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Circulation. published online September 10, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

DOI: 10.1161/CIRCULATIONAHA.112.112607

Long-Term Cardiovascular Risk of NSAID Use According to Time Passed After First-Time Myocardial Infarction: A Nationwide Cohort Study

Running title: *Olsen et al.; NSAIDs and Long-Term Risk after MI*

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Journal Subject Codes: [4] Acute myocardial infarction; [8] Epidemiology; [27] Other Treatment; [135] Risk Factors

DOI: 10.1161/CIRCULATIONAHA.112.112607

Abstract:

Background - The cardiovascular risk after the first myocardial infarction (MI) declines rapidly during the first year. We analyzed whether the cardiovascular risk associated with using nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with the time elapsed following first-time MI.

Methods and Results - We identified patients aged 30 years or older admitted with first-time MI in 1997–2009 and subsequent NSAID use by individual-level linkage of nationwide registries of hospitalization and drug dispensing from pharmacies in Denmark. We calculated the incidence rates of death and a composite endpoint of coronary death or nonfatal recurrent MIs associated with NSAID use in 1-year time intervals up to 5 years after inclusion and analyzed risk by using multivariable adjusted time-dependent Cox proportional-hazard models. Of the 99,187 patients included, 43,608 (44%) were prescribed NSAIDs after the index MI. There were 36,747 deaths and 28,693 coronary deaths or nonfatal recurrent MIs during the 5 years of follow-up. Relative to non-current treatment with NSAIDs, the use of any NSAID in the years following MI was persistently associated with an increased risk of death (hazard ratio (HR) 1.59 (95% confidence interval (CI) 1.49–1.69) after 1 year and HR 1.63 (CI 1.52–1.74) after 5 years) and coronary death or nonfatal recurrent MI (HR 1.30 (CI 1.22–1.39) and HR 1.41 (CI 1.28–1.55).

Conclusions - The use of NSAIDs is associated with persistently increased coronary risk regardless of time elapsed after first-time MI. We advise long-term caution in using NSAIDs for patients after MI.

Key words: mortality; myocardial infarction; prognosis; non-steroidal anti-inflammatory drugs (NSAIDs); selective cyclooxygenase (COX)-2 inhibitors

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Introduction

There has been much focus recently on the cardiovascular risk of commonly used nonsteroidal anti-inflammatory drugs (NSAIDs). In 2007, the American Heart Association published a focused update discouraging the use of NSAIDs for patients with established cardiovascular disease.[1] Despite this, many patients with cardiovascular disease receive NSAIDs, albeit for shorter periods. We have previously demonstrated not only that NSAIDs are harmful among patients with myocardial infarction(MI) or heart failure but also that this risk is prevalent even after short treatment periods.[2] Establishing the cardiovascular safety profile of NSAIDs is imperative since patients with established cardiovascular disease and the general population widely use NSAIDs. MI is associated with a high risk of death and recurrent cardiovascular events, especially immediately following MI. The risk of death or recurrent MI after the first MI is elevated in the year after the initial event but approximates baseline levels after 5-10 years. Because using NSAIDs after the first MI has been demonstrated to increase the risk of death or recurrent MI, understanding the long-term trends in this condition is important: whether using NSAIDs presents the greatest risk in the first year after the first MI and declines as the years pass or whether using NSAIDs changes the declining incidence of cardiovascular risk in the years after the first MI. If the latter is true, long-term caution with these agents after MI may need to be recommended. This uncertainty prompted us to examine the cardiovascular risk associated with episodes of NSAID use in relation to time elapsed after MI in a nationwide cohort of patients with first-time MI in Denmark.

Methods

Study Design and Data Sources

This study was a nationwide cohort study of patients with first-time MI in Denmark. The study

period began on January 1, 1997 and ended on December 31, 2009. All residents of Denmark are provided with a permanent and unique personal identification number that enables linkage between administrative registries. Our nationwide cohort study linked national registry data relevant to hospitalization, pharmacy prescription claims and deaths.

The Danish National Patient Registry has registered all hospital admissions in Denmark since 1978.[3] Each admission is registered by one primary diagnosis and, if appropriate, one or more secondary diagnoses according to the International Classification of Diseases (ICD): by the 8th revision (ICD-8) until 1994 and by the 10th revision (ICD-10) after 1994.

The Danish Registry of Medicinal Product Statistics has recorded all prescriptions dispensed from pharmacies in Denmark since 1995.[4] The Registry classifies each drug according to the international Anatomical Therapeutic Chemical (ATC) system and includes information about strength, formulation, date of dispensing and quantity dispensed.

We obtained information about patients' vital status (dead or alive) from the Civil Registration System through Statistics Denmark. The Centralized Civil Registry keeps records on vital status and registers all deaths within 14 days. We obtained the cause of death from the Danish Registry of Causes of Death, in which immediate and underlying causes are recorded using ICD-10.

The Integrated Database for Labour Market Research provided data on socioeconomic status. The Database is based on information on taxed income gathered by government tax authorities. We defined socioeconomic status according to average annual gross household income during the 5 years before the index MI excluding the year of the index MI. We divided the cohort into quintiles according to the average annual income of the patients.

Participants

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In the Danish National Patient Registry, we identified a cohort of all patients 30 years or older with first-time admission for MI (ICD-10 I21–I22) from 1997 to 2009. The diagnosis of MI has been validated with a specificity exceeding 90%.[5] The first admission for MI implied that the Danish National Patient Registry had not registered any earlier admission for MI in the previous 19 years. This method has been used previously.[2,6] To avoid selection bias in the exposure allocation caused by the high mortality associated with the MI, the cohort was restricted to individuals still alive 30 days after discharge. We followed the patients until the outcome of interest, emigration or the end of the study period (December 31, 2009), whichever came first.

Drug Use

Denmark's health care system reimburses some medicine expenses, and all pharmacies are thus required to register all dispensed drug prescriptions, which ensures complete registration. During the study period, the only NSAID available in Denmark over the counter without a prescription was ibuprofen (since November 1, 2001) and only in low (200-mg) doses and in limited quantity (100 tablets) at each dispensing. All other NSAIDS analyzed were available by prescription only. We identified all filled prescriptions for NSAIDs (ATC code M01A) in the Danish Registry of Medicinal Product Statistics. We performed separate analyses for the two selective cyclooxygenase (COX)-2 inhibitors celecoxib (M01AH01) and rofecoxib (M01AH02) and the most commonly used non-selective NSAIDs: ibuprofen (M01AE01), diclofenac (M01AB05) and naproxen (M01AE02). All other NSAIDs excluding glucosamine (M01AX05) were combined in a common group called "other NSAIDs". Concomitant treatment status was defined for the following cardiovascular drugs: beta-blockers (ATC C07), angiotensin-converting enzyme (ACE) inhibitors and angiotensin-2 receptor blockers ([ARBs] ATC C09), loop diuretics (ATC C03C) and spironolactone (ATC C03D). We defined pharmaceutically treated diabetes using

prescriptions of glucose-lowering medication (ATC A10), as done previously.[7]

Dose and Duration of Treatment

The Danish Registry of Medicinal Product Statistics does not include information on the prescribed daily dosage of the medication. We therefore estimated the daily dosage when each new prescription was dispensed by calculating the average dosages from up to 7 consecutive prescriptions. This method allowed the dosage to change when a new prescription was dispensed. The method used to determine the dose and treatment duration has been described previously.[8, 9]

Comorbidity

We defined comorbidity using diagnoses at discharge from index MI as specified in the Ontario acute MI mortality prediction rules.[10] To further enhance the comorbidity index, we identified discharge diagnoses up to 1 year before the index hospitalization.[11] To define high-risk patients, we used concomitant use of loop diuretics or glucose-lowering drugs as proxies for heart failure or diabetes, respectively.[9]

Study Outcome

The study outcomes examined were: 1) all-cause death and 2) the combined endpoint of death caused by coronary artery disease (coronary death, ICD-10 codes I20–I25) or readmission for nonfatal MI (ICD-10 codes I21–I22).

Statistical Analysis

We calculated unadjusted rates of death and of the composite endpoint of coronary death or the incidence of nonfatal recurrent MI per 100 person-years for NSAID treatment in general. We used time-dependent Cox proportional hazard models to analyze the risk of death and the risk of the composite endpoint of coronary death or nonfatal recurrent MI associated with NSAID use.

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Terms for all individual NSAIDs were included, with the reference composed of those not taking any NSAIDs at that time. Exposure to NSAIDs was included as a time-dependent covariate in the models, ensuring that patients were only considered at risk when exposed to the respective drug. Each individual could have multiple independent treatment courses with the same drug but also with different drugs. To analyze time variation in risk, we defined 6 exposure periods up to 5 years after discharge from the first MI and included them as time-dependent covariates in the proportional hazard models. All models were adjusted for age, sex, year of index hospitalization, concomitant medication, comorbidity and socioeconomic status. **Table 1** lists the variables. We found the assumptions on proportional hazards, the linearity of continuous variables and lack of interaction to be valid unless otherwise indicated.

We performed Cox proportional hazard analysis with time-dependent variables and incidence rates using the Stata statistical package, version 11 (Stata-Corp LP, College Station, TX, USA). We performed all other statistical analysis and data management using the SAS statistical software package, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patients

From 1997 to 2009, 128,418 patients were admitted with first-time MI; 99,187 (77%) were alive 30 days after discharge and were included in the study. Men comprised 64% of the study cohort, and the mean age was 69 (standard deviation (SD) 13.0) years. **Table 1** and **Figure 1** describe in detail the baseline characteristics of the study cohort and the distribution between NSAID groups.

Of the 99,187 patients included, 43,608 (44%) filled at least one prescription of NSAIDs

during follow-up.

Figure 1 in the supplemental material shows the use pattern of NSAIDs in the cohort during the study period. For each separate year, the percentages of the cohort receiving NSAID one year after the first MI increased from 1997 to 2001. From 2001 and especially after 2003, the NSAID use declined.

Outcomes

During follow-up, 36,747 (37%) patients died and 28,693 (29%) experienced a composite event of coronary death or nonfatal recurrent MI. The death rates per 100 person-years were calculated for NSAID treatment in general and for the individual NSAIDs compared with non-current treatment (**Figure 2** and **Supplemental Figure 2a–f**). **Figure 2** shows a persistently increased risk of death associated with the use of NSAIDs in general. The results from the Cox proportional hazard model showed a consistently increased risk of death among patients receiving any NSAID during the 5 years of follow-up relative to non-current use of NSAIDs. Use of diclofenac was associated with the highest risk (**Figure 3**).

We calculated the incidence rates of the composite endpoint of coronary deaths or nonfatal recurrent MIs per 100 person-years for NSAID treatment in general and for the individual NSAIDs (**Figure 4** and **Supplemental Figure 3a–f**). We found a persistently increased rate of the composite outcome associated with using NSAIDs relative to the non-current use of NSAIDs. The Cox proportional hazard model showed significantly increased risk among patients using NSAIDs in general and for each drug separately, especially for diclofenac (**Figure 5**).

Sensitivity Analysis

The effect of unmeasured confounders cannot be excluded. Our calculations showed that, if 20%

of the cohort treated with NSAIDs had an unmeasured confounder or a combination of confounders, the confounder would have to elevate the risk by a factor of 4.4–5.4 to explain the increased risk of all-cause mortality observed in our study (**Supplemental Figure 4**). Using the Wald test, we examined interactions between the use of NSAID and the available covariates and found no clinically important interactions. Terms for all individual NSAIDs were included, with the reference composed of those not taking any NSAIDs at that time. To determine whether the prevalence of use of the various other medicines affected the estimates, we repeated the models with the reference group only comprising the patients who did not take any NSAID at any time. The results remained the same (not shown). To analyze the impact of adjusting the Cox models, we calculated the crude hazard ratios for all-cause mortality (**Supplemental Table 1a**) and coronary death or nonfatal recurrent MI (**Supplemental Table 2a**). Further, we analyzed the effect of age and sex (**Supplemental Tables 1b–c** and **2b–c).**Additional sensitivity Cox analysis demonstrated that malignancy, use of loop or glucose lowering drugs at baseline were more likely to predict use of NSAIDs. (**Supplemental Table 3**).

Discussion

We examined the cardiovascular risk of NSAIDs in relation to the time elapsed after first-time MI in this nationwide study. We demonstrated that the proportional increase in the risk of death and of a composite endpoint of coronary death or nonfatal recurrent MI in post-MI patients receiving NSAIDs was independent of the time elapsed after their first MI. Notably, the risk associated with using NSAIDs remained virtually unchanged throughout all 5 years after discharge from hospital after the first MI.

The risks of cardiovascular mortality and morbidity are well-known complications after MI. The risk is highest soon after the MI but declines as time passes and eventually corresponds

to the risk of the background population after 5–10 years.[12] However, knowledge about the cardiovascular safety of NSAIDs in the years following MI is limited. Although we also previously reported an increased risk of death and reinfarction associated with using NSAID among such patients, we did not specifically analyze whether the risk associated with NSAIDs depended on the time elapsed after the primary event in that study.[9] We demonstrated dose-related excess mortality associated with the use of NSAIDs, and our results indicated an acute or subacute effect of NSAIDs, since the events were closely tied to the timing of taking the drugs. To our knowledge, the present study is the first one designed to focus on the risk of death and a composite of coronary death and nonfatal MI associated with NSAIDs in relation to the time elapsed after MI. We found that the use of NSAIDs was associated with a persistently increased cardiovascular risk in the years following MI, thus indicating that the cardiovascular risk of taking NSAIDs during the first year after MI remains similar to that after 5 years. The incidence rates showed persistent increased absolute risks during the 5 years among the patients taking any NSAID, whereas the risk among the patients not taking NSAIDs declines: for example, the risk decreases substantially after the first MI (**Figures 2 and 4**). Since these drugs are widely used and concern about their safety is growing, further investigation is needed to clarify whether long-term caution in using these agents after MI should be recommended. It would seem prudent to limit NSAID use among patients with cardiovascular disease and to get the message out to clinicians taking care of these patients that NSAIDs are potentially harmful, even 5 years after MI. Thus, a persistent focus on the risk of NSAIDs is warranted among patients who have experienced MI.

Clinical Implications

Along with other recent reports of the adverse cardiovascular effects of NSAIDs, the current data

provide further evidence that using COX-2 inhibitors and non-selective NSAIDs may increase the risk of severe adverse cardiovascular events.[13-23] The results from the past decades have shown that the cardiovascular safety of pharmacotherapy can have massive implications, and the risk–benefit ratio of all NSAIDs and the over-the-counter availability of nonselective NSAIDs such as diclofenac or ibuprofen in many countries should be reconsidered. Physicians should consider alternatives to NSAID therapy based on individual patient characteristics, but it is worrying that the use of NSAIDs remains high[24] even though the risk of these drugs is well established in the literature, and particularly worrying that some NSAIDs remain available over the counter.[9, 25] Among the conventional nonselective NSAIDs, the cardiovascular risk of naproxen has been much debated, but it is widely accepted that naproxen is probably the NSAID with the safest cardiovascular risk profile, and some reports have even suggested that naproxen protects against cardiovascular risk.[22, 26, 27] In accordance with other studies, we found that naproxen was the NSAID with the lowest relative cardiovascular risk, and the results might indicate that naproxen should be preferred if NSAID treatment cannot be avoided. Nevertheless, naproxen was associated with a higher risk of gastrointestinal bleeding than rofecoxib, and gastrointestinal bleeding among patients with MI is associated with poor prognosis.[28] Indeed, the adverse prognostic effects of gastrointestinal bleeding further support a very conservative approach to using NSAIDs among patients with MI. The absence of large-scale comparative trials of long-term safety and efficacy hampers determining the appropriate pain relief for patients with established cardiovascular disease. Thus, large systematic reviews of the risks and benefits of a broad range of various analgesic agents are warranted.[29, 30] Epidemiological studies such as ours cannot establish causality, but in a field of research with no randomized controlled trials, we find it particularly important to report associations between drugs and adverse events

that can affect patient prognosis.

Strengths and Limitations

The strength of this study lies in its completeness of data from a whole country. The Danish National Patient Registry and the Danish Registry of Medicinal Product Statistics are known to be accurate.[3, 4] This complete registration of all residents of Denmark, including those outside the labour market, diminishes the risk of selection bias. All pharmacies in Denmark are required to register all dispensed drug prescriptions, ensuring complete registration.[4,5] During our study period, the only NSAID that was available over the counter in Denmark was ibuprofen (since November 1, 2001), but only in low dosage (200 mg) and with a maximum purchase of 100 tablets. Such NSAID use having major effects in this study is therefore unlikely. To confirm our results, we performed sensitivity analysis with the study period ending on November 1, 2001. The results remained unchanged (not shown). The main limitation is inherent in the observational nature of the study. Information about important clinical parameters is lacking and effects of unmeasured confounders therefore cannot be excluded. The existence of such a confounder or combination of confounders is highly unlikely but not impossible. Our calculations showed that, if an unmeasured confounder or a combination of confounders were present in 20% of the cohort treated with NSAIDs, the confounder would have to elevate the risk of all-cause mortality by a factor of 4.4–5.4.

Confounding by indication may have contributed to the results, and we acknowledge that lack of information about the indications for NSAID treatment is a limitation of the study. However, such confounding probably cannot fully explain our results. To test for these biases, we performed sensitivity analysis that supported our results. Rheumatic diseases are common reasons for NSAID use, and previous studies have reported an increased risk of coronary artery

disease among patients with rheumatoid arthritis.[31-33] We therefore performed the analysis excluding patients with rheumatoid arthritis, which did not change the results (not shown). The risk differed between the individual NSAIDs, which are used for similar indications, and the degree of COX-2 inhibition (as reported in the literature) was clearly correlated with the risk, which also indicates the predominant importance of the drugs (rather than the drug indications) for the results. Moreover, we have previously reported a clear dose-dependent increase in risk associated with NSAIDs.[9] Further, given the evidence from randomized controlled trials and other observational studies of adverse cardiovascular effects of selective COX-2 inhibitors and nonselective NSAIDs,[13-23] we do not believe that confounding by indication alone could have driven the results. This is further supported by the fact that an unmeasured confounder had to elevate the risk more than 4-fold to explain the risk increase by NSAIDs we demonstrated. We found a stronger relation to all cause mortality ratherr than cause specific mortality, which may be due to an underestimation of the cardiovascular component in death registration of these patients. We were studying a group of patients with a major coronary event and we therefore find it likely that most deaths in this population are influenced by the coronary component. Thus when these patients die from pulmonary disease, infection etc –then death was influenced by their heart disease.

Aspirin is available over the counter, which explains why the fraction of patients who fill prescriptions for aspirin is relatively low. Another consequence of this is that we do not have information on whether using NSAIDs may lead to prematurely discontinuing aspirin. We assume that most patients who did not fill a prescription for aspirin were treated with over-the-counter aspirin, since medication adherence has been documented to be high among patients in Denmark after MI.[27,34] Our use of prescription data without knowing whether patients adhere to

treatment is another possible bias. Patients may not take their prescribed medication, and unfortunately, there is no way around this problem in observational studies. Nevertheless, nonadherence would tend to dilute the observed association between the exposure and outcome. Information bias is another limitation, as patients do not necessarily take their medicines as prescribed and in temporal sequence.

Conclusion

In conclusion, our study demonstrated that NSAID use among patients with first-time MI was associated with persistently increased risk of all-cause mortality and of a composite of coronary death or nonfatal recurrent MI, respectively, for at least 5 years thereafter. These results support previous findings that NSAIDs have no apparent safe treatment window among patients with MI. Further studies are warranted to evaluate the cardiovascular safety of NSAIDs, but at this point the overall evidence suggests advising caution in using NSAIDs at all times after MI.

Funding Sources: Anne-Marie Schjerning Olsen has received an unrestricted grant from the Department of Cardiology, Copenhagen University Hospital Gentofte, Denmark. The funding source had no influence on study design, interpretation of the results or the decision to submit the article.

Conflict of Interest Disclosures: None.

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DOI: 10.1161/CIRCULATIONAHA.112.112607

Table 1. Baseline characteristics of the total study population and individual treatment groups.

			Exposure group						
Characteristic	**Total population** N (%)	**No NSAID** N (%)	**Overall NSAID** N (%)	**Rofecoxib** N (%)	**Celecoxib** N (%)	**Ibuprofen** N (%)	**Diclofenac** N (%)	**Naproxen** N (%)	**Other NSAIDs** N (%)
Total patients	99,187(100)	55,579(56.0)	43,608(44.0)	3,635(3.7)	3,761(3.8)	26,428(26.6)	14,543(14.7)	2,406(2.4)	13,266(13.4)
Mean age (SD), y	68.9(13.2)	70.2(12.9)	66.1(12.9)	70.1(12.2)	70.2(11.8)	64.4(12.9)	64.7(12.5)	64.7(12.4)	67.4(12.5)
Women	36,102(36.4)	20,853(37.5)	15,249(35.0)	1,760(49.0)	1,842(49.0)	8,497(32.2)	4,683(32.2)	732(30.4)	5,229(39.4)
Men	63,085(63.6)	34,726(62.5)	28,359(65.0)	1,875(51.0)	1,919(51.0)	17,931(67.8)	9,860(67.8)	1,674(69.6)	8,037(60.6)
Co-morbidity									
Cardiac arrhythmias	10,515(10.6)	6,977(12.6)	3,538(8.1)	352(9.7)	344(9.2)	1,873(7.1)	1,095(7.5)	156(6.5)	1,090(8.2)
Peripheral vascular disease	1,543(1.6)	1,005(1.8)	538(1.2)	55(1.5)	63(1.7)	289(1.1)	162(1.1)	24(1.0)	174(1.3)
Cerebral vascular disease	4,646(4.7)	3,136(5.6)	1,510(3.5)	164(4.5)	162(4.3)	799(3.0)	456(3.1)	65(2.7)	456(3.4)
Diabetes with complications	4,470(4.5)	2,773(5.0)	1,697(3.9)	149(4.1)	145(3.9)	1,014(3.8)	555(3.8)	91(3.8)	472(3.6)
Acute renal failure	854(0.9)	651(1.2)	203(0.5)	23(0.7)	17(0.5)	105(0.4)	49(0.3)	9(0.4)	49(0.4)
Chronic renal failure	1,338(1.4)	1,044(1.9)	294(0.7)	26(0.7)	20(0.5)	157(0.6)	75(0.5)	10(0.4)	71(0.6)
Malignancy	680(0.7)	481(0.9)	199(0.5)	10(0.3)	16(0.4)	109(0.4)	63(0.4)	6(0.3)	51(0.4)
Shock	1,001(1.0)	692(1.3)	309(0.7)	32(0.9)	22(0.6)	152(0.6)	95(0.7)	27(1.1)	94(0.7)
COPD	994(1.0)	660(1.2)	334(0.8)	31(0.9)	28(0.7)	167(0.6)	97(0.7)	19(0.8)	120(0.9)
Gastric ulcer	1,516(1.5)	985(1.8)	531(1.2)	82(2.3)	68(1.8)	259(1.0)	137(0.9)	21(0.9)	179(1.4)
Concomitant medical treatment									
Beta-blockers	73,313(73.9)	40,251(72.4)	33,062(75,8)	2,478(68.2)	2,598(69.1)	20,409(77.2)	11,244(77.3)	1,826 (75.9)	9,926 (74.8)
ACE inhibitors	44,834(45.2)	26,248(47.2)	18,586(42.6)	1,434(39.5)	1,529 (40.7)	11,121(42.1)	5,993(41.2)	1,007(41.9)	5,546(41.8)
Statins	61,269(61.8)	34,447(62.0)	26,822(61.5)	1,485(40.9)	1,601(42.6)	17,119(64.8)	9,068(62.4)	1,446(60.1)	7,582(57.2)
ASA	57,450(57.9)	34,004(61.2)	23,446(53.8)	1,386(38.1)	1,489(39.6)	14,578(55.2)	7,591(52.2)	1,250(52.0)	6,671(50.3)
Clopidogrel	44,642(45.0)	27,190(48.9)	17,452(40.0)	605(16.6)	773(20.6)	11,116(42.1)	5,515(37.9)	873(36.3)	4,682(35.3)
Spironolactone	8,437(8.5)	5,444(9.8)	2,993(6.9)	290(8.0)	322(8.6)	1,654(6.3)	873(6.0)	165(6.9)	889(6.7)
Loop-diuretics	38,587(38.9)	23,658(42.6)	14,929(34.2)	1,647(45.3)	1,675(44.5)	8,214(31.1)	4,503(31.0)	794(33.0)	4,856(36.6)
Glucose lowering drugs	12,176(12.3)	7,238(13.0)	4,938(11.3)	429(11.8)	442(11.8)	2,956(11.2)	1,653(11.4)	257(10.7)	1,510(11.4)
PCI	32,094(32,4)	18,734(33.7)	13,360(30.6)	558(15.4)	607(16.1)	8,645(32.7)	4,435(30.5.)	736(30.1)	3,588(27.1)
Socioeconomic factors									
Yearly family income in quintiles									
0	19,347(19.5)	11.255(20.3)	8,092(18.6)	1,052(28.9)	1,018(27.1)	4,428(16.8)	2.478(17.0)	462(19.2)	2,895(21.8)
1	19.302(19.5)	11,362(20.4)	7,940(18.2)	883(24.3)	946(25.2)	4,297(16.3)	2,469(17.0)	401(16.7)	2,649(20.0)
2	19,793(20.0)	11,285(20.3)	8,508(19.5)	641(17.6)	655(17.4)	5,165(19.5)	2,825(19.4)	435(18.1)	2,638(19.9)
3	20,177(20.3)	10,846(19,5)	9,331(21.4)	619(17.0)	669(17.8)	6,033(22.8)	3,301(22.7)	586(24.2)	2,675(20.2)
4 (highest)	20,568(20.7)	10,831(19.5)	9,737(22.3)	440(12.1)	473(12.6)	6,505(24.6)	3,470(23.9)	522(21.7)	2,409(18.3)

SD: standard deviation; MI: acute myocardial infarction; COPD: chronic obstructive pulmonary disease; ACE-inhibitors: angiotensin converting enzyme-inhibitors; ASA: acetylsalicylic acid; PCI: percutaneous coronary intervention

DOI: 10.1161/CIRCULATIONAHA.112.112607

Figure Legends:

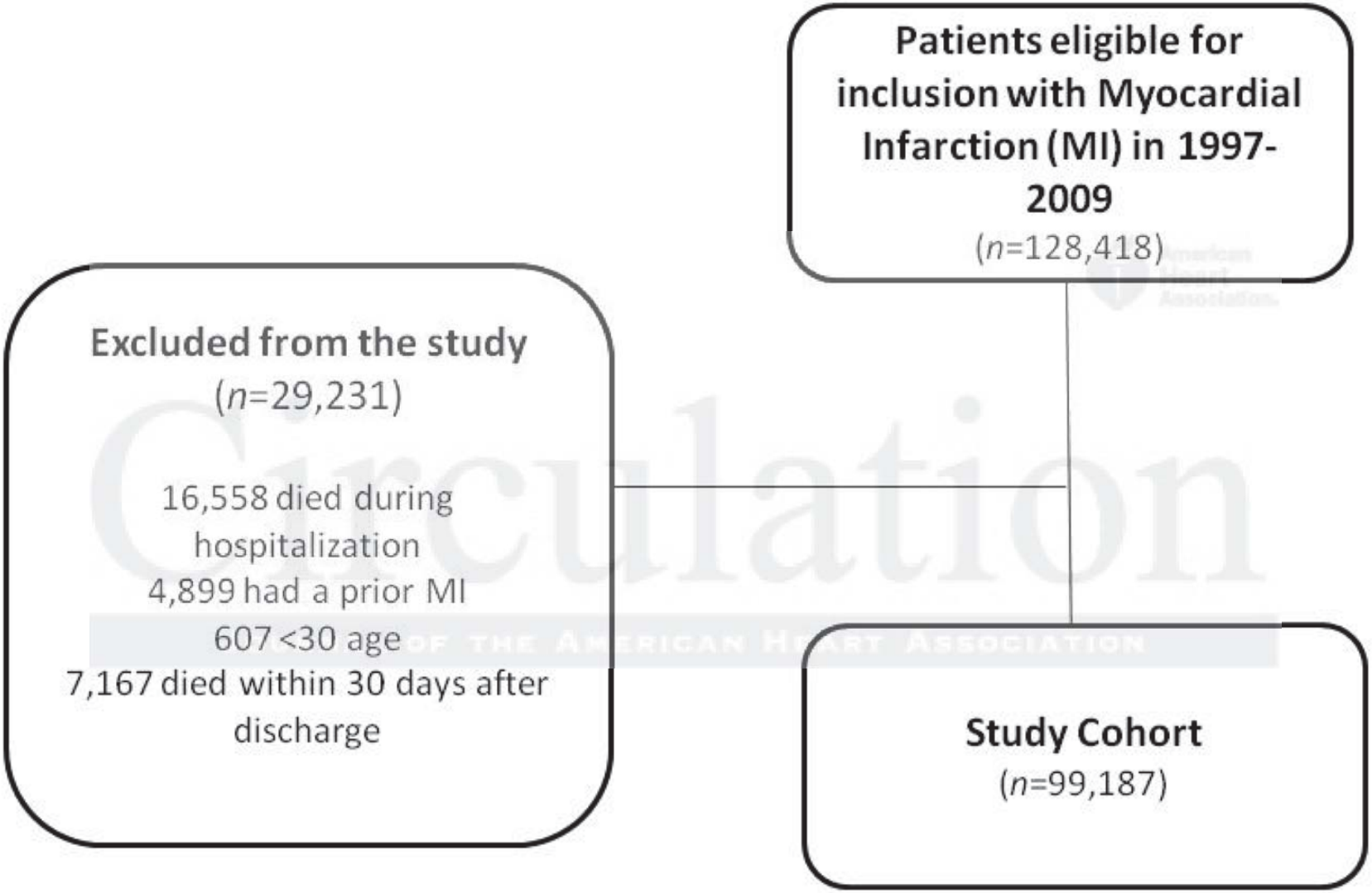
Figure 1. Study flow diagram.

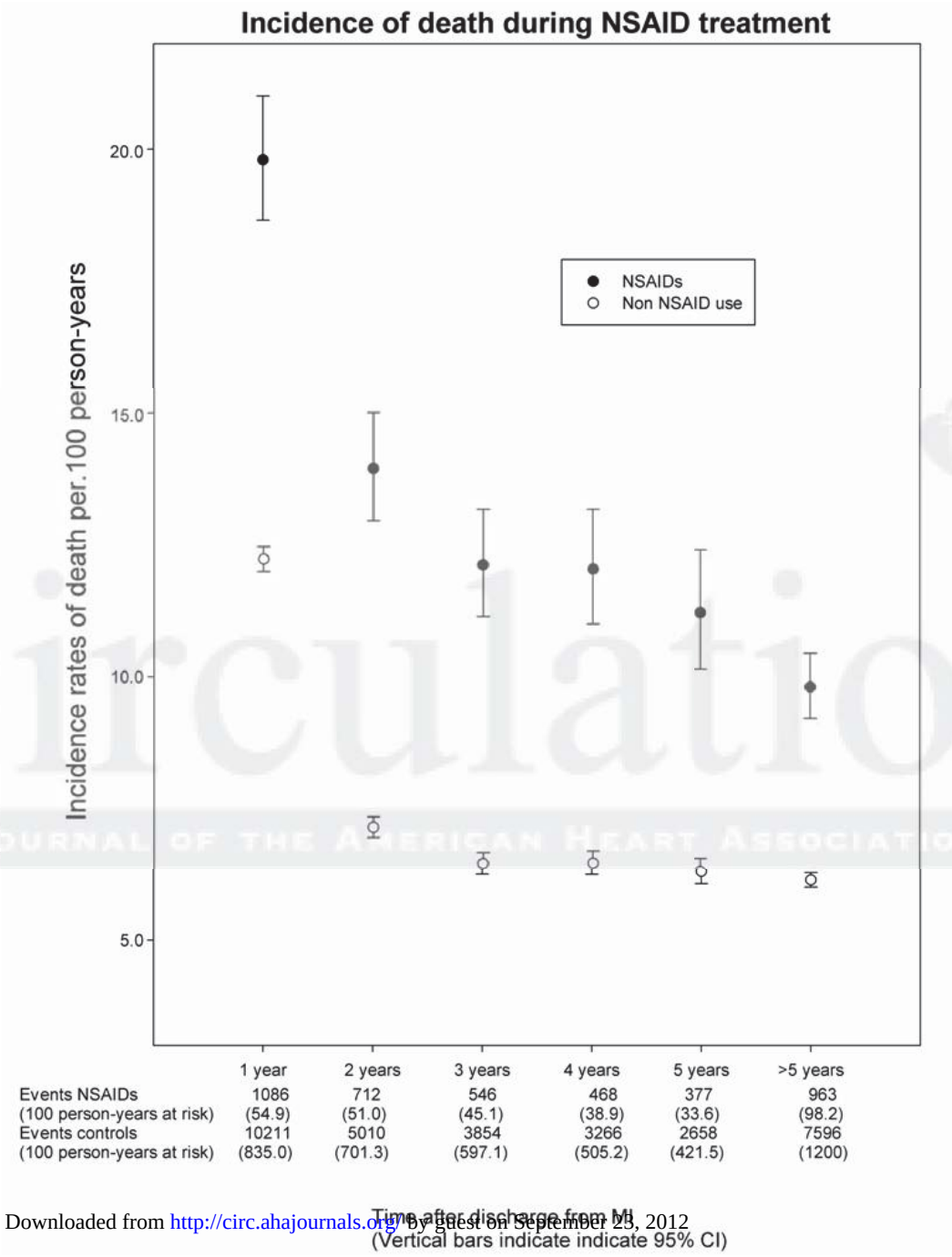
Figure 2. Death rates per 100 person-years during treatment with NSAIDs in general. The treatment periods are divided for each year up to 5 years after myocardial infarction (MI). The vertical bars indicate 95% confidence intervals.

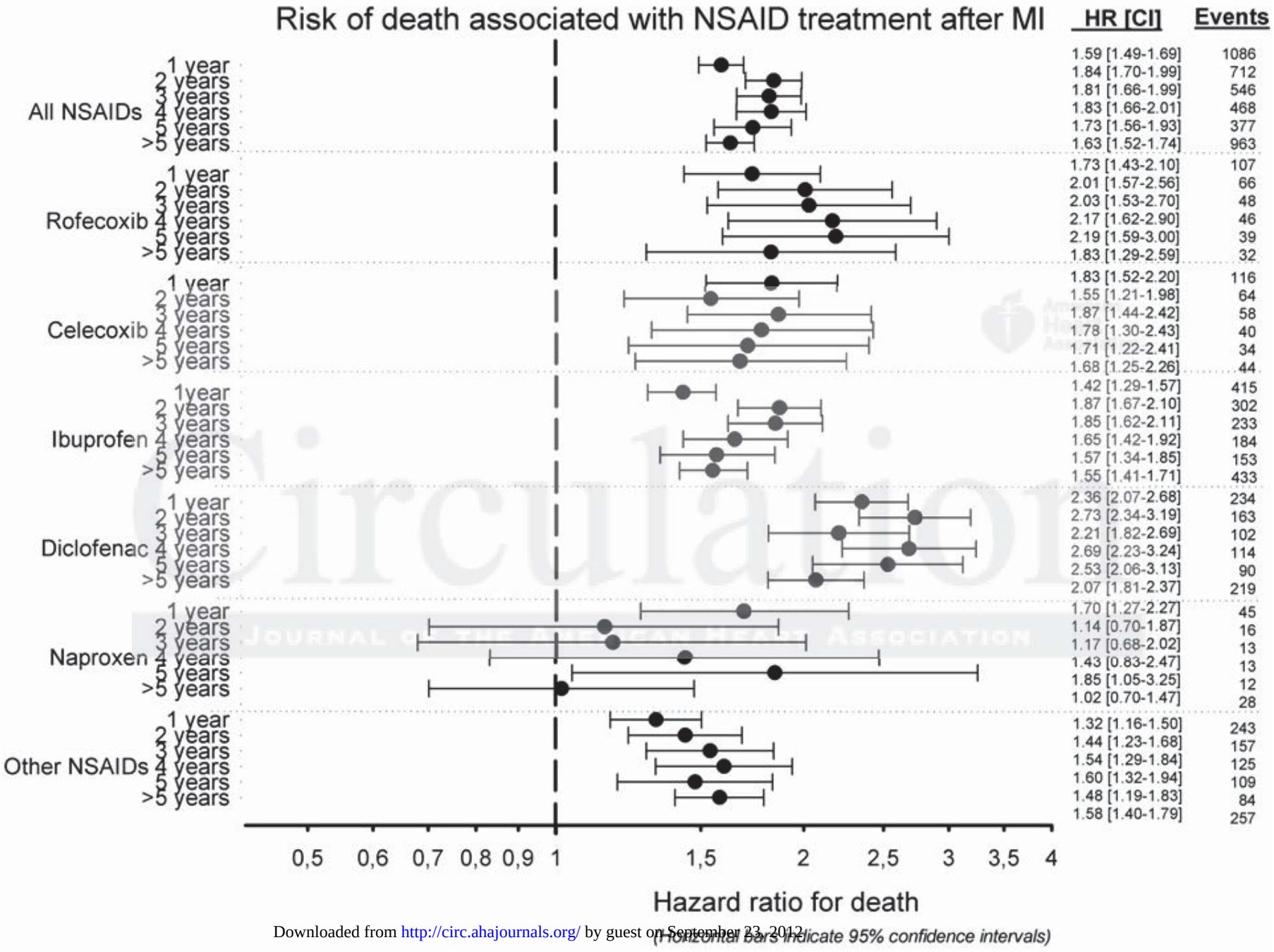
Figure 3. Time-dependent Cox proportional-hazard analysis of the risk of death according to the time of NSAID treatment among patients with prior myocardial infarction (MI).

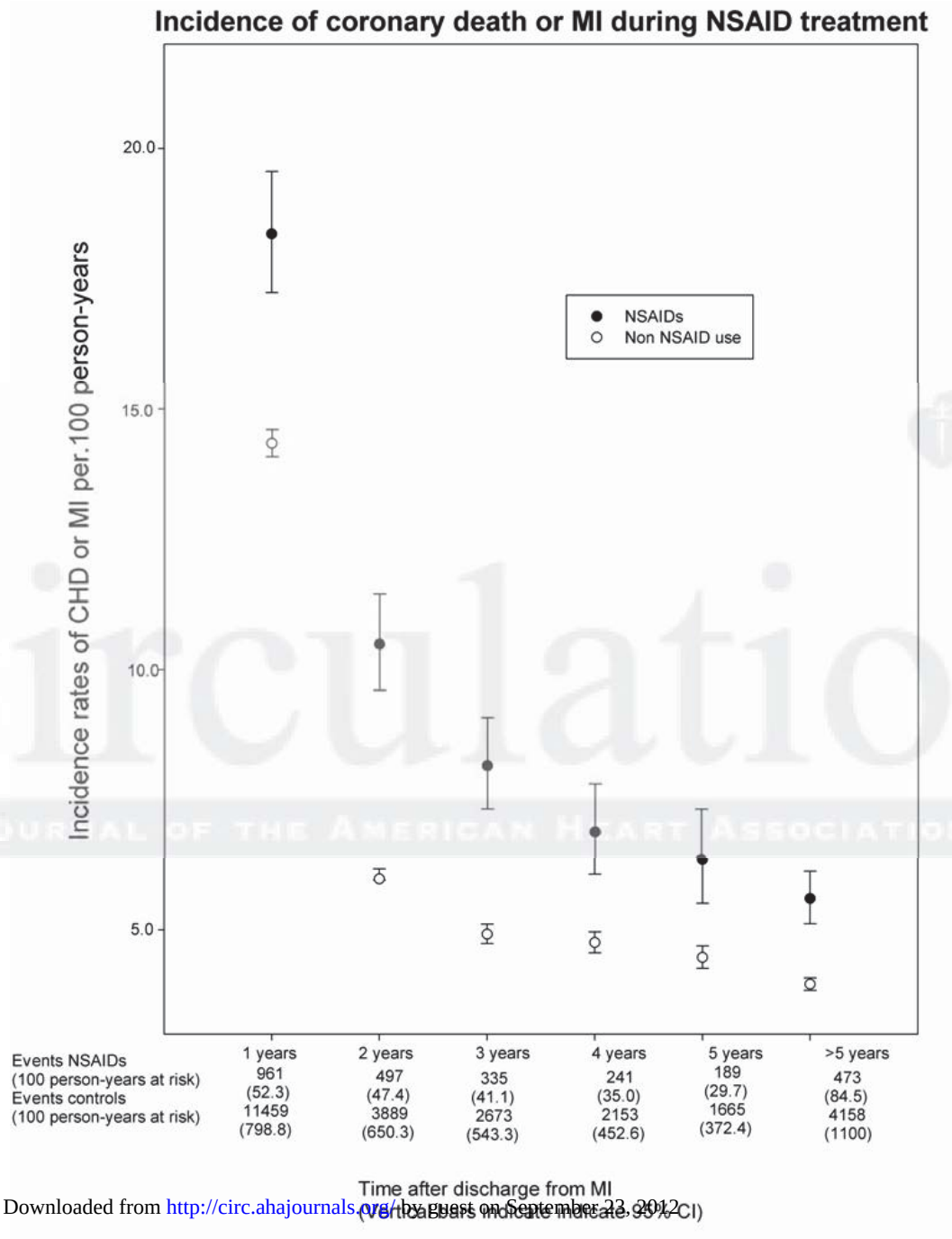
Figure 4. Incidence rates of coronary death (CHD) or nonfatal myocardial infarction (MI) per 100 person-years during treatment with NSAIDs in general. The treatment periods are divided for each year up to 5 years after MI. The vertical bars indicate 95% confidence intervals.

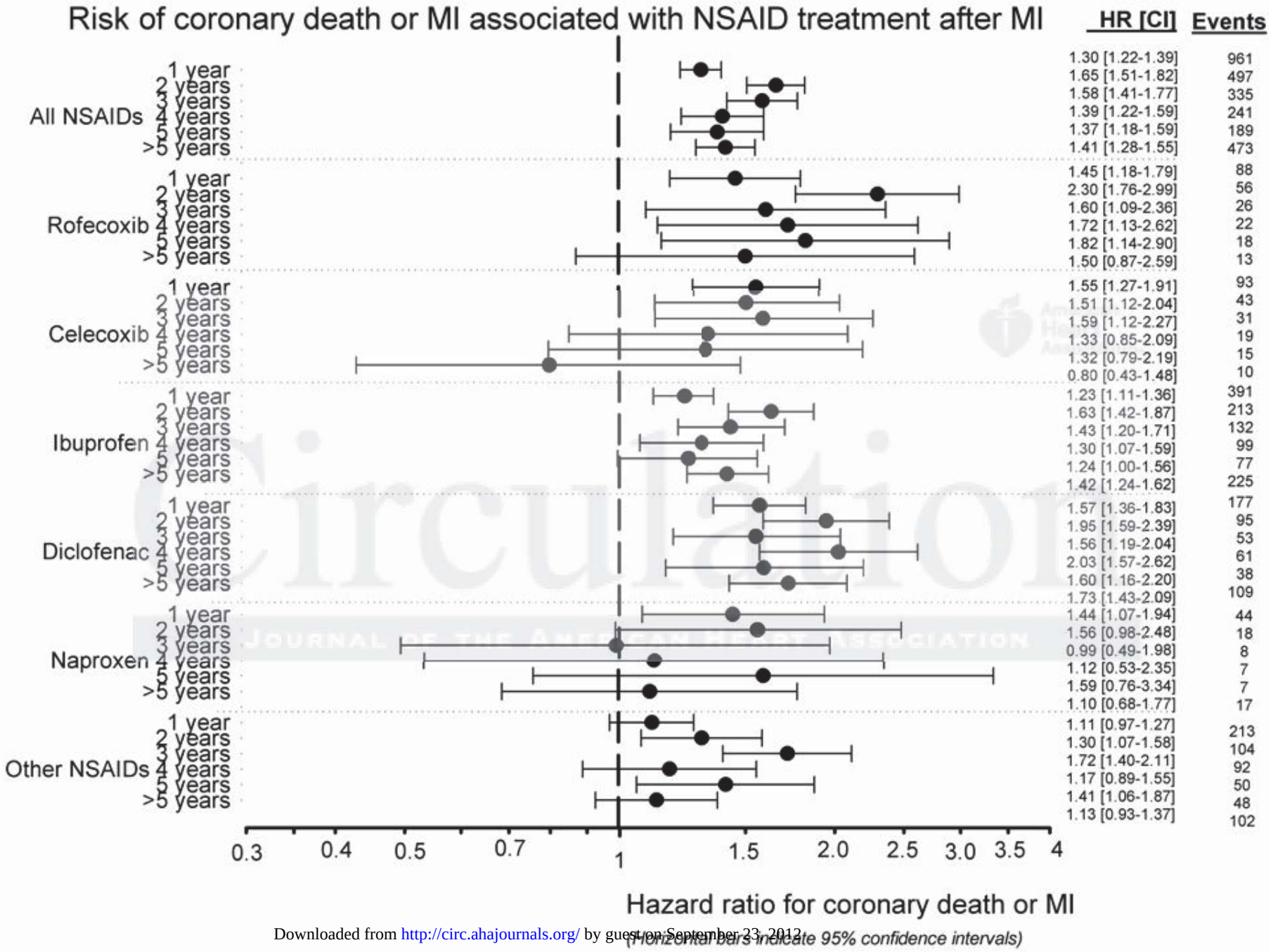
Figure 5. Time-dependent Cox proportional-hazard analysis of the risk of coronary death or nonfatal myocardial infarction (MI) according to the time of NSAID treatment among patients with prior MI.











“SUPPLEMENTAL MATERIAL”

Supplemental figure legends

Supplemental Figure 1 The utilization pattern of NSAID treatment. Percent of the cohort receiving NSAIDs, a year after discharge from myocardial infarction, in the study period 1997-2008

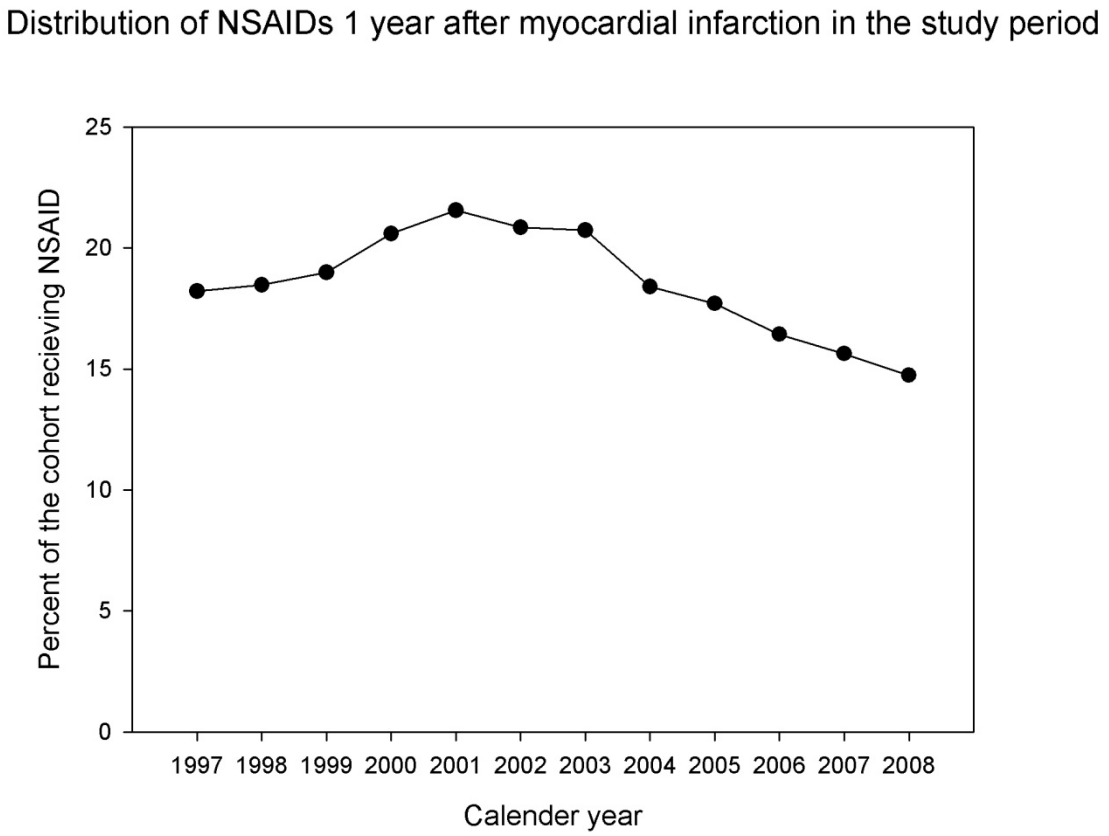
Supplemental Figure 2a- f. Incidence rates of death per 100 person years during treatment with the individual NSAID. Treatment periods are divided for each year up to 5 years after myocardial infarction (MI). Vertical bars indicate 95% confidence intervals.

Supplemental Figure 3a-f Incidence rates of coronary death (CHD) or nonfatal myocardial infarction per 100 person years during treatment with the individual NSAID. Treatment periods are divided for each year up to 5 years after myocardial infarction (MI). Vertical bars indicate 95% confidence intervals

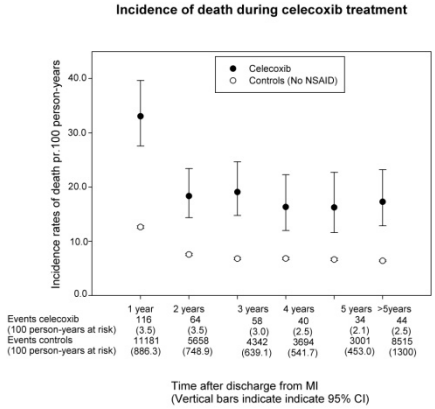
Supplemental Figure 4 Required size for an unmeasured confounder 20%.

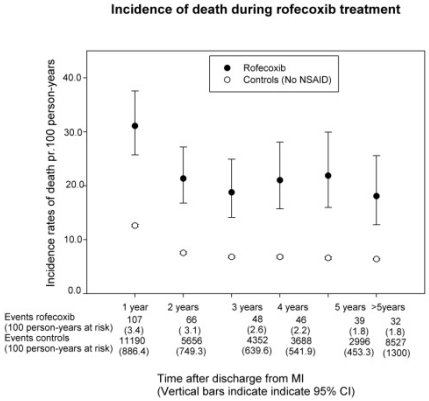
OREC =association between drug use category and confounder; RRCD=association between confounder and all cause mortality.

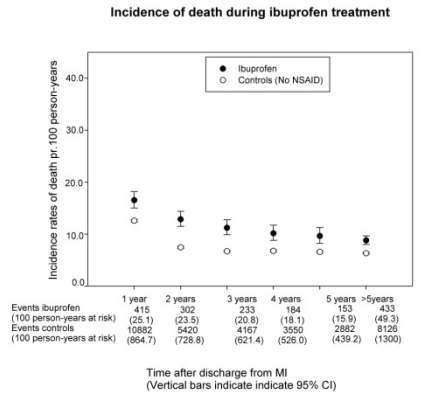
Supplemental Figure 1

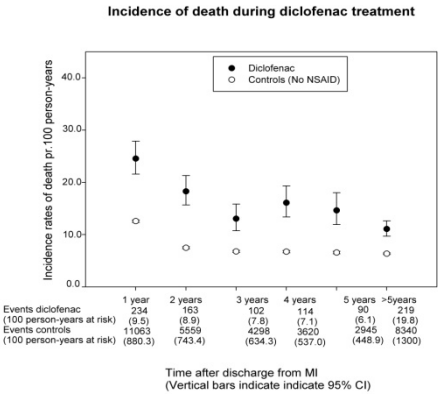


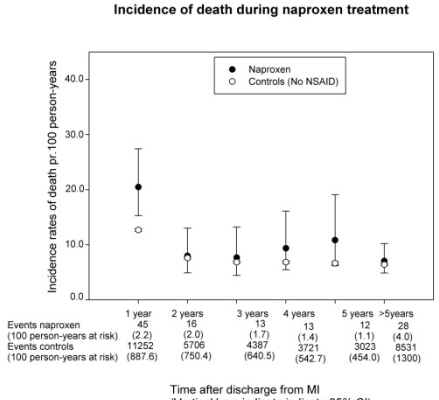
Supplemental Figure 2a-f

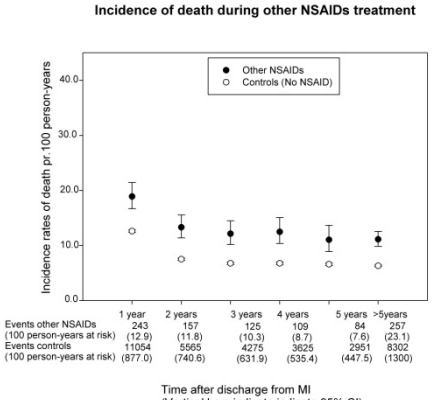




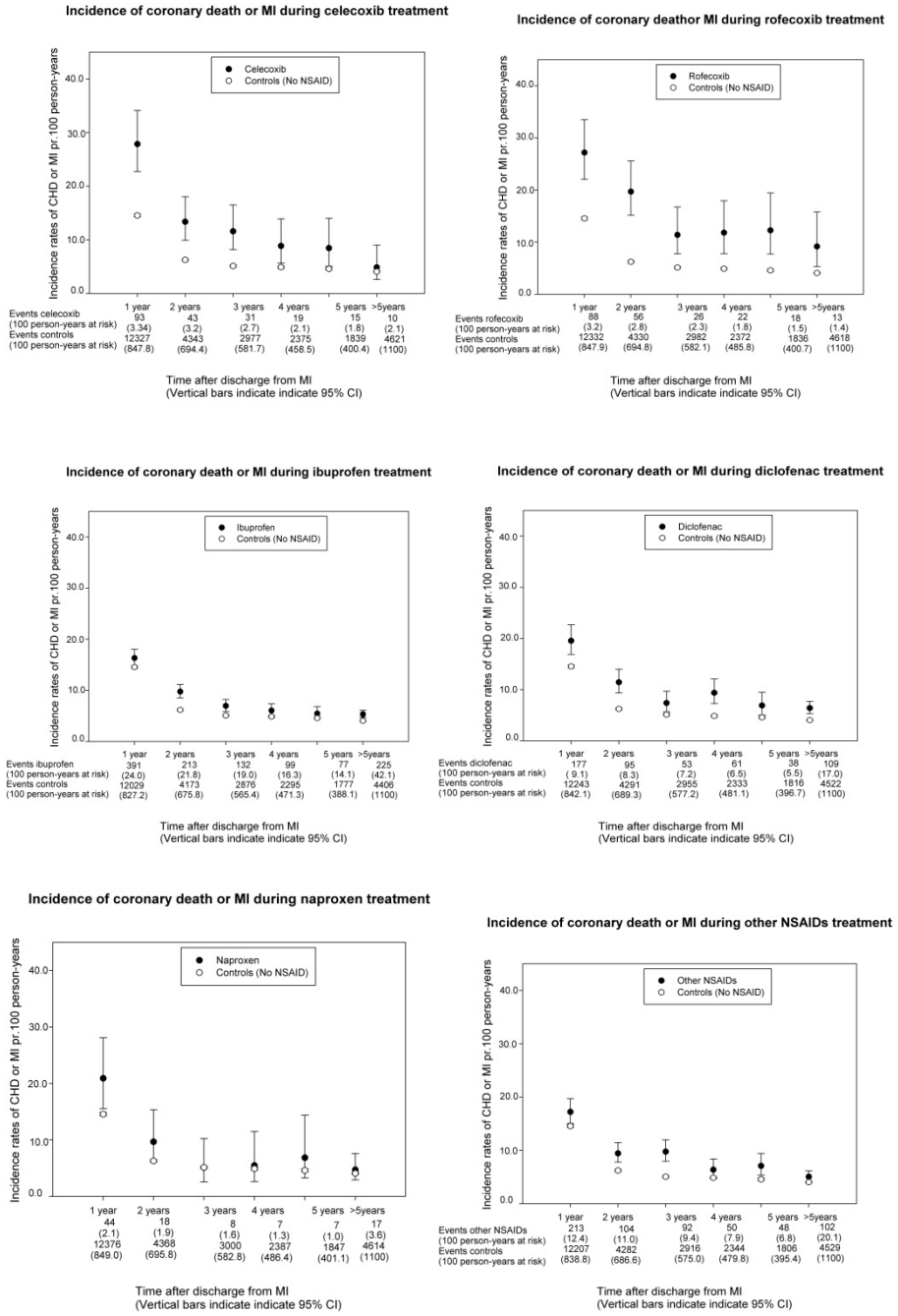




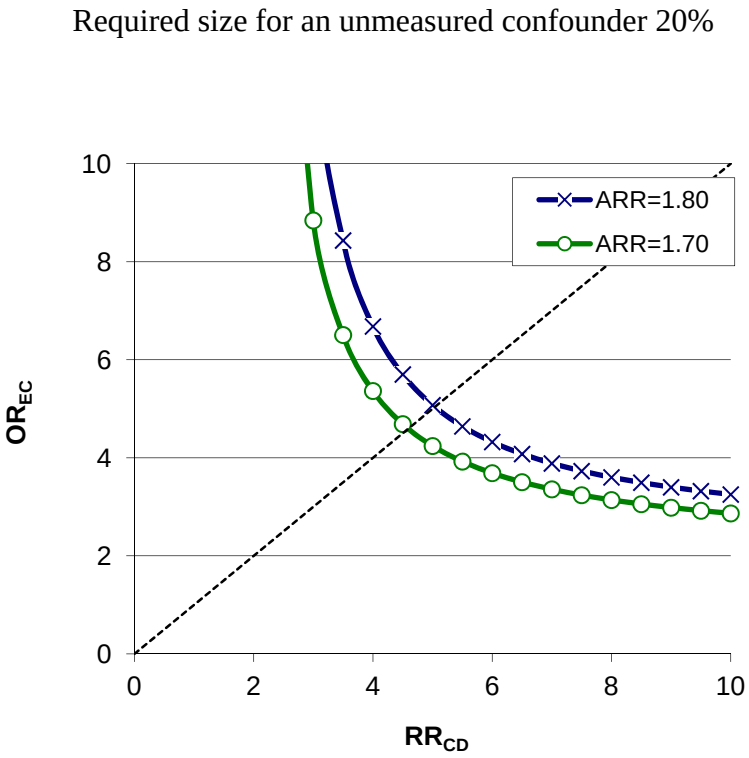




Supplemental Figure 3a-f



Supplemental Figure 4



Supplemental table 1a: Crude Hazard ratios for all-cause mortality

NSAID	Crude Hazard ratio for all-cause mortality	p-value	Confidence intervals 95 %	
Overall NSAID				
1 year	1.69	<0.001	1.59	1.80
2 year	1.95	<0.001	1.81	2.11
3 year	1.88	<0.001	1.72	2.05
4 year	1.86	<0.001	1.69	2.05
5 year	1.78	<0.001	1.60	1.98
>5 years	1.60	<0.001	1.49	1.71
Rofecoxib				
1 year	2.50	<0.001	2.07	3.02
2 year	2.76	<0.001	2.16	3.52
3 year	2.72	<0.001	2.04	3.61
4 year	3.07	<0.001	2.29	4.10
5 year	3.21	<0.001	2.34	4.41
>5 years	2.78	<0.001	1.97	3.94
Celecoxib				
1 year	2.68	<0.001	2.23	3.22
2 year	2.38	<0.001	1.86	3.04
3 year	2.74	<0.001	2.12	3.55
4 year	2.33	<0.001	1.71	3.18

5 year	2.33	<0.001	1.66	3.27
>5 years	2.68	<0.001	1.99	3.60
Ibuprofen				
1 year	1.37	<0.001	1.23	1.50
2 year	1.71	<0.001	1.52	1.92
3 year	1.67	<0.001	1.46	1.90
4 year	1.50	<0.001	1.29	1.74
5 year	1.46	<0.001	1.24	1.72
>5 years	1.40	<0.001	1.27	1.53
Diclofenac				
1 year	2.03	<0.001	1.78	2.31
2 year	2.42	<0.001	2.07	2.83
3 year	1.91	<0.001	1.57	2.32
4 year	2.38	<0.001	1.98	2.87
5 year	2.23	<0.001	1.81	2.75
>5 years	1.74	<0.001	1.52	1.99
Naproxen				
1 year	1.68	0.001	1.25	2.25
2 year	1.05	0.841	0.64	1.72
3 year	1.13	0.658	0.66	1.95
4 year	1.37	0.254	0.80	2.37
5 year	1.62	0.097	0.92	2.85
>5 years	1.08	0.684	0.75	1.57

Other NSAID				
1 year	1.53	<0.001	1.35	1.74
2 year	1.74	<0.001	1.49	2.04
3 year	1.78	<0.001	1.49	2.12
4 year	1.83	<0.001	1.51	2.21
5 year	1.65	<0.001	1.33	2.05
>5 years	1.75	<0.001	1.55	1.98

Supplemental table 1b: Hazard ratios only adjusted of age for all cause mortality

NSAID	**Crude Hazard ratio for all cause mortality**	**p-value**	**Confidence intervals 95 %**	
Overall NSAID				
1 year	1.64	<0.001	1.54	1.74
2 year	1.89	<0.001	1.75	2.05
3 year	1.87	<0.001	1.71	2.04
4 year	1.87	<0.001	1.70	2.06
5 year	1.78	<0.001	1.60	1.99
>5 years	1.67	<0.001	1.56	1.78
Rofecoxib				
1 year	1.81	<0.001	1.50	2.19
2 year	2.18	<0.001	1.71	2.77

3 year	2.17	<0.001	1.63	2.88
4 year	2.32	<0.001	1.73	3.10
5 year	2.41	<0.001	1.76	3.31
>5 years	2.15	<0.001	1.52	3.04
Celecoxib				
1 year	2.01	<0.001	1.67	2.41
2 year	1.76	<0.001	1.37	2.25
3 year	2.12	<0.001	1.63	2.74
4 year	1.92	<0.001	1.41	2.63
5 year	1.85	<0.001	1.32	2.59
>5 years	1.91	<0.001	1.42	2.56
Ibuprofen				
1 year	1.48	<0.001	1.34	1.63
2 year	1.88	<0.001	1.68	2.12
3 year	1.87	<0.001	1.64	2.13
4 year	1.67	<0.001	1.44	1.93
5 year	1.61	<0.001	1.36	1.89
>5 years	1.56	<0.001	1.42	1.72
Diclofenac				
1 year	2.32	<0.001	2.04	2.64
2 year	2.75	<0.001	2.35	3.21
3 year	2.21	<0.001	1.81	2.68
4 year	2.75	<0.001	2.28	3.31

5 year	2.58	<0.001	2.09	3.19
>5 years	2.08	<0.001	1.82	2.38
Naproxen				
1 year	1.81	<0.001	1.35	2.42
2 year	1.14	<0.001	0.70	1.86
3 year	1.19	<0.001	0.69	2.05
4 year	1.41	<0.001	0.82	2.44
5 year	1.90	<0.001	1.08	3.36
>5 years	1.12	<0.001	0.77	1.63
Other NSAID				
1 year	1.34	<0.001	1.18	1.52
2 year	1.47	<0.001	1.26	1.72
3 year	1.58	<0.001	1.32	1.89
4 year	1.68	<0.001	1.39	2.03
5 year	1.53	<0.001	1.23	1.90
>5 years	1.62	<0.001	1.43	1.83

Supplemental table 1c: Hazard ratios only adjusted of sex for all-cause mortality

NSAID	**Crude Hazard ratio for all-cause mortality**	**p-value**	**Confidence intervals 95 %**	
Overall NSAID				
1 year	1.65	<0.001	1.55	1.76

2 year	1.92	<0.001	1.77	2.07
3 year	1.85	<0.001	1.70	2.03
4 year	1.84	<0.001	1.67	2.02
5 year	1.76	<0.001	1.58	1.96
>5 years	1.59	<0.001	1.48	1.70
Rofecoxib				
1 year	2.31	<0.001	1.91	2.80
2 year	2.59	<0.001	2.03	3.30
3 year	2.55	<0.001	1.92	3.39
4 year	2.89	<0.001	2.16	3.87
5 year	3.00	<0.001	2.19	4.12
>5 years	2.62	<0.001	1.85	3.70
Celecoxib				
1 year	2.49	<0.001	2.07	2.99
2 year	2.21	<0.001	1.73	2.83
3 year	2.56	<0.001	1.98	3.32
4 year	2.18	<0.001	1.60	2.98
5 year	2.21	<0.001	1.57	3.09
>5 years	2.51	<0.001	1.87	3.38
Ibuprofen				
1 year	1.36	<0.001	1.23	1.49
2 year	1.71	<0.001	1.52	1.92
3 year	1.68	<0.001	1.47	1.92

4 year	1.50	<0.001	1.29	1.74
5 year	1.47	<0.001	1.25	1.73
>5 years	1.40	<0.001	1.27	1.54
Diclofenac				
1 year	2.04	<0.001	1.79	2.32
2 year	2.45	<0.001	2.10	2.86
3 year	1.96	<0.001	1.61	2.38
4 year	2.43	<0.001	2.01	2.92
5 year	2.28	<0.001	1.85	2.81
>5 years	1.77	<0.001	1.55	2.03
Naproxen				
1 year	1.68	0.001	1.25	2.25
2 year	1.06	0.805	0.65	1.74
3 year	1.14	0.635	0.66	1.97
4 year	1.38	0.245	0.80	2.38
5 year	1.63	0.090	0.93	2.88
>5 years	1.08	0.679	0.75	1.57
Other NSAID				
1 year	1.48	<0.001	1.30	1.68
2 year	1.68	<0.001	1.43	1.97
3 year	1.71	<0.001	1.43	2.05
4 year	1.76	<0.001	1.46	2.13
5 year	1.59	<0.001	1.28	1.97

>5 years	1.70	<0.001	1.50	1.92

Supplemental table 2a: Crude Hazard ratios for coronary death or Re-MI

NSAID	**Crude Hazard ratio for coronary death or recurrent myocardial infarction**	**p-value**	**Confidence intervals 95 %**	
Overall NSAID				
1 year	1.38	<0.001	1.30	1.48
2 year	1.76	<0.001	1.60	1.93
3 year	1.66	<0.001	1.48	1.86
4 year	1.45	<0.001	1.27	1.65
5 year	1.42	<0.001	1.22	1.65
>5 years	1.41	<0.001	1.29	1.56
Rofecoxib				
1 year	1.96	<0.001	1.59	2.41
2 year	3.11	<0.001	2.39	4.05
3 year	2.21	<0.001	1.50	3.25
4 year	2.40	<0.001	1.58	3.65
5 year	2.61	<0.001	1.64	4.16
>5 years	2.19	0.005	1.27	3.77

Celecoxib				
1 year	2.05	<0.001	1.67	2.51
2 year	2.11	<0.001	1.57	2.85
3 year	2.23	<0.001	1.57	3.18
4 year	1.78	0.012	1.13	2.79
5 year	1.77	0.027	1.07	2.95
>5 years	1.17	0.629	0.63	2.17
Ibuprofen				
1 year	1.21	<0.001	1.10	1.34
2 year	1.57	<0.001	1.37	1.82
3 year	1.37	<0.001	1.15	1.63
4 year	1.24	0.035	1.02	1.52
5 year	1.19	0.129	0.95	1.50
>5 years	1.33	<0.001	1.16	1.52
Diclofenac				
1 year	1.46	<0.001	1.26	1.70
2 year	1.83	<0.001	1.49	2.24
3 year	1.44	<0.001	1.09	1.88
4 year	1.94	<0.001	1.50	2.50
5 year	1.51	0.012	1.09	2.08
>5 years	1.58	<0.001	1.31	1.91
Naproxen				
1 year	1.55	0.004	1.16	2.09

2 year	1.54	0.066	0.97	2.45
3 year	1.00	0.998	0.50	2.00
4 year	1.12	0.766	0.53	2.35
5 year	1.49	0.295	0.71	3.12
>5 years	1.15	0.575	0.71	1.85
Other NSAID				
1 year	1.27	<0.001	1.11	1.45
2 year	1.50	<0.001	1.24	1.83
3 year	1.91	<0.001	1.56	2.36
4 year	1.29	0.071	0.98	1.71
5 year	1.54	0.003	1.16	2.05
>5 years	1.25	0.028	1.02	1.52

Supplemental table 2b: Hazard ratios only adjusted of age for coronary death or Re-MI

Overall NSAID	**Hazard ratio for coronary death or recurrent myocardial infarction**	**p-value**	**Confidence intervals 95 %**	
1 year	1.36	<0.001	1.27	1.45
2 year	1.72	<0.001	1.56	1.88
3 year	1.65	<0.001	1.47	1.84
4 year	1.44	<0.001	1.26	1.65

5 year	1.42	<0.001	1.22	1.65
>5 years	1.44	<0.001	1.31	1.58
Rofecoxib				
1 year	1.57	<0.001	1.27	1.93
2 year	2.61	<0.001	2.00	3.40
3 year	1.85	0.002	1.25	2.72
4 year	1.95	0.002	1.28	2.97
5 year	2.09	0.002	1.31	3.33
>5 years	1.79	0.036	1.04	3.09
Celecoxib				
1 year	1.67	<0.001	1.36	2.05
2 year	1.71	<0.001	1.27	2.31
3 year	1.85	0.001	1.30	2.64
4 year	1.52	0.069	0.96	2.39
5 year	1.54	0.095	0.93	2.56
>5 years	0.93	0.821	0.50	1.73
Ibuprofen				
1 year	1.28	<0.001	1.16	1.41
2 year	1.66	<0.001	1.45	1.91
3 year	1.46	<0.001	1.23	1.74
4 year	1.32	0.006	1.08	1.62
5 year	1.26	0.047	1.00	1.58
>5 years	1.41	<0.001	1.24	1.62

Diclofenac				
1 year	1.58	<0.001	1.36	1.83
2 year	1.97	0.001	1.61	2.42
3 year	1.57	<0.001	1.20	2.07
4 year	2.10	<0.001	1.63	2.70
5 year	1.64	0.002	1.19	2.26
>5 years	1.76	<0.001	1.46	2.13
Naproxen				
1 year	1.60	0.002	1.19	2.15
2 year	1.61	0.043	1.01	2.56
3 year	1.02	0.956	0.51	2.05
4 year	1.13	0.738	0.54	2.38
5 year	1.63	0.198	0.78	3.42
>5 years	1.17	0.515	0.73	1.89
Other NSAID				
1 year	1.15	0.041	1.01	1.32
2 year	1.34	0.003	1.10	1.63
3 year	1.76	<0.001	1.43	2.17
4 year	1.21	0.179	0.92	1.60
5 year	1.44	0.012	1.08	1.92
>5 years	1.16	0.137	0.95	1.41

Supplemental table 2c: Hazard ratios only adjusted of sex for coronary death or Re-MI

Overall NSAID	**Hazard ratio for**	**p-value**	**Confidence intervals 95 %**

	coronary death or recurrent myocardial infarction			
1 year	1.37	<0.001	1.28	1.47
2 year	1.74	<0.001	1.58	1.91
3 year	1.65	<0.001	1.47	1.85
4 year	1.44	<0.001	1.26	1.64
5 year	1.41	<0.001	1.21	1.64
>5 years	1.41	<0.001	1.28	1.55
Rofecoxib				
1 year	1.89	<0.001	1.53	2.33
2 year	3.02	<0.001	2.32	3.92
3 year	2.14	<0.001	1.46	3.15
4 year	2.33	<0.001	1.53	3.54
5 year	2.52	<0.001	1.59	4.01
>5 years	2.12	0.007	1.23	3.66
Celecoxib				
1 year	1.98	<0.001	1.61	2.42
2 year	2.04	<0.001	1.51	2.75
3 year	2.16	<0.001	1.51	3.07
4 year	1.72	0.019	1.09	2.70
5 year	1.72	0.036	1.04	2.87

>5 years	1.13	0.694	0.61	2.11
Ibuprofen				
1 year	1.21	<0.001	1.09	1.34
2 year	1.57	<0.001	1.37	1.80
3 year	1.37	<0.001	1.15	1.63
4 year	1.24	0.034	1.02	1.52
5 year	1.19	0.126	0.95	1.50
>5 years	1.33	<0.001	1.16	1.52
Diclofenac				
1 year	1.46	<0.001	1.26	1.70
2 year	1.84	<0.001	1.50	2.26
3 year	1.45	0.007	1.11	1.90
4 year	1.95	<0.001	1.51	2.51
5 year	1.52	0.011	1.10	2.10
>5 years	1.59	<0.001	1.32	1.92
Naproxen				
1 year	1.56	0.003	1.16	2.09
2 year	1.55	0.063	0.98	2.47
3 year	1.00	1.000	0.50	2.00
4 year	1.12	0.767	0.53	2.35
5 year	1.49	0.292	0.71	3.13
>5 years	1.15	0.578	0.71	1.84
Other NSAID				

1 year	1.25	0.001	1.09	1.43
2 year	1.48	<0.001	1.22	1.79
3 year	1.88	<0.001	1.53	2.31
4 year	1.27	0.094	0.96	1.68
5 year	1.51	0.005	1.13	2.01
>5 years	1.23	0.043	1.00	1.49

Supplemental Table 3 Cox analysis of factors predicting NSAID use.

Supplemental Table 3

Characteristic	***Hazard Ratio***	***95 % confidence Limits***	
Year			
1998	0.91	0.75	1.11
1999	0.94	0.77	1.14
2000	0.97	0.80	1.18
2001	0.99	0.82	1.21
2002	0.94	0.77	1.15
2003	0.93	0.76	1.13
2004	0.87	0.71	1.06
2005	0.85	0.70	1.04
2006	0.80	0.65	0.98
2007	0.77	0.63	0.94
2008	0.70	0.57	0.85
2009	0.69	0.56	0.86
Age	0.99	0.99	0.99
Sex	0.98	0.96	1.00
Co-morbidity			
Cardiac arrhythmias	0.87	0.84	0.91
Peripheral vascular disease	1.02	0.94	1.11
Cerebral vascular disease	0.90	0.85	0.95

Diabetes with complications	0.97	0.91	1.04
Acute renal failure	0.83	0.72	0.95
Chronic renal failure	0.75	0.67	0.84
Malignancy	1.33	1.16	1.54
Shock	1.02	0.91	1.15
COPD	0.98	0.88	1.10
Gastric ulcer	0.91	0.83	0.99
Concomitant medical treatment			
Beta-blockers	0.95	0.93	0.97
ACE inhibitors	0.94	0.92	0.96
Statins	0.99	0.97	1.01
ASA	1.02	1.00	1.04
Clopidogrel	1.02	0.99	1.05
Spironolactone	0.92	0.88	0.96
Loop-diuretics	1.07	1.04	1.09
Glucose lowering drugs	1.05	1.01	1.10
PCI	0.97	0.94	1.00
Socioeconomic factors	0.97	0.96	0.97