

Electronic Supplementary Material

Cardiovascular Risk Associated with Nonsteroidal Anti-Inflammatory Drug Use in Individuals With and Without Hypertension: A Case-Crossover Study

Drugs and Therapy Perspectives.

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Supplementary Resources

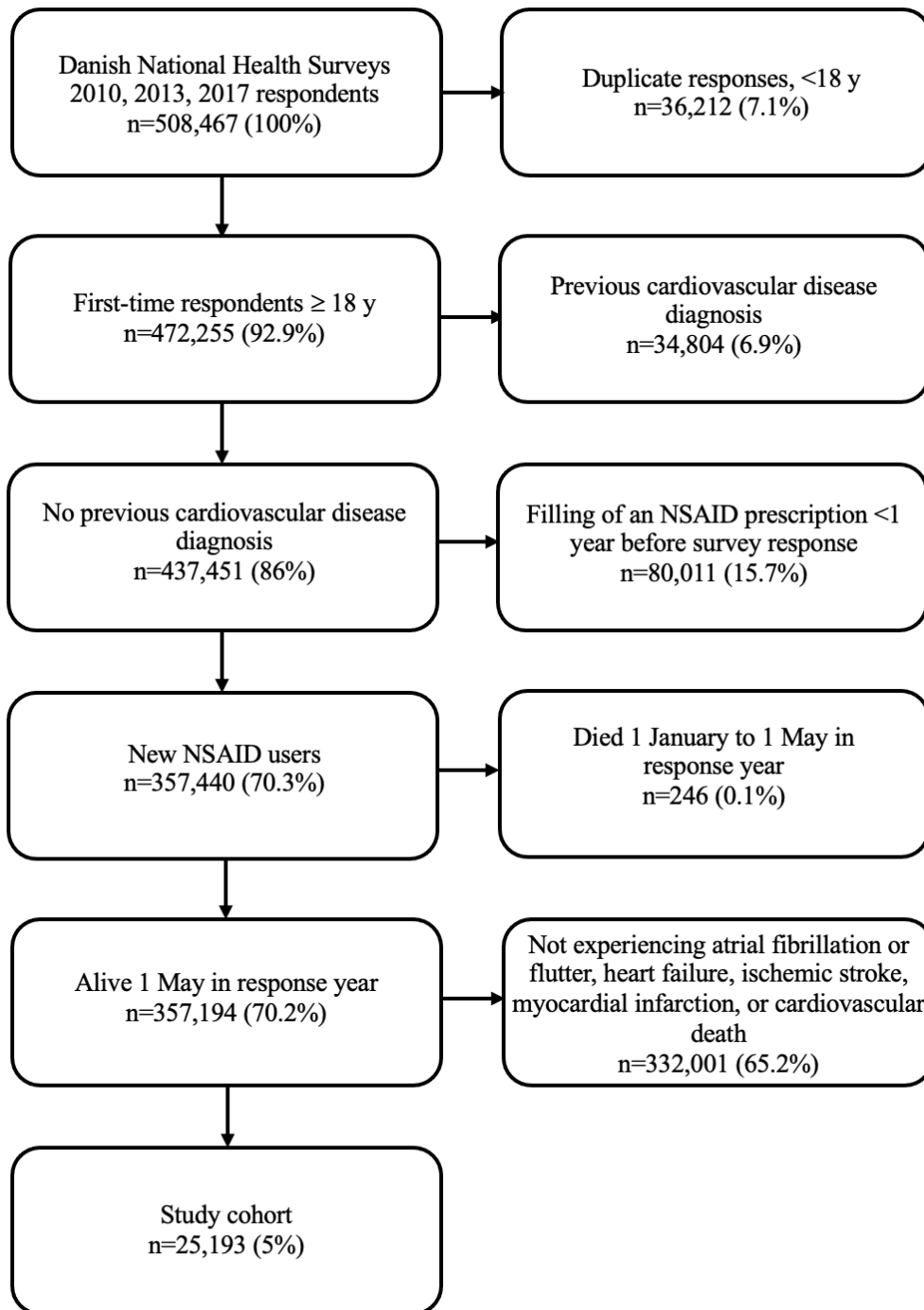
Supplementary Resource 1. *International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical classification (ATC) codes used in the study*

Exposure	Codes
Ibuprofen	ATC: M01AE01, M02AA13
Naproxen	ATC: M01AE02, M01AE52, M01AE56, M02AA12
Diclofenac	ATC: M01AB05, M01AB55, M02AA15
Outcome	Codes
Atrial fibrillation or flutter	ICD-10: I48 (in/outpatient, primary/secondary diagnoses)
Heart failure	ICD-10: I130, I132, I420, I426–I429, I500–I503, I508–I110 (only inpatient, primary diagnoses)
Ischemic stroke (including transient ischemic attack)	ICD-10: G459, I63–I64 (only inpatient, primary diagnoses)
Myocardial infarction	ICD-10: I21 (only inpatient, primary diagnoses)
Comorbidities	Codes
Dementia	ICD-10: F00–F03, F051, G30, G311
Chronic pulmonary disease	ICD-10: I278, I279, J40–J47, J60–J67, J684, J701, J703
Rheumatologic disease	ICD-10: M05, M06, M315, M32–M34, M351, M353, M360
Mild liver disease	ICD-10: B18, K700–K703, K709, K713–K715, K717, K73, K74, K760, K72–K764, K768, K769, Z944
Diabetes with chronic complications	ICD-10: E102–E105, E107, E112–E115, E117, E122–E125, E127, E132–E135, E137, E142–E145, E147
Hemiplegia or paraplegia	ICD-10: G041, G114, G801, G802, G81, G82, G830–G834, G839
Renal disease	ICD-10: I120, I131, N032–N037, N052–N057, N18, N19, N250, Z490–Z492, Z940, Z992
Any malignancy, including leukemia and lymphoma	ICD-10: C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97
Moderate or severe liver disease	ICD-10: I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767
Metastatic solid tumor	ICD-10: C77–C80
AIDS/HIV	ICD-10: B20–B22, B24
Peptic ulcer disease	ICD-10: DK221, DK25, DK26, DK27, DK28
Diabetes without chronic complications	ICD-10: E100, E101, E109–E111, E119–E121, E129–E131, E139–E141, E149
Affective disorder	ICD-10: F30–F34, F38, F39
Comedication	Codes
Antiplatelets	ATC: B01AC
Anticoagulants	ATC: B01AA, B01AB, B01AE, B01AF
Angiotensin-converting enzyme inhibitors	ATC: C09A, C09B
Angiotensin receptor blockers	ATC: C09C, C09D
Beta blockers	ATC: C07
Calcium channel blockers	ATC: C07F, C08, C09BB, C09DB
Diuretics	ATC: C03, C07B–C07D, C08G, C09BA, C09DA
Statins	ATC: C10AA
Glucocorticoids	ATC: H02AB, R03BA
Opioids	ATC: N02A
Acetaminophen	ATC: N02BE01
Anti-migraine drugs	ATC: N02C
Proton pump inhibitors	ATC: A02BC
Antidiabetics	ATC: A10A, A10B
Antidepressants	ATC: N06A
Alfa-adrenergic blockers	ATC: C02A–C02B
Vasodilators	ATC: C02DB, C02DD, C02DG, C04, C05

Supplementary Resource 2. Categorization of hypertension status according to question and response categories used in the Danish National Health Survey

Categories of hypertension status	Question and response options
	<i>For each of the following diseases and health problems, please indicate whether you have it now or have had it in the past.</i>
	Stated for high blood pressure.
Never	No, I have never had it.
Former	Yes, I have had it previously.
Current	Yes, I have it now.

Supplementary Resource 3. Flowchart of study cohort



Abbreviations: y, years of age; NSAID, non-steroidal anti-inflammatory drug.

Supplementary Resource 4. Odds ratios for individual cardiovascular outcomes associated with ibuprofen, naproxen, and diclofenac use in self-controlled case-crossover analyses

Cardiovascular outcomes	Ibuprofen	Naproxen	Diclofenac
	Odds ratio (95% confidence interval)		
Atrial fibrillation or flutter	1.43 (1.24–1.64)	2.28 (1.26–4.13)	2.00 (1.17–3.43)
Heart failure	1.35 (0.94–1.94)	8.90 (0.86–91.61)	0.22 (0.02–2.15)
Ischemic stroke	1.35 (1.07–1.70)	1.61 (0.54–4.82)	1.22 (0.59–2.49)
Myocardial infarction	1.31 (1.02–1.66)	1.60 (0.57–4.51)	1.95 (0.78–4.85)
Cardiovascular death	1.31 (0.97–1.78)	2.73 (0.98–7.60)	2.41 (1.09–5.34)

Note: Odds ratios represent, among individuals experiencing an outcome, the odds of non-steroidal anti-inflammatory drug use on the outcome date but not on a reference date compared with the odds of use on a reference date but not on the outcome date.

Supplementary Resource 5. Direct drug-to-drug case-crossover comparisons of major adverse cardiovascular events for naproxen vs. ibuprofen, diclofenac vs. ibuprofen, and diclofenac vs. naproxen, overall and by hypertension status

	Naproxen vs. ibuprofen	Diclofenac vs. ibuprofen	Diclofenac vs. naproxen
	Odds ratio (95% confidence interval)		
Overall	1.54 (0.99–2.38)	1.18 (0.82–1.71)	0.83 (0.47–1.46)
Hypertension status			
Never	1.18 (0.54–2.55)	1.15 (0.64–2.06)	1.01 (0.38–2.68)
Former	1.09 (0.29–4.17)	1.05 (0.29–3.78)	0.94 (0.16–5.66)
Current	1.70 (0.83–3.51)	1.08 (0.58–2.03)	0.64 (0.26–1.60)

Notes: Odds ratios represent, among individuals experiencing a major adverse cardiovascular event, the odds of exposure to the first-listed non-steroidal anti-inflammatory drug (NSAID) on the outcome date but to the second-listed NSAID on a reference date with the odds of exposure to the second-listed NSAID on the outcome date but to the first-listed NSAID on a reference date. Major adverse cardiovascular events were defined as the composite of atrial fibrillation or flutter, heart failure, ischemic stroke, myocardial infarction, and cardiovascular death.

Supplementary Resource 6. Direct drug-to-drug case-crossover comparisons of individual cardiovascular outcomes for naproxen vs. ibuprofen, diclofenac vs. ibuprofen, and diclofenac vs. naproxen

	Naproxen vs. ibuprofen	Diclofenac vs. ibuprofen	Diclofenac vs. naproxen
Cardiovascular outcomes	Odds ratio (95% confidence interval)		
Atrial fibrillation or flutter	1.61 (0.88–2.97)	1.44 (0.83–2.50)	0.90 (0.40–2.03)
Heart failure	6.89 (0.65–72.76)	0.19 (0.02–1.77)	— ^a
Ischemic stroke	1.22 (0.40–3.73)	0.90 (0.42–1.90)	0.75 (0.20–2.79)
Myocardial infarction	1.25 (0.43–3.62)	1.49 (0.58–3.82)	1.51 (0.36–6.25)
Cardiovascular death	2.13 (0.73–6.18)	1.78 (0.76–4.18)	1.06 (0.26–4.31)

Notes: Odds ratios represent, among individuals experiencing an outcome, the odds of exposure to the first-listed non-steroidal anti-inflammatory drug (NSAID) on the outcome date but to the second-listed NSAID on a reference date with the odds of exposure to the second-listed NSAID on the outcome date but to the first-listed NSAID on a reference date.

^aNot applicable because of few events.

Supplementary Resource 7. Odds ratios for major adverse cardiovascular events associated with ibuprofen, naproxen, and diclofenac use in self-controlled case-crossover analyses, by age group and sex

	Ibuprofen	Naproxen	Diclofenac
	Odds ratio (95% confidence interval)		
Age group (years)			
< 60	1.33 (1.12–1.57)	1.29 (0.63–2.64)	1.80 (0.96–3.37)
60–70	1.49 (1.24–1.78)	2.49 (1.22–5.09)	1.33 (0.65–2.75)
70–80	1.15 (0.93–1.42)	2.07 (0.77–5.59)	1.87 (0.91–3.82)
≥ 80	2.00 (1.46–2.73)	15.33 (1.75–134.01)	1.43 (0.64–3.19)
Sex			
Male	1.35 (1.18–1.54)	2.36 (1.34–4.15)	1.50 (0.91–2.45)
Female	1.44 (1.23–1.68)	1.76 (0.82–3.79)	1.60 (0.90–2.86)

Notes: Odds ratios represent, among individuals experiencing a major adverse cardiovascular event, the odds of non-steroidal anti-inflammatory drug use on the outcome date but not on a reference date compared with use on a reference date but not on the outcome date. Major adverse cardiovascular events were defined as the composite of atrial fibrillation or flutter, heart failure, ischemic stroke, myocardial infarction, and cardiovascular death.