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Effects of Non-Steroid Antirheumatic Drugs on the Cardiovascular System

Giuseppe Cocco[1*] and Philipp Amiet[2]

[*1]*Cardiology Office, Marktgasse 1oA, CH-4310 Rheinfelden*

[2]*Medical Office, Schiffackerweg2, CH-4310 Rheinfelden*

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ABSTRACT

Objective: To assess the effects of non-steroid antirheumatic drugs (NSARDs) on the occurrence of major adverse cardiac events (MACEs) in cardiac patients.

Methods: This is a retrospective observational study. Statistical analysis was performed by self-controlled case-series design. All patients had cardiac diseases. Patients who did not use NSARDs were compared to patients who used these drugs. Laboratory and hemodynamic data were compared at baseline and at the end of the observation (occurrence of either a MACE or, 1 year after begin). MACEs were recorded and related to the use of NSARDs.

Results: MACEs were significantly related to the use of ibuprofen plus paracetamol. Diclofenac, lornoxicam, mefenamin, naproxen, acemetacin, celecoxib and rofecoxib also reduced renal function and increased LDL-C but we did not find an increased risk of MACEs. However, the chance of detecting MACEs is reduced by the fact that these NSARDs were used less frequently than ibuprofen.

The use of NSARDs was associated with decreased renal function and increased blood pressure and LDL-C. NSARDs favored the occurrence of MACEs mainly by reducing renal function.

A confounding condition ought to be considered, because patients taking NSARDs have a reduced physical activity, which is a risk for the occurrence of cardiovascular complications.

Conclusion: Our results confirm previous reports that have shown that the use of NSARDs is associated with an increased risk of MACEs. The regression model analysis shows that MACES are related to the use of ibuprofen plus paracetamol and that this adverse event is statistically related to a decreased renal function.

Keywords: Non-steroid antirheumatic drugs, Adverse cardiovascular events, Renal function

BACKGROUND

Non-steroid antirheumatic drugs (*NSARDs*) are frequently used for the treatment of many conditions and many of these drugs can be bought over the counter. NSARDs differ in chemical structure, pharmacodynamics and pharmacokinetics. These agents block different isoenzymes of cyclooxygenase (*COX*).The inhibition of COX-1 brings about a decrease of prostaglandins at inflammatory sites. The inhibition of COX-2 is associated with alleviation of pain, partly due to reducing levels of prostaglandins in the central nervous system. COX-3 inhibitors interfere with hypothalamic endothelial cells and block COX synthesizing prostaglandins near sensory receptors of sub-diaphragmatic vagal afferents.

It is established that treatment with NSARDs is a potential risk for a decline in renal function and the occurrence of major cardiovascular adverse events (*MACEs*) [1-3].

The mechanisms of adverse events of NSARDs are not fully deciphered. Yet, it is possible that the imbalance between by-products of the COX-1 (thromboxane A2) and COX-2 (prostaglandin) pathways, with an increase of the former and a decrease of the latter, may be responsible for vasoconstriction, platelet activation, subsequent hypertension, and accelerated atherosclerosis [1]. The inhibition of renal prostaglandins may also lead to the sodium retention, peripheral edema, and decompensation of heart failure [1-5]. COX-1 inhibitors induce adverse gastrointestinal side effects, worsen the renal function and increase the risk of MACEs [1-5]. Patients taking COX-1 inhibitors are on average four times more likely to develop gastrointestinal complications than people not taking these drugs [2]. COX-2 inhibitors may also worsen the renal function and favor the occurrence of MACEs [1].

The COX-3 inhibitor paracetamol (acetaminophen) has the potential for hepatic toxicity and, when used at doses of more than 1000 mg, may exert similar adverse events as COX-1 inhibitors [1,6].

Corresponding author: Giuseppe Cocco, M.D., Cardiology Office, Marktgasse 1oA, CH-4310 Rheinfelden, Tel: 004161 831 45 55, Fax: 0041 61 833 97 56; E-mail: praxis@cocco.ch

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The relative risk for the occurrence of MACEs during treatment with NSARDs has been one of the most studied adverse drug reactions and ranges from 1 to 2 [2]. However, the real propensity of different NSARDs in inducing MACEs is as yet a matter of debate. Discording results might be explained not only by dissimilar drug use and quality of observational studies, which lead to high heterogeneity among studies and a possible misjudgment of effects [1,2].

The different propensity of NSARDs in inducing MACEs is likely to be explained by dissimilar effects on prostacyclin and thromboxane A_2 synthesis, endothelial function, nitric oxide production, blood pressure, volume retention and other renal effects [1]. Furthermore, dissimilar pharmacokinetics may contribute to the toxicity profile because the individual half-lives of NSARDs are likely to interfere with different cardiovascular complications.

Systematic reviews have highlighted apparent differences in cardiovascular risk between COX-1 and COX-2 inhibitors. Yet, data on the impact of COX-2 inhibitors on the occurrence of MACEs are conflicting. Indeed, previous studies [6] claimed that the use of COX-2 inhibitors is associated with an increased risk of MACEs. In contrast, a recent meta-analysis [2] found no clear relation between COX-2 inhibitors and MACEs. Furthermore, it is unlikely that an increased cardiovascular risk is a class effect of COX-2 inhibitors, because COX-2 inhibitors may exert different effects on the COX system [1-5]. Indeed, the frequency of MACEs is increased by rofecoxib but is seems to be decreased by celecoxib [4]. A possible explanation for the contrasting effect of these two COX-2 inhibitors might be related to their different pharmacokinetics, the half-life of rofecoxib being long and that of celecoxib short.

Cardiac patients frequently use NSARDs, mostly because of rheumatic pathologies. On the basis of uncertain data on the propensity of NSARDs in inducing MACEs we analyzed the effect of the use of NSARDs in our cardiac patients.

STUDY DESIGN

This is a retrospective observational study. We analyzed data from January 1998 till January 2017.

Population and Definitions

We studied 406 patients with cardiovascular pathologies: coronary artery disease (*CAD*), arterial hypertension, valval heart disease, cardiac arrhythmias, and peripheral arterial disease. CAD was diagnosed by presence of a relevant stenosis in the coronary arteries, and/or a myocardial infarction, in most cases with previous revascularization. Arterial hypertension was classified according to the 2013 ESH/ESC Guidelines [7]. Valval heart disease was diagnosed by the presence of hemodynamically relevant aortic stenosis and/or regurgitation, and of mitral regurgitation. Cardiac arrhythmias were diagnosed from symptomatic premature beats or atrial fibrillation. Peripheral arterial disease was diagnosed from relevant stenosis in non-coronary arteries (e.g. carotid, abdominal aorta and leg arteries).

'Traditional' cardiovascular risk factors were: age, sex, smoking status, blood pressure, glomerular filtration rate (*GFR*), glucose, low-density lipoprotein cholesterol (*LDL-C*), body weight and family history for cardiovascular diseases. Patients who never smoked or stopped since >3 years were considered non-smokers. Physical activity was assessed recording the daily walking steps. Rheumatic pathologies, pulmonary diseases, cancer, thyroid dysfunction, cerebral stroke, psychic disorders, liver pathologies, hemoglobin disorders and psoriasis may influence the occurrence of cardiovascular events and were recorded. Hepatic dysfunction was defined by >3 fold normal values for ASAT / ALAT.

MACEs were defined as all-cause events or re hospitalization or death for a cardiovascular related illness (myocardial infarction, congestive heart failure, cerebral stroke).
The patients were divided into two groups: a) control group (*COGR*), 254 patients (63%) who did not or less than twice per month used NSARDs, and b) observational group (OBGR), 152 patients (37%) who used NSARDs on a regular basis.

STATISTICAL ANALYSIS

Analysis was performed with Statgraphics Centurion software. All statistical tests were two-tailed, and P values of <0.05 were considered to indicate statistical significance. The statistical analysis was based on the self-controlled case-series design [8]. Baseline data were compared to those of the observation period, i.e., the interval from before the use of NSARDs and either the occurrence of MACEs or after 1 year. The observation time was truncated in this manner to minimize time varying confounding, since the self-controlled case-series design does not control for time varying confounding. We included in our analysis patients who had at least one MACE during the observation period.

RESULTS

Demographics (Table 1)

Sex: 100 COGR patients (39%) were male and 154 (61%) female. 62 OBGR patients (41%) were male and 90 (59 %) female. The female/male ratio is similar in both groups. Age was similar in both groups (60 to 63 years).
Weight: in both groups males were significantly (p <00001) heavier than females. The male/female weight difference was similar in both groups.
Smoking status: 64 COGR patients (15%) and 40 OBGR patients (16%) were smokers.

Family history: in both groups 28% of patients had a positive family history for cardiovascular pathologies.

Table 1. Demographics

	COGR (254 patients)		OBGR (152 Patients)	
	Males	Females	Males	Females
Number	100	154	62	90
Age	60 ± 8	61 ± 8	62 ± 7	63 ± 7
Weight	88 ± 12	73 ± 10	84 ± 11	73 ± 10
FA	32	38	32	24
Smokers	39	25	22	18

Legend
Age: years, mean ± 1SD.
Weight: kg, mean ± 1 SD.
FA: Number of patients with positive familial history.
Smokers: Number of smokers.

Concomitant pathologies (Table 2)
47 COGR patients (19%) had degenerative rheumatic pathologies. All OBGR patients had rheumatic disorders. 150 (98%) had degenerative pathologies and 2 (1%) had rheumatoid arthritis.

Lung pathologies (chronic obstructive lung disease, or asthma, or overlap syndrome) were present in 55 COGR patients (22%) and in 35 OBGR patients (23%).

13 COGR patients (5%) had cancer: prostatic cancer(1 man) orchronic lymphopoietic cancers (1man and 8women). 6 OGRP patients (4%) had cancer: prostatic cancer (1 man) or chronic lymphopoietic cancers (6 women).

Thyroid pathology: 28 COGR patients (11%) had a dysfunction,. A man had hyperthyroidism and 27 patients (3 men and 24 women) had hypothyroidism. 15 OBGR patients (10%) (1 man, 14 women) had hypothyroidism. In both groups hypothyroidism was more frequent in females than in males.

Cerebral stroke: 38 COGR patients (15%) and 19 OBGR patients (13%) had a previous cerebral stroke.

32 COGR patients (13%) and 20 OBGR patients (13%) had psychic disorders (anxiety or depressive mood): In both groups women were thrice more frequent than men.

10 COGR patients (4%) and 5 OBGR patients (3%) had mild hepatic dysfunction.

15 COGR patients (6%) and 9 OBGR patients (6%) had psoriasis.

Table 2. Concomitant pathologies

	COGR (254 patients)		OBGR (152 Patients)	
	Number of patients		Number of patients	
	Men	Women	men	Women
Rheumatism	18	29	62	90
Diabetes	20	31	11	20
Lung pathologies	32	23	18	17
Cancer	6	7	2	4
Hyperthyroidism	1	0	0	0
Hypothyroidism	3	24	1	14
Cerebral stroke	18	20	4	15
Psychiatrics	10	22	2	18
Hepatic dysfunction	5	5	1	4
Psoriasis	5	10	2	7

Concomitant medications (Table 3)
Except for NSARDs concomitant medications were similar in the two groups.

Table 3: Concomitant medications

	COGR (254 patients)		OBGR (152 Patients)	
	Number	Percentage	Number	Percentage
ACE-inhibitors	130	51	79	52
A2-blockers	124	48	73	48
β-blockers	190	75	116	76
Bipyridin calcium antagonists	200	79	119	78
Platelets aggregation inhibitors	200	79	119	78
Factor Xa inhibitors	38	15	19	13
Diuretics	190	75	116	76
Statins	220	87	132	87
Oral antidiabetics	51	20	31	20
Insulins	12	5	8	5
Glucocorticoids + β-sympathicomimetics	40	16	23	15
β-sympathicomimetics + anticholinergics	55	22	35	23
Bisphosphonates	78	31	50	33
Denosumab	5	2	3	2
Calcium & vitamin D	78	31	50	33
Antidepressants	32	13	20	13
Benzodiazepines	20	8	13	9
Alfuzosin / Tamsulosin	35	14	19	13
Proton pump antagonists	180	71	108	71
L-thyroxin	27	11	1	14

NSARDs (Table 4)

110 OBGR patients (88%) took COX-1 inhibitors. 86 patients (58%) took ibuprofen, and 2 took dexibuprofen. 33 patients (22%) took diclofenac and 2 lomoxicam; 30 patients(20%) took acemetacin; 10 patients (7%) took naproxen; and 6 (4%) mefenamin.

70 patients (46%) took COX-2 inhibitors. 42 patients (28%) celecoxib and 3 patients (3%) took rofecoxib. 50 patients (33%) took paracetamol in combination with celecoxib, and 2 patients (1.4%) in combination with rofecoxib.

	Number	Percentage
COX 1 inhibitors	110	72
• **Ibuprofen / dexibuprofen**	88	58
• **Diclofenac / lornoxicam**	35	23
• **Mefenamin**	6	4
• **Naproxen**	10	7
• **Acemetacin**	30	20
Coxibs	42	28
- **Celecoxib**	39	26
- **Rofecoxib**	3	2
COX 3 inhibitor	69	45
• **Paracetamol (acetaminophen)**	69	45

Variables (Table 5)

Blood pressure at baseline was similar in both groups. At follow-up blood pressure was unchanged in the COGR but increased significantly (p = 0.0001) in the OBGR.

Heart rate at baseline was similar in both groups. It decreased significantly (p <0.00001) in both groups, but significantly (p <0.00001) less in the OBGR.

Serum glucose a baseline was similar in both groups and it did not change during the follow-up.

LDL-C at baseline was similar in both groups. At follow-up it did not change in the COGR but increased significantly (p = 0.0002) in the OBGR.

Hemoglobin at baseline was similar in the two groups. At follow-up it decreased significantly (p <0.5) in the OBGR.
GFR at baseline was similar in both groups. At follow-up it did not change in the COGR but decreased highly significantly (p <0.00001) in the OBGR.

Physical activity was significantly smaller (p <0.00001) at baseline in the OBGR and decreased significantly at follow-up.
6 MACES occurred in the COGR: 3 hospital admissions for acute coronary syndromes, 1 for cerebral embolic stroke and 1 for congestive heart failure. 10 MACEs occurred in the OBGR: 5 hospital admissions for acute coronary syndromes, 2 for cerebral embolic stroke and 3 for congestive heart failure. The occurrence of MACES was statistically significantly different (p< 0.05) in the two groups. In the OBGR all MACEs occurred in patients taking ibuprofen plus paracetamol. The P value for the Poisson regression analysis of variance between GFR and MACEs is <0.05, showing a statistically significant relationship between the variables at the 95% confidence level. We found a significant association between the use of ibuprofen plus paracetamol and the occurrence of MACEs.

Two COGR patients with cancer and 2 OBGR patients with cancer died for non-cardiac reasons.

Table 5. BP, HR, glucose, LDL-C, hemoglobin and walking steps

	Base	Check	Base	Check
	SBP		DBP	
COGR	143 ± 8	142 ± 8	83 ± 5	79 ± 6
OBGR	143 ± 7	149 ± 6	82 ± 5	85 ± 6
	HR		Glucose	
COGR	73 ± 9	70 ± 7	6.6 ± 0.9	6.3 ± 0.9
OBGR	74 ± 9	72 ± 7	6.4 ± 1.0	6.4 ± 1.4
	LDL-C		Hemoglobin	
COGR	3.2 ± 0.4	3.1 ± 0.4	145 ± 12	145 ± 12
OBGR	3.2 ± 0.4	3.3 ± 0.6	146 ± 13	141 ± 13
	GFR		Steps	
COGR	83 ± 11	82 ± 10	7461 ± 1870	7503 ± 1800
OBGR	84 ± 11	69 ± 10	44209 ± 1265	4196 ± 1291
	MACEs		Non-cardiac deaths	
COGR	0	6	0	2
OBGR	0	10	0	2

Legend

Base	*Values at baseline.*
Check	*Values at the check-up control.*
SBP	*Sitting systolic blood pressure, mm Hg, mean ± 1 SD.*
DBP	*Sitting diastolic blood pressure, mm Hg, mean ± 1 SD.*
Heart rate	*Sitting, beats per minute, mean ± 1 SD.*
Glucose	*Fasting glucose, mmol/l, mean ± 1 SD.*
LDL-C	*Low density cholesterol, mmol/l, mean ± 1 SD.*
Hb	*Hemoglobin, g/l, mean ± 1 SD.*
Steps	*Number of daily walking steps, mean ± 1 SD.*
GFR	*Estimated glomerular function rate (CKD-EPI), ml/min/1.73 m^2, mean ± 1 SD*
MACEs	*Number of patients with MACEs at the follow-up.*
Non cardiac deaths	*Number of non-cardiac deaths at the follow-up*

DISCUSSION

Our data confirm previous reports [1-3] based on observational evidence, that NSARDs increase significantly blood pressure and LDL-C and decrease highly significantly GFR. The regression analysis of variance between GFR and MACEs is statistically significant for the use of ibuprofen plus paracetamol and the occurrence of MACEs. Our data confirm the results of the meta-analysis by Damman and Testani [10] that NSARDs increase the risk of MACEs by reducing the renal function [1-3]. The heart and the kidneys are interdependent in regulating salt and water of the body. Irrespective of cause, a decline in GFR is associated with a 60 up to 80% higher all-cause mortality [11]. Not only the extent, but also the timing and the duration of decline of renal function are important [12].

Diclofenac, lornoxicam, mefenamin, naproxen, acemetacin, celecoxib and rofecoxib also increased blood pressure and LDL-C and reduced the GFR, but we did not find a significant association with the occurrence of MACEs. However, these NSARDS were only used in small numbers of patients which is certainly insufficient to assess their possible triggering effect on MACEs. Therefore, our data should not be interpreted to assume that these NSARDs are safe in cardiovascular patients.

A confounding factor ought to be considered: probably because of the rheumatic pathologies physical activity was significantly smaller than in patients using NSARDs and decreased significantly at follow-up,. Reduced physical activity might be a risk factor for the occurrence of MACEs in rheumatic patients with cardiovascular pathologies.

Our results are based on evidence from a retrospective observational study. We have sufficient data for the combined use of ibuprofen and paracetamol. It is recommended to have retrospective prospective observational data for more comprehensive evaluation of adverse cardiovascular effects of NSARDs. Nonetheless, lacking prospective data we feel that our data provide evidence on the effects of NSARDs on the cardiovascular system.

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