

Effectiveness of the CardioPain initiative in reducing inappropriate NSAID prescriptions in pain therapy among high cardiovascular risk patients: an informative Italian survey

Valentina Orlando¹, Enrica Menditto¹, Francesca Guerriero¹, Raffaele Rotunno²

¹CIRFF, Center of Pharmacoeconomics, Federico II University of Naples, Naples - Italy

²Cardiology Department CCU, Roccadaspide Hospital, Salerno - Italy

ABSTRACT

Aims: Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors (COXIBs) may be associated with increased cardiovascular (CV) risk and mortality in CV patients. After the release of Note 66 by *Agenzia Italiana del Farmaco* (AIFA) to reduce inappropriate prescribing of NSAIDs and COXIBs, the CARDIOPAIN initiative was started in Italy to include such recommendations into the hospital discharge letter of patients with high CV risk. We evaluated the effect of the CARDIOPAIN initiative on the prescription of analgesic drugs by general practitioners (GPs).

Methods: An online interview was proposed to 414 Italian GPs. A descriptive statistic was reported.

Results: Three groups of GPs were identified: those who found the Note 66 recommendations in most hospital discharge letters (the "MOST" group), those who found them in only few cases (the "FEW" group) and those who never found the recommendations (the "NO" group). In patients with high CV risk, the percentage of GPs prescribing NSAIDs as first choice in pain management was lower in the MOST group compared with the "FEW" or "NO" groups. GPs belonging to the "MOST" group prescribed NSAIDs in 28% of cases, compared with 50% of cases observed for GPs belonging to the "NO" group. The more severe the pathology the fewer the NSAID prescriptions, in favor of opioid agents administration.

Conclusions: Our results suggest that the inclusion of the AIFA Note 66 in the discharge documents of high CV risk patients may have contributed to lower inappropriate NSAID prescriptions in Italian GPs. Presumably, a wider diffusion of the CARDIOPAIN initiative might improve the prescription appropriateness of analgesic drugs.

Keywords: Inappropriate prescription, NSAIDs, Cardiovascular risk, Questionnaire

Introduction

Drug prescription appropriateness represents a major target in Public Health, especially with the aim to increase drug safety, to reduce potentially dangerous adverse events and to lower direct and indirect sanitary costs (1). Recent studies demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors (COXIBs), apart from their well-known risk of gastrointestinal bleeding (especially in the

elderly) (2-4), are also associated with an increased risk of cardiovascular events (5-13) and mortality (14, 15). In addition, NSAID treatment duration appears to be independent from the increased risk of mortality, at least in patients with prior myocardial infarction; therefore, even short-term treatments should be limited (16). A 2012 amendment of a previous Italian legislative decree (first published in 2009), the Note 66 (17), released by the Italian drug regulatory authority *Agenzia Italiana del Farmaco* (AIFA), accepting the indications of other international drug regulatory agencies such as EMA (European Agency for the Evaluation of Medicinal Products) and FDA (Food and Drug Administration), stated the absolute need to reduce inappropriate prescribing of NSAIDs and COXIBs in patients with cardiovascular diseases, limiting the prescription of such drugs to a specific list of orthopedic, rheumatic and oncologic pathologies. In particular, NSAIDs and COXIBs are both contraindicated in patients with severe heart failure (HF), whereas COXIBs are contraindicated in patients with moderate HF, cerebrovascular diseases (CVD), peripheral artery diseases (PAD) and coronary artery disease (CAD). AIFA has recently acknowledged a spontaneous initiative (started from the local

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Corresponding author:

Valentina Orlando
CIRFF, Center of Pharmacoeconomics
Federico II University of Naples
D. Montesano 49
80131 Naples, Italy
valentina.orlando@unina.it



health presidium of Roccaspide Hospital, Salerno, Italy) aimed at implementing the dispositions of AIFA Note 66 among general practitioners (GPs). The initiative, entitled "CARDIOPAIN", aimed at reducing the inappropriate prescribing of NSAIDs and COXIBs by GPs in patients with HF, CAD, CVD and PAD after hospital discharge. The initiative consisted of an explicit warning written in the hospital discharge letter to reduce inappropriate NSAID prescriptions in patients with cardiac, cerebral, and peripheral vascular diseases. To date, the initiative has been adopted by 73 Italian hospitals.

After about 15 months from the beginning of the CARDIOPAIN initiative, an informative survey was carried out to assess whether the indications of AIFA Note 66 have been correctly interpreted by local GPs and successfully implemented in their prescribing habits in pain management of high cardiovascular risk patients. To this end, a questionnaire exploring the attitude to prescribing anti-inflammatory drugs was distributed to more than 400 GPs operating in various Italian regions. Answers to the questionnaire were used to assess how the Note 66 indications were perceived and possibly translated into reduced inappropriate prescribing of NSAIDs and COXIBs. The preliminary results of this informative survey are reported for the first time in this work.

Material and methods

Subjects

Four hundred and fourteen GPs (351 males/63 females; mean age 59 years) were enrolled over the entire Italian territory. The main local hospital of reference was in the north of Italy for 212 (51%) GPs, in the center of Italy for another 89 (22%) and in the south of Italy (including islands) for the remaining 113 (27%) GPs.

Questionnaires

The proposed questionnaire was to be completed through a dedicated web portal, requiring user authentication. Thirteen questions were aimed at quantifying the impact of adding to the hospital discharge letter the AIFA Note 66 recommendations on prescribing anti-inflammatory drugs by GPs in high cardiovascular risk patients needing analgesic therapy for pain management. In particular, specific questions addressed the inclusion of such treatment recommendations in pain management of assisted patients with HF (Question no. 1), acute CAD (Question no. 2), PAD (Question no. 3) and CVD (Question no. 4). The subsequent seven questions elicited GPs on their preferred choice of drug among the classes of anti-inflammatory agents (namely, paracetamol, COXIBs, NSAIDs, opioids and others) when treating pain in patients who had been discharged from hospital with acute CAD (Question no. 5), stable heart disease (ejection fraction [EF]>50%) (Question no. 6), moderate HF (Question no. 7) and severe HF (Question no. 8), PAD (Question no. 9) and CVD (Question no. 10). As patients with cardiovascular disease are generally on polypharmacy, Question no. 11 asked which drugs/drug classes (NSAIDs, COXIBs, opioids) were their main concern with regard to possible interactions with CV medications.

Statistics

When not otherwise stated, all numerical data are reported as absolute values and percentages. Due to the nature of data retrieved by the questionnaires, statistics were only descriptive.

Results

Based on the answers given to Questions 1-4, three groups of responder GPs were identified: those who found the Note 66 recommendations in most hospital discharge letters (the "MOST" group), those who found them in only few cases (the "FEW" group) and those who found no Note 66 recommendations in the hospital discharge letters (the "NO" group).

Table I shows the drugs of choice for pain therapy in patients with moderate HF, divided by the frequency of occurrence of the Note 66 alert in the patient discharge letter (recommendation present in most cases, "MOST" group; in few cases, "FEW" group; in no cases, "NO" group). It can be perceived that the percentage of GPs prescribing NSAIDs as first choice in pain management is reduced in those who found the Note 66 recommendations in the discharge letter of most patients ("MOST" group, 1.37%) compared with those who did not ("NO" group, 1.91%). Conversely, the percentage of GPs prescribing opioids as first choice in pain management are increased in the "MOST" group (20.55%) compared with "NO" group (10.53%). Tables II, III and IV reported the same data, relative to patients with severe HF, PAD and CVD, respectively. In both severe HF and PAD patients, the presence of Note 66 recommendations in the discharge letters produced an apparent reduction in NSAID prescriptions among GPs and a parallel increase of opioid prescriptions. Overall, paracetamol was the preferred drug, independent of pathology, followed by opioids, and then by NSAIDs and COXIBs. Paracetamol prescribed as the first-choice analgesic drug by GPs in the "MOST" group was reduced compared with those in the "NO" group.

Interestingly, GPs belonging to the "MOST" group prescribed NSAIDs in no more than 28% of patients with PAD, compared to GPs belonging to the "NO" group, who prescribed NSAIDs in 50% of cases. Again, the presence of Note 66 alert in the discharge letter appeared to influence the prescribing habits of NSAID agents among GPs. To further estimate how

TABLE I - First-choice drugs in patients with moderate heart failure, divided by frequency of occurrence of the Note 66 statements in the patient discharge letter

	ALL (n = 414)	MOST (n = 73)	FEW (n = 132)	NO (n = 209)
Paracetamol (%)	76.09	63.01	80.30	77.99
NSAIDs (%)	1.69	1.37	1.52	1.91
COXIBs (%)	2.17	5.48	0.76	1.91
OPIOIDS (%)	10.87	20.55	6.06	10.53

Recommendation present in most cases = MOST; in few cases = FEW; in no cases = NO. Percentage values are calculated on the total of each group.

TABLE II - First-choice drugs in patients with severe heart failure, divided by frequency of occurrence of the Note 66 statements in the patient discharge letter

	ALL (n = 414)	MOST (n = 73)	FEW (n = 132)	NO (n = 209)
Paracetamol (%)	69.32	61.64	70.45	71.29
NSAIDs (%)	0.48	0.00	0.00	0.96
COXIBs (%)	1.45	4.11	1.52	0.48
OPIOIDS (%)	16.43	19.18	15.15	16.27

Recommendation present in most cases = MOST; in few cases = FEW; in no cases = NO. Percentage values are calculated on the total of each group.

TABLE III - First-choice drugs in patients with peripheral artery disease, divided by frequency of occurrence of the Note 66 statements in the patient discharge letter

	ALL (n = 414)	MOST (n = 47)	FEW (n = 131)	NO (n = 236)
Paracetamol (%)	65.46	59.57	66.41	66.10
NSAIDs (%)	7.25	4.26	6.87	8.05
COXIBs (%)	1.69	0.00	0.76	2.54
OPIOIDS (%)	14.25	19.15	12.21	14.41

Recommendation present in most cases = MOST; in few cases = FEW; in no cases = NO. Percentage values are calculated on the total of each group.

TABLE IV - First-choice drugs in patients with cardiovascular disease, divided by frequency of occurrence of the Note 66 statements in the patient discharge letter

	ALL (n = 414)	MOST (n = 50)	FEW (n = 148)	NO (n = 216)
Paracetamol (%)	73.19	66.00	72.30	75.46
NSAIDs (%)	4.35	4.00	5.41	3.70
COXIBs (%)	1.45	4.00	0.68	1.39
OPIOIDS (%)	11.59	18.00	8.78	12.04

Recommendation present in most cases = MOST; in few cases = FEW; in no cases = NO. Percentage values are calculated on the total of each group.

the severity of the underlying pathology may have influenced NSAID prescriptions in the three different groups of GPs, the percentages of GPs prescribing NSAIDs in each group were analyzed by pathology, in order of severity (from the most [severe HF] to the least severe [PAD]). These results are reported in Figure 1, and suggest that the more severe the pathology, the more reduced are the NSAID prescriptions.

Furthermore, by examining individual molecules within each drug class adopted by GPs in patients with acute CAD (Question no. 5), etoricoxib was shown to be the preferred choice among COXIB agents (18.4%), whereas ibuprofen was the most prescribed NSAID (56.1%), and oxycodone-naloxone

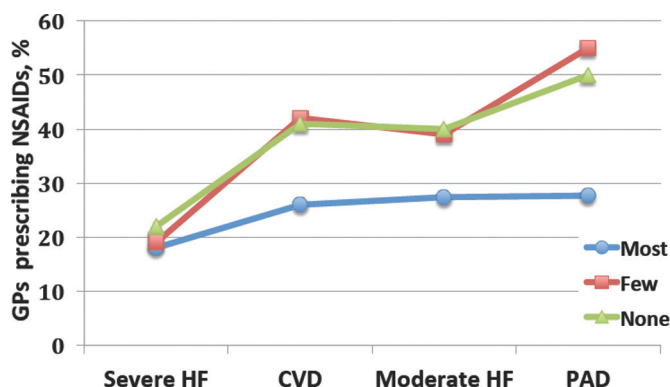


Fig. 1 - Percentage of GPs prescribing NSAIDs, divided by main pathology, from the most (severe heart failure) to the least severe (peripheral artery disease), and by frequency of occurrence of the Note 66 statements in the patient discharge letter. Recommendation present in most cases = MOST, indicated by circles and blue line; in few cases = FEW, indicated by squares and red line; in no cases = NO, indicated by triangles and green line.

association was most frequently prescribed among the opioids (46.1%).

Interestingly, GPs answers to Question no. 6, regarding the preferred anti-inflammatory drug in patients with stable cardiovascular disease (EF>50%), showed that, after the main choice of paracetamol (79.2%), opioids hold second place in the choice of drugs for pain therapy (8.2%), distantly followed by COXIBs (2.7%) and NSAIDs (2.2%).

A final point of interest derived from the GPs' answers to Question no. 11, pertaining to the fear of the possible interactions between drugs generally administered for pain treatment (NSAIDs, COXIBs and opioids) and medication routinely prescribed in patients with cardiovascular diseases. GPs reported a major concern regarding possible interactions between NSAIDs and the following drugs: warfarin (89.6%), oral anticoagulants (85.9%), aspirin (74.8%), and clopidogrel (62.8%), whereas the concern was much less pronounced for opioids (warfarin 43%, oral anticoagulants 33.8%, aspirin 14.25%, and clopidogrel 14.01%).

Discussion

This is the first survey addressing how the inclusion of an alert about the potential risks of NSAIDs and COXIBs in patients with cardiovascular diseases (consistent with the AIFA Note 66) into the hospital discharge letter of patients with CAD, CVD, PAD and HF, may have contributed to increasing the appropriateness of pain therapy prescriptions by GPs, in particular by reducing inappropriate NSAID prescriptions. It is well known, indeed, that pharmacological agents such as NSAIDs and COXIBs are largely used for a variety of conditions requiring pain management, but recently in the elderly and in cardiovascular-risk patients the safety profile of these drug classes has been reconsidered in light of the significant increase in risk of cardiovascular events (5-13, 18-22). For example, as regards etoricoxib (the most prescribed COXIB among acute CAD patients), an AIFA note recommended caution in patient with arterial hypertension, whereas for ibuprofen



(the most prescribed NSAID among acute CAD patients) it has been demonstrated that the association with paracetamol may lead to dangerous adverse events, with only a modest increase in pain control (23). As a consequence, the inappropriate prescription of NSAIDs and COXIBs should be significantly reduced, limiting their use to certain pathologies only, especially in older patients (24, 25) and in those with previous cardiovascular disease, such as acute myocardial infarction. In addition, it appears necessary to reduce to a minimum the short-term treatment with these drug classes in high cardiovascular risk patients, as it has been demonstrated that the increase in NSAID-associated mortality is independent from treatment duration (16).

The main novel finding of the present informative survey is that the inclusion of an alert, consistent with Note 66 in the discharge letter of high-risk patients, probably contributed to the observed lower number of NSAID prescriptions as first-choice drugs for pain management by many GPs, above all in patients with moderate and severe HF (Tabs. I and II), and PAD (Tab. III). Conversely opioids, which represent the second preferred class of analgesic drugs, after paracetamol, were in prescribed more by GPs belonging to the "MOST" group than in those belonging to the "NO" group (20.55% vs. 10.53%, respectively, in patients with moderate HF, 19.18% vs. 16.27% in patients with severe HF, 19.15% vs. 14.41% in patients with PAD and 18.00% vs. 12.04% in patients with CVD) (Tabs. I-IV). These results suggest that, if a reduction of inappropriate prescribing occurred in NSAIDs and COXIBs due to the recommended addition of Note 66 to the patients' discharge letter, then a trend to increase the prescription of opioid agents was also achieved. A finding that parallels this observation is that the prescription of paracetamol, which represents the preferred drug for pain therapy in all pathologies, was reduced by GPs belonging to the "MOST" group compared with those belonging to the "NO" group (63.01% vs. 77.99%, respectively, in patients with moderate HF, 61.64% vs. 71.29% in patients with severe HF, 59.57 vs. 66.10 in patients with PAD and 66.00 vs. 75.46 in patients with CVD). All these findings support the idea that the role of opioids among pain-management drugs is becoming relevant in patients at high cardio- and cerebrovascular risk. Two possible explanations of this rising relevance of opioid therapy may come from the increasing ease of prescription of opioid agents in Italy (probably favored by recent decrees, as law no. 38/2010) and by the increased availability of new molecules, which have dramatically reduced the occurrence of the main adverse event associated with opioid therapy, i.e. constipation (see Morlion et al 2015 (26), for a recent review). As a matter of fact, when the choice of individual agents within each class was considered in our survey, the oxycodone/naloxone association was the most frequently reported first-choice drug among opioid agents in pain treatment for patients with acute ischemic heart disease (46.1%). According to the results of the present survey regarding the fear of the possible interactions between drugs generally administered for pain treatment (NSAIDs, COXIBs and opioids) and medications routinely prescribed in patients with cardiovascular diseases, GPs fearing interactions of oxycodone/naloxone with warfarin, clopidogrel, or oral anticoagulant drugs in lower percentages than those observed for NSAIDs or COXIBs.

The results reported in Figure 1 show that the more severe the pathology, the more reduced were the NSAID prescriptions. Moreover, the difference between NSAID prescriptions by GPs belonging to the "MOST" group and those of the "NO" group decreased with the increasing severity of the clinical condition (18 vs. 22% in severe HF and 28 vs. 50% in PAD). This finding suggests that the efficacy of the CARDIOPAIN initiative was more pronounced for diseases perceived by GPs as less severe. Maybe, this is due to the fact that GPs are generally more careful in prescribing NSAIDs to patients with more severe conditions.

Interestingly, the analgesic prescriptions of NSAIDs indicated by the GPs of the "FEW" group are more similar to those of the "NO" group than to those of the "MOST" group, at least in CVD, moderate HF and PAD patients (Fig. 1). This suggests that the addition of the Note 66 recommendations in only a few discharge letters may have been somehow "confusing" for most GPs in the decision process of the analgesic treatment. It is therefore probable that a wider diffusion of the CARDIOPAIN initiative might improve the prescription appropriateness of analgesic drugs, as stated in Note 66 (21), among Italian GPs. As the CARDIOPAIN initiative has only involved 73 centers at the time of this survey, we can presume that a further reduction in inappropriate NSAID prescriptions for pain therapy in high-risk patients might be achieved when the project is extended to cover the whole national territory.

In conclusion, this informative survey demonstrated that the inclusion of AIFA Note 66 recommendations in the hospital discharge documents of high-risk patients, such as those with moderate and severe HF, CVD and PAD, may have contributed to the reduction of inappropriate NSAID and COXIB prescriptions by Italian GPs.

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