

Establishing a Safe Administration of ASA in Cardiovascular Patients with Nonsteroidal Anti-Inflammatory Drug Hypersensitivity with Skin and/or Respiratory Involvement

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Keywords

Nonsteroidal anti-inflammatory drugs · Challenge · Desensitization · Coronary angioplasty · High-risk patients

Abstract

Background: A history of nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity with cross-intolerance to several drugs is common in some patients with coronary artery disease. We present a series of patients with acute coronary syndrome undergoing ASA desensitization prior to a possible stent to evaluate the short- and long-term efficacy and safety. The aim was to evaluate the outcomes of an ASA desensitization protocol developed by our center based on the guidelines proposed by the EAACI drug allergy expert recommendations. **Methods:** We developed a desensitization protocol that was based on both the patient characteristics and onset of reaction after NSAIDs, including premedication with a leukotriene antagonist and the H1-antagonist antihistamine. The clinical entities were NSAID-induced urticaria and/or angioedema in the absence of chronic spontaneous urticaria (NIUA) and NSAID-exacerbated respiratory disease (NERD). **Results:** A total of 23 patients were challenged or desensitized with ASA: 19 NIUA and 4 NERD. All patients tol-

erated the protocol at the different times of 30, 45, 90, and 120 min. The dosages of oral ASA that were given included 10, 21, 41, 81, and 162 mg (cumulative dose 315 mg). One patient reacted during the procedure and 1 during follow-up. Symptoms were limited to the skin without manifestations in other organs. All patients tolerated the required dose of ASA within 30–120 min. Those requiring urgent catheterization were desensitized within 90 min. **Conclusions:** Our protocol addresses challenge or desensitization with the contribution of a specialist allergist. It provides an effective, dynamic, safe, and short administration of 81 mg or higher of ASA in patients with a history of NSAID hypersensitivity with skin involvement.

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Introduction

ASA therapy is indicated for primary prevention of the first myocardial infarction in patients with risk factors [1, 2] and as secondary prevention in patients with existing cardiovascular disease [2], especially those with a coro-

Each of the authors contributed equally to this manuscript.

Table 1. Previously published studies

Study	Dose (start), mg	Dose (per step), mg	Interval, min	Total time	ASA tolerated, n/N
Wong [12]	0.1	0.1–163	15–20	3 h	9/11
Silberman [13]	1–5	1–100	30	2.5–3.5 h	15/16
Lee [14]	5	5–80	30	2 h	20/24
Hobbs [15]	1	0.1–125	15	3.5 h	12/13
Rossini [16]	1	1–100	30–120	5.5 h	23/26
Christou [17]	0.1	0.1–325	15–25	2.25 h	11/11
Cortellini [18]	0.1–10 ^a	0.1–50	20–45	3 h to 3 h 40 min	58/61
Córdoba-Soriano [19]	0.1	0.1–100	15	1.75 h	24/24
McMullan [20]	1	1–325	15	1.5 h	25/26
De Luca [21]	1	1–250	30	4.5 h	42/43
Díez-Villanueva [22]	12.5	12.5–100	30	1.5 h	10/10
Cortellini [23]	0.1 ^a	0.1–35	20–30	3 h 20 min	145/147
	10 ^a	10–50	20–30	1 h 40 min	163/163
Rossini [24]	1	1–100	30–120	5.5 h	315/330
Al Rashed (this study)	10–41 ^a	10–162	30–120	0.5–4 h	25/25

^a Protocols based on patient risk stratification.

nary stent [3]. There is a 46% odds ratio reduction in major cardiovascular events for patients with unstable angina [4]. The American Heart Association/American College of Cardiology [5] recommends dual therapy with ASA and clopidogrel for patients in need of a percutaneous intervention, followed by indefinite continuation of ASA therapy [6], without addressing any suitable alternative for cases of ASA hypersensitivity. However, the European Society of Cardiology [7] and European Association for Cardio-Thoracic Surgery (EACTS) [4] include rapid desensitization as a procedure that may be performed in patients with ASA hypersensitivity who require ASA therapy to be continued indefinitely. Discontinuation of ASA treatment in patients with coronary artery disease leads to a 3-fold increase in major cardiovascular events that is boosted in patients who have intracoronary stents with an estimated odds ratio of 89.78 (29.9–269.6) [8]. The prevalence of ASA hypersensitivity ranges from 0.5 to 1.9%, reaching up to 25.6% in patients with nasal polyposis and bronchial asthma and 27–35% in patients with chronic urticaria who present with skin symptoms after nonsteroidal anti-inflammatory drug (NSAID) intake. According to the recently proposed ENDA classification, 5 major entity groups are recognized: (1) NSAID-exacerbated respiratory disease (NERD), (2) NSAID-exacerbated cutaneous disease (NECD), (3) NSAID-induced urticaria and angioedema in the absence of chronic spontaneous urticaria (NIUA),

(4) single NSAID-induced urticaria, angioedema, and/or anaphylaxis (SNIUAA), and (5) NSAID-induced delayed hypersensitivity response (NIDHR) [9].

Drug allergy desensitization is the “induction of temporary clinical unresponsiveness to a drug” [10] and drug allergy challenge is a diagnostic procedure to check the tolerability of the drug [11]. Both procedures should be performed by a trained allergist with the understanding of the pathophysiology of these reactions and the ability to differentiate the severity of reactions as well as decide on an appropriate challenge or desensitization protocol. In NSAID hypersensitivity, desensitization with ASA essentially implies a gradual increase in drug dose until the patient reaches the desired dose without further reaction. If a response occurs at any step, it is treated and the process is restarted after symptoms have been cleared. The aim of this study was to evaluate the short- and long-term outcomes of a risk-stratified, dynamic protocol developed in our center. This approach is shorter than those previously published protocols for challenge and/or desensitization to NSAID hypersensitivity for coronary artery disease [12–24].

Following ENDA classification [9] the most frequent clinical entity is NIUA followed by SNIUA and NERD according to different studies [25–27]. Many desensitization studies have been carried out in patients with NERD [28] whereas patients presenting with NECD can present a challenge to the allergists owing to increased rates of unsuccessful desensitization [12, 29] (Table 1).

Materials and Methods

We performed a prospective single-center challenge or desensitization study that included all individuals with cardiac referrals for NSAID hypersensitivity reactions who were in need of ASA in a coronary care unit (CCU) setting. This was carried out in our tertiary Al-Rashed Allergy Reference Centre and subjects were submitted from all public health systems in the State of Kuwait.

The recruitment period was 3 years, from September 2013 to July 2016. Ethical approval was granted from our institution's ethical committee. All patients were informed about the risk and outcomes of the procedure and provided their informed consent.

Because referrals were previously labelled as allergic to NSAIDs either by nonallergist medical staff or the patient themselves, a full evaluation by a trained allergist was mandatory. This included the clinical characteristics of all previous reactions to NSAIDs, drugs eliciting a reaction, the administration of NSAIDs afterwards, confounding factors at the time of the reaction such as concomitant drugs and exercise, food, infection, the presence of chronic spontaneous urticaria (CSU), recurrent anaphylaxis, or other comorbidities. Based on these data, a trained allergist decided on an appropriate challenge or desensitization protocol. Patients were defined as confirmed hypersensitivity to NSAIDs by clinical history in cases with more than 2 episodes to NSAIDs from different chemical groups and in NERD patients with underlying asthma or rhinitis who develop respiratory symptoms after NSAID administration [30].

Patients with a history of hypersensitivity reaction to ASA were considered as NIUA, due to the unlikely possibility that these patients were IgE selective responders to ASA [31]. Patients with a contraindication for challenge or desensitization were not considered. This included the following: bullous exanthemas, DRESS (drug reaction with eosinophilia and systemic symptoms), Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis. Patients with symptoms that did not suggest hypersensitivity to ASA received ASA without challenge or desensitization. Uncontrolled asthma was not a contraindication for desensitization and an individualized approach including the severity of asthma and emergency for ASA administration is granted by allergy and cardiology services. If a patient was not allowed for ASA challenge or desensitization, an alternative therapy was granted by the treating cardiologist.

All patients underwent a challenge or desensitization with ASA in CCU with continuous monitoring by a nurse and allergist up to 2 h after the last dose was administered. Premedication with 10 mg of cetirizine and 10 mg of montelukast was given from the moment we were asked for consultation. Beta-blockers were withheld 24 h prior to the procedure.

Based on clinical history, our patients were stratified by an allergist in accordance to the risk of receiving inotropic drugs (epinephrine, beta-agonists) during the possible reaction to NSAIDs. High risk was considered when severe comorbidities were present, the initial reaction occurred after a low (81 mg) or unknown dose of ASA, and/or they had anaphylaxis. For these patients, an initial dose of 21 mg of ASA was given followed by a 21-mg dose. In patients presenting with anaphylaxis, a starting dose of 10 mg followed by a 21-mg dose was administered. Severe comorbidities were defined as any condition that could significantly increase the risk of acute injury in case of anaphylaxis with special

consideration to the respiratory system. Low-risk was considered for the remaining patients. In this group, 41 mg of ASA was given as the starting dose, with further 41-mg doses until the required ASA dose determined by cardiology was reached. The interval between doses was at least 15 min longer than the time required to present a reaction after the initial administration of NSAIDs, with a minimum of 30 min. When information regarding this period was unclear or unknown, a 120-min interval was used.

Cardiology staff decided the indication and dosing for ASA therapy prior to coronary angiography and possible stent placement. They also determined other indications and dosing for ASA therapy in CCU. Follow-up with patients occurred between 3 months and 2 years and were reviewed for ASA compliance and possible reactions as well for the need for a stent after ASA challenge or desensitization.

Statistical Studies

A descriptive analysis of variables, including sex, male/female ratio, mean age, and the number of episodes, was conducted.

Results

We had 38 consultations with previous reactions to NSAIDs in patients requiring coronary angiography and in need for ASA. None of these presented contraindications to ASA due to severe cutaneous adverse reactions. Among them, 13 were allowed to safely administer 81 mg of ASA as they had already taken NSAIDs after the initial reaction with good tolerance. Two patients were desensitized but not included in the study due to delayed reactions or the patient failing to remember initial symptoms at the time of NSAID exposure. The remaining 23 patients completed the full ASA challenge or desensitization protocol and were included in the study (Fig. 1). The male-female ratio was 1.30, with an average age of 61.48 years (SD 11.42); 82.60% of the patients were compatible with NIUA (Table 2). None reported a previous history of CSU.

Fourteen NIUA patients were desensitized with 81 mg of ASA according to their cardiology recommendation. In the remaining 5 patients, a loading dose of 325 mg was given to 3 patients, and 750 and 162 mg, respectively, to the other 2 patients. All NIUA patients were able to tolerate challenge or desensitization up to 81 mg of ASA. Among the remaining 4 NERD cases, all were able to tolerate challenge or desensitization up to 81 mg of ASA.

A total of 13 patients presented with a confirmed clinical diagnosis of NSAID hypersensitivity, with 7 presenting as high risk, including 1 patient with anaphylaxis, and they were able to achieve the required dose of ASA in 30–160 min. Among the 10 patients with a nonconfirmed

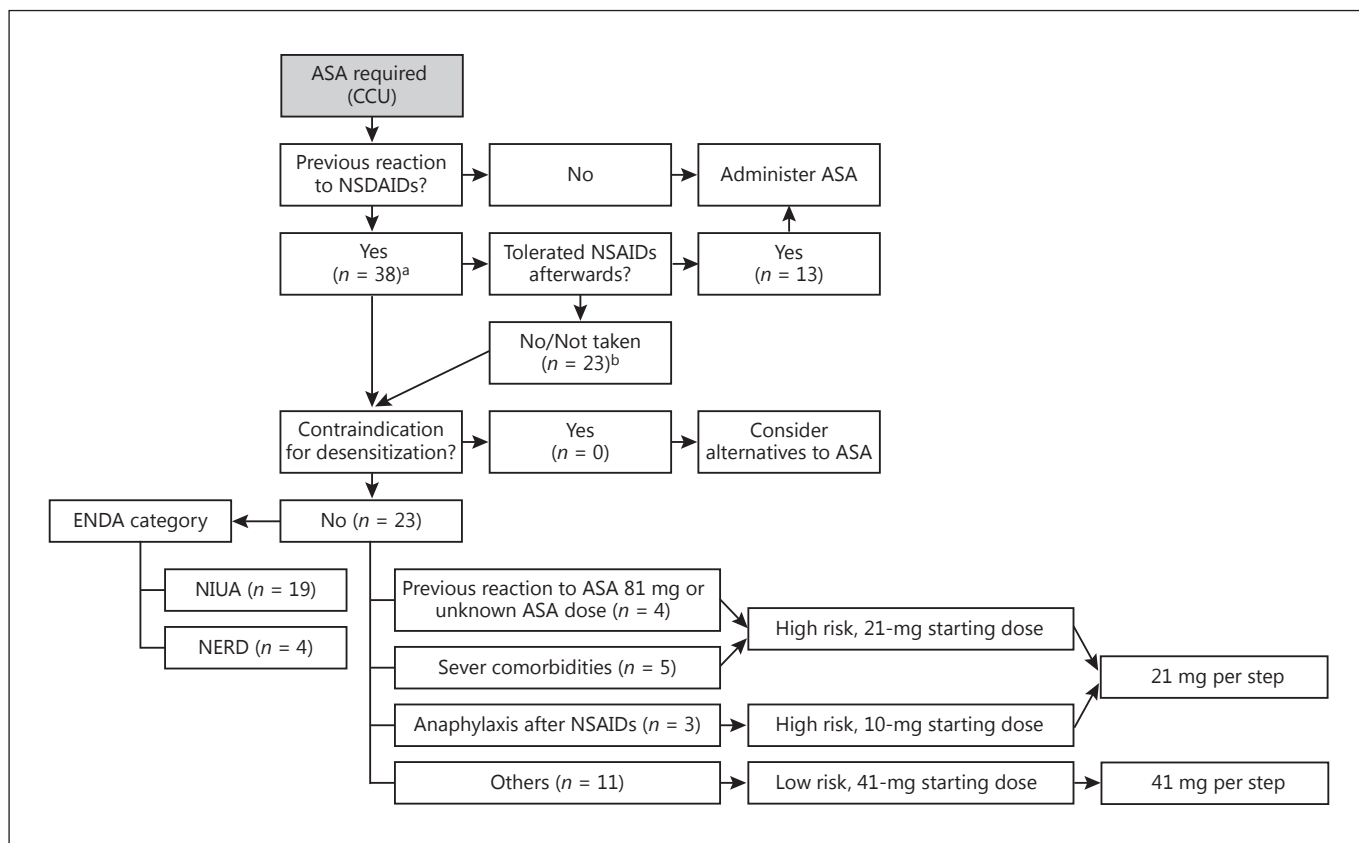


Fig. 1. Protocol for ASA challenge or desensitization, including ENDA categories. ^a Only included patients who were referred to the drug allergy unit for ASA desensitization. ^b Two patients were excluded due to unknown or delayed reactions to NSAIDs.

clinical diagnosis of NSAID hypersensitivity, 5 presented as high risk, including 3 patients with anaphylaxis, and they were able to achieve the required dose of ASA in 30–240 min. One patient in each of the groups presented with a reaction during the protocol.

Five patients were considered to constitute a high-risk group due to comorbidities: Patient 2 was 87 years old with COPD; Patient 4 was a 59-year-old heavy smoker with COPD; Patient 6 was 66 years old with bronchial asthma and had suffered a cerebrovascular accident; Patient 8 was 76 years old with morbid obesity, bronchial asthma, and lung fibrosis due to radiotherapy postmastectomy; Patient 20 was 60 years old with cerebral vein thrombosis. A further 7 patients were included in the high-risk group owing to their initial reaction to an 81 mg or unknown dose of ASA or anaphylaxis, as stated in Materials and Methods. All these patients were able to tolerate at least 81 mg of ASA, with 2 cases presenting with a transitory reaction that was finally well tolerated at 81 mg.

Patient 1 presented with perioral urticaria for 5 min after a cumulative dose of 200 mg of ASA. When the patient was asked to increase the doses she refused, but maintained an 81-mg daily dose of ASA without further reaction. Patient 16 tolerated challenge with ASA of 81 mg, but on the second day of follow-up the patient presented with perioral angioedema that was controlled with the introduction of antihistamines without ASA discontinuation. The 11 patients included in the low-risk group tolerated 81 mg of ASA without reactions, including Patient 13, who was given four 81-mg ASA tablets without a step-wise approach by the nursing staff (Table 2).

Two patients were administered 81 mg of ASA without presenting any further reaction, but were excluded from our data analysis. Patient 24 reported an initial reaction consisting of a single, blue, macular eruption in the arms without skin detachment or systemic symptoms on 2 separate occasions at 8 and 24 h. After the first and second doses of 81 mg ASA, because of the low likelihood of a

Table 2. Study outcomes

Patient No.	Age, years	Sex	Indication	Risk	Clinical diagnosis of NSAID hypersensitivity	Dose eliciting response in the history	Reaction (initial)	ENDA category	ASA tolerated, mg	Protocol, mg	Interval, min ¹	Reaction (challenge)	Reaction (follow-up)
1	65	Female	ACS/unstable	High	Confirmed	ASA ? mg Ibuprofen 600 mg	Urticaria/AE	NIUA	200	21-21-21-21-41-41-41	30	Yes	No
2	87	Female	ACS/unstable	High	Confirmed	ASA 325 mg Ibuprofen 600 mg	Urticaria	NIUA	81	21-21-41	30	No	No
3	60	Male	ACS/stable	High	Not confirmed	ASA ? mg	Urticaria	NIUA	162	21-21-21-21-41-41	30	No	No
4	59	Male	ACS/stable	High	Confirmed	ASA 325 mg Diclofenac 50 mg	Urticaria/AE	NIUA	81	21-21-21-21	30	No	No
5	78	Female	ACS/stable	High	Confirmed	Several NSAIDs	Anaphylaxis	NIUA	81	10-21-21-29	45	No	No
6	66	Female	NSTEMI	High	Not confirmed	ASA 81 mg	Anaphylaxis	NIUA	81	10-21-21-29	45	No	No
7	41	Male	NSTEMI	High	Confirmed	ASA 81 mg Ibuprofen 600 mg	Urticaria/AE	NIUA	81	21-21-21-21	45	No	No
8	76	Female	ACS/stable	High	Confirmed	Diclofenac 50 mg ASA 325 mg	Urticaria	NIUA	81	21-21-21-21	30	No	No
9	62	Male	NSTEMI	Low	Confirmed	Diclofenac 50 mg ASA 325 mg Other NSAIDs	Urticaria	NIUA	81	41-41	120	No	No
10	63	Male	ACS/unstable	Low	Not confirmed	ASA 325	Urticaria/AE	NIUA	81	41-41	30	No	No
11	55	Male	ACS/stable	Low	Not confirmed	ASA 81 mg	Urticaria	NIUA	81	41-41	45	No	No
12	63	Female	ACS/stable	Low	Confirmed	ASA 325 mg	Urticaria	NIUA	81	41-41	90	No	No
13	60	Male	ACS/stable	Low	Not confirmed	Ibuprofen 600 mg ASA 325 mg	Urticaria	NIUA	324	324		No	No
14	71	Female	NSTEMI	Low	Confirmed	ASA 325 mg Paracetamol	Urticaria	NIUA	325	41-41-41-41-41-41	30	No	No
15	54	Male	ACS/stable	Low	Not confirmed	ASA 325 mg	Urticaria	NIUA	81	41-41	30	No	No
16	50	Male	NSTEMI	Low	Not confirmed	ASA 162 mg	Urticaria	NIUA	81	41-41	120	No	Yes
17	53	Male	ACS/stable	High	Not confirmed	Unknown single NSAID	Urticaria	NIUA ²	81	21-21-21-21	30	No	No
18	58	Female	NSTEMI	High	Not confirmed	Diclofenac 50 mg	Anaphylaxis	NIUA ²	81	10-21-21-29	30	No	No
19	44	Male	Pericarditis	High	Not confirmed	Ibuprofen 600 mg	Anaphylaxis	NIUA ³	750 mg	10-21-41-81-160-437	60	No	No
20	69	Female	NSTEMI	High	Confirmed	ASA 325 mg	Wheezing	NERD	81	21-21-21-21	40	No	No
21	74	Female	ACS/stable	Low	Confirmed	ASA 325 mg	Wheezing	NERD	81	41-41	30	No	No
22	43	Male	ACS/stable	Low	Confirmed	ASA 325 mg	Wheezing	NERD	81	41-41	30	No	No
23	63	Male	NSTEMI	Low	Confirmed	Diclofenac 50 mg	Wheezing	NERD	81	41-41	120	No	No

AE, angioedema; ACS, acute coronary syndrome.

¹ Interval between administrations of each step of the protocol. ² Considered NIUA as patients did not tolerate other NSAIDs. ³ Patient considered as NIUA prior to procedure.

systemic reaction, a straight dose of 81 mg of ASA was given. Patient 25 failed to remember the initial symptoms that presented during hospitalization for giant cell arteritis, and the reaction did not involve hypotension or respiratory symptoms. A low-risk group protocol was considered, despite the unknown dose of NSAID.

Our patients were followed up after achieving the challenge or desensitization for up to 2 years. Among the 16/23 (69.57%) patients who were successfully contacted for follow-up, 10 underwent successful stent placement, whereas the other 6 did not meet the requirements for a stent after coronary angiography. All patients remained on a daily treatment of 81 mg of ASA after challenge or desensitization. No long-term reactions to 81 mg of ASA were reported among our group of patients.

Discussion

Dual antiplatelet therapy significantly reduces the rate of cardiovascular events in acute coronary syndromes and coronary stents. However, in a recent systematic review survey [32], a surprising 56% of cardiologists do not perform challenge or desensitization procedures, but manage ASA hypersensitivity using alternative treatments. The most common monotherapy in this survey was clopidogrel.

Several protocols for ASA challenge or desensitization in patients with cardiovascular diseases were published prior to our study [12–24] and are summarized in Table 1. A European expert panel of the ENDA group has recently agreed on guidelines on this topic [23], but no position paper has been published so far. All previous studies did not specifically exclude patients who tolerated NSAIDs after the initial reaction, and in most cases did not assess the patterns of response, including reactions to other NSAIDs and the presence of previous CSU [12–24]. The most commonly used protocol starts with 0.1–1 mg of ASA with 30-min intervals between doses, and is performed after allergy consultation in only 47% of cases [32]. In previously published studies, most of the patients presenting with unsuccessful desensitization belonged to the group with chronic urticaria, although no severe reactions were reported [12–16, 18, 20, 21, 23]. With exception of the studies by Cortellini et al. [18, 23], most previously published protocols did not include risk stratification and all patients were managed equally, disregarding their individual characteristics [12–17, 19–22, 24]. With our approach, the time required for challenge or desensitization can be shortened and, hence, all the direct and

indirect medical costs for patient care can be reduced significantly (Table 1).

Recent data support the inclusion of anaphylaxis within the NIUA clinical entity [33]. In our study, 1 patient who presented with anaphylaxis has reacted to more than 1 NSAID.

Most of our patients were desensitized up to 81 mg of ASA, and we are aware that, following dual antiplatelet therapy with clopidogrel and ASA, there is no clear data in favor of 325 mg versus 81 mg of ASA during the initial 24–48 h to prevent in-stent stenosis [7, 34]. Moreover, patients might have a trigger dose for reaction higher than 81 mg [11, 35] and an ENDA-EAACI expert panel suggests reaching a cumulative ASA dose between 75 and 150 mg [23]. To our knowledge, none of the previous studies on ASA administration in patients with ischemic heart disease and NSAID hypersensitivity have tried to compare between patients with a confirmed or nonconfirmed prior diagnosis of NSAID hypersensitivity [12–24].

In the recent American Academy of Asthma Allergy and Immunology (AAAAI) guidelines for practice parameters [11], a protocol for ASA induction of drug tolerance in NERD patients recommended a starting dose of 20.25 mg, followed by 40.5, 81, 162.5, and 325 mg at 90-min intervals, and stated that almost no patient reacted to 20.25 mg, with only an occasional reaction occurring at 40.5 mg.

In the guidelines published by EAACI/GA²LEN on provocation tests for the diagnosis of ASA hypersensitivity [36], it was recommended that a starting dose of 10 mg be used for patients presenting with anaphylaxis to NSAIDs, but we are aware of previous studies in which the severity of the initial reaction showed no significant difference compared to ASA oral challenge in NERD patients, especially in patients receiving leukotriene modifier drugs (LTMDs), such as montelukast [37]. Hope et al. [38] showed that few patients with NERD will react to doses lower than 30–40 mg of ASA, and proposed a starting dose of 20–30 mg for patients with a history of emergency department visits for asthma and low baseline FEV1. Previous protocols and recommendations for patients without cardiovascular disease in need of ASA administration despite presenting with an NSAID allergy supports the inclusion in our self-designed protocol of a 10- to 21-mg initial dose for high-risk patients and a 41-mg dose for low-risk patients. Based on EAACI/GA²LEN recommendations, if anaphylaxis requires ICU care, a challenge or desensitization must be started with an initial dose of 10 mg of ASA. In our study, neither of the 2

patients who reacted presented with severe symptoms, which further supports our protocol as a safe and dynamic approach, even though we started with much higher doses than in previously published protocols (Table 1).

We are aware that some patients will not remember the exact interval between ASA intake and initial reaction [39], so a 120-min interval between doses was allowed when the patient was unsure. For patients who initially reacted to ASA in less than 15 min, our group determined a minimum interval of 30 min between doses. We did not inform the patient about the details of our protocol in order to avoid a biased decision towards longer or shorter protocols.

Leukotriene receptor blockage obtained by LTMDs is effective for patients presenting with an increased release of Cys-LT following COX-I inhibition [40], and it has been routinely included in protocols for ASA desensitization for NERD patients, but that has not been used with ASA desensitization protocols in an acute setting for cardiac patients [12–24]. All our patients received pretreatment with montelukast and this may have increased our success rate of ASA desensitization, but further studies with a larger number of patients are required to confirm the obtained clinical effect. Montelukast rapidly reaches therapeutic concentrations in plasma, with T_{max} at 2.8 h, which is not affected by the age of the patients [41].

Since the publication from the ENDA expert panel group in 2017 [23], our present protocol has been modified as follows. (1) For a patient with unstable acute coronary syndrome in whom ASA administration cannot be achieved in ≤2 h: administer clopidogrel 600 mg + tirofiban 25 mg/kg within 5 min and then 15 mg/kg/min for up to 24 h and perform challenge or desensitization in the next 24 h. (2) For stable patients: the cumulative challenge dose has been incremented to 110 mg for challenges lasting less than 2.5 h, and to 160 mg for the remaining cases. (3) Severe anaphylactic reactions have been excluded for ASA administration and patients with nonsevere anaphylactic reactions are desensitized following the ENDA expert panel group protocol. The protocol in patients presenting with an initial reaction to a COX-1 inhibition higher than the dose of ASA administered during the procedure could be defined as challenge, while in the remaining patients it could be defined as desensitization in order to adapt a similar terminology to that used in the ENDA guidelines [23]. We have described 13 patients with a confirmed and 10 with a nonconfirmed diagnosis to NSAID hypersensitivity who received the required dose of ASA from cardiology staff. However, we are not sure that this dose was enough to induce desensitization as it

is lower than the dose needed to trigger a reaction in a significant number of NSAID-hypersensitive patients [35]. This has been discussed extensively and remains a controversial issue. Moreover, in a recent, elegant multicenter study [23], nearly all patients tolerated ASA administration following 2 different protocols (challenge and desensitization). However, both protocols used a maximum cumulative dose of 160 mg, which could be below the required threshold.

One of the limitations of the previously published studies and our own work is the number of patients desensitized [12–24]. Other limitations have also been outlined in a recent meta-analysis [32], which, besides the low number of patients, includes the heterogeneity of self-reported adverse reactions, among others [42]. In our study the entities were well defined [9] with a further stratification being performed in order to assess risk and the time of the protocol.

In conclusion, our protocol dynamically addresses desensitization in patients with NIUA and NERD based on a risk assessment and montelukast premedication as decided by a trained allergist. This allows for an effective and safe short protocol with an 81-mg ASA dose in patients with a history of NSAID hypersensitivity.

Statement of Ethics

All patients were informed about the risks and outcomes of the procedure and provided their signed informed consent.

Disclosure Statement

None of the authors have any conflicts of interest to declare.

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