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Clinical approach on challenge and desensitization procedures with aspirin in patients with ischemic heart disease and NSAID hypersensitivity

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Abstract

Background: Hypersensitivity to acetylsalicylic acid (ASA) constitutes a serious problem for subjects with coronary artery disease. In such subjects, physicians have to choose the more appropriate procedure between challenge and desensitization. As the literature on this issue is sparse, the present study aims to establish in these subjects clinical criteria for eligibility for an ASA challenge and/or desensitization.

Methods: Collection and analysis of data on ASA challenges and desensitizations from 10 allergy centers, as well as consensus among the related physicians and an expert panel.

Results: Altogether, 310 subjects were assessed; 217 had histories of urticaria/angioedema, 50 of anaphylaxis, 26 of non-immediate cutaneous eruptions, and 17 of bronchospasm related to ASA/NSAID intake. Specifically, 119 subjects had index reactions to ASA doses lower than 300 mg.

Of the 310 subjects, 138 had an acute coronary syndrome (ACS), 101 of whom underwent desensitizations, whereas 172 suffered from a chronic ischemic heart disease (CIHD), 126 of whom underwent challenges. Overall, 163 subjects underwent challenges and 147 desensitizations; 86 of the latter had index reactions to ASA doses of 300 mg or less. Ten subjects reacted to challenges, 7 at doses up to 500 mg, 3 at a cumulative dose of 110 mg. The desensitization failure rate was 1.4%.

Conclusions: In patients with stable CIHD and histories of non-severe hypersensitivity reactions to ASA/NSAIDs, an ASA challenge is advisable. Patients with an ACS and histories of hypersensitivity reactions to ASA, especially following doses lower than 100 mg, should directly undergo desensitization.

Introduction

Cardiovascular and ischemic heart diseases (IHDs) affect 50% and 35% (1) of the general population, respectively, whereas hypersensitivity to cyclooxygenase (COX-1) inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs) affects around 0.6 - 5.7 % of it (2, 3). It is, therefore, relatively common to see hypersensitivity to acetylsalicylic acid (ASA, aspirin) or to COX-1 inhibiting NSAIDs in patients who require an urgent assessment due to an acute coronary syndrome (ACS) or an elective investigation due to chronic IHD (CIHD).

The application of drug eluting or non-eluting stents under coronary angiography requires a dual anti-platelet therapy for 6-12 months with ASA and thienopyridine drugs (selective, irreversible ADP receptor/P2Y12 inhibitors) (4), which can be problematic in patients with NSAID hypersensitivity, even though the recommended dose of ASA is 100 mg or less daily. In effect, the CURRENT OASIS 7 trial (5) demonstrated that in patients with an ACS, who were referred for an invasive strategy, there was no significant difference between higher-

dose ASA (300 to 325 mg daily) and lower-dose ASA (75 to 100 mg daily), with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke.

Therefore, the collaboration between allergists and cardiologists is essential (6, 7) for two reasons: a) to ensure these patients get the best therapy, rather than going for a second choice, namely coronary artery bypass grafting; b) to decide which of the following procedures is applicable: 1) an ASA challenge test, which is a diagnostic procedure aiming to verify the tolerability of ASA at an anti-platelet dose of 100 mg (or 150 mg, in the acute phase) (8) or an ASA desensitization, which is a procedure aimed at inducing a pharmacological or immunological tolerance to ASA.

The literature on this topic is currently insufficient and uneven with regard to the procedures used (6, 7, 9-14).

It also does not explain the clinical indications for when to use the tolerance (challenge) test or, instead, desensitization to ASA. In particular, the published series differ in terms of number of patients studied, antihistamine pre-medication, intervals between ASA doses, total time of administration, cumulative dose reached, and time of observation after procedure is finished (15-27) (Table 1).

Moreover, the medical history is frequently unclear, in both cardiological (e.g., CIHD or ACS) and allergological (presence of either anaphylactic symptoms, or skin reactions only, or NSAID-Exacerbated Respiratory Disease - NERD) terms.

Therefore, in the first phase the present study collected data on ASA challenges and desensitizations in subjects with CAD and histories of ASA/NSAID hypersensitivity reactions, who were assessed in 10 allergy centers. In the second phase, the collected data were analyzed and discussed in a meeting in order to establish a consensus on the clinical

criteria for eligibility for an ASA challenge or desensitization among the related physicians and an expert panel, and create a common protocol for ASA desensitization. In the third phase, this protocol was applied by all centers.

Methods

A multicenter study was performed from October 2013 to April 2015. In the first phase, data on ASA challenges and desensitizations from each of the 10 enrolled centers were collected. Each center belonged to the European Network on Drug Allergy (ENDA)/European Academy of Allergy and Clinical Immunology (EAACI) Drug Allergy Interest Group (DAIG).

The inclusion criteria were age over 18 years and presence of a well-established IHD or a suspect IHD requiring a coronary study, as well as a history of ASA or NSAID hypersensitivity. The exclusion criterion was a history of severe anaphylactic reactions to ASA.

Data concerning heart diseases, culprit NSAIDs, types of ASA/NSAID hypersensitivity reactions, and allergological and cardiological outcomes were also collected (Tables 2 and 3).

In the second phase, the collected data were analyzed and discussed in a consensus meeting (during the ENDA autumn meeting, October 2014, Florence, Italy), in which the physicians of the 10 centers and an expert panel participated. The key points in consensus were: 1) to create homogeneous cardiological and allergological criteria to decide which patients are eligible for the challenge procedure and which are eligible for the desensitization (primary endpoint); 2**)** to create a common, simple protocol for desensitization procedures (secondary endpoint); and 3) to understand and determine allergological and cardiological outcomes of both procedures (secondary endpoint).

In the third phase, from November 2014 to April 2015, the 10 centers applied a common desensitization protocol.

Statistical analysis

Statistical analysis (absolute and percentage frequency, average data, and standard deviation) was performed. Data were analyzed with the Stata package (Stata Statistical Software: Release 10; StataCorp. 2007, College Station, TX, USA). The continuous variables are expressed as the mean [SD], and were compared by using a t-test. Categorical data are given as numbers of cases and percentages, and were compared by using a chi-square test. A P-value of 0.05 or less indicates statistical significance.

We examined the following variables: gender, type of reactions to ASA/NSAIDs (urticaria/angioedema, anaphylaxis, asthma, and cutaneous non-immediate reactions), single reactors to ASA, reactors to ASA and other NSAIDs, index reactions at a 300 mg or lower dose of ASA, index reactions at a dose higher than 300 mg, heart disease (ACS, ACS and myocardial infarction, CIHD), cardiological procedures (medicated stenting, not-medicated stenting, and simple angioplasty), allergological outcome (symptoms during the procedure), and cardiological outcome (cardiovascular accidents, death) (Tables 2 and 3).

Results

Clinical features

The clinical characteristics of patients are shown in Tables 2 and 3. Altogether, 310 subjects were assessed; 163 underwent challenges and 147 desensitizations. The average age of subjects desensitized was significantly higher than that of subjects who underwent challenges. Among subjects who were desensitized, the number of males was significantly higher than that of females (91 *vs* 56; $p<0.001$) (Table 2).

Of the 310 subjects, 217 had histories of urticaria/angioedema, 50 of anaphylaxis, 26 of non-immediate cutaneous eruptions, and 17 of bronchospasm related to ASA or NSAID intake. Of the 106 subjects with histories of hypersensitivity reactions only to ASA, 104 had experienced urticarial and/or angioedematous or anaphylactic reactions and, according to Kowalski et al (28), were classified as having had a single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), whereas 2 suffered from asthma and rhinosinusitis, had experienced bronchospasm after ASA intake, and were classified as having had a NERD.

In the desensitization group, the number of subjects with histories of hypersensitivity reactions only to ASA was significantly higher than the one of the challenge group (Table 2).

According to the clinical histories, a dose of 300 mg or less of ASA was able to induce symptoms in 119 patients (38.4%), while in the remaining 191 patients (61.6%) symptoms were caused by a dose of ASA higher than 300 mg (Table 2).

The number of subjects with histories of hypersensitivity reactions to ASA at doses of 300 mg or less who underwent desensitization was significantly higher than that of patients challenged. On the other hand, the number of subjects with histories of hypersensitivity reactions to ASA at doses higher than 300 mg who underwent challenges was significantly higher than that of patients desensitized (Table 2).

With regard to the cardiological characteristics, 138 (44.5%) of the 310 subjects had an ACS, whereas 172 (55.5%) suffered from CIHD. The number of subjects with an ACS desensitized was significantly higher than that of patients challenged (101 *vs* 37; $p<0.001$) (Table 3).

Of the 138 subjects with an ACS, 87 underwent angioplasty and/or coronary stent placement (drug-diluting, non-diluting, and simple angioplasty in 56, 20, and 11 cases, respectively). The other 51 patients underwent simple coronarography, without angioplasty or stent placement.

In the group with stable CIHD, the number of subjects who underwent challenges was significantly higher than that of patients desensitized (Table 3).

As far as challenges are concerned, 143 subjects underwent them before the consensus meeting: 95 subjects at ASA doses up to 160 mg, and 48 at doses up to 500 mg; whereas 20 were challenged after the consensus meeting, all at a cumulative dose of 110-160 mg, according to the protocol of the present study (Table 4). Overall, 10 subjects reacted to challenges, 7 at doses up to 500 mg, 3 at a cumulative dose of 110 mg. Three of the 10 subjects positive to ASA challenges had a history of anaphylaxis (cutaneous and respiratory symptoms), and were effectively treated with ASA desensitization. The remaining 7 patients, with a history of urticaria/angioedema, had to stop the study for clinical reasons or personally decided to interrupt (Table 3).

With regard to desensitizations, 92 subjects were treated before the consensus meeting, 82 (all Italians) with the protocol by Cortellini et al (23), the remaining 10 with the protocol by Wong et al (15), with slight modifications and a final ASA dose of 162 mg. Fifty-five subjects were desensitized after the consensus meeting, all with the protocol of the present study (Table 5).

During desensitizations, only 12 patients (8.2%) had hypersensitivity symptoms; 10 of them reached an effective ASA 100 mg tolerance, while the other 2 had to stop the procedure (Table 3).

Regarding cardiovascular outcomes, the procedure of desensitization was significantly associated with stenting. With regard to the 12-month cardiological outcomes, there was no difference in cardiovascular accidents between subjects desensitized and subjects challenged; on the other hand, there were major accidents (4 deaths) only in the desensitization group (Table 3).

Recommendations

General

On the basis of the analysis of the data on ASA challenges and desensitizations collected in the first phase of the study, as well as of literature data (15-27) and the expert panel opinion, there was a consensus that the access to procedures of both challenge and desensitization should be implemented in every clinical subset of acute hypersensitivity to NSAIDs provided by the position paper on "Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs" (28). Moreover, there was a consensus that the challenge procedure is safe and has to be implemented in patients with stable CIHD and a history of hypersensitivity to ASA at an anti-inflammatory dose (over 300 mg), as well as at an anti-platelet dose (75-100 mg), and non-severe clinical symptoms (e.g., urticaria). Challenge steps are determined on the basis of literature data (23, 29-34) and the cumulative ASA dose should be 110 to 160 mg.

On the other hand, the desensitization procedure should be chosen as a safer alternative in patients with: 1) ACS and NSAID hypersensitivity; 2) a previous positive ASA challenge at an anti-platelet dose; and 3) a history of non-severe anaphylaxis due to ASA or other NSAIDs (Fig. 1).

Clinical subsets

1) Regarding the challenge procedure for patients with:

a) NERD and b) NSAID-exacerbated cutaneous disease (NECD), the procedure is well documented in the EEACI/GA2LEN guidelines (30);

c) NSAID-induced urticaria/angioedema (NIUA), the procedure is well documented in the aforesaid EEACI/GA2LEN guidelines (30) and in some studies which evaluated subjects with histories of hypersensitivity reactions to ASA/NSAIDs (29, 31-34). On the basis of studies performed by some members of the expert panel on large samples of such subjects, including subjects with NIUA (32, 34), it was agreed that more than 50% of patients with NIUA might tolerate an ASA dose lower than 100 mg;

d) SNIUAA, there is a higher level of risk for the challenge procedure, which is not recommended in patients with a history of severe anaphylaxis.

2) Regarding the desensitization procedure, taking also into account the recommendations of the aforesaid position paper (28) and those of another position paper regarding general considerations on rapid desensitization for drug hypersensitivity (35):

a) it was agreed that the challenge procedure is risky in subjects with an ACS (Table 3) and that desensitization is the option of choice in ACS patients with:

1) an unclear history of ASA hypersensitivity, desensitization being safer than challenge;

2) a history of hypersensitivity to NSAIDs and/or ASA at anti-inflammatory doses, but it is not mandatory. In effect, in these patients, desensitization may be unnecessary, but due to time pressure it is better to be done instead of a challenge.

b) desensitization is mandatory in patients with:

1) an ACS and a history of hypersensitivity to ASA at an anti-platelet dose;

2) an ACS and a history of non-severe anaphylactic reactions to ASA/NSAIDs;

3) a previous positive ASA challenge at an anti-platelet dose (Fig. 1).

c) desensitization is not recommended in subjects with histories of severe anaphylactic reactions.

It was agreed that NERD and NECD patients generally need a desensitization procedure with longer intervals between the doses to reach the cumulative dose (19, 24, 25). However, such longer intervals are impractical for subjects with unstable CAD (15).

The expert panel recommended choosing a single homogeneous procedure protocol for each patient regardless of cardiological or allergological features. This procedure could be suitable especially for cardiologists or other physicians who have no experience in drug allergy.
In a patient without a clear clinical history, hospitalized for an ACS in the coronary intensive unit (Table 3), it is also imperative to perform the desensitization procedure as soon as possible.

The panel of allergists suggests to choose a very low starting dose, and to continue with short time intervals (20-30 minutes) until the cumulative dose of 40 mg is reached. Subsequent time intervals, in particular in NERD/NECD patients, may be longer (60-90 minutes), preferably within a cumulative time of administration of 300 minutes.

STEPS: On the basis of literature data (Table 1), the desensitization procedure can vary between 5 and 12 steps; in the present study, the majority of patients of the 10 centers underwent desensitization in 10 steps (Table 5). The time interval between steps was 20-30

minutes until the dose of 40 mg was reached and 60-90 minutes thereafter until the dose of 100 mg was reached.

Starting dose: Because of the possibility of IgE-mediated reactions (36), a low starting dose is advisable. According to literature data (15-27) (Table 1), such dose varies between 0.1 mg and 10 mg; in the present study, a starting dose of 0.1-1 mg was used.

Cumulative dose: According to the literature data (15-27) (Table 1), it ranges between 150 mg (16) and 799 mg (18). On the basis of a cardiological consensus (8), the ENDA-EAACI expert panel suggests reaching a cumulative dose between 75 and 150 mg.

Desensitization in "primary PCI (percutaneous coronary intervention)": In the case of an ACS (Table 3), in patients with ST-segment elevation (ACS-STEMI), the primary percutaneous coronary intervention (pPCI) is a safe and effective therapeutic strategy. For this feature it is mandatory to perform the desensitization procedure in a very short time (less than 2 hours) to diminish further myocardial damage. The oral dose of ASA to reach is 150 mg (8).

However, in patients with ACS-STEMI, usually there is not enough time for performing an ASA desensitization procedure before the pPCI. Therefore, according to the expert panel opinion and literature data (27, 37, 38), a safe choice would be using an alternative anti-platelet drug (e.g., clopidogrel, an adenosine diphosphate receptor antagonist) along with a platelet glycoprotein IIb/IIIa inhibitor (i.e., abciximab, eptifibatide, or tirofiban), as a temporary measure before performing an ASA desensitization. Then, within 12-72 hours, an

ASA desensitization with the normal schedule can be performed.

In effect, the aforesaid glycoprotein IIb/IIIa inhibitors block the final common pathway leading to platelet aggregation, thus reducing thrombotic complications in patients with ACS-STEMI undergoing pPCI (37). Most data regard abciximab (39-42); in some comparison studies (43-45), however, no differences in outcome (i.e., 30-day mortality, reinfarction at 30 days, post-procedural Thrombolysis In Myocardial Infarction [TIMI] flow grade 3, and ST-segment resolution) have been found between standard-dose abciximab (i.e., a bolus of 0.25 mcg/kg and a maintenance infusion of 0.125 mcg/kg/min over 12 hours) and a high-loading dose of tirofiban (i.e., 25 mcg/kg over 3 min) followed by a 12-hour infusion of 0.15 mcg/kg/min. In particular, a meta-analysis by De Luca et al (43) showed among STEMI patients undergoing pPCI similar results between abciximab and tirofiban, as well as between abciximab and eptifibatide, in terms of angiographic, electrocardiographic, and clinical outcome.

In our case series, we had 4 ACS-STEMI patients who underwent a successful desensitization procedure after pPCI with a course of tirofiban therapy.

Summary

ASA therapy is mandatory for all patients who need a coronary angiography, possibly followed by stenting. Collaboration between cardiologist and allergist is fundamental in cases with these clinical features. However, on this topic there is a lack of guidelines for cardiologists, allergists, and specialists in internal medicine to support their clinical decisions. Therefore, a consensus on this topic in an expert panel was desirable.

According to the consensus reached in the present study, the procedure of desensitization must be implemented in all cases of in-hospital patients with hypersensitivity to

ASA/NSAIDs and ACS.

It is recommended that, before any evaluation procedures, patients with an ACS and a history of anaphylactic reactions when exposed to anti-platelet doses of ASA to be assessed by an allergist, who together with the cardiologist can decide the appropriate procedure (Fig. 1).

In any case, in high-risk ACS patients the desensitization procedure appears to be the best and safest choice, even in those with histories of non-severe anaphylactic reactions to ASA/NSAIDs.

In patients with stable CIHD, a challenge test is advisable. However, considering the results of the CURRENT-OASIS 7 trial (5), it is crucial to identify subjects with histories of hypersensitivity to ASA doses higher than 100 mg, as such subjects might not need any further allergological workup**.**

With regard to the common desensitization protocol of the present study (Table 5), the low starting ASA dose is due to the documented possibility of IgE-mediated reactions (36). Regarding these rare conditions, the suitable schedule may be of brief (20-30 minutes) incremental steps, reaching the cumulative dose of 40 mg of ASA. On the other hand, longer intervals are advisable in order to diminish the risk of reactions mediated by a pharmacological mechanism in subjects with NERD, NECD, or NIUA, which represent the cross-reactive types of non-allergic NSAID hypersensitivity (28). The pathogenic mechanism of these reactions has been associated with the inhibition of COX-1. In fact, NSAIDs – such as ASA, pyrazolones, indomethacin, ketoprofen, ibuprofen, piroxicam, ketorolac, etc. – inhibit the constitutive isoform of COX-1, and thus reduce the generation of protective prostaglandin (PG)E2, as well as increase the unrestrained synthesis of cysteinyl leukotrienes (Cys-LTs) and the release of mediators such as PGD2 from mast cells and eosinophils. This mechanism, which is well-established in ASA-induced asthma (46), has also been supported

by biochemical observations in ASA-induced urticaria (47). Specifically, Mastalerz et al (47) found that baseline urinary LTE4 levels, believed to reflect global cys-LTs biosynthesis, were markedly increased in both NERD and NECD patients and that ASA released PGD2 in both NERD and NECD patients. In effect, the risk of reactions mediated by a pharmacological mechanism increases in NERD patients at an ASA dose of 40 mg (48). With regard to these hypersensitivity reactions, after reaching this dose, it is reasonable to use longer steps (60-90 minutes) to reach the cumulative dose of 100 mg. In any case, the procedure has to be quick and has to finish within 6 hours, including the subsequent clinical observation.

A limitation of our study is the absence of randomization of the patients. However, in the first phase the study was set as a collection of real life data in the enrolled centers. Moreover, randomization was not approved for this study, because it would have been unethical.

In conclusion, we state that desensitization with ASA is a safe procedure in subjects with an ACS and ASA/NSAID hypersensitivity, while in patients with stable CIHD and ASA/NSAID hypersensitivity, a provocation test is the option of choice.

Author Contributions

Gabriele Cortellini, chair of the multicenter study, contributed to the conception paper, general structure, and general writing of the paper, diagnostic algorithm elaboration and approval, management of references, and data collection. Antonino Romano promoted the multicenter study and contributed scientific advice in writing the manuscript and intellectual input for the manuscript. Annalisa Santucci contributed to statistical analysis, data collection, and management of references. Patrizia Bonadonna contributed with data collection and intellectual input for the manuscript, and promoted the ENDA meeting on the study. Sevim Bavbek contributed scientific advice in writing the manuscript and intellectual input for the manuscript. Miguel Blanca contributed with data collection, scientific advice in writing the manuscript, and intellectual input for the manuscript. Joanna Makowska and Donatella Bignardi contributed with intellectual input for the manuscript and management of references. Sergio Testi and Jose Julio Laguna collected data and contributed intellectual input for the manuscript. Ingrid Terreehorst contributed with scientific advice in writing the

manuscript and to the general structure of the paper. Annick Barbaud, Maria Teresa Costantino, Javier Dionicio Elera, Laura Losappio, Domenico Lippolis, Carla Lombardo, Elide Anna Pastorello, Vincenzo Patella, and Oliviero Quercia collected data and wrote the draft of the manuscript. Alla Nakonechna promoted the study and contributed scientific advice in writing the manuscript and intellectual input for the manuscript and to the management of references, elaboration of the general structure of the paper, and approval. Daniele Grosseto contributed with scientific advice, analyzing cardiological data. Josefina R Cernadas contributed scientific advice in writing the manuscript and intellectual input for the manuscript and to the promotion of the study, elaboration, approval, and final reviewing. All authors were involved in the development of the study concept, critically reviewed the manuscript, and gave permission for publication.

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Disclosure of Potential Conflicts of Interest

None of the authors have anything to disclose about this paper.

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FIG. 1 Flow chart for patients with coronary artery disease and histories of hypersensitivity reactions to acetylsalicylic acid (ASA) who need ASA therapy.

Table 1 Rapid protocols of acetylsalicylic acid (ASA) desensitization

Author	No. of patients treated	Total time (min)	Starting dose (mg)	Final dose (mg)	Cumulative dose (mg)	No. of protocol steps	Time interval between doses (min)	Success rate %
Wong TJ (15)	11	100-300	0.1-10	81-325	155.4-642.4	10	10-30	81.8%
Silberman S (16)	7	210	1	100	227	8	30	85.7%
	9	150	5	75	150	5	30	100.0%
Alijotas-Reig J (17)	4	135	0.1	100-125	254.4-279.4	9*	15	100.0%
Hobbs L (18)	13	210	1	325	799	11	15-40	92.3%
Rossini R (19)	26	330	1	100	176	6	30-120	88.5%
Dalmau G (20)	5	120-240	0.1	100	189.3	8	15-20	100.0%
Ortega-Loayza AG (21)	3	240	0.5	100	227.5	9	30	66.7%
Cristou A (22)	11	135	0.1	325	648.4	8	15-25	100.0%
Cortellini G (23)	31	220	0.1	50	151.6	12	20	90.3%
DeLuca G (24)	43	240	1	250	502	9	30	97.6%
Lee JK (25)	24	120	5	80	155	5	30	83.3%
McMullan KL (26)	26	90-120	1	325	636	7	15-20	88.5%
Córdoba-Soriano JG (27)	24	105	0.1	100	189.4	8	15	100.0%¶

*If no adverse effects appeared, the ASA dose of 100 or 125 mg was repeated the next day.
¶Actually, one patient experienced an urticarial reaction after the 10-mg dose and completed the protocol in about 4 hours.

Table 2 Demographic characteristics of the 310 patients and types of reactions to acetylsalicylic acid (ASA)

	Number (%)	Challenge (%)	Desensitization (%)	Pearson chi^2/ t test
Total number of patients	310	163	147	
Average age, years [SD]	63.9	60.4 [SD 14.2]	67.9 [SD 10.1]	p<0.001
Males	141/310 (45.5)	50/141 (35.5)	91/141 (64.5)	p<0.001
Females	169/310 (54.5)	113/169 (66.9)	56/169 (33.1)	p<0.001
Urticaria/angioedema	217/310 (70.0)	118/163 (72.4)	99/147 (67.3)	p=0.333
Anaphylaxis	50/310 (16.1)	22/163 (13.5)	28/147 (19)	p=0.185
Asthma	17/310 (5.5)	7/163 (4.3)	10/147 (6.8)	p=0.333
Cutaneous non immediate reactions	26/310 (8.4)	16/163 (9.8)	10/147 (6.8)	p=0.339
Hypersensitivity only to ASA*	106/310 (34.2)	38/163 (23.3)	68/147 (46.3)	p<0.001
Multiple ASA/NSAID hypersensitivity**	204/310 (65.8)	125/163 (76.7)	79/147 (53.7)	p<0.001
Symptoms after ASA dose				
≤300 mg#	119/310 (38.4)	33/163 (20.2)	86/147 (58.5)	p<0.001
>300 mg¶	191/310 (61.6)	130/163 (79.8)	61/147 (41.5)	p<0.001

ASA: acetylsalicylic acid; NSAID: nonsteroidal anti-inflammatory drug; SD: standard deviation; p: correlation coefficient.
* Patients with histories of hypersensitivity reactions only to ASA.
** Patients with histories of hypersensitivity reactions to ASA and at least one other NSAID.
# Patients with histories of hypersensitivity reactions to ASA at doses of 300 mg or less.
¶ Patients with histories of hypersensitivity reactions to ASA at doses higher than 300 mg.

Table 3 Cardiological characteristics of the 310 patients and both allergological and cardiological outcomes

	Number (%)	Challenge (%)	Desensitization (%)	Pearson chi^2/t test
Total number of patients	310	163	147	
Cardiological characteristics				
Acute coronary syndrome (ACS)	90/310 (29.0)	23/163 (14.1)	67/147 (45.6)	p<0.001
ACS and myocardial infarction	48/310 (15.5)	14/163 (8.6)	34/147 (23.1)	p<0.001
Chronic ischemic heart disease	172/310 (55.5)	126/163 (77.3)	46/147 (31.3)	p<0.001
Stenting				
Medicated	56/310 (18.1)	8/163 (4.9)	48/147 (32.7)	p<0.001
Not medicated	20/310 (6.5)	8/163 (4.9)	12/147 (8.2)	p=0.244
Simple angioplasty	11/310 (3.5)	4/163 (2.5)	7/147 (4.8)	p=0.273
Allergological outcome				
Symptoms during the procedure*	22/310 (7.1)	10/163 (6.1)	12/147 (8.2)	p=0.487
Desensitization failure	-	-	2/147 (1.4)	
12-month cardiological outcome				
Major adverse cardiac events (MACE)	26/310 (8.4)	12/163 (7.4)	14/147 (9.6)	p=0.493

* Hypersensitivity reactions experienced by the patients during challenge or desensitization procedures.

Table 4 Acetylsalicylic acid (ASA)* challenge protocol

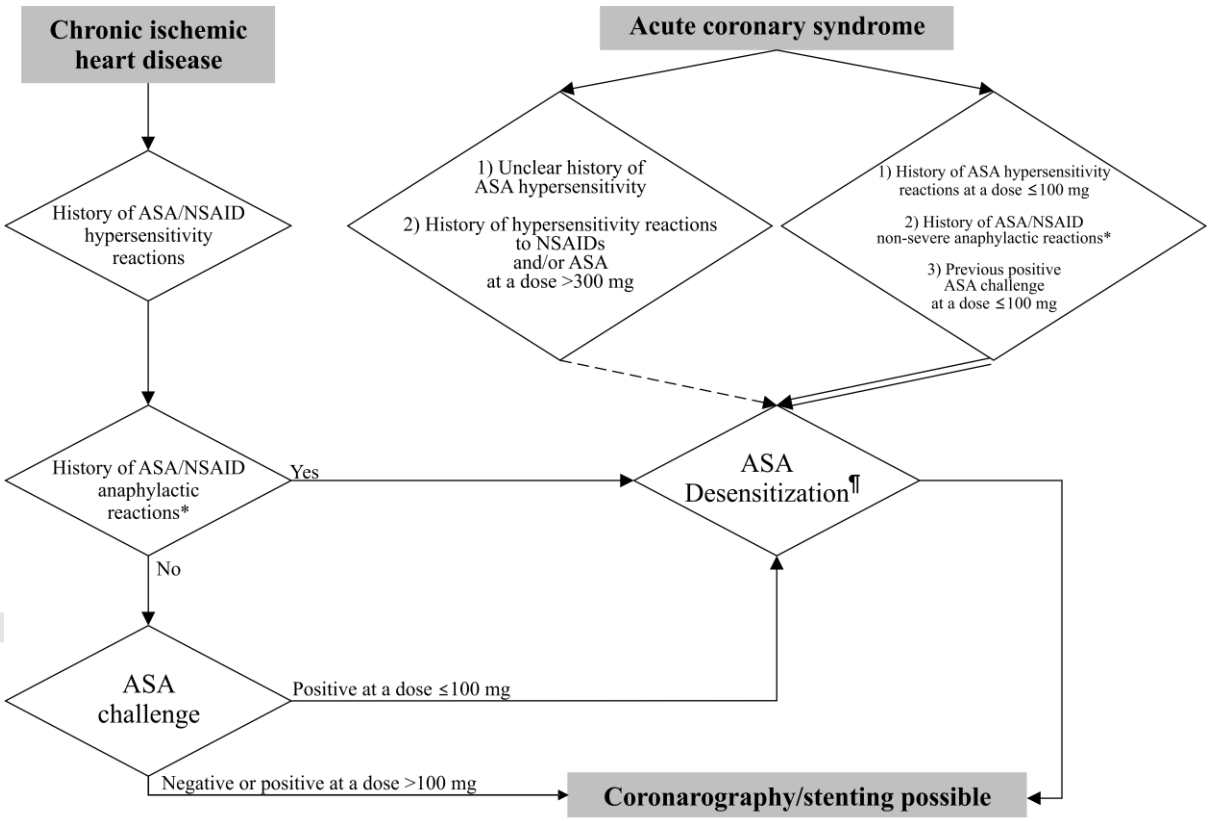
Minute	ml of L-ASA solution	ASA dose (mg)	Cumulative dose (mg)
0	0 (placebo)	0	0
20	1	10	10
65	2.5	25	35
110	2.5	25	60
155**	5	50	110
200**	5[#]	50[#]	160[#]

* 288 mg of lysine acetylsalicylate (L-ASA), equivalent to 160 mg of ASA, dissolved in 16 ml of water were used.
** 1-2 h observation after procedure.
[#] The default cumulative dose is 110 mg; in case of specific request by cardiologist it becomes 160 mg.

Table 5 Acetylsalicylic acid (ASA)* desensitiziation protocol

Minute	ml of L-ASA solution	ASA dose (mg)	Cumulative dose (mg)
0	0 (placebo)	0	0
20	0.01	0.1	0.1
40	0.1	1	1.1
60	0.2	2	3.1
80	0.3	3	6.1
100	0.4	4	10.1
120	0.5	5	15.1
140	1	10	25.1
180	1.5	15	40.1
240	2.5	25	65.1
300**	3.5	35	100.1

* 288 mg of lysine acetylsalicylate (L-ASA), equivalent to 160 mg of ASA, dissolved in 16 ml of water were used.
** 1-2 h observation after procedure.



*Challenge and desensitization are not recommended for patients with a history of severe anaphylaxis.
¶The dashed line indicates an optional choice.
¶The double line indicates a mandatory choice (see also text).