

Early aspirin desensitization in unstable patients with acute coronary syndrome: Short and long-term efficacy and safety

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Abstract

Background: Aspirin hypersensitivity is not a rare condition among patients with acute coronary syndrome. However, despite the publication of several successful desensitization protocols, the procedure is not as widespread as expected. We present a cohort of patients with acute coronary syndrome undergoing aspirin desensitization to evaluate its short- and long-term efficacy and safety and to reinforce data from previous studies.

Methods: Of 1306 patients admitted to our Coronary Care Unit between February 2011 and February 2013, 24 (1.8%) had a history of aspirin hypersensitivity. All 24 patients underwent an eight-dose aspirin desensitization protocol (0.1, 0.3, 1, 3, 10, 25, 50 and 100 mg of aspirin given by mouth every 15 minutes) after premedication with antihistamines and corticosteroids or antileucotrienes. Previously prescribed β blockers and angiotensin-converting enzyme inhibitors were not discontinued. All patients were desensitized within 72 hours of admission. Those requiring urgent catheterization (five patients with ST segment elevation myocardial infarction) were desensitized within 12 hours of catheterization and the remainder before catheterization.

Results: All patients were successfully desensitized and only one presented with an urticarial reaction. The five patients with ST segment elevation myocardial infarction were treated with abciximab until desensitization was complete. All but one patient underwent catheterization and 20 underwent percutaneous coronary intervention, most (66%) with the implantation of a bare metal stent. At follow-up (a minimum of 6–24 months), only two patients had discontinued aspirin, both due to gastrointestinal bleeding, and no hypersensitivity reaction had occurred.

Conclusions: Aspirin desensitization is effective and safe in unstable patients with acute coronary syndrome in both the short and long term.

Keywords

Aspirin allergy, aspirin desensitization, acute coronary syndrome, coronary stenting, ischaemic heart disease

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Introduction

Aspirin (ASA) has been the foundation of antithrombotic treatment for all acute coronary syndromes (ACS) since the ISIS-2 trial¹ and guidelines^{2,3} recommended that it should be used from the beginning of treatment and then continued indefinitely, irrespective of the type of ACS and treatment

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modality. These are regarded as class IA or IB recommendations. ASA hypersensitivity is the second most common cause of hypersensitivity to drugs after penicillin.⁴ Although the true prevalence of this condition is not well known, it ranges from 0.6 to 2.5% in the general population and reaches 10% in patients with asthma.⁵

Despite the existence of several effective, safe ASA desensitization (AD) protocols^{6–13} there is no universally accepted protocol¹⁴ and there is still a lack of evidence about the best way to perform early, quick desensitization in patients with ACS. In the current European guidelines for the management of patients with ST segment elevation myocardial infarction (STEMI)³ and non-ST-segment elevation ACS (NST-ACS),¹⁵ the only references to AD are the statements ‘patients with a history of hypersensitivity to ASA can undergo desensitization and continue therapy indefinitely’³ and ‘an option in selected patients’,¹⁵ with no established recommended levels or explanation about how to accomplish desensitization. This may be one of the reasons why knowledge and implementation of these protocols is still low among cardiology departments, as demonstrated in a recent survey of UK cardiology departments in which only seven of 40 percutaneous coronary intervention (PCI) centres had ever performed AD.¹⁶

We report here the efficacy and safety of a quick and early AD protocol, based on previously tested protocols, performed on all unstable patients with a history of ASA hypersensitivity admitted to our Coronary Care Unit (CCU) over a three-year period. We also describe the events and current state of ASA intake during a follow-up period of at least six months in all these patients. Our main objective is to reinforce the evidence from previous studies about AD in coronary artery disease (CAD) and to encourage cardiologists to perform desensitization when it is indicated.

Methods

Population

A prospective registry of all patients undergoing AD was performed. In February 2011, we started to use an AD protocol for all patients admitted to our CCU for NST-ACS or STEMI with a history of ASA hypersensitivity in its various forms, except chronic idiopathic urticaria; in most instances this was registered in their medical records. Patients were classified into five groups according to the type of reaction based on the classification of Gollapudi et al.⁴ (Table 1). Patients reporting ASA intolerance in other forms, such as gastroenteric symptoms or bleeding, did not undergo AD.

Protocol

Aspirin doses were prepared from 500 mg of chewable ASA diluted in water with lactose at a concentration of 1

mg/0.5 cm³. The different doses of a soluble master formula were separated, individually packaged and marked with the dose to avoid confusion.

The patients were strictly monitored (heart rate, blood pressure, peripheral oxygen saturation, heart rhythm and clinical status, with special attention to cutaneous and respiratory symptoms) in the CCU. All patients had a stable respiratory and cutaneous status and signed an informed consent document before starting the challenge/desensitization procedure.

We used premedication in all patients. We initially used prednisone 60 mg plus cetirizine 10 mg by mouth, but after an adverse event occurred in one patient with STEMI, we revised the protocol and, in agreement with an allergist, we used premedication with montelukast 10 mg plus cetirizine 10 mg from May 2012. Premedication was administered 12 hours before and repeated four hours prior to the challenge/desensitization for the patients with NST-ACS and once, four hours before AD, for the patients with STEMI. We usually maintained β blockers and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) in all patients for whom they were previously prescribed.

AD was performed within 72 hours and before cardiac catheterization in the patients with NST-ACS or in those not undergoing urgent PCI for STEMI, and within 12 hours after primary PCI in patients with STEMI or in those undergoing urgent PCI for other reasons (e.g. instability or shock). For patients requiring urgent PCI, bare metal stents (BMS) are often used until it is certain that AD is successful and, if patients have other lesions suitable for PCI, a scheduled procedure is performed after AD is complete. Drug-eluting stents (DES) are used based on operator criteria. Until AD was performed, the patients received an adenosine diphosphate receptor antagonist (clopidogrel, prasugrel or ticagrelor depending on the current antiplatelet regimen protocol in our centre) and full anticoagulation with unfractionated heparin. Some patients (those without a high risk of bleeding), especially those undergoing primary PCI with stent implantation, received an IIB–IIIa glycoprotein inhibitor until AD was performed.

The protocol consisted of eight escalating doses of ASA by mouth every 15 minutes, starting with 0.1 mg in all patients (Table 2). AD was complete within 105 minutes. If, during the challenge, any mild to moderate reaction occurred, it was suitably treated depending on its type (with corticosteroids and antihistamines for cutaneous reactions, with oxygen support and inhaled β agonists for asthma attacks, and with subcutaneous adrenaline for more severe reactions) and AD was restarted, once the patient had recovered, at the last tolerated dose. In patients with a severe reaction, the challenge was definitively stopped. Mild reactions were defined as an itchy skin, rhinitis, sneezing or coughing; moderate reactions as urticaria with skin rash, wheezing, swelling of the lips or mild dyspnoea due to the exacerbation of asthma; and severe reactions as oedema

Table 1. Classification of patients desensitized according to the classification of Gollapudi et al.⁴ of hypersensitivity reactions to aspirin.

Type of hypersensitivity reaction	Clinical manifestations	No. (%) patients
I (COX-I mediated)	Respiratory symptoms, rhinitis, asthma exacerbation, nasal polyps, sinusitis	6 (25)
II (COX-I mediated)	Urticaria/angioedema with chronic idiopathic urticaria	0
III (COX-I mediated)	Urticaria/angioedema with NSAIDs cross-reactions and first exposure manifestation	14 (58)
IV (immunological ^a)	Urticaria/angioedema without NSAIDs	2 (8)
V (immunological ^a)	cross-reactions and with more than first exposure needed Anaphylactic reactions: hypotension, swelling, laryngeal oedema, generalized pruritus, tachypnoea and lapses in consciousness	2 (8)

COX-I: cyclooxygenase-I enzyme; NSAIDs: non-steroidal anti-inflammatory drugs.

^aPresumed to be mediated by drug-specific IgE antibody production.

Table 2. Escalating doses and timing of aspirin desensitization protocol.

Time (min)	Dose (mg)	Cumulative dose (mg)
0	0.1	0.1
15	0.3	0.4
30	1	1.4
45	3	4.4
60	10	14.4
75	25	39.4
90	50	89.4
105	100	189.4

of the tongue or face, severe asthmatic crisis and anaphylactic shock. After successful AD, the patients were strictly monitored in the CCU for at least four hours. We avoided AD in patients who were unconscious and in Killip class $\geq$ III patients until they were stable.

Statistical analysis

Categorical variables are reported as a number (%) and continuous variables as mean (standard deviation) or median according to the variable distribution. All analyses were performed with SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA)

Results

From February 2011 to February 2013, 1306 patients were admitted to the CCU with a diagnosis of ACS (60% STEMI, 34% non-STEMI and 4% unstable angina). In total, 68 patients reported ASA intolerance (5.2%), 24 due to ASA hypersensitivity (1.8%), 29 (2.2%) for gastrointestinal intolerance and 15 (1.2%) for other reasons such as epistaxis, nasal polyposis or headache. Patients with ASA hypersensitivity all underwent AD. All but four patients

presenting in Killip class II were Killip class I at the time of AD and no patient was excluded as a result of heart failure. Four of the desensitized patients had previously undergone PCI with BMS implantation and all received clopidogrel as the only antiplatelet drug due to ASA hypersensitivity as we did not conduct AD at that time. Table 1 shows each type of reaction according to the Gollapudi classification.⁴ The overall baseline characteristics are given in Table 3 and the individual patient characteristics in Table 4. Table 5 shows the angiographic and procedure characteristics of all patients undergoing catheterization.

Cardiac catheterization was performed in all but one patient (patient 23); cardiac catheterization was performed urgently before AD in five (22%) patients, all as primary PCI for STEMI. The remainder (18.78%) were performed within the first 72 hours (34 $\pm$ 12 hours) after the completion of AD. Of the three patients with STEMI who did not undergo primary PCI, one was a result of fully evolved STEMI ($>$ 36 hours) and two patients underwent thrombolysis. No complications occurred during the procedures. BMSs were more frequently used than DESs and four of the five patients undergoing primary PCI received a BMS. The patient not undergoing catheterization was number 10 in our series (Table 4) and died suddenly 24 hours after AD as a result of an acute cardiac rupture. Premedication in this patient had been performed with prednisone and, after this death and in agreement with an allergist, the premedication protocol was changed to montelukast. PCI was not performed in two patients due to three-vessel disease; these patients were referred for coronary artery bypass grafting (CABG). No patient had a prolonged stay in the CCU (median 5 days).

AD was immediately successful without any reaction in 23 patients and was completed in 105 minutes. One patient with a history of type III hypersensitivity developed urticaria and pruritus after the 10 mg dose; this was quickly resolved with intravenous methylprednisolone 60 mg and dexchlorfeniramine 5 mg. Two hours later, when all symptoms had

Table 3. Baseline characteristics of patients.

Baseline characteristics	No. (%) patients
Male	16 (66.7)
Mean age (years)	69±12
Hypertension	21 (87.5)
Diabetes ^a	12 (50)
Hypercholesterolaemia	12 (50)
Current or previous smoker	11 (45.8)
Ischaemic cardiomyopathy background	4 (16.7)
Previous percutaneous coronary intervention	4 (16.7)
Type of acute coronary syndrome	
STEMI	8 (33)
NSTEMI	14 (58.3)
Unstable angina	2 (8.3)
Pharmacological treatment	
Clopidogrel	20 (83)
Prasugrel	3 (12.5)
Ticagrelor	1 (4)
Abciximab	5 (21)
Tirofiban	2 (8.3)
ACEI or ARB	15 (62.5)
Beta blocker ^b	11 (46)

ARB: angiotensin receptor blocker; ACEI: angiotensin converting enzyme inhibitor; NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction.

^aAll type 2 diabetes.

^bCardio-selective β blocker (carvedilol).

resolved, the protocol was restarted at that point (10 mg dose) and successfully completed.

In all patients, including those who underwent CABG, indefinite treatment with ASA was prescribed with an emphasis on the need to maintain it to conserve the desensitized status. For patients who had stents implanted or who did not undergo CABG, an adenosine diphosphate receptor antagonist (clopidogrel, prasugrel or ticagrelor) was prescribed for six months if a BMS was implanted or 12 months if a DES or no stent was used. All patients received at least six and up to 24 months of follow-up. Two patients discontinued ASA due to gastrointestinal bleeding requiring hospitalization at three and six months, respectively; both were treated with omeprazole at the time of the bleeding event. No new desensitization was performed and both were discharged with receiving treatment with clopidogrel for a full 12 months. One patient was re-admitted for cardiac causes: a new onset of heart failure without the need for a new revascularization. No Major Adverse Cardiovascular Events (MACE) was reported.

Discussion

Aspirin remains one of the cornerstones of treatment in ACS in both primary¹⁷ and secondary prevention. In the CAPRIE trial,¹⁸ clopidogrel did not demonstrate superiority in MACE reduction compared with ASA after an ACS.

Based on this study, the guidelines recommended ASA as the first choice long-term antiplatelet treatment for secondary prevention and clopidogrel instead of ASA only for allergic or intolerant patients. The latter treatment is not evidence-based because no randomized trial has compared combined antiplatelet regimens with any other antiplatelet drug used alone other than ASA after ACS. ASA plays a key role, especially in patients undergoing PCI with stent implantation. A recent large one-year prospective multicentre study found that patients who did not receive ASA before PCI were at higher risk of mortality and stroke.¹⁹ Furthermore, ASA has proved to be a more cost-effective treatment in patients with CAD compared with a regimen of tylenopiridine alone.²⁰

Pathophysiology of ASA hypersensitivity and AD

As indicated in the Gollapudi classification,⁴ ASA hypersensitivity may be the result of two types of physiopathological mechanisms: pseudo-allergic reactions (types I, II and III) and true allergy reactions (types IV and V). The first reactions are mediated by an excessive production of leukotrienes by 5-lipoxygenase.^{4,21,22} In contrast, it is thought that true allergic reactions are mediated via ASA-directed immunoglobulin E (IgE) antibodies,^{21,22} but a specific IgE against ASA has not yet been found¹⁴ and these reactions are called anaphylactoid and not anaphylactic reactions. The exact mechanism of AD is not well known, but for pseudo-allergic reactions it is thought that the gradual dose escalation of ASA exhausts leukotrienes and downregulates leukotriene receptors.²¹ For true allergic reactions, mechanisms similar to desensitization with penicillin are assumed.²³ It is hypothesized that there is a gradual saturation of antibody-binding sites on granulocytes and a depletion of inflammatory cytokines. Another study suggests that the suppression of IL-4 synthesis by ASA explains the therapeutic benefit.²⁴

Prevalence of ASA hypersensitivity

The available data concerning the incidence of ASA hypersensitivity among patients with CAD ranges between 2.6%⁸ and 3.1%¹¹; the incidence of ASA intolerance in a large registry of patients with CAD²⁵ was 1.5%. In our population, the incidence of ASA hypersensitivity was 1.8% over three years. Therefore the number of patients who might benefit from AD is not negligible.

No provocation test to confirm the hypersensitivity was performed, but most patients had a recorded history of allergy. Provocation tests are currently the only way to demonstrate ASA hypersensitivity, administering the drug by mouth, bronchially or nasally. There is no available in vitro technique and skin tests have failed to give consistent and reliable wheal and flare responses.^{5,23} Provocation tests are contraindicated in unstable patients with ACS,⁵ although

Table 4. Main characteristics of patients undergoing aspirin desensitization.

Patient No.	Age (years)	Sex	Allergy type ^a	ACS event	Killip class at time of AD	Urgent catheterization	Stenting	Time of AD	Complications of AD	Aspirin withdrawn on follow-up	Observations
1	71	F	III	NSTEMI	I	No	No	Pre	No	Yes	CABG, UGIB
2	69	M	V	NSTEMI	I	No	Yes (BMS x1)	Pre	No	No	
3	84	F	III	STEMI	I	No	Yes (DES x4)	Pre	No	No	Thrombolysis New hospitalization for HF
4	79	F	III	STEMI	II	Yes	Yes (BMS x1 and DES x1) ^b	Post	No	No	
5	77	M	I	NSTEMI	I	No	Yes (DES x2)	Pre	No	No	
6	47	F	III	STEMI	I	Yes	Yes (BMS x1)	Post	No	No	
7	66	M	III	NSTEMI	I	No	Yes (BMS x3)	Pre	No	No	
8	83	M	I	NSTEMI	II	No	Yes (BMS x1)	Pre	No	No	
9	83	M	I	NSTEMI	I	No	Yes (BMS x1)	Pre	No	Yes	UGIB
10 ^c	84	F	III	STEMI	II	No	No	Pre	No	No	Death due to left ventricle free wall rupture
11	52	M	III	STEMI	I	Yes	Yes (BMS x1)	Post	Urticaria	No	Urticaria treated and AD successfully finished
12	60	F	III	UA	I	No	No	Pre	No	No	CABG
13	59	M	III	STEMI	II	Yes	Yes (BMS x1)	Post	No	No	
14	66	M	III	NSTEMI	I	No	Yes (BMS x2)	Pre	No	No	
15	83	M	IV	NSTEMI	I	No	Yes (DES x1)	Pre	No	No	
16	67	F	III	UA	I	No	Yes (BMS x1)	Pre	No	No	
17	55	M	III	STEMI	I	No	Yes (BMS x1)	Pre	No	No	Thrombolysis
18	77	M	IV	NSTEMI	I	No	Yes (BMS x1)	Pre	No	No	
19	56	M	V	NSTEMI	I	No	Yes (BMS x1; DES x1)	Pre	No	No	
20	66	M	III	NSTEMI	I	No	Yes (BMS x1)	Pre	No	No	
21	46	M	III	STEMI	I	Yes	Yes (DES x2)	Post	No	No	
22	83	M	I	NSTEMI	I	No	Yes (BMS x1)	Pre	No	No	
23	76	F	I	NSTEMI	I	No	Yes (BMS x2)	Pre	No	No	
24	80	M	I	NSTEMI	I	No	No	Pre	No	No	Balloon angioplasty without stent implantation

^aAllergy type according to the classification of Gollapudi et al.⁴^bDES in second procedure.^cPatient died before catheterization as a result of acute left ventricle free wall rupture.

ACS: acute coronary syndrome; AD: aspirin desensitization; BMS: bare metal stent; CABG: coronary artery bypass grafting; DES: drug-eluting stent; HF: heart failure; NSTEMI: non-ST segment elevation myocardial infarction; Pre: before catheterization; Post: after catheterization; STEMI: ST segment elevation myocardial elevation; UA: unstable angina; UGIB: upper gastrointestinal bleeding.

Table 5. Angiographic characteristics and procedures.

Angiographic characteristics	No. (%) patients
Left main disease	0
LAD disease	12 (50)
Cx disease	10 (41.7)
RC disease	15 (62.5)
Secondary vessel disease ^a	11 (45.8)
Multivessel disease ^b	11 (45.8)
PCI	21 (87.5) (one balloon angioplasty in secondary vessels with small calibre)
BMS implanted: 20	No. of patients receiving each type of stent
DES implanted: 11	BMS DES BMS+DES
	14 4 2
Stents per patient	BMS DES
1	13 3
2	2 2
3	1 0
4	0 1
Median overall stent length per patient (mm)	22 (15–71)
Mean no. of stents per patient	1.8

Lesions were considered significant angiographically when there was an estimated narrowing $\geq 50\%$ for the left main vessel and $\geq 70\%$ for all other vessels.

^aSecondary vessel disease was defined when any branch other than the main branches with calibre ≥ 1.5 mm was affected.

^bMultivessel disease was defined when two or more main branches presented significant lesions.

BMS: bare metal stent; DES: drug-eluting stent; Cx: circumflex coronary artery; LAD: left descending anterior coronary artery; PCI: percutaneous coronary intervention; RC: right coronary artery.

the difference between a diagnostic, multistep graded challenge and AD can be a little hazy²⁶ and, according to 2010 drug allergy practice parameters, it is thought that graded drug challenges of more than four or five steps may induce drug tolerance. There is thus a grey area when determining crossover from a graded challenge to AD.²⁶ Nevertheless, given the good results reported here, it seems reasonable to be cautious and perform AD instead of directly administering ASA to patients reporting ASA hypersensitivity, even when the suspicion is low.

Protocol used: premedication or no premedication

We used a modified protocol of Dalmau et al.⁹ with eight doses of ASA by mouth every 15 minutes, therefore completing desensitization within 105 minutes with the minimum six steps recommended for challenge/desensitization.²⁹ This protocol was shorter than most other published protocols and similar in duration that of McMullan et al.¹²

Although some researchers recommend different doses for starting the challenge/desensitization^{4,6} depending on the type of reaction, we decided to use the same initial dose irrespective of the type of reaction to simplify the protocol.

Premedication with cetirizine and corticosteroids was used in the first 10 patients and with montelukast and cetirizine in the remainder. Most studies not using premedication report a high percentage of success (Table 6), but the only benefit of not using premedication may be the lack of delay in performing desensitization. We believe that any such delay would not be long enough to be significant and when a delay could be most dangerous – for instance, after stent implantation – we reduced the time between premedication and the start of AD. For patients with NST-ACS, the guidelines recommend that PCI should be performed in the following 72 hours and all our patients with NST-ACS underwent catheterization within the first 72 hours with a mean time for AD of 34 hours. Furthermore, four of the five patients with STEMI, and some of the other patients, were treated with abciximab or tirofiban added to treatment with an adenosine diphosphate receptor inhibitor. We think that this is a good strategy until AD is complete, as reported by Schiano et al.²⁷ Premedication can also make patients more likely to tolerate the complete procedure. In fact, we achieved success in 100% of patients, with only one patient presenting a mild cutaneous adverse reaction; however, even in this patient we were able to successfully complete the procedure.

The premedication used was changed because there was a case of confirmed acute cardiac rupture in an 84-year-old woman with a diagnosis of evolved STEMI pre-treated with corticosteroids the night before and four hours before AD. The procedure was successful, but the patient died before catheterization could be performed. Despite controversies about the role of non-steroidal anti-inflammatory drugs, corticosteroids and the risk of cardiac rupture in the acute–subacute phase of ACS,^{28,29} we decided, in agreement with the allergist, to change the premedication to montelukast, an anti-leukotriene drug which has been previously proposed as a protective agent, particularly in patients with an asthmatic type I reaction.^{14,24,30}

Concomitant medications

The discontinuation of treatment with β blockers and ACE inhibitors has been proposed to prevent reactions during the procedure, especially for patients with asthma (β blockers) and because of an association with angioedema (ACE inhibitors). Only Silberman et al.⁷ have reported the discontinuation of β blockers; McMullan et al.¹² reported systematic non-cessation without further adverse effects. De Luca et al.¹¹ reported that almost 70% of their patients were being treated with β blockers and 50% with ACE inhibitors. We tend not to discontinue these treatments in patients for whom they are indicated and, as demonstrated here and in

Table 6. Aspirin desensitization in patients with coronary artery disease: literature review.

Reference	Incidence (%)	No. of patients	ACS/SCAD	Pre-treatment	Protocol (mg)	Interval (minutes)	Success (no. (%) of patients)	Adverse reactions	Follow-up
Silberman et al. ⁷	–	16	10/6	No	1, 2, 4, 8, 16, 32, 64, 100	30	14 (87.5)	Angioedema (2) Dyspnoea (1)	1–35 months, no suspensions/allergic reactions
Rossini et al. ⁸	2.6	26	16/10	No	1, 5, 10, 20, 40, 100	30–120	23 (88.4)	Urticaria (2) Asthma crisis (1)	12 months, 1 suspension for peptic ulcer
Dalmau et al. ⁹	–	5	5/0	No	0.1, 0.3, 1, 3, 10, 25, 50, 100	15–20	5 (100)	–	5–46 months, no suspensions/allergic reactions
Christou et al. ¹⁰	–	11	6/5	No	0.1, 0.3, 10, 30, 40, 81, 162, 325	15–25	11 (100)	–	6–19 months, no suspensions/allergic reactions
De Luca et al. ¹¹	3.1	43	23/20	No	1, 2, 4, 8, 16, 32, 64, 128, 250	30	42 (97.6)	Urticaria (1)	1–12 months, no suspensions/allergic reactions
Wong et al. ⁶	–	11	2/7	Loratadine or cetirizine or hydroxyzine or diphenhydramine and prednisone (two patients)	0.1, 0.3, 1, 3, 10, 30, 40, 81, 162, 325	10–20	10 (91)	Asthmatic crisis (1)	1–24 months, angioedema hours after the procedure
McMullan et al. ¹²	–	89 ^a	–	Leukotriene antagonists, antihistamines, steroids ^b	1, 10, 20, 40, 80, 160, 325	15	84 (94.3)	Angioedema (8)	45 patients with available follow-up data; 2 discontinued ASA (cough and urticarial, respectively)
Díez-Villanueva et al. ¹³	–	13	11/2	Leukotriene antagonists and dexchlorfeniramine in one patient	0.1, 0.3, 1, 3, 10, 25, 50, 100	20	13 (100)	Urticaria (6) Asthmatic crisis (3) Chest pain (1) –	Median 27.5 months, no suspensions/allergic reactions

Studies above the grey line were without antiallergic pre-treatment and studies below the grey line were with antiallergic pre-treatment.

ASA: aspirin; ACS: acute coronary syndrome; SCAD: stable coronary artery disease.

Numbers in parentheses indicate how many patients were affected by each adverse reaction in each study.

^aInpatient and outpatient desensitization procedures.

^bNot specified how many patients received pre-treatment.

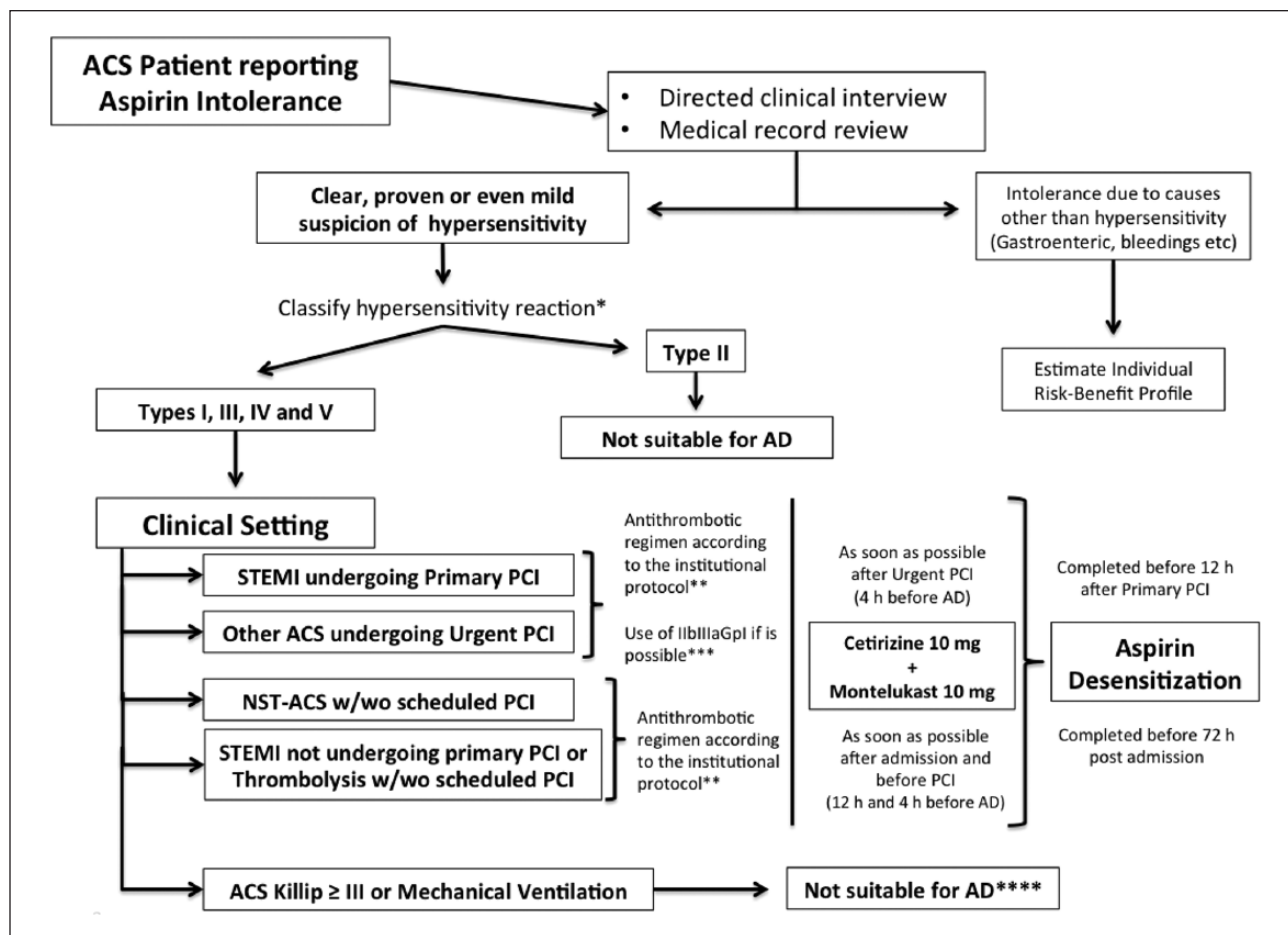


Figure 1. Decision-making algorithm for aspirin desensitization in patients with acute coronary syndromes.

*Classification based on Gollapudi et al.⁴ (see Table 1).

**Adenosine diphosphate receptor antagonist and anticoagulation regimen for each type of acute coronary syndrome and patient should be treated according to the current institution protocol or cardiologist decision because there is no evidence of which is the better strategy.

***Especially in patients receiving a stent after urgent PCI and before AD, but also in patients with NST-ACS, a IIb–IIIa glycoprotein antagonist such as abciximab or tirofiban may be a good alternative when there is no high risk of bleeding and until AD is performed.

****In patients unable to take aspirin by mouth, intravenous aspirin was used for desensitization.

ACS: acute coronary syndrome; AD: aspirin desensitization; PCI: percutaneous coronary intervention; NST-ACS: non-ST segment elevation acute coronary syndrome; STEMI: ST segment elevation acute coronary syndrome; w/wo: with or without; IIb–IIIaGpl: IIb–IIIa glycoprotein inhibitors.

other studies, the rate of adverse events does not appear to increase, whereas their utility in the acute–subacute phase of ACS²⁶ is universally demonstrated.

Safety of AD in the early phase of ACS

Our search at MEDLINE found eight studies with more than three patients (summarized in Table 6). All of these studies include both stable and unstable patients. In our study, we only included unstable patients, all admitted to our CCU for an ACS before 72 hours of AD. To our best knowledge, this is the largest published series of unstable patients undergoing AD. Only one patient had an adverse non-immediate cutaneous reaction with a cumulative dose of 14.4 mg. We resumed the protocol two hours after treating the reaction and completed it successfully. Adverse reactions during the procedure reported in other studies

were not frequent, were mostly cutaneous and asthmatic, usually well tolerated and quickly resolved with drugs commonly used to treat allergic reactions. No case of anaphylactic shock, death or myocardial infarction has been reported. Other studies have reported successful re-challenge/desensitization in patients developing symptoms during the first attempt.

Long-term efficacy and safety

Patient follow-up was for at least six and up to 24 months and all but two patients continued under treatment with ASA without recorded hypersensitivity reactions. Two patients discontinued ASA due to upper gastrointestinal bleeding requiring admission to hospital and no re-challenge was performed. The two patients were being treated with omeprazole at the time of bleeding. Only one patient

was admitted for cardiovascular causes: a new onset of heart failure. Only one of the previously published studies reported the discontinuation of ASA due to allergy symptoms in two of 45 patients with available follow-up.

Conclusions

This study reinforces data from previous reports: AD is effective and safe in patients with ASA hypersensitivity and acute coronary syndrome, allowing them the early benefit of ASA in the secondary prevention of ischaemic cardiomyopathy and prevention of stent thrombosis. Furthermore, AD should be performed in patients undergoing CABG to decrease the risk of graft occlusion. These types of procedure should be generalized to all cardiology departments with a protocol based on the published data and in collaboration with an allergist. As a result of the relatively low prevalence of ASA hypersensitivity, future large multicentre registries could help to improve our knowledge about the efficacy and safety of these procedures and encourage their more widespread use by cardiologists. With the results of our experience, we propose a decision-making algorithm which may guide the decision and the time taken to perform the procedure (Figure 1).

Limitations

Several limitations of the current study warrant consideration. First, not all patients had a confirmed diagnosis of ASA hypersensitivity, but, as previously reported, it seems prudent to be cautious and to perform the AD protocol before administration. Second, it is difficult to establish clear conclusions or recommendations from a small number of patients, although the results of all the studies published to date are similar in efficacy and safety. Finally, it is necessary to consider that the recommendations previously stated and the algorithm suggested are based on our own experience and published evidence, so caution is necessary when starting to apply AD. Despite this, the present study reinforces current data on the efficacy and safety of AD protocols.

Conflict of interest

The authors declare that there is no conflict of interest.

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