

Aspirin Desensitization in Patients With Coronary Artery Disease

Results of the Multicenter ADAPTED Registry (Aspirin Desensitization in Patients With Coronary Artery Disease)

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Background—There are limited data on aspirin (ASA) desensitization for patients with coronary artery disease. The aim of the present study was to assess the safety and efficacy of a standard rapid desensitization protocol in patients with ASA sensitivity undergoing coronary angiography.

Methods and Results—This is a prospective, multicenter, observational study including 7 Italian centers including patients with a history of ASA sensitivity undergoing coronary angiography with intent to undergo percutaneous coronary intervention. A total of 330 patients with history of ASA sensitivity with known/suspected stable coronary artery disease or presenting with an acute coronary syndrome, including ST-segment–elevation myocardial infarction were enrolled. Adverse effects to aspirin included urticaria (n=177, 53.6%), angioedema (n=69, 20.9%), asthma (n=65, 19.7%), and anaphylactic reaction (n=19, 5.8%). Among patients with urticaria/angioedema, 13 patients (3.9%) had a history of idiopathic chronic urticaria. All patients underwent a rapid ASA (5.5 hours) desensitization procedure. The desensitization procedure was performed before cardiac catheterization in all patients, except for those (n=78, 23.6%) presenting with ST-segment–elevation myocardial infarction who underwent the desensitization after primary percutaneous coronary intervention. Percutaneous coronary intervention was performed in 235 patients (71%) of the overall study population. The desensitization procedure was successful in 315 patients (95.4%) and in all patients with a history of anaphylactic reaction. Among the 15 patients (4.6%) who did not successfully respond to the desensitization protocol, adverse reactions were minor and responded to treatment with corticosteroids and antihistamines. Among patients with successful in-hospital ASA desensitization, 253 patients (80.3%) continued ASA for at least 12 months. Discontinuation of ASA in the 62 patients (19.7%) who had responded to the desensitization protocol was because of medical decision and not because of hypersensitivity reactions.

Conclusions—A standard rapid desensitization protocol is safe and effective across a broad spectrum of patients, irrespective of the type of aspirin sensitivity manifestation, with indications to undergo coronary angiography with intent to perform percutaneous coronary intervention.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02848339.

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■ percutaneous coronary intervention

Aspirin (ASA) is the cornerstone of antithrombotic therapy in patients with coronary artery disease (CAD), both in the acute and the chronic phase of treatment.^{1–3} However, ≈2% of patients have hypersensitivity to ASA.⁴ Although

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clopidogrel is recommended in practice guidelines as the antiplatelet agent of choice for patients who are unable to

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WHAT IS KNOWN

- Aspirin therapy is recommended in patients with coronary artery disease, especially after coronary stent implantation. Notably, $\leq 2\%$ of patients do not receive aspirin therapy because of hypersensitivity.
- Aspirin desensitization can be attempted in patients with aspirin hypersensitivity; however, many desensitization protocols require several days to be completed, contributing to the limited experience with applying aspirin desensitization protocols in real-world practice in patients with coronary artery disease.

WHAT THE STUDY ADDS

- The present study explored a rapid standardized aspirin desensitization protocol in a large cohort of patients undergoing coronary angiography for both acute and stable clinical conditions.
- The study demonstrates that a rapid standardized protocol is safe and effective in patients with coronary artery disease, irrespective of the type of sensitivity, and highly feasible, including in patients with acute coronary syndrome.
- The present desensitization protocol can be easily performed, allowing for aspirin administration after percutaneous coronary intervention even in patients with a history of aspirin hypersensitivity.

take aspirin because of hypersensitivity or intolerance, ASA desensitization also represents an alternative approach.⁵ This is particularly relevant for patients requiring dual antiplatelet therapy, including ASA and a P2Y₁₂ receptor, such as in patients experiencing an acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) with stent implantation. Desensitization protocols generally involve gradual increases in patient exposure to ASA with the goal of mitigating or abolishing immune-mediated reaction.^{4,6} However, many desensitization protocols require several days to be completed, making them impractical. This may also contribute to the limited experience with applying ASA desensitization protocols in real-world practice in patients with CAD.

We previously reported the results of a pilot investigation supporting the feasibility of performing a rapid (<6 hours) ASA desensitization protocol in patients undergoing PCI with stent implantation.⁷ The encouraging findings from our pilot feasibility investigation prompted the design of a larger scale multicenter investigation aimed to assess the safety and efficacy of a rapid ASA desensitization protocol in patients with a history of ASA hypersensitivity undergoing coronary angiography.

Methods

Study Design and Data Collection

The ADAPTED registry (Aspirin Desensitization in Patients With Coronary Artery Disease) is a prospective, multicenter, observational

study assessing the safety and efficacy of a rapid desensitization protocol in patients with ASA hypersensitivity undergoing coronary angiography. A total of 7 centers in Italy, including both academic and nonacademic hospitals, participated in this registry. In particular, consecutive patients with a history of ASA hypersensitivity scheduled to undergo coronary angiography with intent to perform PCI were enrolled. ASA hypersensitivity was self-reported and assessed based on patients' clinical history. No patient was excluded, except from those who were unwilling to provide written informed consent to participate in the desensitization protocol. The study included stable patients with known or suspected CAD and patients presenting with an ACS, including ST-segment-elevation myocardial infarction (STEMI). Patients underwent a rapid ASA desensitization protocol, as described below. At each participating hospital, demographic and clinical data, adverse reactions associated with ASA hypersensitivity, PCI details, and details of antiplatelet treatment regimen were recorded. All patients were followed up for desensitization procedure success, description of reactions because of the desensitization procedure, and in-hospital major adverse cardiac events. All patients were also followed up for 12 months to assess their long-term risk of major adverse cardiac events, compliance with ASA therapy, and late occurrence of side reactions because of ASA sensitivity. In case of ASA withdrawal, the causes of discontinuation were assessed. The study protocol was approved by the ethics committee at each participating center, and all patients provided their written informed consent to participate in the study. The study was conducted in accordance with the principles contained in the Declaration of Helsinki and Good Clinical Practice guidelines.

Aspirin Desensitization Procedure

ASA desensitization was performed before coronary angiography in all patients except for those presenting with STEMI in whom the desensitization protocol was performed after primary PCI. In patients with a history of ASA sensitivity presenting with a STEMI, in whom the desensitization procedure was performed after PCI, periprocedural use of glycoprotein IIb/IIIa inhibitors was left at the discretion of the treating physician. Details of the ASA desensitization protocol used in this study have been previously reported.⁷ Briefly, intravenous access was obtained in all patients before desensitization. Six sequential doses of aspirin (1, 5, 10, 20, 40, and 100 mg) were administered orally for 5.5 hours (Figure). Blood pressure, pulse, and saturation were measured every 30 minutes, and mucocutaneous, naso-ocular, and pulmonary reactions were monitored closely until 4 hours after the end of the procedure. ASA administration was immediately discontinued if mucocutaneous, respiratory, or systemic signs of hypersensitivity occurred. The desensitization procedure was generally performed before cardiac catheterization, with the exception of those with an indication to undergo urgent/emergent coronary angiography. After desensitization, patients were instructed to continue aspirin 100 mg daily because sensitivity may recur within a few

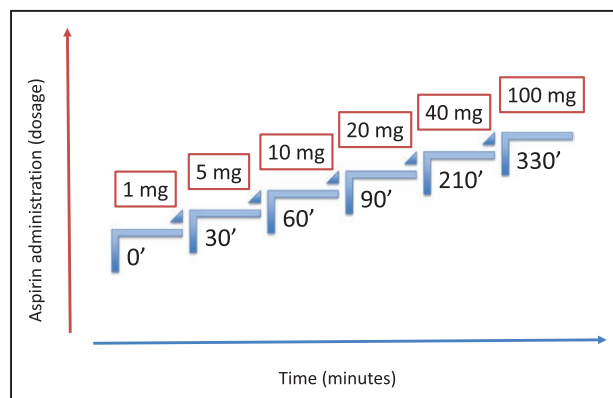


Figure. Rapid aspirin desensitization protocol. Six sequential doses of aspirin (1, 5, 10, 20, 40, and 100 mg) administered orally for 5.5 h.

days after discontinuation. In all elective cases, the use of steroids, antihistamines, and antileukotrienes was stopped for 7 days before desensitization.

Definitions

Major adverse cardiac events were defined as the composite of cardiac death, myocardial infarction, probable/definite stent thrombosis (ST), unstable angina, or stroke. Death was considered cardiac in origin unless obvious noncardiac causes could be identified. Myocardial infarction was diagnosed in case of troponin elevation with ischemic symptoms and new pathological Q waves on the ECG.⁸ ST was defined according to the Academic Research Consortium (ARC) definitions.⁹ Unstable angina was defined as the occurrence of ischemic symptoms requiring hospitalization or repeat coronary angiography, without any biochemical evidence of myocardial necrosis. Stroke was defined as an ischemic cerebral infarction caused by an embolic or thrombotic occlusion of a major intracranial artery.

Study Oversight

The overall management of the ADAPTED registry was led by the Italian Society of Invasive Cardiology (GISE). No unrestricted grant support was provided. The principal investigator (R.R.) was responsible for the study design, maintenance of the database, data validation, analyses, and study-center co-ordination. The first, second, and senior authors wrote the first draft of the article, and the writing committee made revisions and made the decision to submit the article for publication.

Statistical Analysis

The safety of the ASA desensitization protocol was assessed in terms of frequency and severity of adverse reactions because of administration of escalating doses of ASA. The efficacy of the ASA desensitization protocol was expressed as the rate of successful desensitization (ie, pill intake with no allergic reaction) after administration of the 100-mg ASA dose. Continuous data are expressed as mean±SD, and categorical data are expressed as frequencies (percent). All statistical analyses were performed using the SPSS 19.0 software.

Results

From May 2010 to February 2015, among a total of 26 550 patients undergoing coronary angiography, 333 patients (1.26%) with a self-reported history of ASA sensitivity and presenting with either an ACS or known/suspected CAD were identified and prospectively enrolled. All patients, except for 3 patients (0.9%), agreed to participate in the protocol. Thus, a total of 330 patients constituted our study population.

A history of mucocutaneous reactions was reported in 246 patients (74.5%) (urticaria in 177 patients [53.6%] and angioedema in 69 patients [20.9%]), respiratory sensitivity (asthma and rhinitis and bronchospasm) in 65 patients (19.7%), and anaphylactic shock in 19 patients (5.8%). Among patients with urticaria/angioedema, 13 patients (3.9%) had a history of idiopathic chronic urticaria. Baseline demographics of the study population are listed in Table 1. There was a larger prevalence of men (64.2% of patients), and 233 patients (70.6%) had an ACS as indication for coronary angiography. A total of 252 patients (76.3%) underwent the desensitization procedure before cardiac catheterization, whereas in 78 patients (23.6%), all with STEMI, the desensitization was performed after primary PCI.

The desensitization procedure was successful in 315 patients (95.4%), including patients with a history of anaphylactic shock or chronic idiopathic urticaria. Among 15 patients

Table 1. Baseline Characteristics and Procedural Data

Clinical Characteristic	330 Patients
Age, y	68±11
Male sex, %	212 (64.2)
Previous PCI, %	80 (24.2)
Previous CABG, %	47 (14.2)
Clinical presentation	
Stable angina, n (%)	67 (20.3)
Unstable angina, n (%)	44 (13.3)
NSTEMI, n (%)	111 (33.6)
STEMI, n (%)	78 (23.6)
Other causes, n (%)	30 (9.1)
Multivessel disease, n (%)	71 (22)
Bare metal stents, n (%)	79 (23.9)
Drug-eluting stents, n (%)	156 (46.1)
Coronary artery bypass graft, n (%)	10 (3)
LV ejection fraction (%)	52±10
Treatment at discharge	
Clopidogrel, n (%)	172 (52.1)
Ticlopidine, n (%)	29 (8.8)
Ticagrelor, n (%)	24 (7.3)
Prasugrel, n (%)	19 (5.8)
Statin, n (%)	242 (73.3)
Nitrates, n (%)	81 (24.5)
ACE-I/ARB, n (%)	211 (63.9)
OAC, n (%)	24 (7.3)

ACE-I indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; LV, left ventricular; NSTEMI, non-ST-segment-elevation myocardial infarction; OAC, oral anticoagulant therapy; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation myocardial infarction.

(4.6%) in whom the aspirin protocol failed, 10 patients presented a mucocutaneous (urticaria and angioedema) reaction, and 5 patients had a respiratory reaction (asthma, dyspnea, or bronchospasm; Table 2). Of note, only 2 of these patients had history of chronic idiopathic urticaria and had experienced urticaria after taking ASA. No serious adverse reactions occurred in patients in whom the procedure failed (Table 2). Particularly, none of them experienced anaphylactic shock, and angioedema was promptly treated. The symptoms subsided after treatment with corticosteroids and antihistamines.

Of the 330 patients, 235 patients (71%) underwent PCI with stent implantation (46% drug-eluting stents). Of the 95 patients who did not undergo PCI, 10 patients (10.5%) underwent coronary artery bypass graft, whereas the remaining 85 patients (89.5%) were medically managed (Table 2). All patients with successful ASA desensitization were discharged on aspirin 100 mg per day. A total of 229 patients (69.4%) were discharged on dual antiplatelet therapy. Table 1 shows the type of P2Y₁₂ inhibitor. Among patients with successful in-hospital ASA desensitization, 62 patients (18%) discontinued

Table 2. Characteristics of Patients With Unsuccessful Desensitization Procedure

Patient	Age, y	Sex	Aspirin Hypersensitivity–Related Reaction	Clinical Presentation	PCI	Stent Type	Stent Length, mm	No. of Lesions Treated With PCI	No. of Vessels Treated With PCI	Pre-PCI Desensitization	Type of Reaction in Unsuccessful Desensitization	Dose of Aspirin at Which Reaction Occurred, mg	Event Resolution	Overall MACE
1	70	F	Asthma	NSTEMI	+	DES	12	1	1	+	Asthma	20	Corticosteroids and antihistamines	None
2	61	M	Glottic edema; chronic idiopathic urticaria	SA	+	DES	15	2	2	0	Urticaria	40	Corticosteroids and antihistamines	None
3	61	M	Urticaria	SA	0	–	–	0	0	+	Urticaria	20	Corticosteroids and antihistamines	None
4	58	M	Urticaria; chronic idiopathic urticaria	UA	0	–	–	0	0	+	Urticaria	20	Corticosteroids and antihistamines	None
5	66	M	Asthma; glottic edema	UA	0	–	–	0	0	+	Dyspnea	100	Corticosteroids and antihistamines	None
6	75	M	Glottic edema	SA	+	DES	32	1	1	+	Angioedema	...	Corticosteroids and antihistamines	None
7	84	M	Urticaria	UA	0	–	–	0	0	+	Urticaria	20	Corticosteroids and antihistamines	None
8	80	M	Urticaria	SA	0	–	–	0	0	+	Perianal erythema	20	Corticosteroids and antihistamines	None
9	76	F	Urticaria	NSTEMI	0	–	–	0	0	+	Urticaria	40	Corticosteroids	Cardiac death
10	86	M	Asthma	STEMI	0	–	–	0	0	+	Bronchospasms	20	Corticosteroids and antihistamines	STEMI
11	59	M	Urticaria	NSTEMI	+	DES	18	1	1	+	Generalized urticaria	40	Corticosteroids and antihistamines	UA
12	75	F	Urticaria	NSTEMI	+	BMS	15	1	1	0	Urticaria	20	Corticosteroids and antihistamines	None
13	79	M	Glottic edema	STEMI	+	–	–	1	1	0	Angioedema	20	Corticosteroids and antihistamines	Cardiac death
14	75	M	Asthma	STEMI	+	DES	28	2	2	0	Asthma, dyspnea	20	Corticosteroids and antihistamines	None
15	75	M	Asthma	Other	0	–	–	0	0	0	Dyspnea, rhinitis	40	Antihistamines	None

BMS indicates bare metal stent; DES, drug-eluting stent; F, female; M, male; MACE, major adverse cardiac event; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.

+, yes; –, not available.

ASA within the first 12 months. In none of the patients, discontinuation was because of hypersensitivity reactions.

Overall major adverse cardiac events at 1 year occurred in 39 patients (11.8%). Of these, 14 occurred in hospital (2 cardiac deaths, of which 1 with probable ST, 7 myocardial infarction, 1 stroke, and 4 unstable angina) and 25 after discharge (4 cardiac deaths, of which 1 with probable ST, 8 myocardial infarction, 1 ST, 1 stroke, and 11 unstable angina).

Discussion

To the best of our knowledge, the present study is the largest to explore the standardized use of an ASA desensitization protocol in a large cohort of patients undergoing coronary angiography for both acute and stable clinical conditions. The study was conducted in the context of a prospective, multicenter registry, which was developed following preliminary findings of a pilot investigation supporting the feasibility of a simple and rapid bedside ASA desensitization protocol. The key findings of our study include (1) a simple and rapid bedside ASA desensitization protocol was effective in an unselected patient real-world cohort of patients known/suspected CAD or ACS, including STEMI, with $\approx 95\%$ of patients responding to the desensitization procedure; (2) the ASA desensitization protocol was safe with no serious adverse reaction at short term and long term (≤ 1 year); and (3) the risk of adverse reactions seemed to be independent of the type of ASA hypersensitivity.

Aspirin, in addition to a P2Y₁₂ inhibitor, is the treatment of choice for the secondary prevention of atherothrombotic events in patients with CAD, including those undergoing PCI with stent implantation.^{1-3,5} However, some patients are unable to tolerate ASA because of hypersensitivity.⁴ Despite the availability of disparate ASA desensitization protocols,^{7,10-12} these are not commonly used in real-world practice.⁶ Indeed, the fact that these may be time-consuming potential leading to treatment delays are potential causes for physicians to not embrace these protocols particularly in settings such as the treatment of patients with CAD. In patients with ASA hypersensitivity and concomitant CAD, data on the safety and efficacy of desensitization therapy are limited to small case series.^{7,10,11} Moreover, the vast majority of these reports were based on retrospective analysis, included different ASA desensitization protocols, and excluded high-risk patients, such as those with history of anaphylactic shock. The ADAPTED registry is a prospective study that included all patients, including high-risk patients, with a history of ASA hypersensitivity in which a user-friendly desensitization protocol, the feasibility of which was previously tested, was consistently applied on a large-scale basis.

Most of the ASA desensitization protocols reported in the literature are time consuming and may take several days for completion.¹³⁻¹⁵ For example, the Scripps Clinic protocol involves small incremental oral doses of aspirin administered over the course of 2 to 3 days, until a dose of 400 to 650 mg is tolerated.¹⁶ Although a long interval between doses can safeguard against undesired reactions, as symptoms can be detected at each given dose, a desensitization procedure requiring several days to be completed is not practical in patients with ACS or those who undergo stent implantation who require immediate administration of ASA. Moreover,

such time delay would not be in line with guideline recommendations, which recommend an early invasive evaluation in most patients with an ACS.¹⁷ In addition, a protocol applicable to patients with different manifestations of ASA hypersensitivity, as in this study, is more practical. The simplified protocol of Silberman et al¹⁰ required only 2.5 hours. However, its validation study included only 16 patients, and patients with ACS were excluded. De Luca et al¹¹ tested a desensitization protocol that consisted of intravenous aspirin administration within 4.5 hours. Out of the 43 patients included in the study, 53% presented with ACS, and the rate of success was higher than 97.6%. However, patients with previous anaphylactic reactions were excluded.

In the present registry, we prospectively investigated the safety and efficacy of a user-friendly desensitization protocol that was overall rapid (5.5 hours) and did not require the use of antihistamines or corticosteroids. The latter approach was used in the series of Wong et al,¹⁸ which, however, included only 11 patients, 10 of whom (90.9%) were pretreated with antihistamines or corticosteroids. Importantly, our population included high-risk patients with 70.6% presenting with ACS and 23.6% of the patients with STEMI. Moreover, among these patients with a history of most severe manifestations of ASA hypersensitivity, including anaphylactic shock, were studied. No serious adverse reactions occurred, even in the 15 patients with unsuccessful desensitization procedure.

In the vast majority of patients affected by idiopathic chronic urticaria, the desensitization protocol was successful, which is not consistent with previous data. In this subset of patients, at the Scripps Clinic,¹⁶ ASA desensitization was not accomplished as they were considered unable to undergo effective ASA desensitization therapy because of recurrent flare-ups of urticaria until the nonsteroidal anti-inflammatory drugs were withdrawn. It should be highlighted that, unlike the Scripps Clinic protocol that used 400 to 650 mg of ASA, in the present study only ≤ 100 mg of ASA was administered.

The present study demonstrates that long-term treatment with ASA is safe after desensitization protocol, as no late (≤ 1 year) adverse reaction was reported. Notably, among patients who decided to discontinue ASA, this was because of medical decision and not because of hypersensitivity reactions.

Study Limitations

The main limitation of the present registry is related to the definition of ASA hypersensitivity, which was self-reported and diagnosed only on history data and was not confirmed by specific tests. However, the desensitization procedure allows administering ASA to patients who otherwise may not be treated with ASA. Second, in patients who failed the desensitization protocol, a new attempt to desensitize was not performed. Indeed, the use of smaller increments of ASA doses could have potentially enhanced our success rate. Finally, although this registry is larger than other reports of aspirin desensitization, the sample size is still limited, particularly for patients with a history of anaphylaxis. Therefore, it is uncertain whether the safety of this protocol can be generalized to all patients with a history of anaphylactic reactions or how this protocol might compare with other desensitization strategies.

Indeed, larger studies are warranted to confirm the safety of our desensitization protocol in these patients.

Conclusions

The present multicenter, prospective study demonstrates that a rapid standardized desensitization protocol in patients with ASA hypersensitivity undergoing coronary angiography is safe and effective, irrespective of the type of sensitivity, including in patients with ACS. Low-dose ASA can be safely continued long term without the occurrence of late adverse hypersensitivity events.

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