Meta-Analysis of Acetylsalicylic Acid Desensitization in Patients With Acute Coronary Syndrome

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Acetylsalicylic acid (ASA) hypersensitivity represents a clinical challenge in acute coronary syndrome (ACS) patients urgently requiring ASA for antiplatelet therapy. ASA desensitization has been reported with successful outcomes in cardiac patients. The aim of this review is to determine the safety and efficacy of ASA desensitization therapy in ACS patients. A PubMed database search was conducted for articles containing combinations of keywords, "aspirin desensitization" or "aspirin hypersensitivity" and "acute coronary syndrome" between January 1, 1990 and August 1, 2018. The primary end point was desensitization protocol success. Secondary end points included hypersensitivity adverse events and ASA discontinuation due to hypersensitivity adverse events at follow-up. Fifteen reports consisting of 480 ACS patients with previous hypersensitivity to ASA were included. The pooled desensitization success rate was 98.3% (95% confidence interval: 97.2% to 99.5%). There was no statistical difference in outcomes between protocols ≤ 2 hours and > 2 hours in duration (96.3[92.3 to 100.3]% vs 97.2[94.6 to 99.8]%; p = 0.71). Protocols with > 6 dose escalations were associated with higher success rates compared to those with ≤ 6 doses (99.2[97.9 to 100.4]% vs 95.4[93 to 97.8]%; p = 0.007). At follow-up between 1 and 46 months (mode 12 months), zero hypersensitivity adverse events were reported. Consequently, no ASA discontinuations were related to hypersensitivity adverse events. In conclusion, ASA desensitization therapy is safe and effective in patients with ACS. Protocols with > 6 dose escalations may be optimal for ASA desensitization in ACS patients. **(Am J Cardiol 2019;124:14−19)**

Acetylsalicylic acid (ASA; aspirin) is avidly used as antiplatelet therapy for the secondary prevention of coronary artery disease (CAD).[1] However, approximately 1.5% of cardiac patients have hypersensitivity reactions to ASA.[2] In CAD patients with hypersensitivity to ASA, American College of Cardiology and American Heart Association (ACC/AHA) guidelines indicate the use of clopidogrel.[3] However, in higher-risk patients with acute coronary syndrome (ACS) requiring ASA, hypersensitivity may alter the choice of stents (bare metal vs drug-eluting stent) or at times prevent the patient from receiving the benefits of percutaneous coronary intervention (PCI) therapy altogether.[3] In such urgent settings, ASA desensitization therapy—successively increasing exposure to ASA at set intervals to eliminate hypersensitivity reactions—has been reported with successful outcomes.[4,5] The aim of this review is to determine the safety and efficacy of ASA desensitization therapy in ACS patients.

Methods

Data for this review were attained through a PubMed database search (National Center for Biotechnology Information, US National Library of Medicine, Bethesda, Maryland) for articles containing combinations of keywords, "aspirin desensitization" or "aspirin hypersensitivity" and "acute coronary syndrome" between January 1, 1990 and August 1, 2018.[6]

Inclusion criteria included: (1) patients with ACS and a known or suspect history of hypersensitivity to ASA; (2) availability of desensitization protocol details with outcomes. Exclusion criteria included: (1) case series with less than 3 patients. No language restrictions were applied. Hypersensitivity reactions were defined as cutaneous (urticaria, angioedema), respiratory (asthma, rhinitis), or systemic (anaphylaxis).[7]

Primary end point: desensitization protocol success defined as the ability to complete the desensitization protocol and sustain aspirin therapy till discharge without any hypersensitivity reactions. Secondary end points: (1) hypersensitivity adverse events at follow-up, and (2) discontinuation of ASA due to hypersensitivity adverse events at follow-up.

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This study was performed in compliance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[8] The search strategy was executed independently by 2 reviewers (AC, PDV). Reports that met inclusion criteria were appraised as complete reports. Authors of individual studies were contacted for incomplete data. All authors reviewed extracted data. Eligible studies were assessed based on methodological items for non-randomized studies score (MINORS) criteria.[9]

Continuous variables were reported as mean (with median or mode) and categorical variables expressed as percent (n/N). Statistical analysis was performed in accordance with a random effects model with inverse variance weighting, computing risk estimates with 95% confidence intervals. All computations were performed using RevMan 5.3 software (The Cochrane Collaboration, The Nordic Cochrane Center, and Copenhagen).

Results

Among 68 articles identified by PubMed database search, 20 included patients with CAD and a history of hypersensitivity to ASA.[10–29] Five reports were excluded for incomplete patient data (n = 3)[10,12,14] and lack of inclusion of ACS patients (n = 2).[11,13] A total of 15 studies met inclusion criteria and were selected for this review.[15–29] Table 1 highlights included study characteristics.

A total of 691 patients presenting with CAD and a history of ASA hypersensitivity were identified. The average age was 67.1 years and included 66% male patients. Four hundred and eighty patients were classified as ACS-ST-segment elevated myocardial infarction (STEMI; 25%) or unstable angina/non-ST-segment elevated myocardial infarction (UA/NSTEMI; 75%) and included in this review. Table 2 highlights patient baseline characteristics. Hypersensitivity history among CAD patients were 74% cutaneous, 18% respiratory, and 8% systemic.

Desensitization protocols had a mean of 7.1 dose escalations and mean duration of 3.3 hours. The range of starting doses among protocols was 0.1 mg to 12.5 mg (modes 0.1 mg and 1 mg). Postdesensitization therapy the sustaining dose range was 75 to 325 mg (mode 100 mg). A recent risk-stratified report was considered an outlier for the above calculations.[29] Table 1 highlights protocol details.

ASA desensitization was successful in 463 of 480 ACS patients with a pooled protocol success rate of 98.3 [95% confidence interval: 97.2 to 99.5]%. Table 3 highlights desensitization failures. There was no statistical difference comparing protocols ≤ 2 hours and > 2 hours in duration (96.3 [92.3 to 100.3]% vs 97.2 [94.6 to 99.8]%; p = 0.71). Protocols with > 6 doses were associated with higher success rates than those with ≤ 6 doses (99.2 [97.9 to 100.4]% vs 95.4 [93 to 97.8]% vs; p = 0.007).

Among successfully desensitized patients at follow-up between 1 and 46 months (mode 12 months), zero ASA hypersensitivity related adverse events were reported. Consequently, no ASA discontinuations were due to hypersensitivity reactions. The cumulative adverse events rate was 8.4(3.2 to 13.6)% and included cardiac deaths, heart failure, gastrointestinal bleeding and events requiring repeat PCI, thrombolysis, and CABG procedures.[15–26,29] Notably, aspirin was withdrawn for 2 patients with gastrointestinal bleeding.[26]

Discussion

Key highlights: (1) High desensitization protocol success rates and zero long-term hypersensitivity related adverse events were reported among ACS patients. (2) Protocols with > 6 dose escalations were affiliated with higher success rates compared to those with ≤ 6 doses. (3) There was no statistical difference between protocols of duration ≤ 2 hours and > 2 hours.

High pooled protocol success rates reported among ACS patients (98.3 [97.2 to 99.5]%) were consistent with ASA desensitization among all CAD patient profiles reported in a recent meta-analysis (93 [89.8 to 96.1]%).[30] Successful desensitization enabled antiplatelet therapy with ASA for 96.5% ACS patients and consequently permitted immediate medical therapy or revascularization with coronary stents. Most patients included in this review received drug-eluting stents and were discharged with dual antiplatelet therapy including ASA. Notably, there were no systemic reactions reported during or after the protocol, highlighting a favorable safety profile for desensitization therapy. The adverse event rate among ACS patients (8.4 [3.2 to 13.6]%) trended lower with that reported in the aforementioned meta-analysis (11.3 [7.5 to 15.2]%) among all CAD patients[30]. At follow-up between 1 and 46 months, zero hypersensitivity adverse events and consequently zero hypersensitivity related ASA discontinuations were reported. ACS patients with ASA hypersensitivity may continue to benefit from antiplatelet therapy with ASA and need not miss out on the proven advantages of PCI therapy.

Notable within this review were high success rates among each included protocol. Use of rapid protocols—protocols less than 5.5 hours in duration—are more relevant to urgent antiplatelet needs of cardiac patients. Duration subgroup analysis highlighted no statistical difference in success rates between “very-rapid” protocols ≤ 2 hours and those > 2 hours (96.3 [92.3 to 100.3]% vs 97.2 [94.6 to 99.8]%; p = 0.71). High success rates in both subgroups highlight the possibility of using shorter duration protocols for ACS patients that urgently require aspirin. However, protocols with > 6 dose escalations were associated with higher success rates when compared to protocols with ≤ 6 doses (99.2 [97.9 to 100.4]% vs 95.4 [93 to 97.8]% vs; p = 0.007). These results suggest the possibility of using shorter duration protocols (≤2 hours) with smaller dose intervals and a higher number of dose escalations. Notably, longer intervals between doses permit close monitoring of possible systemic reactions between doses, adding to the safety profile of the desensitization protocol. Although no systemic reactions were reported among ACS patients in this review, more data is required to determine the optimal treatment strategy between protocols ≤ 2 hours with > 6 doses and those > 2 hours with > 6 doses.

Most hypersensitivity reactions reported among included ACS patients could be classified as nonsteroidal anti-inflammatory drug (NSAID)-induced urticaria/angioedema (NIUA) or NSAID-exacerbated respiratory disease (NERD).[7] The putative mechanisms were related to the

Table 1
Included study characteristics

Study	Ref.	Study type	Protocol type	Desensitization Protocol (doses in mg*)	Cumulative dose (mg)	Protocol duration (hours)	Sustaining dose (mg)	Follow-up period mean/ range (months)	Minors score
Silberman et al. 2005	[15]	Retrospective	Oral	A) 1, 2, 4, 8, 16, 32, 64, 100	A) 227	A) 3.5	A) 100	13.7 (1 - 34)	5
				B) 5, 10, 20, 40, 75	B) 150	B) 2.5	B) 75		
Rossini et al. 2008	[16]	Retrospective	Oral	1, 5, 10, 20, 40, 100	176.0	5.5	100	12 (0 - 12)	6
Dalmau et al. 2009	[17]	Case series	Oral	0.1, 0.2, 1, 3, 10, 25, 50, 100	189.3	2.2	100	5 - 46	4
Ortega et al. 2010	[18]	Case series	Oral	0.5, 1, 2, 4, 8, 16, 32, 64, 100	227.5	4.0	81	12	5
Christou et al. 2011	[19]	Case series	Oral	0.1, 0.3, 10, 30, 40, 81, 162, 325	648.4	2.3	100	6 - 19	5
De Luca et al. 2012	[20]	Prospective	Endovenous	1, 2, 4, 8, 16, 32, 64, 125, 250	502.0	4.0	100	1 - 12	6
Lee et al. 2013	[22]	Retrospective	Oral	5, 10, 20, 40, 80	155.0	2.0	80	15.6 (1 - 53)	6
Veas et al. 2013	[21]	Case series	Oral	1, 5, 10, 20, 40, 100	176.0	5.5	100 - 325	7.8 (3 - 14)	4
Díez-Villanueva et al. 2014	[23]	Prospective	Oral	0.1, 0.3, 1.0, 3.0, 10.0, 25, 50, 100	189.4	2.3	100	23.7 (2 - 47)	6
Díez-Villanueva et al. 2016	[25]	Retrospective	Oral	12.5, 25, 50, 100	187.5	1.5	100	7.9 (2 - 16)	4
Vega et al. 2016	[24]	Case Series	Oral	0.1, 0.3, 1, 10, 25, 50, 100	186.4	2.0	100	10.4 (2 - 20)	5
Córdoba-Soriano et al. 2016	[26]	Prospective	Oral	0.1, 0.3, 1, 3, 10, 25, 50, 100	189.4	1.8	100	14 (6 – 24)	7
Rossini et al. 2017	[27]	Prospective, multicentre	Oral	1, 5, 10, 20, 40, 100	176.0	5.5	100	12	6
Cortellini et al. 2017 [Desensitized subset]	[28]	Prospective, multicentre	Oral	0.1, 1, 2, 3, 4, 5, 10, 15, 25, 35	100.1	5.0	100	12	7
Al-Ahmad et al. 2018	[29]	Prospective	Oral	A) 21, 21, 21, 21, 41, 41, 41	A) 207	A) 3.0	81	24	5
				B) 21, 21, 41	B) 83	B) 1.0			
				C) 10, 21, 21, 29	C) 81	C) 2.25			
				D) 21, 21, 21, 21	D) 84	D) 2.25			
				E) 41, 41	E) 82	E) 2.0			
				F) 41, 41	F) 82	F) 0.5			
				G) 41, 41, 41, 41, 41, 41	G) 246	G) 2.5			
				H) 10, 21, 21, 29	H) 81	H) 1.5			
				I) 21, 21, 21, 21	I) 84	I) 2.0			

Abbreviations/Notations: MINORS = methodological items for non-randomized studies.
Ref. – indicates reference number.
Symbols: *mg – milligrams.

Table 2
Patient characteristics and desensitization protocol outcomes

Study	Population (N)	Age (mean, years)	Male	Cutaneous reaction	Respiratory reaction	Anaphylaxis reaction	Desensitization success in ACS patients (m/n)*	STEMI	NSTEMI/ UA
Silberman et al. 2005	16	66.0	68.8%	81%	19%	0%	9/10	50%	50%
Rossini et al. 2008	26	61.8	76.9%	61.5%	38.5%	0%	15/16	25%	75%
Dalmau et al. 2009	5	-	-	100%	0%	0%	5/5	0%	100%
Ortega et al. 2010	3	58.7	100%	66.7%	0%	33.3%	2/3	0%	100%
Christou et al. 2011	11	56.0	54.5%	72.7%	27.3%	0%	6/6	16.7%	83.3%
De Luca et al. 2012	43	66.0	81.3%	58.1%	41.9%	0%	22/23	21.7%	78.3%
Lee et al. 2013	24	64.0	67%	91.7%	4.2%	4.2%	12/13	15.4%	84.6%
Veas et al. 2013	4	56.5	100%	50%	0%	50%	4/4	25%	75%
Díez-Villanueva et al. 2014	13	72.5	84.6%	91.7%	0%	8.3%	11/11	54.5%	45.5%
Díez-Villanueva et al. 2016	10	70.2	50%	100%	0%	0%	10/10	20%	80%
Vega et al. 2016	12	71.9	58%	66.7%	8.3%	0%	10/10	20%	80%
Córdoba-Soriano et al. 2016	24	69.0	67%	66.7%	25%	8.3%	24/24	33.3%	66.7%
Rossini et al. 2017	330	68.0	64.2%	74.5%	19.7%	5.8%	223/233	33.5%	66.5%
Cortellini et al. 2017 [Desensitized subset]	147	67.9	64.5%	74.1%	6.8%	19%	99/101	4%	96%
Al-Ahmad et al. 2018	23	61.5	56.5%	65.2%	17.4%	17.4%	11/11	9%	91%

Abbreviations/Notations: ACS = acute coronary syndrome; NSTEMI/UA = Non-ST segment elevated myocardial infarction/unstable angina pectoris; STEMI = ST-segment elevated myocardial infarction.

Symbols: *m/n – successfully desensitized ACS patients/total number of ACS patients.

Notes: ACS classification data reported as % of ACS patients (m). Hypersensitivity reactions included: Quincke edema (n = 3),[15] Widal syndrome (n = 3),[15] glottic edema (n = 2).[27] Hypersensitivity reactions excluded: patients with no recollection of their hypersensitivity reaction type (n = 3)[24].

inhibition of cyclo-oxygenese-1 (COX-1) enzyme or presumed immunoglobulin-E (IgE) mediated, however, not confirmed due to technology limitations.[7] These hypersensitivity reactions occurred after the first few doses of ASA administration during the protocol[21,26,27] or after the protocol (within few hours).[15,18,20,22,27,29] Urticaria[20,22,26,27] and asthma[16,27] were the most commonly reported reactions, however, were easily managed with antihistamines and corticosteroids.[20,22,26,27] In few instances, tolerance to aspirin was attained by restarting the protocol or continuing from previous steps of the protocol.[15] In 14 cases the protocol was terminated, no further attempts at desensitization were made and the protocol was termed a desensitization failure (see Table 3). A higher risk of reactions has been noted in patients with a history of chronic idiopathic urticaria (CIU; reaction rate: 20% to 30%), however, a recent registry reported successful desensitization for this patient subset among CAD patients.[27] In the present analysis, only 1 ACS patient who failed desensitization suffered from a history of CIU.

Among ACS patients included within this review, hypersensitivity was not verified by an ASA challenge.[15–29] Thus the true incidence of hypersensitivity or desensitization may not be determined. However, for ACS patients with a history of ASA/NSAID-induced hypersensitivity and an urgent requirement for ASA, confirming hypersensitivity or cross reactivity via an aspirin challenge is considered to be a higher risk strategy.[31] Available data suggests UA/NSTEMI patients typically undergo desensitization before the elective PCI.[15–29] For STEMI patients, desensitization is reported 72 hours post-PCI with thienopyridines and glycoprotein IIb/IIIa inhibitor provided as interim antiplatelet therapy.[16,20–28]

Relevant to desensitized ACS patients in the follow-up period is the need to remain on aspirin therapy without interruption. For desensitized ACS patients stopping aspirin for 2 to 5 days may result in reoccurrence of hypersensitivity symptoms[32] and require use of alternate antiplatelet agents that do not have the proven efficacy of ASA.[1]

The limitations of this meta-analysis were as follows: First, clinical literature on ASA desensitization for ACS patients predominantly consists of small, nonrandomized, retrospective studies. Second, cardiovascular detail was missing for adverse event data from 3 reports[20,27,28] and for 3 desensitization failures.[20,28] These patients were considered to be ACS patients and the reports were included in our review. Notably, the calculated pooled adverse event rate did not impact the safety claims of our analysis. Third, the covariate distribution was relatively uneven for the duration and dose sub-group analysis. More data is needed to substantiate these results. In contrast, high protocol success rates in this review included a lack of repeat attempts to desensitize patients and may be viewed as an advantage of this analysis.

In conclusion, aspirin desensitization therapy is a viable alternative among ACS patients with a hypersensitivity to ASA. ASA desensitization enables continuation of ASA and consequently allows these patients to benefit from the advantages of PCI therapy.

Disclosures

None. All authors declare no relationships with industry and no conflicts of interest.

Contributions

All authors have contributed to and approve this manuscript.

Table 3
Desensitization failures

No.	Age (Years)	Gender	History of Aspirin/ NSAID Hypersensitivity	ACS Classification	Presentation of Hypersensitivity Reaction	Timeframe of Reaction	Treatment	Follow-up Adverse Events	Desensitization Protocol (Doses in mg*)	Ref.
1	49	Male	Widal Syndrome	STEMI	Asthma, nasal swelling	1 hour after last dose	Inhaled Salbuterol	-	1, 2, 4, 8, 16, 32, 64, 100	15
2	70	Female	Asthma	NSTEMI	Asthma	After 1mg dose	Inhaled Salbuterol	-	1, 5, 10, 20, 40, 100	16
3	62	Male	Urticaria	Unstable Angina	Rash, Itchiness	18 hours after last dose	Diphenhydramine	-	0.5, 1, 2, 4, 8, 16, 32, 64, 100	18
4	39	Male	Angioedema	NSTEMI	Periorbital oedema	1.5 hours after last dose	Antihistamine	-	5, 10, 20, 40, 80	22
5	70	Female	Asthma	NSTEMI	Asthma	After 20mg dose	Corticosteroids, antihistamines	-	1, 5, 10, 20, 40, 100	27
6	58	Male	Chronic Idiopathic Urticaria	Unstable Angina	Urticaria	After 20mg dose	Corticosteroids, antihistamines	-	1, 5, 10, 20, 40, 100	27
7	66	Male	Asthma; Glottic edema	Unstable Angina	Dyspnea	After last dose	Corticosteroids, antihistamines	-	1, 5, 10, 20, 40, 100	27
8	84	Male	Urticaria	Unstable Angina	Urticaria	After 20mg dose	Corticosteroids, antihistamines	-	1, 5, 10, 20, 40, 100	27
9	76	Female	Urticaria	NSTEMI	Urticaria	After 40mg dose	Corticosteroids	Cardiac death	1, 5, 10, 20, 40, 100	27
10	86	Male	Asthma	STEMI	Bronchospasms	After 20mg dose	Corticosteroids, antihistamines	STEMI	1, 5, 10, 20, 40, 100	27
11	59	Male	Urticaria	NSTEMI	Urticaria	After 40mg dose	Corticosteroids, antihistamines	Unstable Angina	1, 5, 10, 20, 40, 100	27
12	75	Female	Urticaria	NSTEMI	Urticaria	After 20mg dose	Corticosteroids, antihistamines	**	1, 5, 10, 20, 40, 100	27
13	79	Male	Glottic edema	STEMI	Angioedema	After 20mg dose	Corticosteroids, antihistamines	Cardiac Death	1, 5, 10, 20, 40, 100	27
14	75	Male	Asthma	STEMI	Asthma	After 20mg dose	Corticosteroids, antihistamines	**	1, 5, 10, 20, 40, 100	27

Abbreviations/Notations: ACS = acute coronary syndrome; NSAID = nonsteroidal anti-inflammatory drug; NSTEMI = Non-ST segment elevated myocardial infarction; STEMI = ST-segment elevated myocardial infarction.

Ref – indicates reference number.

Symbols: *mg - milligrams.

Notes: Desensitization failure detail not available for 3 patients.[20,28]

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