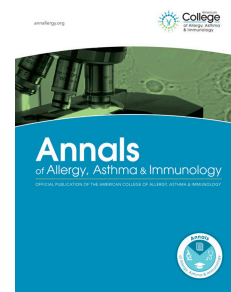


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Emily H. Liang, MD, Cy Y. Kim, MD, Javed Sheikh, MD, Shefali A. Samant, MD



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Higher Dose Starting Protocols In Coronary Artery Disease Patients With Aspirin Hypersensitivity

Emily H. Liang, MD¹; Cy Y. Kim, MD²; Javed Sheikh, MD¹; Shefali A. Samant¹, MD

From the Department of Clinical Immunology and Allergy¹ and the Department of Cardiology², Southern California Permanente Medical Group, Los Angeles, California

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Abbreviations/ Acronyms:

CAD: coronary artery disease

ACS: acute coronary syndrome

AERD: aspirin exacerbated respiratory disease

CIU: chronic idiopathic urticaria

NSAID: non-steroidal anti-inflammatory drug

STEMI: ST-segment elevation myocardial infarction

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Figure: Figure 1 Higher and lower starting dose aspirin protocols

Table: Table 1 Baseline characteristics, safety and efficacy of aspirin protocols

Address correspondence to:

Shefali Samant, MD

1515 North Vermont Ave. 5th Floor

Los Angeles, CA 90027

Telephone: (323)371-4693

Fax: (323)783-4646

Email: Shefali.A.Samant@kp.org

Aspirin is first-line treatment in coronary artery disease (CAD) patients, but in patients with acute coronary syndrome (ACS) or who require dual antiplatelet therapy after myocardial revascularization, aspirin therapy becomes critical and time-sensitive¹. Approximately 1.5% of CAD patients report aspirin allergy². Most reactions are considered non-immunologic, related to aspirin's inhibition of cyclo-oxygenase causing allergic-like symptoms³. A subset of patients has aspirin exacerbated respiratory disease (AERD) or chronic idiopathic urticaria (CIU) exacerbated by aspirin.

Allergists are often asked to evaluate aspirin allergy in CAD patients after patients develop active cardiac symptoms. Past aspirin challenge or desensitization excluded ACS patients and/or used low starting doses between 0.1 to 5 mg aspirin. Protocols have never been standardized, but reported success rates ranged from 81.8% to 100%³⁻⁷. Most failures were CIU patients. Studies in AERD, however, have shown an eliciting reaction dose between 45 to 100 mg aspirin⁸. Recent protocols⁹ propose higher starting doses with fewer steps, achieving aspirin's antiplatelet effects more quickly. A 2019 meta-analysis of 15 studies⁷ including 480 ACS patients with aspirin hypersensitivity found only one study¹⁰ that evaluated the safety and efficacy of higher starting dose protocols using 10 to 41 mg aspirin. The safety and efficacy of these newer protocols have therefore not been established.

We conducted a retrospective chart review at Kaiser Permanente Los Angeles Medical Center for all inpatient consultations to the Allergy Department for self-reported aspirin allergy in a patient with cardiac indication for aspirin from January 1, 2007 to December 31, 2017. Two categories of aspirin protocols were evaluated (Figure 1). Depending on clinical history, within the higher starting dose group patients either received no premedication (challenge group, starting median dose aspirin 40.5 mg) or at least 1 premedication (challenge-desensitization

group, starting median dose 20.25 mg). The lower starting dose group received a combination premedication regimen with starting dose aspirin 0.1 mg. Our study aimed to evaluate the safety and efficacy of higher starting doses compared to lower starting doses.

The protocol chosen was the allergist's discretion based on clinical history, including reaction and severity, reaction dose, reaction drug(s), last known exposure, cardiac symptoms, history of asthma and nasal polyposis concerning for AERD, and history of CIU. Most patients with isolated cutaneous symptoms did not receive premedication, unless there was a history of CIU for which all except one patient received premedication with an anti-histamine. Patients with a history of lower respiratory symptoms received a leukotriene antagonist. If there was a clinical history of nasal polyposis and asthma, patients were considered possible AERD, even without diagnostic challenge, and underwent a separate modified protocol⁸. All patients with anaphylaxis underwent the low dose protocol.

Overall, 179 aspirin procedures were completed in patients with suspected CAD and aspirin allergy, though 5 ultimately did not have CAD. Patients' past reactions included urticaria/ angioedema (59.8%), rhinitis/ asthma/ bronchospasm (50%), anaphylaxis (11.4%), and unknown (8.4%). About 25.7% reacted to both aspirin and a non-steroidal anti-inflammatory drug (NSAID) suggesting class effect, 25.7% reacted to aspirin only at antiplatelet doses greater than 100 mg, 6.1% reacted to aspirin only at less than 100 mg, 5% to NSAID only, and 37.4% did not know their reaction dose or drug.

There were 144 protocols completed in the higher starting dose (challenge and challenge-desensitization) group and 35 in the lower starting dose group. Baseline characteristics including patient cardiac status or presenting symptom did not seem to influence protocol choice (Table 1). Overall, 133 (74.3%) presented with ACS, including 19 with ST-segment elevation myocardial

infarction (STEMI). Most protocols were prior to cardiac revascularization. All STEMI patients underwent urgent revascularization, receiving aspirin post-revascularization.

To determine protocol safety, all reactions were graded for severity. Mild reactions included isolated skin and subcutaneous symptoms. Moderate included respiratory, cardiovascular or gastrointestinal symptoms. Severe included hypoxia, hypotension, or neurologic symptoms such as lightheadedness or confusion.

All three groups had high median and cumulative aspirin doses at reaction. The combined higher starting dose group had a higher reaction rate (12.5%) compared to lower dose group (5.7%), though the finding did not reach significance ($p=0.10$) and most reactions were mild. Fourteen of 18 reactions in this higher dose group were challenge-desensitization patients (Table 1). This higher than expected number of reactions included three of 14 suspected AERD patients who had reactions consistent with their presumptive diagnosis⁸ and four patients who had initially undergone challenge with reactions, then underwent challenge-desensitization. Removing these patients from the analysis, the higher starting dose reaction rate was 7.6%.

There were no direct cardiovascular complications from any aspirin protocol. Observed reactions poorly correlated with symptom history, though a history of rash/urticaria was most consistent with itching. Of the 3 CIU patients, only 1 challenge patient reported itching, but ultimately tolerated daily aspirin with an anti-histamine. Of the four patients with history of aspirin-induced anaphylaxis, three were asymptomatic during low starting dose protocol. One patient with Systemic Mastocytosis experienced anaphylactic shock but ultimately tolerated low dose aspirin.

Overall efficacy was high, at 98.6% for the higher starting dose group and 100% in the lower starting dose group (Table 1). One challenge patient aborted protocol due to respiratory

symptoms refractory to treatment. This patient declined desensitization and received an alternative medication. Another patient in the challenge-desensitization group experienced delayed angioedema and discontinued aspirin three days later. Amongst both higher and lower starting dose protocol patients, 98.4% discharged on aspirin were still taking aspirin at one month, indicating low rates of long-term hypersensitivity-related adverse events.

Our study shows that higher starting dose protocols (challenge or challenge-desensitization) for aspirin-allergic CAD patients without a history of anaphylaxis can be as safe and effective as lower starting dose protocols. Our center showed success in a large number of ACS patients, in most cases prior to cardiac revascularization, without increase in adverse cardiovascular outcomes. There was a high median and cumulative aspirin dose at reaction for all protocols, providing further evidence that low starting doses are unnecessary. Our findings support our center's trend of replacing lower dose with higher starting dose protocols, achieving aspirin's antiplatelet effect more quickly.

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Table 1: Patient characteristics, safety and efficacy of aspirin protocols

	Higher starting dose protocol		Lower starting dose protocol
	No premedication “Challenge”	With premedication “Challenge-Desensitization”	
Total attempted	62	82	35
Goal dose			
81 mg (%)	31 (50)	13 (15.9)	2 (5.7)
325 mg (%)	31 (50)	69 (84.1)	33 (94.3)
Baseline Characteristics			
Median Age, years	65	63	74
Male (%)	36 (58)	51 (62.1)	18 (51.4)
CIU	1	2	0
AERD	0	14	0
Cardiac status			
Pre-revascularization (%)	57 (91.9)	69 (84.1)	29 (82.6)
Post-revascularization (%)	5 (8.1)	13 (15.9)	6 (17.1)
Presenting symptom (%)			
ACS (%)	48 (77.4)	59 (72)	26 (74.3)
Abnormal cardiac stress test (%)	10 (16.1)	11 (13.4)	8 (22.9)
Cardiomyopathy (%)	4 (6.5)	8 (9.8)	0
Arrhythmia/ Cardiac arrest (%)	0	4 (4.9)	1 (2.9)
Safety			
Total reactions (%)	4 (6.5)	14 (17.1)*	2 (5.7)
Mild	3	11	1
Moderate	1	3	0
Severe	0	0	1
Reaction treatment(s)			
Antihistamine	4	12	2
Bronchodilator	1	1	0
Decongestant	0	2	0
Corticosteroid	1	4	1
Epinephrine	0	1	1
No treatment	0	1	0
Median dose at reaction			
Aspirin dose $\pm$ S.D. (mg)	81 $\pm$ 20.2	131.5 $\pm$ 157.7	89 $\pm$ 79.1
Cumulative dose $\pm$ S.D. (mg)	100.6 $\pm$ 38.6	151.9 $\pm$ 161.6	302.7 $\pm$ 379.4
Efficacy			
Discharged on aspirin (%)	56 (90.3)	76 (92.7)	34 (97.1)

Not discharged on aspirin (%)	6 (9.7)	6 (7.3)	1 (2.9)
No CAD	1	3	1
Alternative agent used	1	0	0
Death	2	1	0
Contraindicated	0	1	0
Protocol aborted	1	0	0
Unknown	1	1	0
Still on aspirin, 1 month (%)	54 (87.1)	76 (92.7)	34 (97.1)
Stopped aspirin, 1 month (%)	2 (3.2)	1 (1.2)	0
Delayed angioedema	1	0	0
Tinnitus	0	1	0
Gastrointestinal bleeding	1	0	0

AERD: aspirin exacerbated respiratory disease

ACS: acute coronary syndrome

CAD: coronary artery disease

CIU: chronic idiopathic urticaria

S.D: standard deviation

* includes 3 AERD patients with expected reactions and 4 reacting challenge patients

	Higher starting dose protocol*			Lower starting dose protocol [‡]
	No premedication “Challenge”	With premedication “Challenge-Desensitization”		
Premedication	None	Non-AERD: Antihistamine ± Leukotriene Antagonist ± Corticosteroid	AERD [†] : Leukotriene Antagonist + Antihistamine + Corticosteroid	Antihistamine + Corticosteroid + Leukotriene Antagonist
Starting dose, ASA in mg (median dose)	10-325 (40.5)	20.25-40.5 (20.25)		0.1
Dosing interval, minutes	60-90	Non-AERD: 30-90	AERD: 90-180	20-30
Number of Steps	1-5	3-6		8-11
Cumulative Dose, ASA in mg	81-629.25	81-851.5		165.9-723.4
Goal Dose, ASA in mg	81 or 325	Non-AERD: 81 or 325	AERD: 325	81 or 325
Example Protocol, ASA in mg	Day 1: 20.25, 40.5, 81, 162, 325	Non-AERD: Day 1: 20.25, 40.5, 81, 162 Day 2: 162, 325	AERD: Day 1: 20.25, 40.5, 81 Day 2: 81, 162, 325	Day 1: 0.1, 0.3, 1, 3, 10, 20, 40, 81 Day 2: 81, 162, 325

Figure 1: Higher and lower starting dose aspirin protocols

* Higher starting dose protocol adapted from White et al. ⁹

[†]AERD protocol adapted from Lee et al. ⁸

[‡]Lower starting dose protocol adapted from Wong et al. ³

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