



Characterization of aspirin allergies in patients with coronary artery disease

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ABSTRACT

Background: Aspirin prevents coronary thrombosis and is used extensively in cardiovascular prophylaxis. However, patients with a prior history of an aspirin “reaction” are routinely denied this medication.

Objective: To characterize the clinical presentation of a cohort of patients with coronary artery disease (CAD) and aspirin reactions.

Methods: Between 2009 and 2012, using a retrospective computer analysis, information was collected on all patients within a county-wide health care system presenting with CAD and a prior history of aspirin reactions.

Results: Of 9,565 patients with CAD, a prior history of aspirin reactions was recorded in 142 patients. Of these 142 patients, 30 (21%) had histories compatible with cutaneous and/or respiratory reactions. The other patients described adverse effects to aspirin, mostly gastrointestinal intolerance and bleeding. Aspirin-induced anaphylaxis was recorded in patients but may have been misdiagnosed, describing instead respiratory hypersensitivity reactions. Of the 142 patients, only 34 (24%) were receiving daily cardiovascular prophylaxis with aspirin. Of 108 patients not receiving aspirin, 25 (17.6%) were prescribed clopidogrel.

Conclusion: Histories of aspirin reactions in patients with CAD are uncommon, occurring in only 1.5% of our study population. The 21% of patients with histories compatible with aspirin hypersensitivities can be challenged and, if the results are positive, successfully desensitized. Moreover, almost all patients with gastric intolerance to aspirin can be treated with aspirin and a proton pump inhibitor. However, both approaches, which result in restoration of cardiovascular prophylaxis, were seriously underused in our study population.

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Introduction

Aspirin, in combination with clopidogrel, has been reported to significantly reduce cardiovascular events on the whole spectrum of acute coronary syndromes, including unstable angina, non–ST-segment elevation myocardial infarctions (NSTEMIs), ST-segment elevation myocardial infarctions (STEMIs), and percutaneous coronary intervention (PCI).^{1–4} However, a small but consequential proportion of patients with coronary artery disease (CAD) present with histories compatible with prior adverse reactions to aspirin, placing them at a significantly elevated risk for thrombotic events if they avoid aspirin. In one study, the prevalence of aspirin reactions in the general population was between 0.3% and 0.9%.⁵ In another study of 1014 patients admitted for cardiac catheterization, 26 (2.6%) had histories that the authors believed were compatible with aspirin hypersensitivity.⁶

Hypersensitivities to aspirin can be divided into 3 subtypes: respiratory sensitivity (asthma and/or rhinitis), cutaneous sensitivity (urticaria and/or angioedema), and anaphylaxis (which is exceedingly rare or more likely nonexistent for aspirin but not for other nonsteroidal anti-inflammatory drugs [NSAIDs]).⁷ In medical records, the term *aspirin allergy* can be used to describe all aspirin reactions, including classic adverse effects, such as gastritis and bleeding. For the purposes of this study, *aspirin reactions* will be used as an umbrella term referencing all aspirin reactions, *aspirin hypersensitivity* will refer to respiratory and/or cutaneous reactions, and *adverse effects* will be used to categorize all other reactions.

Aspirin hypersensitivity can be managed by desensitizing patients so they can take daily aspirin after the desensitization is performed. This procedure involves the elimination of pharmacologic and immunologic reactions by exposing a patient to increasing doses of oral aspirin.⁸ Since 1988, there have been a total of 87 documented cases of patients who underwent aspirin desensitization. Of note, Silberman et al⁹ successfully desensitized 15 of 16 patients in the acute care setting. More recently, aspirin desensitization was extended into the outpatient arena when 8 of 9 patients were successfully desensitized using a multiday protocol.¹⁰

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Thus far, patients with both CAD and aspirin reactions have been described only in a small series of cases. The purpose of this retrospective analysis then is to characterize the clinical presentation of aspirin reactions in a large cohort of such patients.

Methods

Study Population and Design

The Scripps Clinic and Scripps Coastal Medical Center provides health care in San Diego County, California, and is composed of more than 600 physicians. All patients in the Scripps Clinic and Scripps Coastal Medical Center database were identified between February 1, 2009, and January 13, 2012, for CAD and aspirin allergies using billing codes data.

Patients with CAD, defined as stable angina, unstable angina, NSTEMI, STEMI, prior history of PCI or coronary artery bypass graft (CABG), or findings of coronary stenosis on cardiac computed tomography (CT), documented by an attending physician were included in the study. Additional inclusion criteria included documentation of aspirin allergy recorded in a history and physical or progress note. Exclusion criteria comprised the following: age of 17 years or younger, pregnancy at the onset of the aspirin allergy or diagnosis of CAD, and dementia linked to the same patient. If the computer identified a patient with an aspirin allergy, then the medical record for that patient was further analyzed by the authors.

Demographic information was collected, including age, sex, aspirin reaction type, aspirin reaction symptoms, additional listed drug allergies, CAD type, whether or not a coronary artery intervention was performed, and whether or not the patient was currently taking aspirin and/or clopidogrel. Aspirin reaction subtypes were categorized according to the medical record descriptions. For example, shortness of breath, hives, and gastrointestinal (GI) upset were documented as respiratory sensitivity, cutaneous sensitivity, and GI intolerance, respectively.

At the same time, demographic information was collected, in a similar manner, on patients taking NSAIDs and those with CAD. All variables and definitions were defined by the authors before data analysis. Each medical record was reviewed by one physician. If there were ambiguities in the data, 2 other allergists clarified the data with their own review of the information, and a consensus was reached.

The study was approved by the institutional review board, with Health Insurance Portability and Accountability Act compliance. There was no external funding source.

Results

Of 9565 patients with a diagnosis of CAD, 185 described aspirin reactions (Fig 1). Individual review of the 185 patient health records revealed that 43 did not, in actuality, have CAD or aspirin reactions (and a few had neither), resulting in a culled total list of 142 patients. Overall, GI bleeding (23.2%) and GI intolerance (26.8%) were the most common types of described reactions, followed by cutaneous hypersensitivities (18.3%) and respiratory hypersensitivities (2.1%) (Table 1). Three patients (2.1%) were recorded as having aspirin-induced anaphylaxis, although the details documented in the medical record leading to the diagnosis of anaphylaxis did not even remotely fulfill the diagnostic criteria for anaphylaxis.¹¹

Miscellaneous reactions included gout and ringing in the ears. Of note, for 32 patients (22.5%), we were unable to ascertain the specific hypersensitivity or adverse event despite the fact that aspirin allergy was recorded and re-recorded in the medical records. In these instances, there were no described events to support the listing of aspirin allergy in the medical records.

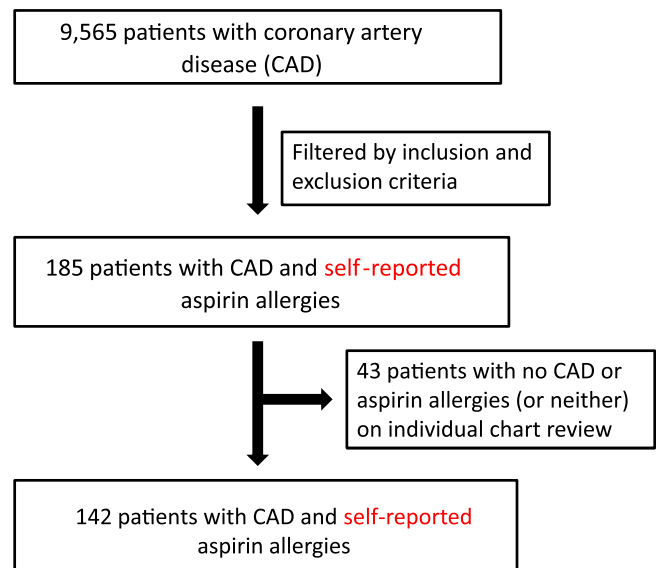


Figure 1. Patient cohort study flow.

Patients with aspirin reactions concurrently reported allergies to other medications as well. Twenty-one patients (14.8%) reported intolerance to NSAIDs. Another 53 patients (37.3%) had recorded allergies to antibiotics, most commonly penicillin and sulfa drugs.

Furthermore, of 142 patients, 44 (31.0%) had documented myocardial infarctions, 11 of whom underwent PCIs and 5 of whom had CABGs procedures performed.

Only 4 patients were referred to an allergist, 3 of whom underwent desensitization (Table 2).⁸ The other patient underwent an oral challenge test, the result of which was negative. Thus, 33 patients with histories of cutaneous and/or respiratory reactions to aspirin were not referred for oral challenge.

Table 1

Clinical and demographic characteristics of patients

Characteristic	CAD and self-reported aspirin allergies (N = 142)
Age, mean, y	76.3
Sex, No. (%)	
Male	58 (41)
Female	84 (59)
Aspirin allergy, No. (%)	
Respiratory	3 (2.1)
Cutaneous	26 (18.3)
Respiratory and cutaneous	1 (0.7)
Anaphylaxis	3 (2.1)
GI	38 (26.8)
GI bleeding	33 (23.2)
Unknown	32 (22.5)
Miscellaneous	6 (4.2)
Other allergies, No. (%)	
NSAIDs	21 (14.8)
Any antibiotics	53 (37.3)
Penicillin	39 (27.5)
Sulfa	24 (16.9)
Clopidogrel	3 (2.1)
CAD subtypes, No. (%)	
MI	28 (19.7)
PCI	29 (20.4)
CABG	19 (13.3)
PCI and CABG	9 (6.3)
MI and PCI	11 (7.7)
MI and CABG	5 (3.5)

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; GI, gastrointestinal; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention.

Table 2

Characteristics of patients who underwent aspirin desensitization

Age, y/sex	CAD type	Self-reported aspirin allergy	Other allergies	Desensitization protocol (aspirin dose in milligrams) ^a	Complications during protocol	Aspirin therapy, mg
85/M	NSTEMI, PCI	Cutaneous	ACE inhibitor	20, 40, 81	None	81
77/M	CABG, PCI, bare metal stent	Cutaneous	Penicillin	1 increasing to 325	None	325
86/M	PCI	Respiratory	Penicillin	30, 60, 100, 150, 325	None	None

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; CAD, coronary artery diseases; MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention.

^aAspirin dose increases in 30-minute intervals.

Aspirin or Clopidogrel

Only 34 patients (23.9%) with CAD and a history of aspirin reactions were taking aspirin: 28 were using 81 mg daily, 4 were using 325 mg daily, and 2 were using 162 mg daily (Table 3). By subtypes, 8 of 26 patients (30.9%) with cutaneous hypersensitivities and 6 of 33 patients (18.2%) with GI bleeding were taking aspirin. One-third of the patients (33.3%) with respiratory hypersensitivities and 12 of 38 patients (31.6%) with GI intolerance were using aspirin (Table 3). A total of 108 patients were not using aspirin, and 25 (17.6%) of these patients were prescribed clopidogrel.

NSAID Allergies and CAD

Of the original pool of 9,565 patients with CAD, 32 patients also described prior NSAID reactions (Table 4). Of these 32 patients, 27 did not have recorded aspirin reactions. GI intolerance (15.6%), cutaneous hypersensitivity (18.8%), and kidney injury (18.8%) were the most common types of reactions listed for patients alleged to be allergic to NSAIDs (Table 4). For 11 patients (34.2%), the reaction was unknown. Among the NSAID reactors, 12 (37.5%) were taking aspirin, indicating that these patients may have had a single NSAID reaction.

Discussion

In patients with CAD, aspirin-induced reactions, although uncommon, are important to identify and overcome if possible. To the best of our knowledge, this is the first study in a large cohort of patients that characterizes the prevalence and nature of these reactions and tracks the medical management of these patients.

In concordance with previous studies,^{5,6} but with a larger sample size of 9,565 patients, our database yielded a prevalence of reported aspirin reactions in 1.5% of patients with CAD. Importantly, only 21% of our patients had histories compatible with aspirin hypersensitivities, whereas the remaining patients had GI

Table 3

Patients taking aspirin and clopidogrel

Aspirin/clopidogrel status	No. (%) of patients (N = 142)
Not taking aspirin	108 (76.1)
Taking any dose of aspirin	34 (23.9)
Taking aspirin by self-reported allergy subtypes	
Cutaneous	8 (5.6)
Respiratory	1 (0.7)
Respiratory and cutaneous	0
Anaphylaxis	0
GI	12 (8.5)
GI bleeding	6 (4.2)
Unknown	6 (4.2)
Miscellaneous	1 (4.2)
Taking clopidogrel, if not taking aspirin	25 (17.6)
Taking aspirin, 81 mg daily	28 (19.7)
Taking aspirin, 162 mg daily	2 (1.4)
Taking aspirin, 325 mg daily	4 (2.8)

Abbreviation: GI, gastrointestinal.

intolerance, GI bleeding, miscellaneous, or unknown reactions. Indeed, all adverse effects to aspirin were categorized under the “allergies” section in medical records, even though they were medication adverse effects that had nothing to do with immunologic hypersensitivity. More likely, when physicians are querying patients about their aspirin reactions, “allergies” are being taken at face value, and distinctions are not being made between medication intolerance and hypersensitivities. At the same time, our electronic medical records do not provide clarifying algorithms to further define drug allergies and thus do not allow physicians to make such distinctions in the first place.

In addition, we did not find any patients who could be decisively diagnosed as having an anaphylactic reaction to aspirin. Instead, what was thought to be anaphylaxis was, more likely, a severe cutaneous or respiratory hypersensitivity reaction, occurring in patients with aspirin-exacerbated respiratory disease (AERD). To date, no cases of IgE-mediated, aspirin-induced anaphylaxis have been convincingly described in the literature. However, aspirin can cause non-IgE anaphylaxis in patients afflicted with AERD. In contrast, other NSAIDs and cyclo-oxygenase 2 inhibitors can cause both IgE and non-IgE anaphylaxis in otherwise healthy individuals.^{12–14}

Of note, a number of patients with aspirin hypersensitivities were taking daily aspirin. The most likely explanation is that these patients never had adverse reactions to aspirin to begin with.

Table 4

Clinical and demographic characteristics of patients with self-reported NSAID allergies

Characteristic	CAD and NSAID allergies (n = 32)
Age, mean, y	75.2
Sex, No. (%)	
Male	12 (37.5)
Female	20 (62.5)
NSAID allergy, No. (%)	
Cutaneous	6 (18.8)
GI	5 (15.6)
GI bleeding	3 (9.4)
Unknown	11 (34.2)
Kidney injury	6 (18.8)
TTP	1 (3.1)
Other allergies, No. (%)	
Any antibiotics	16 (50.0)
Penicillin	6 (18.8)
Sulfa	9 (28.1)
Aspirin	4 (12.5)
CAD subtypes, No. (%)	
MI	6 (18.8)
PCI	6 (18.8)
CABG	3 (9.4)
PCI and CABG	2 (6.3)
MI and PCI	3 (9.4)
MI and CABG	1 (3.1)

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention; TTP, thrombotic thrombocytopenic purpura.

Instead, either they were prescribed aspirin by their physician and no adverse effect occurred or they inadvertently started using aspirin on their own. In a recently submitted manuscript, we found that 37 of 40 patients who believed that they were allergic to aspirin or an NSAID were in fact nonreactors with negative challenge test results. This false assignment of a prior drug reaction makes it even more difficult to determine which patients, if any, have aspirin hypersensitivities in the first place.

If, when evaluating an aspirin allergic patient, the details of the reported reaction are uncertain or sound like a hypersensitivity reaction, then an allergy referral is warranted, and a single blinded oral challenge can be performed. If a patient has aspirin hypersensitivity and desensitization is being considered, then an allergist will find out whether a patient has AERD and whether a previous history of reactions to other NSAIDs is present, because these facts are integral to deciding how the desensitization protocol will proceed. Notably, in our cohort of 37 patients with histories compatible with cutaneous and/or respiratory sensitivity, an allergy referral was initiated in only 4 instances, leaving 33 patients without the opportunity to undergo oral graded challenge.

One might argue that if aspirin desensitization was not possible for some patients, because of logistical reasons, then the substitution of clopidogrel as an alternative is a reasonable clinical decision.¹⁵ However, we found that only 19% of patients who had aspirin hypersensitivities and were not taking daily aspirin were prescribed clopidogrel instead. This leaves 61% of patients with histories compatible with aspirin hypersensitivities without any cardiovascular prophylaxis. Indeed, this finding represents an important area of continuing education for both primary care physicians and cardiologists.

A large percentage of patients with recorded aspirin reactions of GI bleeding or GI intolerance could also benefit from aspirin if a proton pump inhibitor (PPI) is prescribed, along with aspirin at 81 mg daily.¹⁶ However, in our study, only 18 of 71 patients with a history of GI adverse effects from aspirin were receiving cardiovascular prophylaxis. The other 53 patients either did not have a PPI prescribed by their physician or never had an adverse reaction to aspirin in the first place. Identifying these subsets of patients should be a priority because a simple addition of a PPI could substantially increase the number of patients who can, with minimal risk, acquire cardiovascular prophylaxis.

This study has limitations inherent in any retrospective medical record review. First, because of incomplete data from medical records, we were unable to determine the specific aspirin allergy subtypes for some of the patients, which likely resulted in underreporting in the prevalence of patients with cutaneous and respiratory hypersensitivities. Second, information gleaned from the medical records was taken at face value—physicians' assessments of the aspirin allergies could not be independently verified. An additional limitation is that the data were obtained from a single health care system. Nevertheless, the geographic spread of the

clinics in this health system, the consequent diversity in patient population, and the initial study cohort of more than 9,000 patients probably ensure that the cross-section that we analyzed is reflective of the United States population as a whole.

In summary, adverse reactions to aspirin in patients with CAD are uncommon but important occurrences. Patients with cutaneous and/or respiratory sensitivity histories can undergo aspirin challenge and desensitization. However, a striking finding is the underuse of allergy referrals. Equally important, patients with GI reactions to aspirin, either bleeding or intolerance, can be successfully treated with a combination of a PPI and low-dose aspirin. Physicians should strive to ensure that all patients who could be taking aspirin are receiving this important prophylactic medication.

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