

Prevalence and management of aspirin hypersensitivity in a cardiology practice

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ABSTRACT

Background: Data are lacking with concern to the prevalence and management of aspirin (ASA) hypersensitivity.

Objective: To study the prevalence, different types of reactions, and implications for clinical management of ASA hypersensitivity in a cardiology practice.

Methods: We conducted an electronic medical record review of 11,375 individuals, 5052 (44%) in the ambulatory setting, and 6323 (56%) admitted for percutaneous coronary intervention (PCI), from January 2012 to December 2013.

Results: The prevalence of ASA hypersensitivity was 1.88% (n = 214). Skin reactions were the most common (40 [19%]), followed by angioedema (10 [4.6%]), respiratory (9 [4.2%]), and anaphylaxis (6 [2.8%]). No records were found for 74 patients (34.5%), and 69 patients (32.2%) were mistakenly labeled as allergic for having gastrointestinal symptoms. Of the 214 patients who had documented ASA hypersensitivity, 108 individuals (50.46%) had coronary artery disease. The medications at discharge were the following: ASA (30 [14%]), thienopyridine (48 [22%]), a combination of ASA and thienopyridine (13 [6%]), anticoagulation only (26 [12%]), and no antiplatelet (97 [43%]).

Conclusion: ASA hypersensitivity is often not documented correctly or is often misdiagnosed or not appropriately managed. There is a need for improved management of ASA hypersensitivity, including appropriate referral for ASA desensitization and combating unnecessary avoidance in patients with intolerance due to adverse effects.

(Allergy Asthma Proc 41:120–125, 2020; doi: 10.2500/aap.2020.41.190032)

Aspirin or acetylsalicylic acid (ASA) acts through the irreversible inhibition of cyclooxygenase 1, ultimately preventing platelet activation and aggregation by reducing the production of thromboxane A₂ downstream.¹ ASA is frequently used in certain patients for both primary or secondary prevention of cardiovascular disease (CVD), and it is considered the antiplatelet agent of choice due to its effectiveness, low cost, and few adverse effects.² Reactions to ASA could be either due to true hypersensitivity or other types of adverse drug reactions. Even though the terms allergy and hypersensitivity are frequently used interchangeably, they are not synonymous.

Hypersensitivity reactions can be allergic (immunoglobulin E or cell mediated) or nonallergic in origin.³ Although it has been reported that 0.6–2.5% of the general population has some form of ASA hypersensitivity, the prevalence of ASA hypersensitivity in patients with CVD is not well established.^{4,5} ASA hypersensi-

tivity can manifest as respiratory symptoms (rhinitis or asthma), cutaneous manifestations (urticaria and/or angioedema), or possibly anaphylaxis.⁶ Adverse reactions to ASA, unrelated to hypersensitivity are also well recognized; however, they are frequently misdiagnosed and/or incorrectly documented in patients. These include gastrointestinal effects, such as gastritis, mucosal erosions, ulcers, and bleeding. These are attributed to a decrease in mucosa-protective prostaglandins by potent inhibition of gastric cyclooxygenase 1 enzyme by ASA.⁷

In the case of ASA hypersensitivity in patients with CVD, clinicians are frequently faced with a challenging therapeutic decision. Although monotherapy with a thienopyridine may be used as an alternative in this population, it is still not as cost-effective as ASA and it carries a higher risk of complications.^{8,9} However, in patients with a definitive need for ASA, desensitization may be a viable option for delivery of treatment.¹⁰ ASA desensitization consists of slowly increasing exposure to ASA to reduce or eliminate the immunologic reaction that causes the allergic symptoms.⁸ However, there is no consistent approach to patients with ASA hypersensitivity, and clinicians rarely refer them for desensitization therapy.^{2,9}

The present study represents one of the largest single-center experiences that looked at the prevalence of reported ASA hypersensitivity in patients with CVD.

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The authors have no conflicts of interest to declare pertaining to this article

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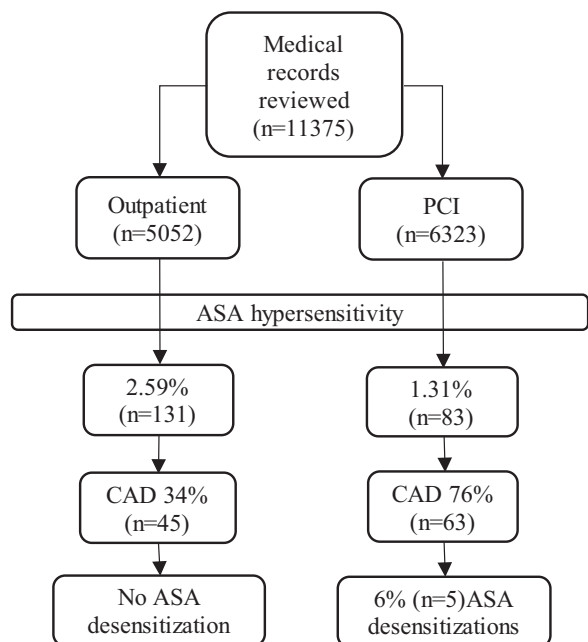


Figure 1. Study design, showing the percentage of patients with documented (ASA) hypersensitivity and the percentage of coronary artery disease (CAD) in the outpatient cardiology service and in the percutaneous coronary intervention (PCI) group.

There were three objectives: first, to determine the prevalence of reported ASA hypersensitivity in a cohort of patients seen in an inpatient and outpatient cardiology practice; second, to report the different types of reactions reportedly caused by ASA hypersensitivity; and third, to report on the different ways that clinicians manage a potential diagnosis of ASA hypersensitivity and/or ASA adverse reactions.

METHODS

After obtaining approval from the Medstar Health Research Institute Institutional Review Board (project 2014-141), we conducted a retrospective search of patients evaluated in the outpatient cardiovascular center as well as those individuals admitted for percutaneous coronary intervention (PCI) between January 2012 and December 2013. The study design is shown in Fig. 1. A total of 11,375 medical records were reviewed, 5052 (44%) in the ambulatory setting, and 6323 (56%) admitted for PCI.

As determined by a chart review for problem-list documentation, the patients with ASA hypersensitivity ($n = 214$) were selected and their electronic medical records were thoroughly reviewed. The following information was collected: type of reaction (anaphylaxis, angioedema, urticarial, respiratory symptoms, gastrointestinal [GI] symptoms, and other problems), documentation of coronary artery disease (CAD), how the alleged allergy was managed, and what were the medications prescribed at the end of the visit or hospitalization. With

regard to referral for ASA desensitization, we relied primarily on the documentation of the managing cardiologist (MM and JW).

RESULTS

A total of 11,375 medical records were reviewed, of which, 5052 (44%) patients were in the ambulatory cardiology setting and 6323 patients (56%) were admitted for PCI. We identified 214 patients (1.88%) with a documented ASA hypersensitivity. Among this group, 153 (71%) were women and 61 (29%) were men. The age of the patients in the cohort ranged from 20 to >80 years old.

The most common type of reactions documented in the cohort were the following: cutaneous reactions ($n = 50$ [23.60%]), which was further subdivided into urticarial response ($n = 40$ [19%]) and angioedema ($n = 10$ [4.60%]); these data are presented in these subgroups of urticaria (denoted as “skin”) and angioedema in Fig. 2. These were followed by respiratory reactions ($n = 9$ [4.2%]) and anaphylaxis ($n = 6$ [2.8%]). Six patients (2.8%) were categorized as being allergic to ASA due to the following adverse reactions: epistaxis ($n = 3$), for which the medication was stopped; thrombocytopenia ($n = 1$), which was considered a contraindication to ASA; bleeding from an arteriovenous fistula during hemodialysis ($n = 1$); and one patient had an unspecified bleeding episode for which ASA was discontinued. In addition, 74 patients (34.5%) had no documentation of the type or severity of the allergic reaction. Furthermore, 69 subjects (32.2%) were mistakenly categorized as having ASA hypersensitivity due to GI adverse reactions (*i.e.*, gastritis, ulcers, GI bleeding, abdominal pain) (Fig. 2).

In the ambulatory cardiology setting, we found that 131 of 5052 patients (2.59%) had documentation of ASA hypersensitivity. Of them, 45 (34%) had documented CAD in their medical records. It was observed that none of the patients in this group were referred for ASA desensitization. At the time of discharge from the visit, 62 patients (47%) were not prescribed any antiplatelet drugs, of whom 14 (23%) had documented CAD. In addition, 16 (12%) were continued on anticoagulation only, 21 individuals (16%) were continued on ASA, 26 (20%) were prescribed a thienopyridine, and 6 (5%) continued on dual antiplatelet therapy with ASA plus a thienopyridine, even though their medical records indicated that they had an active allergy to ASA.

However, 83 of 6323 patients (1.31%) admitted to the hospital for PCI were found to have documented ASA hypersensitivity. The majority of these patients ($n = 63$ [75%]) had documented CAD, and 16 of them (19%) required some type of intervention (angioplasty [$n = 1$], cardiac stent [$n = 5$], and coronary artery bypass graft [$n = 10$]). There were five referrals (6%) for ASA

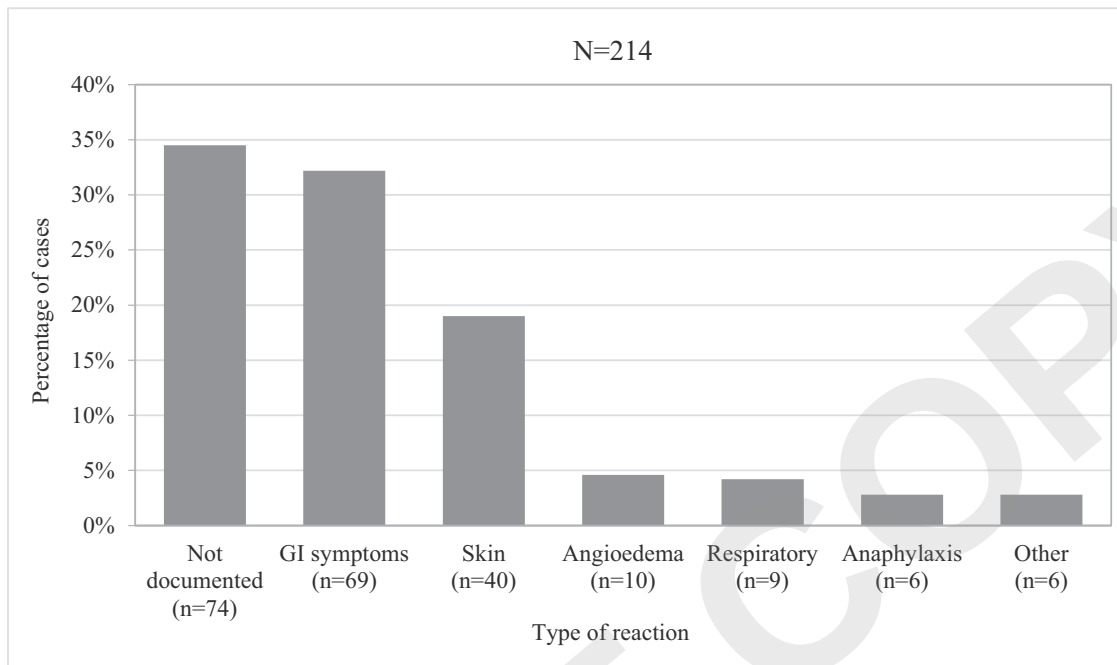


Figure 2. Type of allergic reactions to acetylsalicylic acid (ASA).

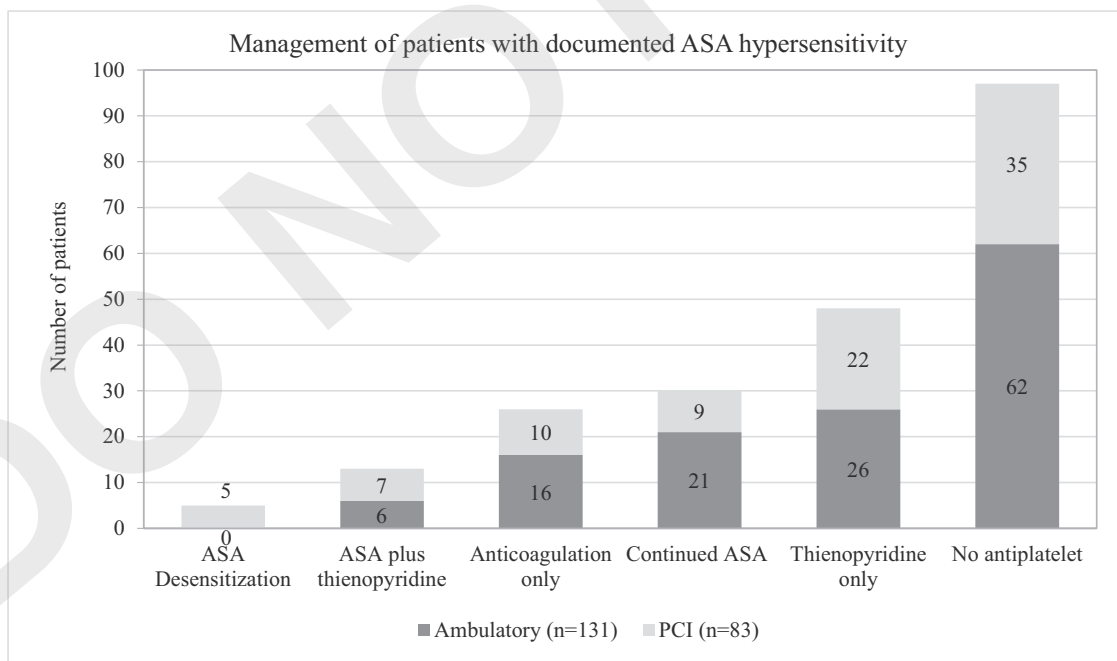


Figure 3. Management of patients with acetylsalicylic acid (ASA) hypersensitivity in the outpatient cardiology service and in the percutaneous coronary intervention (PCI) group.

desensitization found in this group (four referrals for outpatient and one inpatient). At the time of discharge, 35 patients (42%) were discharged without a prescription for any antiplatelet medication despite the fact that 21 (60%) of them had documented CAD. Ten patients (12%) were on anticoagulation only, and a prescription to ASA was given to 9 (11%), 22 (27%)

received a thienopyridine, and 7(8%) were prescribed dual antiplatelet therapy despite the documented allergy. The management of patients with documented ASA hypersensitivity in the outpatient and inpatient cardiology setting is shown in Fig. 3.

The management of the individuals with ASA hypersensitivity with and without documented CAD

Medications at discharge	Documented CAD (n=108)	No documented CAD (n=106)	Total Patients (n=214)
No antiplatelet	35 (32)	62 (58)	97 (43)
Thienopyridine only	37 (34)	11 (10)	48 (22)
Continued ASA	17 (16)	13 (12)	30 (14)
Anticoagulation only	8 (7)	18 (17)	26 (12)
ASA and thienopyridine	11 (10)	2 (2)	13 (6)

N (%), CAD= Coronary artery disease, ASA=acetylsalicylic acid

Figure 4. Medications at discharge classified by the presence or absence of documented coronary artery disease (CAD).

is shown in Fig. 4. Of the patients with a history of CAD, 43 of 108 (40%) were not discharged on any antiplatelet therapy, whereas 37 (34%) were managed with only a thienopyridine. We also observed that, despite their presumed diagnosis of ASA hypersensitivity, 17 patients (16%) were continued on ASA and 11 (10%) were on dual antiplatelet therapy (10%) at discharge. Meanwhile, in the group of individuals without documented CAD, 80 (74%) were not discharged on any antiplatelet therapy, 11 (10%) were continued on a thienopyridine, 13 (12%) were on ASA, and 2 (2%) were on dual antiplatelet therapy. In summary, of the 214 patients with documented ASA hypersensitivity, 97 (43%) were not taking any antiplatelet medications, 48 (22%) were managed by discontinuing ASA and prescribing a thienopyridine instead, 30 (14%) were continued on ASA, 26 (12%) were on anticoagulation only, and 6 (13%) on dual-antiplatelet therapy at the time of discharge.

DISCUSSION

The prevalence of ASA hypersensitivity in our study was 1.88%, which falls within the range of averages (0.6–2.5%) reported in the literature.^{3,4,11} More than 32% of the patients who presented to our aforementioned clinical settings and were mistakenly labeled as allergic to ASA due to reported GI problems introduces a unique yet common scenario. Reported GI issues are a common adverse effect of ASA and nonsteroidal anti-inflammatory drug use and not specifically an indication of allergy or hypersensitivity. Commonly, reporting of these symptoms does not infer that a patient has sensitivity to ASA. However, adverse effects, *e.g.*, GI symptoms, are commonly associated with higher dosing of ASA.¹² Therefore, these 69 patients can receive ASA as a potential therapy in their cardiovascular artery disease management. This provides important therapeutic implications for prescribing physicians.

A recently published meta-analysis showed that, among 10 CVD primary prevention trials, ASA therapy increases the risk of GI bleeding (odds ratio, 1.58 [95% confidence interval], 1.29–1.95).¹³ This has raised concern with regard to the use of ASA for primary prevention of CVD in individuals with a low 10-year risk

of cardiovascular events. When it comes to secondary prevention of CVD, a lower-dose ASA provides a theoretically lower bleeding risk.^{14–16} Therefore, potential management with 81 mg of ASA can be a viable option to these patients. Specifically, patients in our clinic who reported this “allergy” could still be provided with ASA. If gastric pain persists, even with low-dose, 81 mg daily, ASA, medications such as proton-pump inhibitors can be added to help alleviate this symptom. This offers better outcomes for the patient as well as a reduced incidence of adverse effects and lower costs of medications compared with therapeutics that are used in lieu of ASA. Although other medications, *e.g.*, thienopyridines, can be used as an alternative antiplatelet agent in case of ASA hypersensitivity, these agents are not as cost-effective as ASA and are also associated with adverse effects.¹⁷

Subsequently, the next most common reported reactions to ASA therapy by our patient population were cutaneous reactions. These reactions included urticarial reactions as well as angioedema. The presence of these reactions, especially many hours after initiation of ASA therapy are in fact not indicative of an allergic reaction to ASA. Therefore, these patients can be treated with ASA 81 mg instead of full-dose ASA with similarly efficacy. This provides further evidence that hypersensitivity reactions may be dose dependent and patients who have not previously tolerated high doses of ASA may be able to tolerate a low dose.¹⁰

In patients who reported respiratory symptoms, reactions associated with aspirin exacerbated respiratory disease (AERD) were reported. In mechanistic terms, it is thought that AERD evolves due to fundamental disturbances in both the production of an end-organ responsiveness to eicosanoids.¹⁸ The least commonly reported reaction to ASA administration by patients was anaphylactic reaction due to immediate hypersensitivity that involves cross-linking of drug-specific immunoglobulin E, this reaction would be considered a true allergy to ASA use.¹⁹ Charts for our six patients with anaphylaxis were reviewed, and these patients did not have any documented features of AERD. Although classified differently, both anaphylactic and AERD reactions seen concomitant with ASA administration are treated by using desensitization

protocols. A consult with an allergist with regard to this treatment can be of great benefit to these patients. With successful progression through desensitization protocols, patients can begin or continue to take daily ASA indefinitely.¹⁰

Furthermore, from our results, we could see the wide variety of reactions reported by patients after their use of ASA as part of therapeutic management. The electronic health record allergy section contains missing reaction details, discrepancies with the patient interview, and data entered by providers with limited drug allergy training and knowledge that lead to improper allergy (ASA) documentation.²⁰ To ameliorate this finding and provide homogeneity and increased documentation of these instances, electronic health records should be improved and updated to require increased documentation from health-care employees when patients are reporting hypersensitivities to medications. Clinical decision supports functionality embedded in electronic health records can present opportunities to enhance patient care and improve safe medication use by prompting staff and providers to both document adverse effects and allergies in the patient chart in greater detail, and to educate patients who are prescribed antibiotics with regard to known adverse effects and adverse reactions.²¹

Further recommendations were developed by the U.S. Department of Health and Human Services Agency for Healthcare Research and Quality. The Agency for Healthcare Research and Quality recommends that health-care professionals be not only knowledgeable about the differences between hypersensitivity and possibly allergic reactions and adverse effects of drugs but to document adverse effects from therapeutic interventions and allergies separately in the electronic health record. Previous studies sought to look at ASA hypersensitivities in patients with established CAD.²² Our study analyzed patients from both an inpatient and outpatient clinical setting. Therefore, our study provided an opportunity to compare and contrast data in these two clinical settings. Furthermore, our study included recommendations to improve hypersensitivity reporting in both inpatient and outpatient settings.

Study Limitations

Our study had several limitations. As a retrospective chart review, documentations were at times missing. We included patients with a history of ASA hypersensitivity based on a chart review and problem-list documentation, which may have relied on patient self-reporting and not actually confirmed by dedicated diagnostic tests. The prevalence of true ASA hypersensitivity in this cohort might be overestimated because some of the patients were continued on this medication. Similarly, the number of referrals

for ASA desensitization in the cohort might be underestimated because we relied primarily on the documentation of referral done by the managing cardiologist. Furthermore, because this was a retrospective study and complete patient records were not always available, we did not specifically denote a control group to compare with the patients with hypersensitivity. Future studies would benefit by comparing the two groups and extracting data on whether standard of care defers for patients with ASA hypersensitivity compared with their peers who are not allergic.

CONCLUSION

ASA therapy has a pivotal role in the prevention and treatment of CVD. The prevalence of ASA hypersensitivity in this large cohort of patients was close to 2%. Misdiagnosis of ASA hypersensitivity is frequently seen and is often due to GI adverse effects, even through a history of upper- or lower-GI bleed is not an absolute contraindication to ASA therapy. Despite the current evidence that supported effectiveness and safety of the ASA desensitization protocols, the sensitization approach seems to be underused. Lastly, the high percentage of these patients in a cardiology practice who were not treated with antiplatelet agents was striking and confirms other studies, which suggests that ASA therapy in particular is underused, and suggests that unnecessary avoidance in some patients is a concern that needs to be addressed. With the data in this study, we hoped to highlight the underutilization of allergy testing and desensitization for this patient subset. In conclusion, there is a need for better diagnosis, documentation, and management of ASA hypersensitivity and adverse reactions, including appropriate referral for ASA desensitization and unnecessary avoidance in patients with intolerance due to adverse effects.

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