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Diagnosis and Management of Hypersensitivity to Antiplatelet Drugs: EAACI Position Paper

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ABSTRACT

Antiplatelet drug (APD) therapy is the cornerstone for the prevention of atherosclerotic cardiovascular disease. The main APDs are aspirin and thienopyridines, particularly clopidogrel. These drugs may induce hypersensitivity reactions (HSRs). The most common reported reactions to these drugs are cutaneous, such as exanthemas associated with thienopyridine and urticaria/angioedema by aspirin, which can also induce respiratory symptoms. APDs other than aspirin, particularly ticlopidine, can also cause hematologic reactions consisting mainly of isolated thrombocytopenia, agranulocytosis, and leukopenia. Immune-mediated reactions to aspirin are very rare. Few data suggest the usefulness of skin testing in patients with cutaneous reactions to APDs other than aspirin, particularly clopidogrel. Therefore, the drug provocation test is the gold standard for diagnosing hypersensitivity to APDs. Low-dose aspirin challenge (i.e., up to 150–180 mg) and aspirin desensitization have emerged as effective

Abbreviations: ACS, acute coronary syndrome; AGEP, acute generalized exanthematous pustulosis; AHS, aspirin hypersensitivity; APD, antiplatelet drug; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CCS, chronic coronary syndrome; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; DAPT, dual antiplatelet therapy; DPT, drug provocation test; DRESS, drug reaction (or rash) with eosinophilia and systemic symptoms; EAACI, European Academy of Allergy and Clinical Immunology; FDE, fixed drug eruption; FDNIH, food-dependent NSAID-induced hypersensitivity; HSR, hypersensitivity reaction; IDT, intradermal test; LDAC, low-dose aspirin challenge; MPE, maculopapular exanthema; NECD, NSAID-exacerbated cutaneous disease; NEFA, NSAID-exacerbated food allergy; NERD, NSAID-exacerbated respiratory disease; NIFA, NSAID-induced food allergy; NIUAA, NSAID-induced urticaria/angioedema/anaphylaxis; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PT, patch test; SJS, Stevens–Johnson syndrome; SNIUAA, single NSAID-induced urticaria/angioedema/anaphylaxis; SPT, skin prick test; ST, skin test; STEMI, ST-segment elevation myocardial infarction; TEN, toxic epidermal necrolysis; TF, task force.

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and safe approaches in patients with suspected or confirmed aspirin hypersensitivity who require aspirin therapy. Both, a short course of oral glucocorticoids without interruption of clopidogrel treatment and desensitization, appears to be effective and safe options in patients with cutaneous HSRs to clopidogrel. This position paper provides data and recommendations regarding the characteristics of HSRs to APDs and related diagnostic procedures in order to make them as safe and effective as possible. Management and treatment options, including desensitization protocols, are also provided.

1 | Introduction

Antiplatelet therapy is the mainstay for the prevention of atherosclerotic cardiovascular disease (ASCVD). Based on their targets, antiplatelet drugs (APDs) can be classified into several classes (Table 1) [1–4].

The most utilized APDs are acetylsalicylic acid—commonly known under the trade name of "aspirin"—and adenosine–diphosphate receptor inhibitors/P2Y12 antagonists, especially clopidogrel [6]. In particular, aspirin is an effective antithrombotic agent when used in doses ranging between 50 and 100 mg/day [5]. Indeed, both the European [7] and American guidelines [8] recommend the so-called dual antiplatelet therapy (DAPT), consisting of the combination of aspirin plus an adenosine–diphosphate receptor antagonist, after percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) to prevent thrombotic events.

The main side effects of aspirin are gastrointestinal (e.g., dyspeptic symptoms, bleeding), which occur mainly with high doses [5, 9]. Aspirin hypersensitivity (AHS) is another important adverse event and represents a serious limitation to its use [9–11]. However, AHS is generally overdiagnosed both because patients who have experienced an aspirin side effect are often given the label of AHS and because in many cases the diagnosis is made on the basis of the clinical history without performing a drug provocation test (DPT). An AHS label often leads to unnecessary drug discontinuation or use of an alternative antiplatelet therapy that may be less effective and/or more expensive.

APDs other than aspirin (Table 1), such as adenosine–diphosphate receptor antagonists [12, 13], glycoprotein IIb/IIIa inhibitors [14], phosphodiesterase inhibitors [15], and triflusal [16, 17] may also cause hypersensitivity reactions (HSRs).

TABLE 1 | Classification and mechanism of action of the main antiplatelet drugs [1–4].

Class	Drugs	Route
Cyclooxygenase inhibitors		
Low-dose aspirin inhibits platelet cyclooxygenase-1 inducing a permanent defect in thromboxane A2-mediated platelet aggregation [5]	Aspirin	Oral
Triflusal (2-acetoxy-4-(trifluoromethyl) benzoic acid) is chemically related to salicylate, but is not a derivative of acetylsalicylic acid. It irreversibly inhibits cyclooxygenase-1 activity reducing production of thromboxane A2 from arachidonic acid and minimizing platelet aggregation [3, 4]	Triflusal	Oral
Adenosine–diphosphate (ADP) receptor inhibitors/$P2Y_{12}$ antagonists		
Thienopyridines They are selective inhibitors of the ADP-induced platelet aggregation, through the irreversible blockade of the ADP receptor $P2Y_{12}$ on the platelet surface	Ticlopidine Clopidogrel Prasugrel	Oral Oral Oral
Nonthienopyridines (Cyclopentyltriazolopyrimidines) They are reversible $P2Y_{12}$ ADP receptor antagonists	Cangrelor Ticagrelor Elinogrel	IV Oral Oral/IV
Glycoprotein IIb/IIIa inhibitors		
Abciximab is a Fab fragment of a chimeric monoclonal antibody (human/murine) that binds nonspecifically to the glycoprotein IIb/IIIa receptor. Eptifibatide, a cyclic heptapeptide, and tirofiban, a nonpeptide, selectively bind to the glycoprotein IIb/IIIa receptor. They block fibrinogen binding to the platelet glycoprotein IIb/IIIa receptors (the "final common pathway" of platelet activation), thereby preventing the development of fibrinogen bridges between platelets	Abciximab Tirofiban Eptifibatide	IV IV IV
Phosphodiesterase inhibitors		
They inhibit platelet aggregation through the increased concentration of cyclic adenosine monophosphate. Dipyridamole also enhances the biosynthesis of prostaglandin I2 and increases the antiplatelet activity of prostaglandin I2	Dipyridamole Cilostazol	Oral/IV Oral

This position paper aims to provide data and recommendations regarding the characteristics of HSRs to APDs and related diagnostic procedures, as well as to indicate management and treatment options, including desensitization protocols. Please note that the diagnosis and management of hematologic reactions are not covered in this manuscript as they are part of hematologic practice.

2 | Methods

A systematic review of the English language literature (up to June 2024) was performed by a European Academy of Allergy and Clinical Immunology (EAACI) task force (TF) using electronic databases (MEDLINE and PubMed), electronic libraries (Science Direct, OVID), Cochrane library, databases of scientific societies, and reports of the European Medicines Agency and United States Food and Drug Administration. The search terms included: antiplatelet drugs, aspirin/acetylsalicylic acid, allergy/hypersensitivity/desensitization, coronary artery disease/cardiovascular diseases drug therapy, and the names of the specific APD classes and individual drugs. The relevance of the articles was evaluated by the TF members, and the selected articles were analyzed during one in-person meeting and three online meetings where the submission of each author was discussed and confirmed or amended. In particular, TF members carefully examined the statements and recommendations, including the classification of the latter A, B, C, and D according to the SIGN criteria (Tables S1 and S2) [18, 19], as outlined in a recent EAACI position paper [20]. Each recommendation was included in the manuscript only when consensus (70%–89% agreement) or strong consensus (≥90% agreement) had been reached.

3 | Classification of Hypersensitivity Reactions

Based on the chronological criterion, HSRs to drugs, including APDs, can be classified as immediate and nonimmediate (also called delayed). The former typically occur within 1 h but in some cases may occur up to 6 h after the last dose [21, 22]. They manifest as isolated symptoms, such as urticaria and/or angioedema, generalized erythema, hypotension, laryngeal edema, bronchospasm, or anaphylaxis.

Delayed reactions are defined as those that occur >6 h after dosing [22]. They are characterized by a wide range of clinical manifestations, including severe ones, such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) [21, 23, 24]. Maculopapular exanthema (MPE), delayed-appearing urticaria, and fixed drug eruption (FDE) are the most common clinical presentations of nonimmediate reactions [23]. Internal organs can be affected either alone or with cutaneous symptoms (e.g., in DRESS, vasculitis, and SJS/TEN) and include hepatitis, nephritis, pneumonitis, anemia, neutropenia, and thrombocytopenia [21, 23, 25].

Immediate reactions are mostly associated with an IgE-mediated pathogenic mechanism, but they may also occur via non-IgE-mediated mast-cell activation [23, 24, 26]. In some nonimmediate reactions, especially DRESS, AGEP, MPE, and FDE, a T-cell-mediated pathogenic mechanism has been demonstrated on the basis of positive responses to patch tests (PTs) and/or delayed-reading intradermal tests (IDTs) [27–31].

Note that, in the World Health Organization's VigiAccess Database [32], immune-mediated HSRs to APDs account for only 1%–4% of all adverse reactions to them.

Among APDs, aspirin occupies a unique place, being also one of the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs). Recently, the EAACI classifications of NSAID HSRs [10, 33] have been updated by adding reactions in which NSAIDs act as aggravating factors or cofactors in food-sensitized subjects [34–36]. These reactions have been defined as NSAID-exacerbated food allergy (NEFA) and NSAID-induced food allergy (NIFA), respectively [34–36]. As exacerbating factors, NSAIDs aggravate HSRs to foods in individuals who have mild HSRs (e.g., oral allergy syndrome) to the foods concerned if ingested alone. When NSAIDs act as a cofactor, patients may fully tolerate a food if ingested alone, but experience a systemic reaction (e.g., urticaria/angioedema, generalized erythema, anaphylaxis) after its ingestion in combination with NSAIDs [36, 37]. Previously, these phenomena had been termed food-dependent NSAID-induced hypersensitivity (FDNIH) reactions [37]. Therefore, immediate reactions to NSAIDs have been classified into five clinical types: NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), NSAID-induced urticaria/angioedema/anaphylaxis (NIUAA), NEFA/NIFA, and single NSAID-induced urticaria/angioedema/anaphylaxis (SNIUAA) (Table 2). The NIUAA type is the most common NSAID HSRs and refers to reactions to ≥2 chemically unrelated NSAIDs that are characterized by urticaria and/or angioedema, and/or involvement of two organ systems (e.g., cutaneous and respiratory; cutaneous and gastrointestinal) in the absence of underlying chronic spontaneous urticaria (CSU), asthma, or chronic rhinosinusitis with nasal polyps (CRSwNP). These reactions involving two organ systems had previously been classified as “blended” reactions [38]. Finally, single NSAID-induced delayed hypersensitivity reactions (SNIDHRs) have been included.

Table 2 shows the phenotypes of HSRs to NSAIDs and provides information on their pathogenic mechanisms and clinical manifestations. The first three types of immediate reactions are mediated by the inhibition of cyclooxygenase-1 associated with defects in arachidonic acid metabolism and eicosanoid alterations [10, 39]. Patients with NERD, NECD, or NIUAA present a pattern of cross-reactivity to different NSAIDs, which share the ability to inhibit cyclooxygenase-1.

SNIUAA and SNIDHR are considered noncross-reactive phenotypes, mediated by immunological mechanisms. SNIUAA and SNIDHR caused by aspirin are very rare [40, 41].

4 | Aspirin Hypersensitivity Reactions: Clinical Presentations and Diagnosis

In an old study [42], the frequency of HSRs to aspirin in a normal population sample composed of 1974 adults without respiratory

TABLE 2 | Classification of hypersensitivity reactions to NSAIDs [35].

Clinical entity	Pathomechanism	Symptom	Underlying disease	Diagnostic methods					Avoid
				ST	BAT	Nasal DPT	Inhaled DPT	Oral DPT	
NERD	Nonimmunologically mediated	Rhinitis/Asthma	CRSwNP/ Asthma	Not indicated	Not indicated	If upper and/or lower airways involved[a]	If lower airways involved[a]	If negative intranasal/ inhaled DPT with aspirin (see also Figure 1)	Strong COX-1 inhibitors (see also Figure 1)
NECD	Nonimmunologically mediated	Urticaria/AE	CSU	Not indicated	Not indicated	Not indicated	Not indicated	(see Figure 1)	
NIUAA	Nonimmunologically mediated	Urticaria/AE/ Anaphylaxis	Atopy	Not indicated	Not indicated	If upper and/or lower airways involved[a]	If lower airways involved[a]	If negative intranasal/ inhaled DPT with aspirin (see also Figure 1)	
NEFA/ NIFA	NSAIDs increase the permeability of intestinal barrier NSAIDs have a direct effect on mast cells/ basophils amplifying their degranulation/ activation	Urticaria/AE/ Anaphylaxis	Food allergy (NEFA)/ Sensitization (NIFA)	For targeted food allergens	Not indicated	Not indicated	Not indicated	With the involved NSAID, if allergy tests with the suspected foods are positive (see also Figure 1)	All NSAIDs 4 h before and after ingestion of foods to which patients are allergic (NEFA)/ sensitized (NIFA)
SNIUAA	It is thought to be mediated by specific IgE or T cells to the culprit NSAID and related chemical group	Urticaria/AE/ anaphylaxis	None	STs: only validated for dipyrone	Only for dipyrone	Not indicated	Not indicated	(see Figure 1)	Only NSAID group involved in the reaction
SNIDHR		MPE, FDE, CD, AGEP, DIHS/ DRESS, SJS/TEN	None	dIDTs. PTs (for CD and FDE)	Not indicated	Not indicated	Not indicated	With the suspected NSAID, in mild reactions with negative PTs/dIDTs	

Abbreviations: AE, angioedema; AGEP, acute generalized exanthematous pustulosis; BAT, basophil activation test; CD, contact dermatitis; COX, cyclooxygenase; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; dIDT, delayed-reading intradermal test; DIHS/DRESS, drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; DPT, drug provocation test; FDE, fixed drug eruption; IDT, intradermal test; MPE, maculopapular exanthem; NECD, NSAID-exacerbated cutaneous disease; NEFA, NSAID-exacerbated food allergy; NERD, NSAID-exacerbated respiratory disease; NIFA, NSAID-induced food allergy; NIUAA, NSAID-induced urticaria/angioedema/anaphylaxis; NSAID, nonsteroidal anti-inflammatory drug; PT, patch test; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis; SNIDHR, single NSAID-induced delayed hypersensitivity reaction; SNIUAA, single NSAID-induced urticaria/angioedema/anaphylaxis; ST, skin test.

[a]In patients with underlying chronic respiratory disorders, NERD diagnosis can be made by clinical history without performing DPTs.

diseases or urticaria was 0.3%: Three participants reported bronchospasm, two urticaria, and one both conditions. A high prevalence of AHS among individuals with underlying respiratory diseases (i.e., CRSwNP and/or asthma) or CSU [38, 43, 44] has been reported. Specifically, in a systematic review [44], the prevalence of aspirin-induced bronchospasm, when determined by oral challenges, was 21% in adults and 5% in children with asthma, respectively. Moreover, the literature data indicate that 20%–30% of patients with CSU may experience an acute and short-lived exacerbation of their disease after taking aspirin [43]. A review of 9565 patients with coronary artery disease (CAD) revealed that 142 patients (1.5%) reported a prior reaction to aspirin [45]. However, the most common reactions described were gastrointestinal bleeding (23.2%) and gastrointestinal intolerance (26.8%), followed by cutaneous (18.3%) and respiratory (2.1%) reactions. Another study [46] reviewed the medical records of 11,375 patients attending an outpatient clinic of cardiology and/or admitted for a PCI; 214 patients (1.9%) with documented AHS were identified. The documented reactions were urticaria/angioedema (23.4%), respiratory reactions (4.2%), and anaphylaxis (2.8%). Note that 69 patients (32.2%) who reported gastrointestinal symptoms were incorrectly labeled as "allergic" and 74 patients (34.5%) had no documentation of the type or severity of the allergic reaction.

4.1 | Diagnosis of AHS and/or Cross-Reactive Types of NSAID Hypersensitivity

A detailed clinical history with an accurate description of the index reaction is crucial as it allows to distinguish side effects from HSRs and provides useful information for choosing an appropriate allergy workup. Additionally, information on underlying chronic respiratory disorders or CSU and a clear history of recent immediate HSRs to NSAIDs may allow to establish the diagnosis of NERD and NECD, respectively, without the need for further testing. Skin testing with aspirin is not useful. The in vitro basophil activation test has also shown to be useful as a complementary tool for the diagnosis of selective HRs to pyrazolones, but not for other NSAIDs [35].

According to International guidelines [10, 22, 33, 36], the DPT represents the gold standard for proving NSAID hypersensitivity. Regarding the cumulative dose of aspirin to be administered in DPTs, tolerance of 325 mg of aspirin generally excludes cyclooxygenase-1 inhibitor hypersensitivity [47].

Figure 1 shows an algorithm for the diagnosis and phenotyping of immediate HSRs to NSAIDs. In two studies that applied a similar algorithm [34, 37], FDNIH and NEFA/NIFA were diagnosed in 52 (15.9%) of 328 patients and 75 (18.1%) of 414 patients with immediate reactions to NSAIDs, respectively. Aspirin was the cofactor or aggravating factor in 15 of the 52 patients with FDNIH reactions [37] and 31 of the 75 patients with NEFA/NIFA [34], in 3 of the latter at an antiplatelet dose (i.e., 75–100 mg).

DPT with a full dose of aspirin allows for accurate diagnosis and, if negative, the use of aspirin at anti-inflammatory doses. In patients who report HSRs to aspirin and/or other NSAIDs and who are at high risk of ASCVD or suffer from chronic coronary syndrome (CCS), it is advisable to perform at least a low-dose aspirin challenge (LDAC) to assess the tolerability of aspirin at an antiplatelet dose (Figure 2) [48, 49]. Indeed, the former patients may need aspirin for primary prevention, while the latter may require DAPT at some point in their life (e.g., need for PCI or occurrence of an ACS). In a multicenter study [48], 163 patients with CAD and histories of HSRs to aspirin and/or other NSAIDs underwent LDACs. The following doses of aspirin were administered every 45 min: doses of 10 mg, 25 mg, 25 mg, 50 mg, and an additional 50 mg if requested by cardiologists, reaching a total cumulative dose of 110 or 160 mg, followed by an observation period of up to 2 h based on the index reaction. At the cardiologist's request, an additional 50-mg loading dose was administered. As in this study [48], doses of aspirin to be administered in LDAC can be drawn from a solution obtained by diluting 288 mg of lysine-acetylsalicylate (a more soluble form of acetylsalicylic acid), corresponding to 160 mg of aspirin, in 16 mL of water. In centers where oral soluble aspirin formulations are not available, LDACs require the use of dedicated low-dose aspirin formulations supplied by the hospital pharmacy. In a recent study [34], DPTs with aspirin were performed by administering 5 mg (only in patients with asthma and CRSwNP), 50, and 100 mg at 1-h intervals on the first day and, in case of negative results, by administering 150 and 300 mg on the second day. This protocol allows identifying patients who react to antiplatelet doses and anti-inflammatory doses, respectively. In another study [50], desensitizations were spared in 15 of 20 patients with CCS and 7 (11.6%) of 60 patients with ≥ 3 risk factors for ASCVD who had reported HSRs to aspirin or cross-reactive types of NSAID hypersensitivity and had tolerated LDACs.

5 | Nonaspirin Antiplatelet Drug Hypersensitivity Reactions: Clinical Presentations and Diagnosis

The rash or exanthema, mainly MPE, is the most frequent presentation of HSRs to thienopyridines, particularly clopidogrel [51–58]. Clopidogrel-associated rash usually appears 5–11 days after exposure [54, 56–58], but it can also occur within 24 h [54, 56], especially in re-exposed patients.

In two large studies [51, 58], the frequency of severe rash and HSRs to clopidogrel was 6% (58 of 9599 patients) and 1.6% (62 of 3877), respectively, leading to premature clopidogrel discontinuation in 1.5% of the patients of the first study [51]. In particular, 49 (79.3%) of the 62 patients of the second study [58] reported generalized, pruritic, exanthematous rash that had predominantly affected the trunk and had then extended to the proximal part of the upper and lower extremities in 9 of them. In a study [58] by Cheema et al., 79.3% of patients reported generalized, pruritic rashes, mainly on the trunk and extremities. In this study [58], patients underwent skin tests (ST) and PTs with clopidogrel, ticlopidine, and prasugrel. Three patients displayed positive responses to immediate readings, and 34 patients to PTs. Biopsies revealed signs of inflammation, similar to those seen in HSR to clopidogrel. However, several reservations should be raised about this study: The method used for intradermal testing does not follow recent European recommendations [31, 59] in particular because of the use of solutions not approved for human use

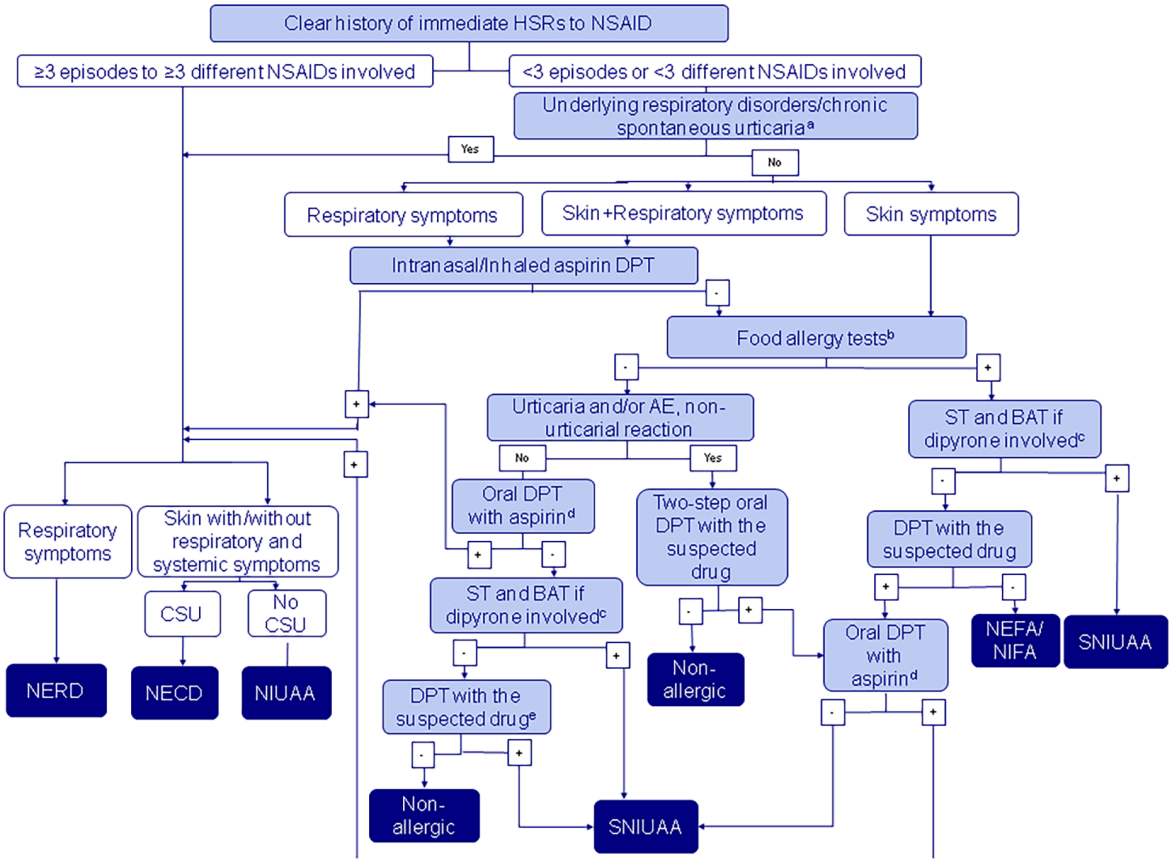

FIGURE 1 | Algorithm for the diagnosis and phenotyping of immediate HSRs to NSAIDs [35] (modified, with permission). The changes made to this figure were approved by the first and last author of the manuscript of origin and were approved by the authors of this manuscript. [a]In patients with underlying chronic respiratory disorders (i.e., chronic rhinosinusitis with nasal polyps and/or bronchial asthma) or chronic spontaneous urticaria and clear histories of recent (i.e., that occurred > 5 years before allergy testing) immediate HSRs to ≥ 1 chemically unrelated NSAIDs, the diagnosis of NERD and NECD, respectively, can be made without performing DPTs. [b]Skin prick tests and specific IgE to targeted foods. [c]Skin prick tests with dipyrone at concentrations of 40–400 mg/mL and intradermal tests at concentrations of 0.4–4 mg/mL. In case of severe reactions, start using concentrations at least 10 times lower due to the risk of developing systemic reactions. [d]Both treatment with leukotriene antagonists in patients with NERD and treatment with antihistamines or anti-IgE in patients with NECD can be maintained. If aspirin is the suspected NSAID, DPT should be performed with another potent cyclooxygenase-1 inhibitor (e.g., ibuprofen, ketoprofen, and indomethacin). [e]Contraindicated in case of severe anaphylactic reactions. AE, angioedema; BAT, basophil activation test; CSU, chronic spontaneous urticaria; DPT, drug provocation test; HSR, hypersensitivity reaction; NECD, NSAID-exacerbated cutaneous disease; NEFA, NSAID-exacerbated food allergy; NERD, NSAID-exacerbated respiratory disease; NIFA, NSAID-induced food allergy; NIUAA, NSAID-induced urticaria/angioedema/anaphylaxis; NSAID, nonsteroidal anti-inflammatory drug; SNIUAA, single NSAID-induced urticaria/angioedema or anaphylaxis; ST, skin test.

and the huge volume injected (0.2 mL, whereas the recommendation is 0.02 mL). These methodological discrepancies could lead to false positives. In addition, the absence of controls in PTs and IDTs reinforces the need to endorse the results with caution.

A retrospective study by Lokhandwala et al. [55] identified 76 patients with cutaneous or hematologic HSRs to clopidogrel or ticlopidine who had also received the other thienopyridine; 38 had reacted to ticlopidine, 24 to clopidogrel, and 14 to both. Rash was reported by 71 (93.4%) of 76 patients and angioedema by 4 patients.

There are also reports of single cases of exanthema associated with prasugrel [60], ticagrelor [61–63], or dipyridamole [15], as well as eczema [16] and photosensitivity [17] associated with triflusal. Allergy tests were performed only in the cases provoked by dipyridamole or triflusal, which were positive to PTs [15, 16] or photo-PTs [17].

Clopidogrel and ticlopidine have also been associated with urticarial/angioedematous or erythematous reactions; delayed reactions [53, 54, 56, 64, 65] were more frequent than immediate ones [55, 58].

A few cases of FDE from ticlopidine [64, 66] or clopidogrel [67] have been described. In one case from ticlopidine [66], the positivity of the in situ PT was confirmed by the positive response to the DPT.

Cases of lupus induced by ticlopidine [68], leukocytoclastic vasculitis [69, 70] and serum sickness-like reaction [71] associated with clopidogrel, as well as ticlopidine-induced cholestatic hepatitis with fever, anemia [72] or eosinophilia [73] have been reported. In the latter two cases [73], the lymphocyte transformation test was positive.

Regarding severe HSRs, there are reports of single cases of AGEP due to ticlopidine [74], ticagrelor [75], or clopidogrel [76], as well

as of SJS/TEN associated with clopidogrel [77] or dipyridamole [78], and DRESS caused by clopidogrel [79, 80], prasugrel [81], or abciximab [82]. Of the patients with AGEP, one was positive for PT [74] and another for the lymphocyte stimulation test [76]. The patient with DRESS caused by abciximab was positive for delayed-reading IDTs with it [82].

There are also reports of anaphylactic reactions to prasugrel [83], dipyridamole [84], and abciximab [85–87]. One of these patients was positive to IDT with abciximab at an unspecified concentration [86], while another was negative to dipyridamole STs [84].

Overall, STs with suspected nonaspirin APDs may be useful to evaluate patients reporting cutaneous HSRs (Grade D). Table 3 shows the highest nonirritating concentrations of APDs for STs and PTs. Skin prick tests (SPTs) should be done with injectable solutions; if the relevant APD is not available in this form, SPTs can be done with any form of commercialized

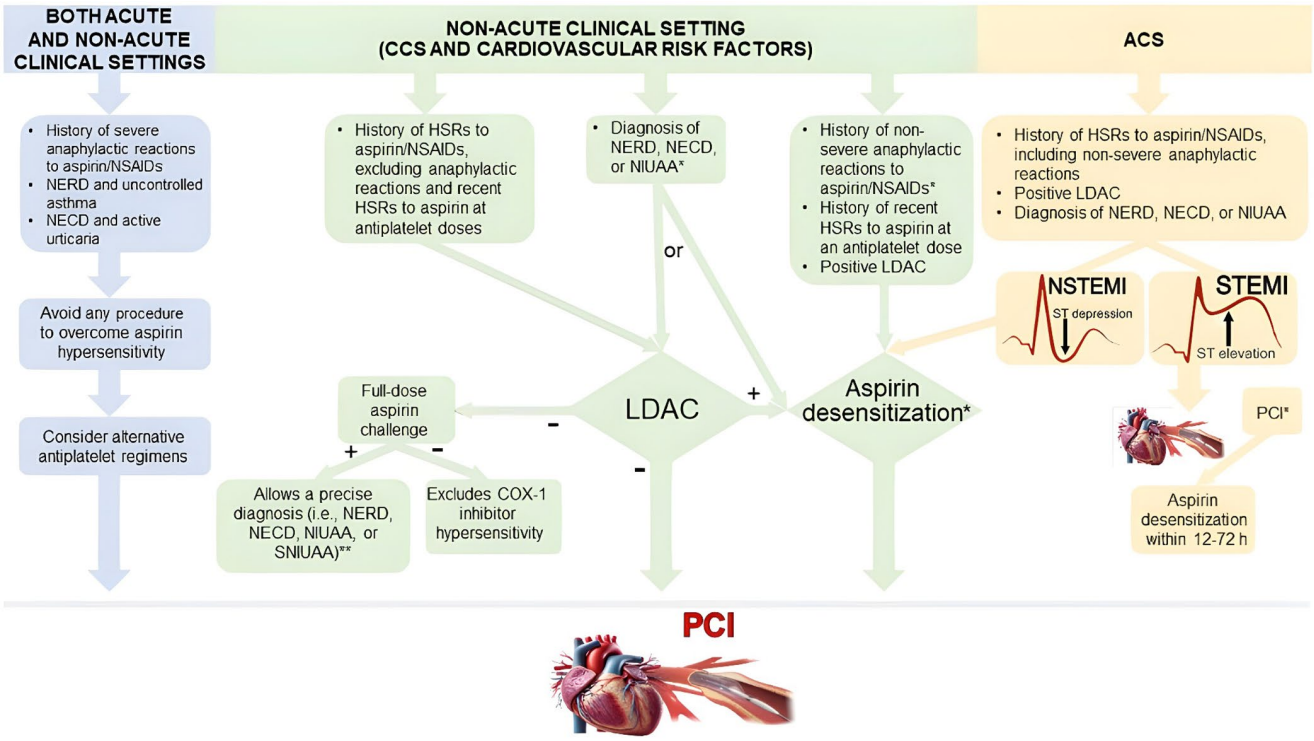

FIGURE 2 | Algorithm for the management of patients with ASCVD and HSRs to aspirin and/or other NSAIDs. ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CCS, chronic coronary syndrome; COX-1, cyclooxygenase-1; HSR, hypersensitivity reaction; LDAC, low-dose aspirin challenge; NECD, NSAID-exacerbated cutaneous disease; NERD, NSAID-exacerbated respiratory disease; NIUAA, NSAID-induced urticaria/angioedema/anaphylaxis; NSAID, nonsteroidal anti-inflammatory drug; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SNIUAA, single NSAID-induced urticaria/angioedema/anaphylaxis; STEMI, ST-segment elevation myocardial infarction. *See text. **Patients who receive the diagnosis of SNIUAA should avoid anti-inflammatory doses of aspirin, while patients who are diagnosed with NERD, NECD, or NIUAA should avoid not only aspirin at anti-inflammatory doses but also other potent cyclooxygenase-1 inhibitors. In these latter patients, provocation tests with selective (e.g., celecoxib, parecoxib, and etoricoxib) or preferential (e.g., meloxicam and nimesulide) COX-2 inhibitors are recommended.

TABLE 3 | Highest nonirritating concentrations of APDs used for skin and patch testing.

Drugs	Skin prick tests	Intradermal tests[c]	Patch tests
Acetylsalicylic acid			10% pet[a]
Clopidogrel	0.75 mg/mL [58]–7.5 g/mL [65]	0.75 mg/mL [58, 65]	20% pet [58]–30% water [58]
Ticlopidine	0.65 mg/mL [58]	0.65 mg/mL [58]	10% pet [74]–75% water [58]
Prasugrel	0.5 mg/mL [58]	0.5 mg/mL [58]	5% water [58]
Dipyridamole			30%[b] pet [15]–30%[b] water [15]
Abciximab	2 mg/mL [82]	2 mg/mL [82]	

Abbreviation: APD, antiplatelet drugs.
[a]Available as ready-to-use material. (Chemotechnique, Velinge, Sweden or SmartPractice Canada).
[b]Asasantin tablets (dipyridamole 200 mg + Aspirin 25 mg).
[c]See text.

APD (Grade D). In case of negative SPT results, IDTs can be performed, for which the use of sterile solutions is mandatory (Grade C).

PTs can be useful in nonimmediate cutaneous reactions, particularly exanthemas associated with thienopyridines [58], and, if done in situ, also in FDE (Grade D) [30, 88].

STs and PTs can be performed both to diagnose allergy to thienopyridines and to assess cross-reactivity among them (Grade D) [58]. In mild/moderate cutaneous reactions, negative STs and/or PTs can be followed by DPTs with the suspected drugs (Grade D). DPTs are also indicated to find safe alternatives (Grade D). Very few DPTs with the suspected drugs have been performed in patients reporting HSRs to nonaspirin APDs [65, 66] and therefore there are no specific protocols to recommend. Anyway, a recent European position paper on DPTs recommends reaching the maximum single therapeutic dose in 1 day and in 1–3 steps, depending on the severity of the reaction [88].

In evaluating patients who experienced severe nonimmediate cutaneous reactions, PTs with suspected APDs could be used as a first line of investigation (i.e., prior to STs). In case of positive results, STs should be avoided, whereas in case of negative results, IDTs could be performed (Grade C) [27, 89]. However, intradermal testing with the suspected drug is contraindicated in patients with SJS/TEN [27, 28, 30, 31, 88].

Lymphocyte transformation or stimulation tests proved to be useful in evaluating a few patients with severe nonimmediate reactions [73, 76]. However, they are not routinely used, and expert consensus on their diagnostic value has not yet been reached [90].

Hematologic reactions are represented mainly by isolated thrombocytopenia, agranulocytosis, leukopenia, aplastic anemia, and even pancytopenia [55, 91]. Among thienopyridines, ticlopidine causes serious hematologic adverse reactions more commonly than clopidogrel [55, 91]. The most reported hematologic hypersensitivity syndrome associated with ticlopidine and clopidogrel is thrombotic thrombocytopenic purpura, a life-threatening multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, neurologic manifestations as fluctuating mental status, and acute kidney failure. Two pathogenic mechanisms were suggested. The first was immunological, mediated by antibodies to ADAMTS13 (a zinc-containing metalloprotease enzyme that cleaves von Willebrand factor) and was associated with > 2 weeks of thienopyridine therapy. The second was nonimmunological and was associated with ≤ 2 weeks of thienopyridine use [91].

Abciximab can also cause thrombocytopenia [14, 92]. In a study of 1342 patients who underwent PCI and received abciximab for at least a second time [92], thrombocytopenia ($< 100 \times 10^9$/L) developed in 5% of patients; profound thrombocytopenia ($< 20 \times 10^9$/L) occurred in 2%. In most patients, thrombocytopenia developed within 48 h of abciximab administration, whereas in eight patients (0.6%) it occurred >48 h after administration (delayed onset). Having a positive human antichimeric antibody before readministration was associated with thrombocytopenia. Another study of 13 patients with delayed-onset thrombocytopenia (median 6–9 days) due to abciximab detected both antibodies specific for murine peptide sequences in abciximab and antibodies capable of recognizing other target epitopes on abciximab-coated platelets [14].

6 | Management

6.1 | Aspirin and Cross-Reactive NSAID Hypersensitivity

The therapeutic choice of the clinician when faced with a patient with ASCVD and a diagnosis of AHS or cross-reactive NSAID hypersensitivity can be difficult due to the lack of specific recommendations in current cardiological guidelines [7, 93, 94]. In particular, the 2019 European Society of Cardiology guidelines on CCS [7] do not provide any recommendations on the use of LDAC or aspirin desensitization in CCS patients [9, 11, 95] and state that they may receive clopidogrel in primary prevention and that prasugrel or ticagrelor monotherapy may be considered after PCI, at least as initial therapy, if DAPT cannot be used because of "aspirin intolerance." The American Heart Association/American College of Cardiology guidelines [8] suggest that patients who present with ACS without persistent ST-segment elevation and are not undergoing PCI (i.e., conservative management) should receive clopidogrel monotherapy in case of AHS. Nevertheless, whether clopidogrel could be as safe and effective as aspirin regardless of AHS remains debated [9]. Furthermore, in ASCVD patients, DAPT including aspirin remains the standard of care and there is no evidence supporting the combination of two different P2Y12 antagonists (e.g., clopidogrel and prasugrel/ticagrelor) as an alternative to replace aspirin [9]. Therefore, when dealing with these patients, it is advisable to choose between the two approaches that can enable the administration of low dose of aspirin: (1) an LDAC, if it has not been done previously; and (2) aspirin desensitization.

Figure 2 shows an algorithm for the management of AHS in patients with ASCVD in different clinical settings. LDAC should be considered the first choice for patients with histories of HSRs to aspirin and/or other NSAIDs who are at high risk of CAD or have CCS [9, 48] (Grade C). LDAC could also be performed in patients diagnosed with NERD, NECD, or NIUAA based on clinical history and/or positive full-dose DPT, as some studies demonstrated the tolerability of the antiplatelet dose in patients who had reacted to an anti-inflammatory dose [48, 50, 96]. In these patients, the choice between LDAC and aspirin desensitization should be made after careful evaluation of their clinical condition and risk profile. However, LDAC should not be performed in patients with ACS, as well as in patients reporting severe anaphylactic reactions to aspirin/NSAIDs and in those with active urticaria or uncontrolled asthma, due to the risk of persistence or worsening of symptoms [9, 48]. LDAC is also not recommended in patients who report recent (i.e., occurring < 5 years prior to allergy testing) HSRs to aspirin at antiplatelet doses or nonsevere anaphylactic reactions to aspirin/NSAIDs, in whom NEFA/NIFA is not suspected (Grade C).

Desensitization is a therapeutic procedure aimed at inducing aspirin tolerance by administering incremental doses of

aspirin at certain time intervals [9, 11, 48, 97–99]. Aspirin desensitization is a cornerstone of the management of patients with acute ASCVD and a history of aspirin/NSAID HSRs, including nonsevere anaphylactic reactions, and/or with a diagnosis of cross-reactive NSAID hypersensitivity (Figure 2). This procedure refers to desensitization for immediate HSRs. Specifically, aspirin desensitization is recommended in all such patients with ACS requiring DAPT after coronary stenting [9, 48] (Grade B). Patients with ACS and non-ST-segment elevation myocardial infarction (NSTEMI) can be safely desensitized before coronarography, possibly followed by stenting [9, 11, 48]. Conversely, in patients with ACS and ST-segment elevation myocardial infarction (STEMI), there is not enough time to desensitize before PCI. Therefore, PCI should be performed before desensitization, and intravenous antiplatelet therapies (i.e., cangrelor or a glycoprotein IIb/IIIa inhibitor) should be used as a bridging strategy to allow a prompt and effective platelet inhibition. Subsequently, within 12–72 h, aspirin desensitization can be performed with the normal regimen [9, 11, 48].

Most low-dose aspirin desensitization protocols tested in patients with CAD demonstrated a success rate of 90%–99% in both acute and chronic settings [9, 11, 48, 98, 99]. A meta-analysis of 15 studies involving a total of 480 ACS patients, who reported HSRs to aspirin (74% cutaneous, 18% respiratory, and 8% systemic), found a pooled protocol success rate of 98.3% [99]. Extended protocols (> 6 doses) showed better performances than shorter ones (< 6 doses) in terms of success rate, but no differences were observed between very rapid protocols (< 2 h) and rapid protocols (> 2 h) [99]. In general, protocols lasting < 6 h are more appropriate for ACS cases requiring rapid coronary stent placement (Grade C).

A significant limitation of the studies on aspirin desensitization in patients with ASCVD is the fact that in many cases the diagnosis of NSAID/aspirin hypersensitivity was based on clinical history alone.

Figure 3 provides information on the rapid desensitization protocols applied in the two studies involving the largest samples of patients with ASCVD [48, 100] and on additional protocol recently developed with the contribution of the coordinators of these two studies [9]. For stable patients receiving low-dose aspirin (75–100 mg), a rapid (240 min) 7-step protocol leading to a total cumulative dose of 98 mg is recommended. In patients with ACS, an extended protocol is recommended including an additional 80-mg dose for a total cumulative dose of 178 mg. This extended protocol allows the administration of an oral loading dose of aspirin (i.e., 150–300 mg) in aspirin-naïve patients to achieve more rapid and complete antiplatelet effects. The use of the same solution to perform the LDAC [48] allows to easily prepare doses of aspirin to be administered orally.

Aspirin desensitization is not recommended in NECD patients with active urticaria and NERD patients with uncontrolled asthma, as well as in patients reporting severe anaphylactic reactions to aspirin and/or other NSAIDs, in whom NEFA/NIFA is not suspected. In these patients, an alternative antiplatelet therapy is indicated (Grade C).

After any successful desensitization, patients should take aspirin every day to perpetuate the temporary clinical unresponsiveness to it (Grade B).

Aspirin desensitization may cause gastrointestinal side effects in predisposed patients who may therefore require proton pump inhibitors for gastroprotection.

Note that triflusal, an APD that, like aspirin, inhibits cyclooxygenase-1 [3, 4], has proven to be safe for patients with AHS, including those with exacerbated respiratory disease [4, 101].

Protocol A[100]			Protocol B[48]				Protocol C[9]			
Minutes	ASA dose (mg)	Cumulative dose (mg)	Minutes	mL of L-ASA solution	ASA dose (mg)	Cumulative dose (mg)	Minutes	mL of L-ASA solution	ASA dose (mg)	Cumulative dose (mg)
0	1	1	0	0 (placebo)	0	0	0	0.1	1	1
30	5	6	20	0.01	0.1	0.1	20	0.2	2	3
60	10	16	40	0.1	1	1.1	40	0.5	5	8
90	20	36	60	0.2	2	3.1	60	1	10	18
210	40	76	80	0.3	3	6.1	80	1.5	15	33
330	100	176	100	0.4	4	10.1	120	2.5	25	58
			120	0.5	5	15.1	240	4	40	98
			140	1	10	25.1	360	8	80	178
			180	1.5	15	40.1				
			240	2.5	25	65.1				
			300	3.5	35	100.1				

FIGURE 3 | Rapid desensitization protocols with aspirin for patients with ASCVD [9, 48, 100]. AHS, aspirin hypersensitivity; ASA, acetylsalicylic acid; ASCVD, atherosclerotic cardiovascular disease; L-ASA, lysine-acetylsalicylate.

6.2 | Nonaspirin APD Hypersensitivity

Given the importance of clopidogrel, three management options have been described for patients reporting HSRs to it: (1) pharmacological treatment without discontinuing clopidogrel; (2) desensitization; and (3) switching to another thienopyridine [12, 13, 102].

In a study [58], 62 patients with HSRs to clopidogrel, mostly delayed rashes, were treated with a single course of oral prednisone, starting at 30 mg twice per day for 5 days followed by a decrease in 5 mg/day every 3 days for 15 days. Complete resolution of symptoms was observed in 61 patients who were able to continue clopidogrel therapy for the minimum recommended duration without recurrence of HSRs after treatment with prednisone. All patients continued aspirin therapy 81 mg daily after completion of clopidogrel therapy, and none of them suffered from stent thrombosis.

Desensitization proved to be an effective procedure to overcome clopidogrel hypersensitivity [103]. In three studies [52–54], a total of 35 patients with cutaneous reactions to clopidogrel were successfully desensitized using protocols lasting between 2 and 7.5 h. These procedures refer to desensitization for immediate and non-immediate HSRs. Figure 4 provides information on a protocol [54] adapted from two previous ones [52, 53] and used to desensitize 24 consecutive patients. In another study [56], eight patients were successfully desensitized using a 2–3-day protocol (Figure 5). A significant limitation of these studies [52–54, 56] is the fact that the diagnosis of hypersensitivity was based only on clinical history.

Both the pharmacological treatment without discontinuing clopidogrel and desensitization are contraindicated in severe reactions and in hematologic ones [13, 54, 103]. In addition, desensitization requires discontinuing the drug for a washout period during which hypersensitivity symptoms regress [52, 54]. Therefore, sometimes it is necessary to switch to an APD other than the one involved in the reaction.

Time	Clopidogrel dose (mg)	Concentration (mg/mL)	mL
8:00 AM	0	0	0.01
8:30 AM	0.005	0.5	0.01
9:00 AM	0.01	0.5	0.02
9:30 AM	0.02	0.5	0.04
10:00 AM	0.04	0.5	0.08
10:30 AM	0.08	0.5	0.16
11:00 AM	0.16	0.5	0.32
11:30 AM	0.3	0.5	0.6
12:00 PM	0.6	0.5	1.2
12:30 PM	1.2	5	0.24
1:00 PM	2.5	5	0.5
1:30 PM	5	5	1
2:00 PM	10	5	2
2:30 PM	20	5	4
3:00 PM	40	5	8
3:30 PM	75	75-mg tablet	/

FIGURE 4 | Clopidogrel 16-step desensitization protocol [54]. The first dose given was solvent only, followed 30 min later by 0.005 mg of clopidogrel in solution. Thereafter, doubled doses of dilute clopidogrel were given every 30 min until a single 75-mg tablet was given.

First day	Clopidogrel dose num.	Dilutions	Dose (mg)	Time (hours)
	1	1 mg/mL	0.1	0
	2	1 mg/mL	0.2	1
	3	1 mg/mL	0.5	2
	4	1 mg/mL	1.0	3
	5	1 mg/mL	2.0	4
Second day: repeat the last dose				
	5	1 mg/mL	2.0	0
	6	1 mg/mL	4.0	1
	7	1 mg/mL	8.0	2
	8	1 mg/mL	16.0	3
	9	1 mg/mL	32.0	4
	10	1 pill as it is	75.0	5
Third day	10		75.0	

FIGURE 5 | Clopidogrel 2–3-day desensitization protocol [56].

Regarding patients with HSRs to a thienopyridine, switching to an alternative thienopyridine carries a significant risk of cross-reactivity, given the similarity of their basic chemical structure. In a study [55], 14 of 52 patients with a cutaneous or hematologic HSRs to clopidogrel had a similar reaction to ticlopidine. Moreover, 14 of the 38 patients reporting cutaneous or hematologic HSRs to ticlopidine developed similar reactions to clopidogrel. Another study found a high degree of cross-reactivity among thienopyridines by performing STs and PTs [58].

A systematic review [104] identified 11 patients with HSRs to clopidogrel who were subsequently treated with prasugrel: Two developed HSRs similar to those of clopidogrel (i.e., rash and urticaria/angioedema, respectively) and nine tolerated prasugrel.

There are reports of patients with cutaneous HSRs to thienopyridines other than clopidogrel who were switched to ticagrelor and tolerated it [81, 105, 106]. Of note, some patients with ticagrelor hypersensitivity were successfully switched to clopidogrel [61, 62, 75, 107].

Due to its different structure, cilostazol may be an alternative in patients with HSRs to ADP receptor antagonists [102, 108].

7 | Statement and Recommendations

- The 1.5%–1.9% of patients with CAD reported a prior reaction to aspirin, being gastrointestinal bleeding/intolerance the most frequent, followed by cutaneous symptoms, mainly manifested as urticaria/angioedema.

- The frequency of HSRs to clopidogrel has been estimated at 1.6%, consisting mostly of a generalized exanthematous rash, which is a typical delayed reaction.
- AHS is often overdiagnosed mainly because in many cases the diagnosis is made only on the basis of the clinical history.
- Aspirin is rarely responsible for SNIUAA or SNIDHR. Therefore, STs and in vitro tests are not recommended in patients who report aspirin HSRs (Grade C).
- NSAIDs may act as aggravating factors or cofactors in some HSRs to foods, which are often misdiagnosed as HSRs to NSAIDs
- The DPT with aspirin plays a crucial role in the diagnosis of cross-reactive types of NSAID hypersensitivity (Grade C).
- LDAC is recommended in patients with CCS and in individuals at high risk of ASCVD with histories of HSRs to aspirin and/or other NSAIDs, excluding anaphylactic reactions and recent HSRs to aspirin at an antiplatelet dose (Grade C).
- In STEMI patients with suspected or ascertained AHS, desensitization should be performed after PCI, and cangrelor or a glycoprotein IIb/IIIa inhibitor should be used as a bridging strategy while the desensitization protocol is performed (Grade C).
- In the management of patients with suspected or confirmed AHS and ACS-NSTEMI, aspirin desensitization should be performed prior to coronary angiography, and intravenous APDs should be used only for bailout situations (Grade B).
- PTs could be useful to evaluate patients reporting non-immediate cutaneous reactions, particularly exanthemas associated with clopidogrel. Since IDTs are generally more sensitive than PTs, the use of IDTs should be recommended not only to identify the culprit drug but also to assess cross-reactivity and find safe alternatives (Grade D).
- DPT is the gold standard for diagnosing hypersensitivity to nonaspirin APDs in patients with mild/moderate reactions and negative STs and/or PTs (Grade D).
- To secure safety and effectiveness of the desensitization to APDs, well-established protocols should be followed (Grade C).
- In patients with delayed cutaneous HSRs to clopidogrel, the use of a short course of oral glucocorticoids, without interrupting clopidogrel treatment, may be useful to manage their reactions (Grade D).
- In patients reporting HSRs to thienopyridines, switching to an alternative thienopyridine is not recommended due to the risk of cross-reactivity (Grade D).

8 | Conclusions

APDs can provoke HSRs, some of which might be life-threatening. LDAC and aspirin desensitization have emerged as effective and safe approaches in patients with HSRs to aspirin who require aspirin therapy. However, both procedures are performed in fewer patients than would be actually indicated.

TABLE 4 | Unmet needs and future research area for HSRs to APDs.

Pathogenesis	• Studies to understand the pathomechanisms of HSRs to APDs other than aspirin
Diagnosis	• Role of STs and PTs in the diagnosis of HSRs to nonaspirin APDs • Multicenter studies to establish optimal drug concentrations and vehicles for STs and PTs with APDs other than aspirin • Unified algorithm for testing with suspected and alternative APDs other than aspirin to assess cross-reactivity • Development and evaluation of in vitro tests to diagnose hypersensitivity to nonaspirin APDs • Multicenter studies to provide the risk stratification of HSRs and establish optimal test doses for DPTs with APDs • Standardization of protocols regarding DPTs, particularly those of DPTs with APDs other than aspirin
Management	• Multicenter studies to standardize and possibly validate glucocorticoid treatment without discontinuing clopidogrel in patients with mild/moderate HSRs to it • Validation of standard protocols to desensitize patients hypersensitive to aspirin and/or other APDs • Identification of nonaspirin APD antigenic determinants responsible for cross-reactivity • Lack of recommendations for performing LDAC and aspirin desensitization in current cardiology guidelines on the management of coronary artery disease • Lack of referral or poor referral of patients with histories of HSRs to APDs to the allergist by other physicians for allergy testing, particularly LDAC, and/or for aspirin desensitization

Abbreviations: APD, antiplatelet drug; DPT, drug provocation test; HSR, hypersensitivity reaction; LDAC, low-dose aspirin challenge; PT, patch test; ST, skin test.

Most studies of patients with nonaspirin APD HSRs are reports of single cases or small series in which the diagnosis was based only on clinical history. In these patients, however, an allergy workup is advisable to establish a firm diagnosis. Data regarding immediate nonaspirin APD HSRs are very limited.

Table 4 shows several unmet needs that require further research on APD-induced HSRs to improve their diagnosis and management.

Author Contributions

Gabriele Cortellini proposed and chaired the task force. He managed and coauthored diagnosis, treatment, and recommendations for aspirin hypersensitivity in cardiovascular disease. Alla Nakonechna was

secretary of the task force and took care of its general drafting; together with Mauro Pagani, she supported the task force and coauthored the introduction, problem dimensions, survey methods, and open questions. Annick Barbaud approved and supported the task force, extensively revised the manuscript, and edited the recommendations. Sevim Bavbek supported the task force, edited the recommendations, and together with Violeta Kvedariene coauthored classification, definition, epidemiology. Gianfranco Calogiuri authored the diagnosis, clinical presentation, and treatment of hypersensitivity to nonaspirin APDs. Inmaculada Doña, first corresponding author of the manuscript, and José Julio Laguna coauthored the pathogenesis and clinic of aspirin hypersensitivity. Serena Liberati coauthored diagnosis and treatment of hypersensitivity to aspirin in cardiovascular diseases. Antonino Romano thoroughly revised the drafting of the manuscript and made original and shared conclusions and recommendations. He coauthored diagnosis, treatment, and recommendations for aspirin hypersensitivity in cardiovascular diseases.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.