Aspirin Hypersensitivity and Desensitisation in Patients with Coronary Heart Disease

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Following acute coronary syndromes and percutaneous coronary angioplasty (PCI), Aspirin is an indispensable agent for preventing serious cardiovascular complications. The prevalence of Aspirin hypersensitivity is estimated to be up to 2.5% of the general population. To date, no safe alternative has been proven effective in replacing Aspirin with another antithrombotic agent following PCI or myocardial infarction. The European Society of Cardiology first provided a low-evidence-based recommendation in its 2019 guidelines for the treatment of chronic coronary syndromes, suggesting that prasugrel or ticagrelor monotherapy may be considered as initial antithrombotic treatment following elective PCI in patients with aspirin hypersensitivity. It is important to note that this recommendation does not extend to acute coronary syndromes.

Aspirin desensitisation is the only treatment method that enables patients with hypersensitivity to receive dual antiplatelet therapy and prevent myocardial infarction (MI) and early ischaemic complications following percutaneous coronary angioplasty (PCI). In the absence of clear guidelines, desensitisation may be overlooked as a treatment option in patients with Aspirin hypersensitivity following PCI. The only absolute contraindications to desensitisation are a history of Aspirin-induced Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis or erythema multiforme (1, 2, 3).

DESENSITISATION

Desensitisation is the temporary clinical suppression of a drug's pharmacological and immunological reactions, which is achieved by gradually increasing the drug dose until reaching the maintenance dose. The mechanisms of Aspirin desensitisation primarily involve a reduction in leukotrienes and their receptors, as well as decreased release of histamine and tryptase from mast cells. Adherence to treatment is important for the long-term success of the desensitisation procedure, as the effect may be lost if the drug is not administered for more than 48 hours. In case of resensitisation, the procedure needs to be repeated under safe conditions (4).

ASPIRIN HYPERSENSITIVITY

Aspirin hypersensitivity is heterogeneous in both its manifestation and pathogenesis. Manifestations can be classified as respiratory, cutaneous and systemic. Based on pathogenesis, hypersensitivity mechanisms can be either pharmacological or immunological. Pharmacological reactions are associated with cyclooxygenase-1 (COX-1) inhibition, resulting in increased leukotriene production, whereas immunological reactions are mediated by specific immunoglobulin E. Pharmacological or cross-reactions can occur with all non-steroidal anti-inflammatory drugs (NSAIDs) (4, 5).

The most common form of pharmacological hypersensitivity is Aspirin/NSAID exacerbated respiratory disease (AERD/NERD), which manifests as bronchial obstruction, dyspnoea or nasal congestion following the administration of Aspirin or other NSAIDs and typically occurs in patients with underlying asthma or chronic rhinosinusitis with polyposis (4, 6, 7).

The second form of pharmacological hypersensitivity is NSAID-induced urticaria or angioedema (NIUA), which may occur in patients without a prior history of chronic spontaneous urticaria. For diagnosis, it is important that symptoms have been triggered by more than one structurally unrelated NSAID. NSAID-exacerbated cutaneous disease (NECD) occurs in patients with pre-existing chronic urticaria.

Cross-reactive NSAID hypersensitivity may also manifest as anaphylaxis (5, 6). Immunological hypersensitivity reactions

may exhibit cross-reactivity within the same NSAID class (e.g., salicylates), but may also be specific to a single NSAID. These are Type I hypersensitivity reactions mediated by IgE and histamine. Clinically, these manifest as urticaria, angioedema, maculopapular exanthema or anaphylaxis. The immunological reaction may be immediate, occurring within one hour after Aspirin administration, or, less commonly, a delayed Type IV cell-mediated hypersensitivity reaction occurring after more than 48 hours (5, 6).

ALTERNATIVES TO DUAL ANTIPLATELET THERAPY

Following PCI, it is necessary to implement temporary dual antiplatelet therapy with Aspirin and a P2Y12-receptor inhibitor, such as clopidogrel, ticagrelor or, less frequently, prasugrel. For patients with Aspirin hypersensitivity, desensitisation is primarily necessary to enable dual antiplatelet therapy, as there is no suitable substitute for Aspirin in this regimen.

Among evidence-based treatment options, there are regimens where Aspirin must be used for at least one month. The first example therapy consists of one month of Aspirin in combination with ticagrelor, followed by ticagrelor monotherapy. GLOBAL LEADERS was a multicentre, randomised study, the follow-up analysis of which showed that one month of dual antiplatelet therapy with ticagrelor and Aspirin, followed by 23 months of ticagrelor monotherapy, is comparable in effectiveness to 12 months of dual antiplatelet therapy with ticagrelor and Aspirin followed by 23 months of Aspirin monotherapy with respect to ischaemic complications and bleeding risk (7).

Ticagrelor or prasugrel monotherapy following PCI or myocardial infarction has not been sufficiently studied. The OPTICA pilot study was a prospective observational study that included 70 patients with non-ST-segment elevation myocardial infarction (NSTEMI) who received a loading dose of prasugrel or ticagrelor before PCI and continued with the respective antiplatelet agent as monotherapy for 12 months. The composite endpoint comprised all-cause mortality, myocardial infarction, stent thrombosis, and stroke occurring within six months after PCI. The endpoint was reached in 4% of patients, with no occurrences of myocardial infarction or stent thrombosis. Until stronger scientific evidence emerges, based on the referenced observational study, it is at least reasonable to consider prasugrel or ticagrelor as monotherapy if Aspirin desensitisation is absolutely contraindicated (8).

Following PCI, early clopidogrel monotherapy should be avoided due to insufficient antithrombotic effect. The STOPDAPT-2-ACS study addressed clopidogrel monotherapy following acute coronary syndromes. After 1-2 months of dual antiplatelet therapy, patients were randomised to either clopidogrel monotherapy or continued dual antiplatelet therapy. Early clopidogrel monotherapy did not demonstrate efficacy equivalent to standard practice. Consequently, clopidogrel monotherapy can be safely initiated only after 3 or 6 months of dual antiplatelet therapy in patients with low ischaemic risk, or after 12 months post-PCI in patients with higher ischaemic risk (3, 9).

Glycoprotein IIb and IIIa inhibitors are useful for preventing early ischaemic complications during PCI in acute coronary syndrome patients with Aspirin hypersensitivity, particularly when desensitisation has not been initiated prior to PCI. The treatment is single-dose and intravenous. These agents cannot be considered as substitutes for Aspirin – oral formulations studied so far have proven ineffective, and long-term treatment is associated with a high risk of ischaemic complications (1, 10).

OPTIMAL DOSE OF ASPIRIN

The maintenance dose of Aspirin varies across desensitisation protocols. The most extensively studied dose is 325 mg, which is considered the minimum maintenance dose after desensitisation in patients with AERD and NERD. Studies recommending high doses of Aspirin primarily used polyp recurrence and rhinosinusitis symptoms as primary endpoints, which were not consistently improved in many studies with doses below 325 mg. In acute coronary syndrome, however, Aspirin tolerance and continuation for at least one month becomes prognostically significant to ensure the minimum duration of dual antiplatelet therapy.

Several studies have shown successful desensitisation with Aspirin doses below 325 mg. An Italian multicentre observational study used data from the ADAPTED registry. In this study, 330 patients with chronic and acute coronary syndrome and Aspirin hypersensitivity of various levels were desensitised to Aspirin using a 100 mg maintenance dose. The procedure was successful in 95.4% of patients, including all 19 cases of Aspirin-induced anaphylaxis. One year later, 80.3% of patients continued to take Aspirin (11, 12).

The Aspirin dose is also important in the context of dual antiplatelet therapy, with the optimal dose being 75-100 mg. The efficacy of ticagrelor is influenced by the Aspirin dose, as shown in the PLATO study, where Aspirin doses above 150 mg reduced the effectiveness of ticagrelor. Since this potential association has not been refuted to date, it is necessary during the acute phase of dual antiplatelet therapy to maintain the daily Aspirin dose below 150 mg (13).

When using clopidogrel and Aspirin concomitantly, Aspirin doses exceeding 100 mg do not provide greater protection against major cardiac complications but are associated with an increased risk of bleeding compared to doses below 100 mg (14, 15, 16).

In the ADAPTABLE study, when used as monother-

apy, Aspirin doses of 81 mg and 325 mg showed no significant difference in the incidence of cardiac complications or bleeding events. Therefore, if desensitisation fails to be maintained at lower doses, the use of a higher Aspirin dose – up to 325 mg – may be considered after the initial period of dual antiplatelet therapy. During the dual antiplatelet therapy period, the abovementioned risks must be taken into account with Aspirin doses higher than 100 mg (17).

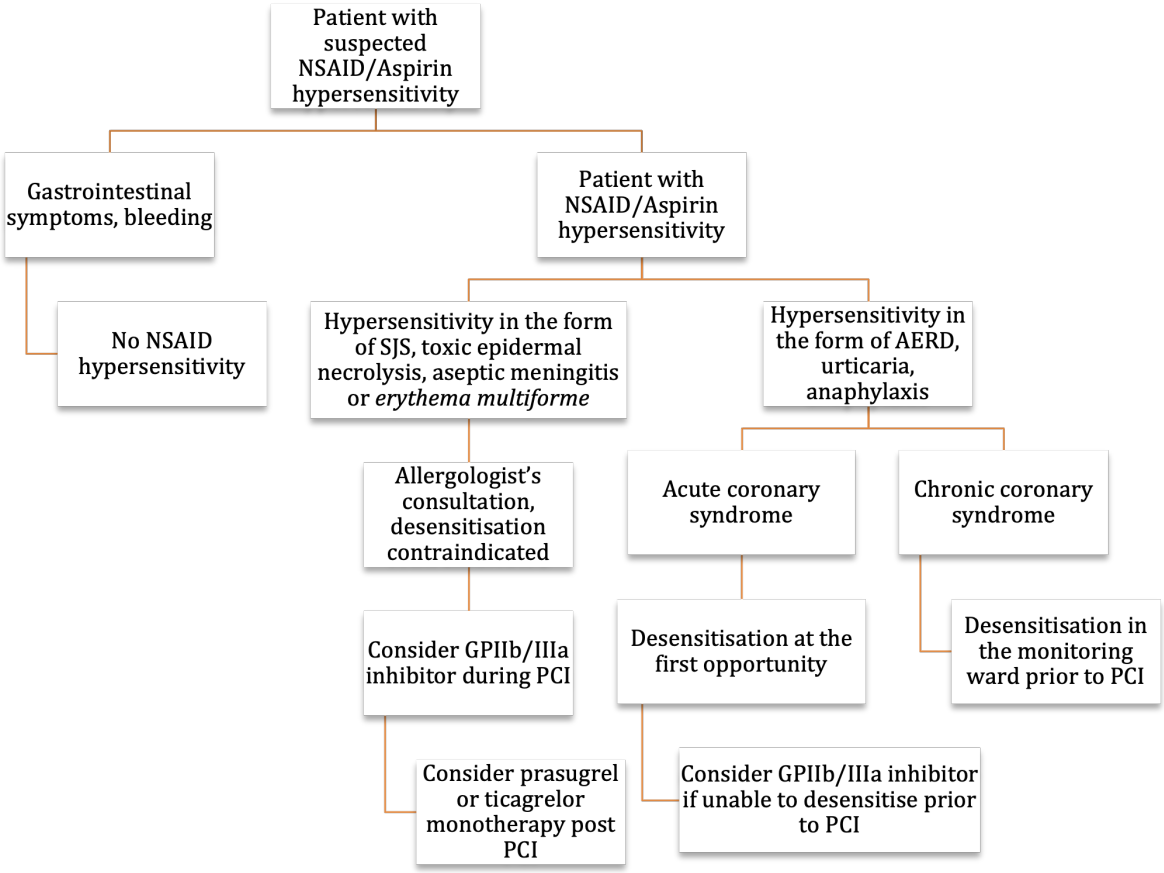
When selecting the Aspirin dose, body weight may also be taken into consideration in some cases. In the meta-analysis by Rothwell et al., which examined the efficacy of Aspirin doses in the context of primary prevention, daily Aspirin doses of 70-100 mg had no effect on reducing cardiac events in patients weighing over 70 kg, and higher doses were required. Although the study results cannot be extrapolated to secondary prevention, this is an important example of possible variation in the most suitable Aspirin dose. An attempt to validate the findings of Rothwell et al. failed in a post-hoc analysis of the ASPREE registry, which included a larger elderly population (18, 19).

ANTICOAGULANTS

Direct oral anticoagulants have not been investigated as a replacement for Aspirin as part of antithrombotic therapy for acute coronary syndromes or following PCI. However, rivaroxaban has demonstrated a favourable effect in reducing ischaemic complications after myocardial infarction when added to antiplatelet therapy containing Aspirin (20).

In case of absolute contraindication to Aspirin, the use of warfarin is a theoretical alternative. Following myocardial infarction, warfarin is associated with a lower incidence of cardiac complications compared to Aspirin; however, this benefit comes at the cost of a significantly increased risk of bleeding (21).

Patients with Aspirin hypersensitivity and atrial fibrillation must use Aspirin for a minimum of one week, followed by 12 months of combined oral anticoagulant and antiplatelet therapy. The use of an antiplatelet agent for more than one year does not reduce mortality or cardiac complications. After this period, lifelong monotherapy with the oral anticoagulant is continued. Atrial fibrillation is therefore associated with a higher risk of restenosis and myocardial infarction; however, due to the minimal bleeding risk and reduced cardioembolic risk, mortality rates are levelled out, resulting in a neutral overall treatment outcome (22, 23).



NSAID – non-steroidal anti-inflammatory drug, PCI – percutaneous coronary intervention, SJS – Stevens-Johnson syndrome, AERD – Aspirin-exacerbated respiratory disease.

Figure 1. Management of patients with Aspirin hypersensitivity and ischaemic heart disease.

Aspirin desensitisation options for patients with ischaemic heart disease

Early desensitisation and assessment of the hypersensitivity history are important (see Figure 1). Patients with acute coronary syndrome are typically admitted to a Level III intensive care unit before and/or after angiography, which provides an ideal environment for desensitisation due to its advanced monitoring capabilities and specialised staff training. Desensitisation protocols typically last one day. In case of test failure, consultation with an allergist is recommended, and increasing the Aspirin dose during the next desensitisation attempt should be considered. A new desensitisation attempt may be initiated immediately after bringing the hypersensitivity reaction under control with corticosteroids or antihistamines (24).

Several desensitisation protocols have been developed for the co-occurrence of acute coronary syndromes and Aspirin hypersensitivity. Although based on small sample sizes, these prospective observational studies report desensitisation success rates ranging from 87.5% to 100%, with no life-threatening systemic hypersensitivity reactions observed. A meta-analysis of 15 observational studies involving patients with both Aspirin hypersensitivity and ischaemic heart disease reported successful desensitisation in 463 of 480 patients. According to the meta-analysis, there was no difference in the success rates between desensitisation protocols lasting less than and more than two hours; however, study protocols involving fewer than six incremental drug doses were associated with lower success rates compared to protocols using more than six doses (99.2% vs. 95.4%; $p = 0.007$).

Maintenance doses varied from 81 mg to 325 mg. The reasons for desensitisation test failure in the meta-analysis were sudden hypersensitivity reactions, primarily presenting as urticaria or asthma, occurring during administration of the first or second dose of Aspirin or within two hours after completion of the desensitisation test. For both cases described in this article, we used a modified version of the Rossini et al. protocol, based on the abovementioned ADAPT-ED registry with the largest sample size, adjusting the Aspirin maintenance dose from 100 mg to 75 mg (see Table 1) (2, 4, 24).

Table 1. Aspirin desensitisation protocols (Rossini et al. and Cordoba-Soriano et al. (1, 11, 25))

Protocol	Rossini et al.	Cordoba-Soriano et al.
Sample	330 patients who underwent percutaneous coronary intervention 23.6% of cases ST-segment elevation myocardial infarction 33.6% Myocardial infarction without ST-segment elevation	24 patients who underwent percutaneous coronary intervention 33.3% Myocardial infarction with ST-segment elevation
Duration	5.5 h	1.8 h
Aspirin doses (mg)	1; 5; 10; 20; 40; 100	0.1; 0.3; 1; 3; 10; 25; 50; 100
Administration frequency	• 0 min – 1 mg • 30 min – 5 mg • 60 min – 10 mg • 90 min – 20 mg • 210 min – 40 mg • 330 min – 100 mg	15-minute intervals
Premedication	None	Antihistamine, corticosteroid
Success rate	95.4%	100%

AVAILABILITY OF LOW-DOSE ASPIRIN

In Estonia, the poor availability of low-dose Aspirin has thus far hindered the implementation of Aspirin desensitisation tests. Specifically, the smallest Aspirin tablet contains 75 mg of the active ingredient. The extemporaneous preparation of smaller tablets, for example, those containing a 1 mg dose, is imprecise and complex.

As of May 2024, the University of Tartu Hospital's Pharmacy will be able to split into doses non-sterile compounded medications using a 3D printer (see Image 1). A printing solution with a specific concentration of active ingredient is placed in the printer using a disposable syringe, and the printer distributes the corresponding dose by weight. The accuracy of each dose is verified by a scale integrated in the printer.

The 3D tablet printer uses a medicinal ink composed of various excipients, to which the active substance is added in the pharmacy prior to printing.

For the desensitisation protocol described in this article, we printed 1 mg, 5 mg and 10 mg Aspirin chewable tablets in the hospital's pharmacy.

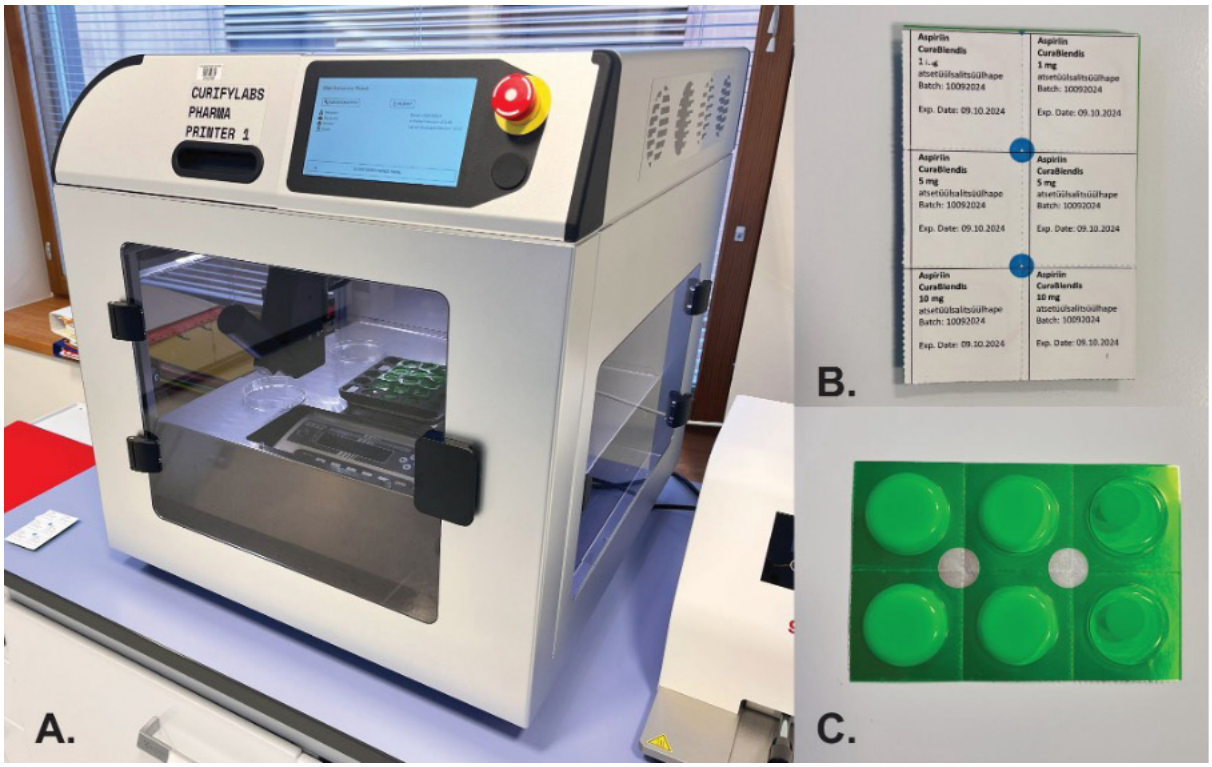


Image 1. A. 3D tablet printer. B. and C. 3D-printed 1 mg, 5 mg and 10 mg Aspirin doses in packaging.

CLINICAL CASE EXAMPLES

Case 1

A 77-year-old female patient was electively hospitalised for coronary angiography due to exertional angina. Computed tomography angiography was performed on an outpatient basis, revealing a calcium score of 1,600 Agatston units. There remained a suspicion of significant stenosis in multiple coronary arteries. In the proximal part of the anterior interventricular branch (A1), findings revealed pronounced calcification, with suspected critical stenosis (pre-occlusion).

SPECT (single-photon emission computed tomography) imaging did not reveal any perfusion defects indicative of myocardial ischaemia. As the angina was typical and progressive, selective coronary angiography was deemed appropriate. The coronary angiography results corresponded with the computed tomography angiography findings.

Selective coronary angiography revealed two-vessel coronary artery disease, with 76-90% stenoses in the proximal segment of the anterior interventricular branch and the posterior interventricular branch. Ad hoc PCI of the aforementioned vessels was performed, with three drug-eluting stents implanted, necessitating dual antiplatelet therapy (aspirin + clopidogrel). The formula for describing the coronary angiography finding: 2 D S (1) A (432) RIM (3) Di1 (2) Di2 (3) C (1 2 0) OM2 (2) D (1 2 2) DIP (4) DPL (1). PCI: A (432) → (112), DiP (4) → (1).

The patient also had hypertension, dyslipidaemia (low-density lipoprotein (LDL) value had previously been up to 4.7 mmol/L without medication) and type 2 diabetes. According to the patient, she could not tolerate aspirin. It had caused skin itching, rash, facial redness and flushing. Ibuprofen and diclofenac also caused skin itching.

An attempt was made to restart aspirin treatment (75 mg), resulting in facial redness; the patient described itching and discomfort; therefore, desensitisation was considered appropriate. No problems occurred during the desensitisation process. We used the following aspirin doses according to the modified Rossini protocol: 1 mg, 5 mg, 10 mg, 20 mg, 40 mg and 75 mg. The patient was monitored in hospital for several additional days, followed by continued follow-up via telephone contact. No skin rashes, redness, flushing, itching or other complaints developed. The patient tolerated the prescribed treatment well.

Case 2

A 56-year-old male patient was admitted to Tartu University Hospital with a diagnosis of anterior ST-segment elevation myocardial infarction. The patient was taken directly to the angiography ward by ambulance, where he also required defibrillation due to ventricular fibrillation. Selective coronary angiography and primary percutaneous coronary intervention were performed; the procedure was successful.

Selective coronary angiography revealed two-vessel coronary artery disease, with an occlusion of the middle segment of the anterior interventricular branch

and a 51-75% stenosis of the ramus intermedius artery. Ad hoc PCI of the anterior interventricular branch was performed, with one drug-eluting stent implanted. The formula for describing the coronary angiography finding: 2 B S (2) A (16–) RIM (3) Di1 (3) C (2 1) D (1 3 2) DIP (3). PCI: A (16–) → (114).

Due to recurrent myocardial infarction and stent implantation, the patient required dual antiplatelet therapy. During the last hospitalisation for ST-segment elevation myocardial infarction, airway obstruction occurred in the cardiac intensive care unit after Aspirin administration. Aspirin was removed from the treatment regimen and ticagrelor + enoxaparin were temporarily selected for antithrombotic therapy.
The patient's comorbidities included hypertension, a previous myocardial infarction, and asthma. The patient had previously suffered a non-ST-segment elevation myocardial infarction in 2019, after which five drug-eluting stents were implanted in the coronary arteries. During the same hospital stay, the patient developed dyspnoea after Aspirin administration, and auscultation revealed obstruction in the lung fields. The episode resolved with the administration of salbutamol. Aspirin was excluded from the treatment regimen as it caused significant exacerbations of asthma. In 2013, the patient reported experiencing shortness of breath following Aspirin administration and called an ambulance. The ambulance team administered a glucocorticoid. The patient also had hypersensitivity to ibuprofen.

After the intensive care period, a decision was made to attempt Aspirin desensitisation. The hospital's pharmacy prepared small aspirin doses for this purpose. The patient was transferred to an observation ward, and the following aspirin doses were administered according to the modified Rossini protocol: 1 mg, 5 mg, 10 mg, 20 mg, 40 mg and 75 mg. Vital signs were recorded and lung fields auscultated hourly, with no change in the patient's condition observed. The patient received 75 mg of Aspirin on each of the following two days, without developing any complaints. Thus, the desensitisation attempt proved successful, and dual antiplatelet therapy was continued with ticagrelor and Aspirin.

SUMMARY
Currently, there is no evidence-based Aspirin-free antithrombotic treatment after percutaneous coronary intervention; therefore, it is important to attempt early desensitisation in patients with Aspirin hypersensitivity. Desensitisation is a rapid and effective procedure, with absolute contraindications being extremely rare (Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis and erythema multiforme).
In case of failed desensitisation, a repeated attempt may be undertaken at the earliest opportunity. If necessary, the maintenance dose of Aspirin may be increased, in consultation with an immuno-allergologist. Desensitisation protocols show similar success rates regardless of duration; however, protocols with more than six different dose steps have demonstrated higher success rates to date. Protocols can be modified according to patient needs and healthcare facility resources.

Aspirin desensitisation can also be performed using the same protocols for optimal management of peripheral arterial disease, ischaemic stroke and prevention of preeclampsia. For obtaining small doses of Aspirin, a 3D tablet printer is available at the Tartu University Hospital's Pharmacy.

Declaration of possible conflict of interest
The authors confirm that they have no conflicts of interest related to this article.

SUMMARY
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It is important to conduct early desensitisation testing in patients with aspirin hypersensitivity due to the lack of evidence supporting aspirin-free antithrombotic therapy after a percutaneous coronary intervention. Desensitisation is a relatively rapid and effective procedure, with absolute contraindications being few and extremely rare (Stevens-Johnson syndrome, toxic epidermal necrolysis, aseptic meningitis and erythema multiforme). After a failed desensitisation attempt, the protocol should be modified and restarted, preferably after increasing the target dose of Aspirin and consulting with an allergist. Desensitisation protocols have comparable efficacy regardless of duration; however, protocols with more than six different

Aspirin doses have demonstrated greater effectiveness. Protocols may be modified to best suit individual patient needs and hospital resources. Aspirin desensitisation using the same protocols can also be performed for the optimal management of peripheral arterial disease, ischaemic stroke and prevention of preeclampsia. For obtaining small Aspirin doses, Tartu University Hospital's Pharmacy utilises a 3D drug printer.

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