

Efficacy and Safety of Available Protocols for Aspirin Hypersensitivity for Patients Undergoing Percutaneous Coronary Intervention

A Survey and Systematic Review

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Background—The most suitable approach for patients with aspirin hypersensitivity undergoing percutaneous coronary intervention remains to be assessed.

Methods and Results—Pubmed, Google Scholar, and Cochrane were systematically searched for papers describing protocols about aspirin hypersensitivity in the percutaneous coronary intervention setting. Discharge from hospital with aspirin was the primary end point, whereas rates of adverse reactions being a secondary outcome. An online international survey was performed to critically analyze rates of aspirin hypersensitivity and its medical and interventional management. Eleven studies with 283 patients were included. An endovenous desensitization protocol was performed on one of them, with high efficacy rate (98%) and a low adverse reaction rate when compared with oral administration. No significant differences were reported among the oral protocols in terms of efficacy (less versus more fractionated [95.8% {95.4%–96.2%} versus 95.9% {95.2–96.5%}]), whereas higher incidence of rash and angioedema were reported for protocols with <6 doses escalation (2.6% [1.1%–4.1%] versus 2.6% [1.9%–3.2%]). In the survey, we collected answer from 86 physician of the 100 interviewed. Fifty-six percent of them managed aspirin hypersensitivity changing the therapeutic regimen (eg, clopidogrel monotherapy and indobufen). Despite the previous safety data, desensitization protocols were adopted by only 42% of surveyed cardiologist.

Conclusions—Available protocols for aspirin hypersensitivity are effective and safe, representing a feasible approach for patients needing dual antiplatelet therapy. (*Circ Cardiovasc Interv.* 2016;9:e002896. DOI: 10.1161/CIRCINTERVENTIONS.115.002896.)

Key Words: angioplasty ■ aspirin ■ hypersensitivity ■ indobufen ■ percutaneous coronary intervention

Aspirin has been demonstrated to play a pivotal role for patients with coronary artery disease, with well-known benefits for reducing recurrent coronary events, and with protective effects toward stent thrombosis for those undergoing percutaneous coronary intervention (PCI).^{1–6}

This aspect becomes particularly relevant in patients with aspirin hypersensitivity, who experience side effects, such as exacerbated respiratory tract disease, urticaria/angioedema, or anaphylaxis, leading to high risk of discontinuation.^{6,7} Although it is an infrequent finding, this problem offers many challenges for physicians managing these patients, particularly because of the limited number of alternatives.

Several other drugs, from cilostazol to cardiren or indobufen, have been tested, although their main limit is represented by the absence of validation on randomized controlled trials or derived from randomized controlled trials with a limited sample size, and with an uncertain effect on prognosis.^{8–11}

At present, the only validated dual antiplatelet therapy (DAPT) regimen is with aspirin plus P2Y₁₂ inhibitors as recommended by current guidelines on myocardial revascularization.¹²

Protocols of aspirin desensitization represent a potentially feasible approach to solve this problem: however, different approaches have been used as well as different timing, leading to contrasting results.^{6,7,13} At the same time, these protocols are fraught with small sample sizes and an

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WHAT IS KNOWN

- Aspirin plays a key role in the secondary prevention of atherothrombotic events and thrombotic complications after stent implantation.
- Aspirin hypersensitivity represents a challenge in the management of patients undergoing stent implantation.

WHAT THE STUDY ADDS

- The majority of cardiologists still manage aspirin hypersensitivity by avoiding aspirin therapy and treating patients with alternative antiplatelets agents. This is not supported by adequate evidence-based medicine.
- Desensitization protocols have demonstrated to be safe and effective and allow cardiologists to use dual antiplatelet therapy.
- Endovenous aspirin desensitization protocols and oral protocols with >6 doses escalation have lower adverse reactions rate compared with dose escalations with <6 doses.

absence of comparisons with a lack of uniformity of behavior among physicians.

Consequently, we performed a meta-analysis to appraise the available up-to-date protocols of desensitization and their positive/negative effects. We performed also a web-based survey to understand physicians' attitude and how aspirin hypersensitivity affects everyday clinical practice.

Methods

Meta-Analysis

This study was performed according to current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, and recommendations from The Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (MOOSE).^{14–19} No temporal or language restrictions were applied.

Search Strategy and Study Selection

Pertinent articles were searched in Pubmed, Medline, Cochrane Library, Biomed Central, and Google Scholar in keeping with established methods^{14–19} with Mesh strategy and with a combinations of the following key words: acetylsalicylic acid (ASA), aspirin, hypersensitivity, desensitization, and protocol. Three independent reviewers (M.B., A.B., and F.D.A.) first screened retrieved citations at title or abstract level, with divergences resolved after consensus. If potentially relevant, they were then appraised as complete reports according to the following selection criteria. Studies were included if they investigated patients: (1) presenting with history of aspirin hypersensitivity reactions, (2) treated with desensitization protocols, (3) undergoing PCI in the same hospitalization, while exclusion criteria were (1) duplicate reporting (in this case the article reporting the largest sample of patients was selected) and (2) case reports with <3 patients.

Data Extraction

Two unblinded independent reviewers (F.D.A. and M.B.) collected data on baseline profile of patients, on symptoms of their hypersensitivity to aspirin and the indication for PCI. Protocols were divided in:

- (1) intravenous, (2) oral with <6 administrations of aspirin doses and, (3) oral with >6 administrations of aspirin doses.

End Point

Success of the protocols was the primary end point (defined as discharge with aspirin as therapy), whereas rates of rash and angioedema during the procedure were secondary outcomes.

Internal Validity and Quality Appraisal

Unblinded independent reviewers (F.D.A. and M.B.) evaluated quality of included studies on prespecified forms. Modifying the MOOSE items to take into account the specific features of included studies they separately abstracted and appraised study design, setting, and data source.

Data Analysis and Synthesis

Continuous variables are reported as mean (SD) or median (interquartile range). Categorical variables are expressed as n/N (%). Statistical pooling was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals. Heterogeneity was evaluated with χ^2 test along with inconsistency. All computations were performed using RevMan 5.2 (The Cochrane Collaboration, The Nordic Cochrane Center, and Copenhagen). Small studies' bias was appraised by graphical inspection of funnel plots. Standard hypothesis testing was set at the 2-tailed 0.05 level.

Survey

A web-based survey was designed and developed by a cardiologist with expertise in data managing and programming (E.C.), and it was hosted in our Web site <http://www.cardiogroup.org>. The development of survey followed the recommendations found in Guidance for Industry, Computerized Systems Used in Clinical Investigations, by the Food and Drug Administration. The engine was built using PHP code language and MySQL client (Oracle corporation).

We invited 100 interventional and clinical cardiologists who were randomly abstracted from national societies data base to take part in an online survey sending an invitation e-mail with a link to our Web site [cardiogroup.org](http://www.cardiogroup.org) where the survey was hosted. Every participant provided informed consent about the survey's purpose and the anonymous management of the data. The survey was made of 22 questions about aspirin's hypersensitivity rate, the management of patients with aspirin hypersensitivity, alternative therapies, and desensitization protocols. All the survey's questions are included in Appendix I in the Data Supplement.

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Results

Meta-Analysis

After initial search, 18 articles were evaluated for inclusion. Five of them have been excluded because of not describing desensitization protocols, whereas another one was removed because it did not include patients with PCI and 2 more because they included <3 patients.^{20–26} Finally, 11 studies with 283 patients were included in the final analysis^{6,7,13,27–33} (Figure 1; Appendix I in the Data Supplement).

Only 1 study tested an intravenous protocol, whereas all the others were focused on oral strategies: moreover other drug (antihistamine) was added in the local medical practice in only 1 case. Most of these research papers were retrospective and performed in Europe (Table 1).

The majority of patients included in our meta-analysis had several cardiovascular risk factors and most of them presented

with acute coronary syndrome. In their medical history, angioedema was the most frequent clinical manifestation of aspirin hypersensitivity (Table 2). In most cases, patients were treated with drug-eluting stents (Table 3), consequently with a need for dual antiaggregant therapy for at least 12 months in acute coronary syndrome (ACS) and a minimum of 6 months for stable coronary artery disease.¹²

All the protocols were successful, without relevant differences among intravenous (98%: 97.9%–98%) and less versus more fractionated (95.8% [95.4%–96.3%] versus 95.9% [95.2–96.5%]; Figure 1).

In regard to side effects, incidence of rash during therapy were lower with intravenous administration and in desensitization protocols with >6 doses escalation when compared with those with <6 doses escalation (0% versus 2.6% [1.9%–3.2%] versus 2.6% [1.1%–4.6%]). The latter was the only reporting a significant incidence of angioedema (3.4% [0.6%–6.3%]), which did not occur with intravenous and with >6 doses escalation desensitization protocols (Figures 2 and 3).

The only study not reporting detailed protocols showed similar rates of adverse events during desensitization, although with a slight tendency to be higher.³⁴

Exclusion of the only study in which patients were pre-treated with antihistamines did not change the significance of the results (data not shown).

Survey Results

We collected 86 answers. Clinical cardiologists slightly outnumbered interventional cardiologists. Most of them were

male, middle aged, from United States or Europe. A total of 94% of physicians interviewed indicated that the prevalence of aspirin hypersensitivity is <10% and that urticaria is the most common adverse reaction for 72% of them, followed by asthmatic type reaction and angioedema.

Surprisingly, 56% of respondents still manage aspirin hypersensitivity by changing the therapeutic regimen and not proceeding to desensitization. The desensitization protocols are adopted only by 42% of cardiologists. Figure 4 shows the different therapeutic strategies proposed as alternatives to aspirin by the respondents. The most common alternative therapeutic strategy is the monotherapy with clopidogrel. Therapy with indobufen (ibustrin) is also a common alternative, and 22% of physicians interviewed used this alternative in patients with aspirin hypersensitivity. Prasugrel and ticagrelor are increasing becoming more prevalent as alternative treatment regimens, particularly in patients with ACS.

The majority of cardiologists who adopt a desensitization protocol uses an oral scheme, starting with an initial dose ranging between 0.1 and 1 mg and increasing every 30 minutes until a final dose between 75 and 100 mg.

Most of them perform the desensitization protocol in the intensive care unit (38%) or in a cardiology ward and day hospital (27% each). Only 2% perform the desensitization in an allergology ward but 47% consults an allergologist before the start of a desensitization protocol.

Desensitization is safe and effective because most of the surveyed doctors reported with a prevalence of anaphylaxis close to 1% and a failure of the protocol in <20% of cases. The

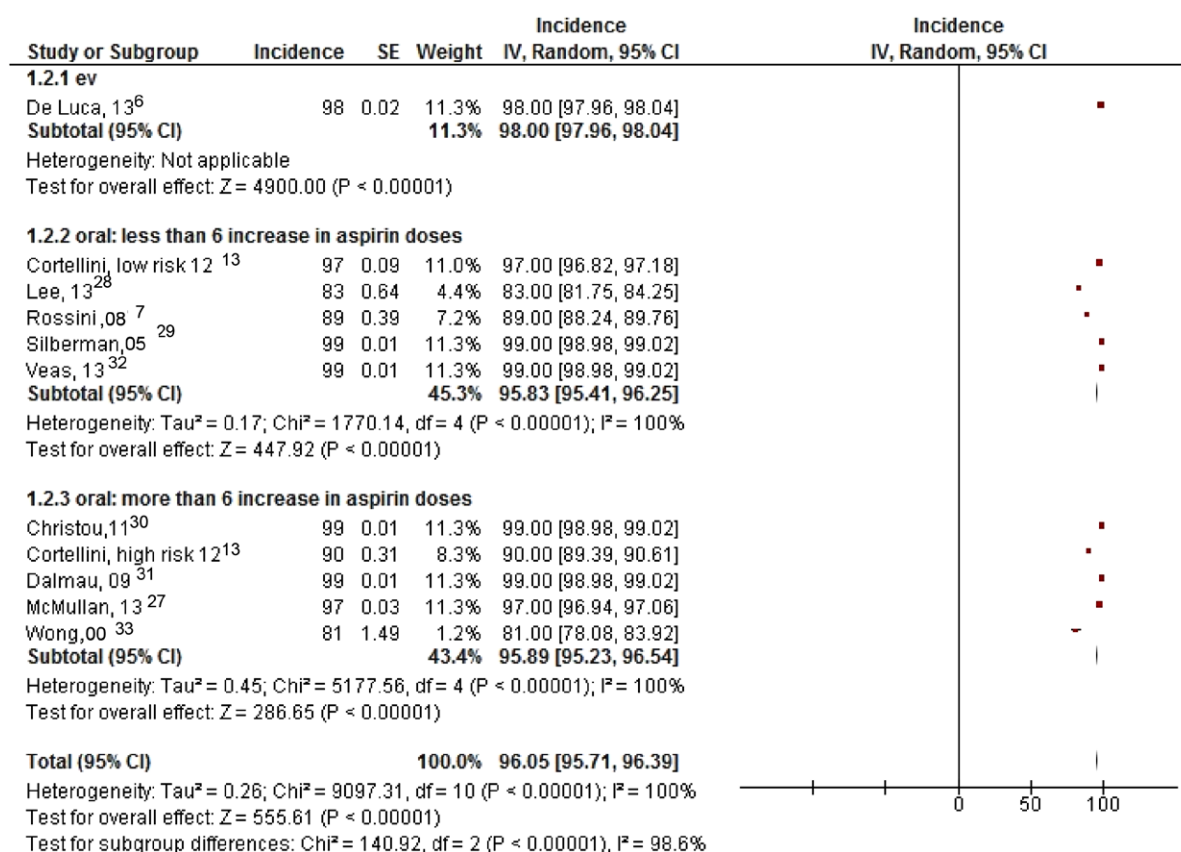


Figure 1. Discharge from hospital with aspirin. CI indicates confidence interval.

Table 1. Main Features of Included Studies

	No. of Patients	Design	Region	Doses, mg	Time, h	Other Drugs Before
Endovenous						
De Luca et al ⁶	43	Prospective	Europe	1, 2, 4, 8, 16, 32, 64, 128, 250	4.5	No
Oral, with <6 increase in aspirin doses						
Cortellini et al, ¹³ low risk	31	Prospective	Europe	10, 15, 25, 20, 50	3.0	No
Lee et al ²⁸	24	Retrospective	Asia	5, 10, 20, 40, 80	3.0	No
Rossini et al ⁷	26	Prospective	Europe	1, 5, 10, 20, 40, 100	5.5	No
Silberman et al ²⁹	16	Retrospective	Europe	5, 10, 20, 40, 75	2.5	No
Veas et al ³²	4	Retrospective	South America	1, 5, 10, 20, 40, 100	5.5	No
Oral, with more than 6 increase in aspirin doses						
Christou et al ³⁰	11	Retrospective	Europe	0.1, 0.3, 10, 30, 40, 81, 162, 325	3.50	No
Cortellini et al, ¹³ high risk	31	Prospective	Europe	0.1, 1.1, 5, 2, 3, 4, 5, 10, 15, 25, 35, 50	3.50	No
Dalmau et al ³¹	5	Retrospective	Europe	0.1, 0.2, 1, 3, 10, 25, 50, 100	2.50	No
Wong et al ³³	11	Prospective	North America	0.1, 0.3, 1, 3, 10, 20, 40, 81, 162, 325	3.50	Antihistamine
McMullan and Wedner ²⁷	81	Retrospective	North America	1, 10, 20, 40, 80, 160, 325	2.0	No

most common adverse effect during desensitization protocols reported by respondents is urticaria for the 31%, followed by asthma for the 23% of interviewed.

Our last 2 questions were (1) are there scenarios where you don't use aspirin desensitization protocol? and (2) do you usually schedule patients for a specific follow-up after desensitization?. Twenty-eight percent of those surveyed do not use desensitization protocols in emergency/urgency, and 8% do not use desensitization in patients with a previous anaphylaxis. Last, >70% of cardiologists surveyed does not plan a specific follow-up for desensitized patients. For complete survey data, see the Appendix I in the Data Supplement.

Discussion

The main findings of our work are (1) literature and real-word practice agree concerning incidence of aspirin hypersensitivity reactions, (2) more than half of the respondents to our survey still manage the hypersensitivity by avoiding aspirin prescription, and (3) aspirin desensitization protocols are safe and effective.

The prevalence of aspirin hypersensitivity ranges from 0.07% to 0.2% for aspirin-induced urticaria in general population to 10% for aspirin-exacerbated respiratory tract disease in patients with asthma.^{35,36} Many patients refer in their clinical history aspirin hypersensitivity because they experienced gastric disturbance after aspirin assumption. It is important to differentiate between aspirin reactions such as gastritis, which can be easily managed with proton-pump inhibitors or other gastric protectors and true aspirin hypersensitivity. The latter is usually a COX-1-mediated reaction causing an increase in leukotriene production that increases eosinophil chemotaxis, vascular permeability, bronchoconstriction, and it has a cross-reactivity with other NSAIDs. More rarely, aspirin hypersensitivity is sustained by an IgE-mediated reaction and in this case cross-reactivity with other NSAID is less common.³⁷ The clinical manifestations can be divided into: skin reactions (urticaria and angioedema), upper and lower respiratory tract reactions (rhinitis and asthma), and anaphylaxis and should be managed with aspirin desensitization or avoiding aspirin administration.³⁸

The diagnosis of aspirin hypersensitivity is often based on the patient's history and this is particularly true in urgency/emergency setting such as ACS where an oral aspirin challenge is not time effective and not safe for the patients. The cardiologist should quickly decide how to manage a patient with aspirin hypersensitivity history and the 2 options are nowadays represented by aspirin desensitization or an alternative drugs regimen. Our survey showed that the majority of physicians prefer using alternative medications or clopidogrel alone in cases of aspirin hypersensitivity. This choice, in particular in ACS subsets, is not supported by data and in case of monotherapy with clopidogrel (normal or double dose) prasugrel or ticagrelor alone could lead to stent thrombosis, early reinfraction or bleedings.^{39,40} To the best of our knowledge, only 2 studies evaluated alternative therapeutic regimens (indobufen, trapidil, and trifusal) in patients with aspirin hypersensitivity

Table 2. Baseline Features of Included Patients (Results Are Reported as Median or Percentages With First and Third Quartiles)

	11 studies, 283 patients
	Value*
Prevalence of aspirin allergy (%)	2.0 (1.2–2.7)
Age (y)	67.0 (62.0–68.0)
Female (%)	31.0 (25.0–39.0)
Hypertension (%)	69.0 (67.0–70.0)
Diabetes mellitus (%)	22.0 (20.0–24.0)
Hypercholesterolemia (%)	60.0 (52.0–68.0)
Indication for PCI (%)	
Stable angina	44.0 (39.0–47.0)
Acute coronary syndrome	55.0 (54.0–60.0)
Symptoms of hypersensitivity (%)	
Angioedema	82.0 (63.0–90.0)
Rash	10.0 (5.0–12.0)
Asthma	10.0 (7.0–13.0)

PCI indicates percutaneous coronary intervention.

*Variables are reported as median or percentages with first and third quartiles.

Table 3. Procedural Features

	11 studies, 283 patients
	Value*
Bare metal stents (%)	5.0 (3.0–7.0)
Drug-eluting stents (%)	95.0 (87.0–98.0)
Length of stent (mm)	29.0 (28.0–30.0)
No. of treated vessels	1.5 (1.0–1.7)
No. of treated lesions	1.0 (1.0–1.4)

*Variables are reported as median or percentages with first and third quartiles.

for a total of 147 patients enrolled.^{41,42} The study from Barilla et al⁴⁰ is the only randomized controlled trial comparing indobufen (100 mg/twice a day) with clopidogrel monotherapy (75 mg/d) and showed superiority of clopidogrel plus indobufen therapy but is limited by a small sample size (n=42).

Intravenous desensitization protocols demonstrated a lower rate of adverse reactions. We hypothesized that this is because of a more stable plasmatic level of aspirin if compared with oral administration. The latter is subjected to gastrointestinal absorption, which could lead to unpredictable plasmatic concentration of aspirin and to a less effective desensitization. Ticagrelor monotherapy after 1 month from coronary stenting is under investigation in the GLOBAL-LEADER trial (DAPT interruption after 1 month followed by ticagrelor monotherapy for 23 months versus standard DAPT). If the results of this trial are positive, ticagrelor monotherapy may be investigated as an alternative to DAPT in patients with aspirin hypersensitivity who undergo PCI, despite the pivotal role of aspirin in the first month and for primary prevention.

Our meta-analysis showed that aspirin desensitization is an easy, safe, and effective strategy to manage aspirin hypersensitivity. We excluded protocols that take several days to perform desensitization such as those used in patients with respiratory manifestations because they are not practical in a setting where urgent PCI and aspirin administration are needed.^{43,44} Both the survey and the meta-analysis confirmed the desensitization's effectiveness with a low percentage of failure. The studies evaluated reported increased failure in patients with chronic idiopathic urticaria.^{7,35,36} The incidence of collateral effects is low and only the faster protocol has an increased rate of angioedema, so we can confirm safety of aspirin desensitization. Despite these data, it is preferable to perform desensitization in a setting such as an intensive care unit to quickly manage adverse reaction. The consultation of an immunologist specialist, as highlighted by the survey, in our opinion, could be useful to set up a desensitization protocol at the beginning but it is not routinely needed. A specific follow-up is not needed but it is important to remember that patients do not interrupt aspirin therapy for >5 days. On the contrary, a new desensitization might be needed.^{35,36}

Limitations

With any meta-analysis, our study is subject to the limitations and the design of the selected studies. The main limitations of our work are (1) no randomized design of the included trials, (2) small number of patients per study, (3) extreme heterogeneity in desensitization protocols, and (4) small number of answers in the survey. These results

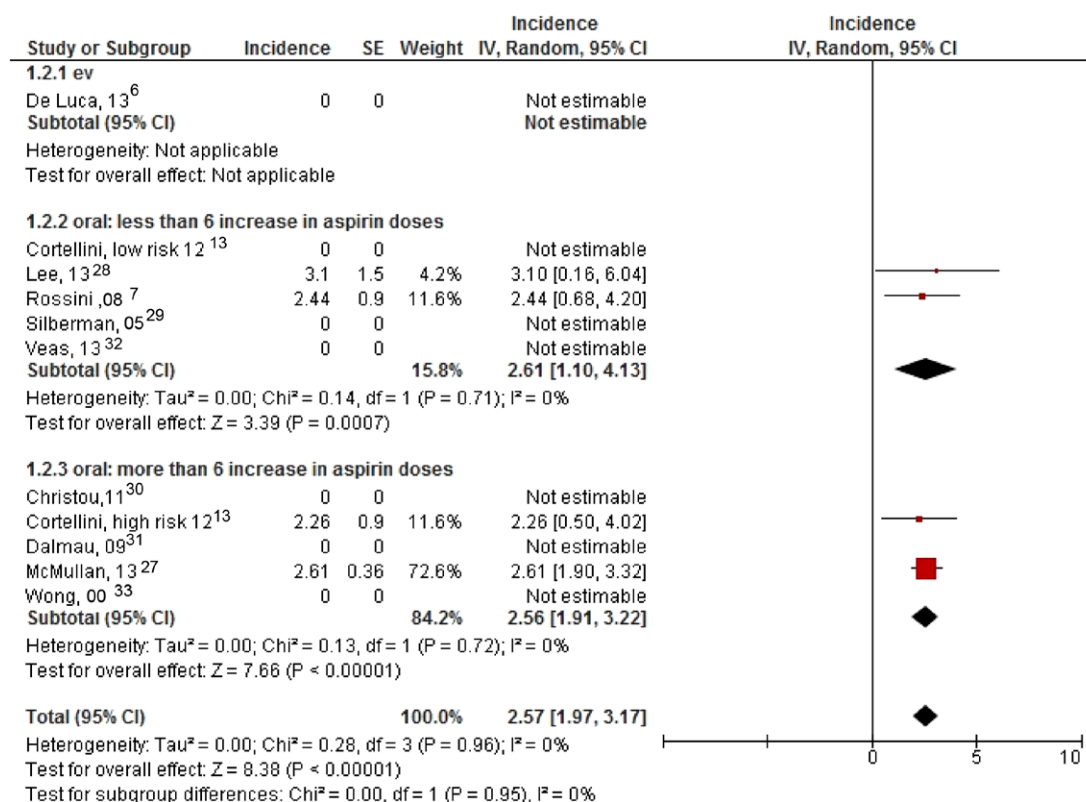


Figure 2. Rate of rash during protocols. CI indicates confidence interval.

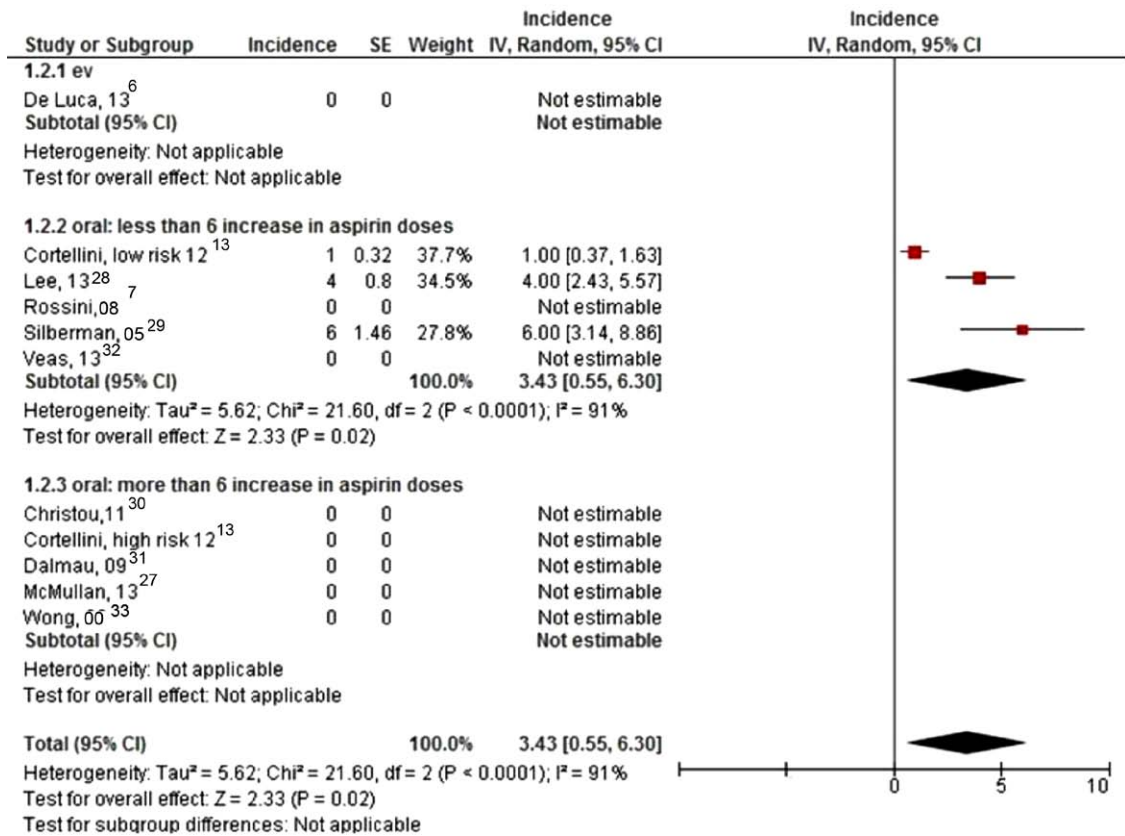


Figure 3. Rate of angioedema during protocols. CI indicates confidence interval.

should not be used to drive inferential data, because no direct comparison between different protocols have been made, but simply aim to provide physicians a rate of success or complications according to different speed of aspirin desensitization.

Conclusions

Aspirin hypersensitivity is still a problem in coronary artery disease patients who undergo a PCI with stent implantation.

For these patients, aspirin is a life-saving medication. Alternative therapeutic regimens are supported by little data. Desensitization protocols have been demonstrated to be safe and effective and allow cardiologists to use DAPT, which is the evidence-based strategy. Desensitization should be the strategy to adopt in case of coronary artery disease and concomitant aspirin hypersensitivity although randomized controlled trials should be performed to confirm the findings of our meta-analysis.

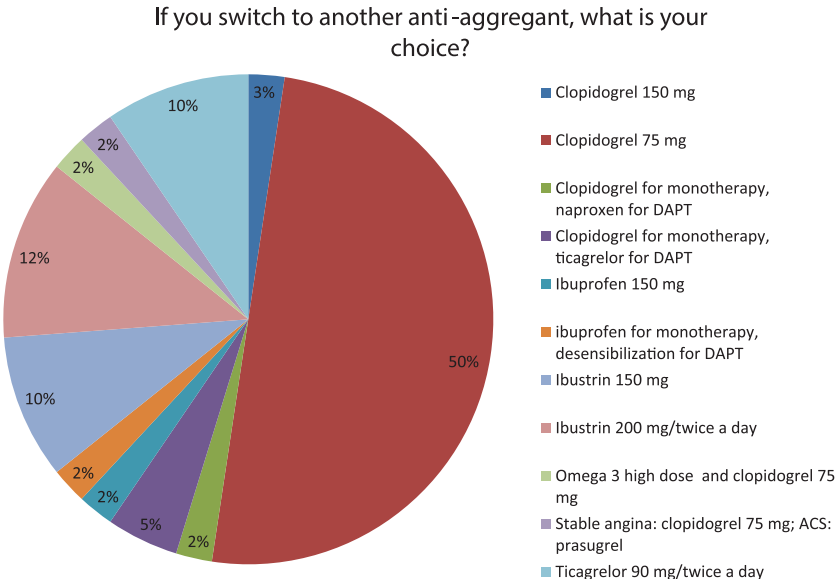


Figure 4. Alternative antiplatelets therapy. DAPT indicates dual antiplatelet therapy.

Disclosures

None.

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Efficacy and Safety of Available Protocols for Aspirin Hypersensitivity for Patients Undergoing Percutaneous Coronary Intervention: A Survey and Systematic Review

Matteo Bianco, Alessandro Bernardi, Fabrizio D'Ascenzo, Enrico Cerrato, Pierluigi Omedè, Antonio Montefusco, James J. DiNicolantonio, Giuseppe Biondi Zoccai, Ferdinando Varbella, Giovanni Carini, Claudio Moretti, Roberto Pozzi and Fiorenzo Gaita

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SUPPLEMENTAL MATERIAL

Supplemental Figures and Figure Legends

1. Figure 1: studies selection
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3. Figure 3: average rate of aspirin hypersensitivity
4. Figure 4: kind of aspirin adverse reactions
5. Figure 5: aspirin hypersensitivity management
6. Figure 6: alternative anti-platelets therapy
7. Figure 7: oral anti-platelets desensitization protocol starting dose
8. Figure 8: time between dose increase in oral protocols
9. Figure 9: final aspirin dose in oral protocols
10. Figure 10: intravenous anti-platelets desensitization protocol starting dose.
11. Figure 11: time between dose increase in intravenous protocols
12. Figure 12: final aspirin dose in intravenous protocols.
13. Figure 13: Have you tried other aspirin desensitization protocol?
14. Figure 14: Where do you perform aspirin desensitization protocol?
15. Figure 15: do you consult an immunologist specialist?
16. Figure 16: prevalence of anaphylaxis crisis
17. Figure 17: protocols failure rate
18. Figure 18: Types and incidence of adverse reactions during desensitization.
19. Figure 19: are there scenarios where do you not use aspirin desensitization protocol?
20. Figure 20: do you usually schedule patients for a specific follow-up after desensitization?
21. Figure 21: age of physician interviewed
22. Figure 22: sex of physician interviewed
23. Figure 23: nationality of physician interviewed
24. Figure 24: Funnel plot

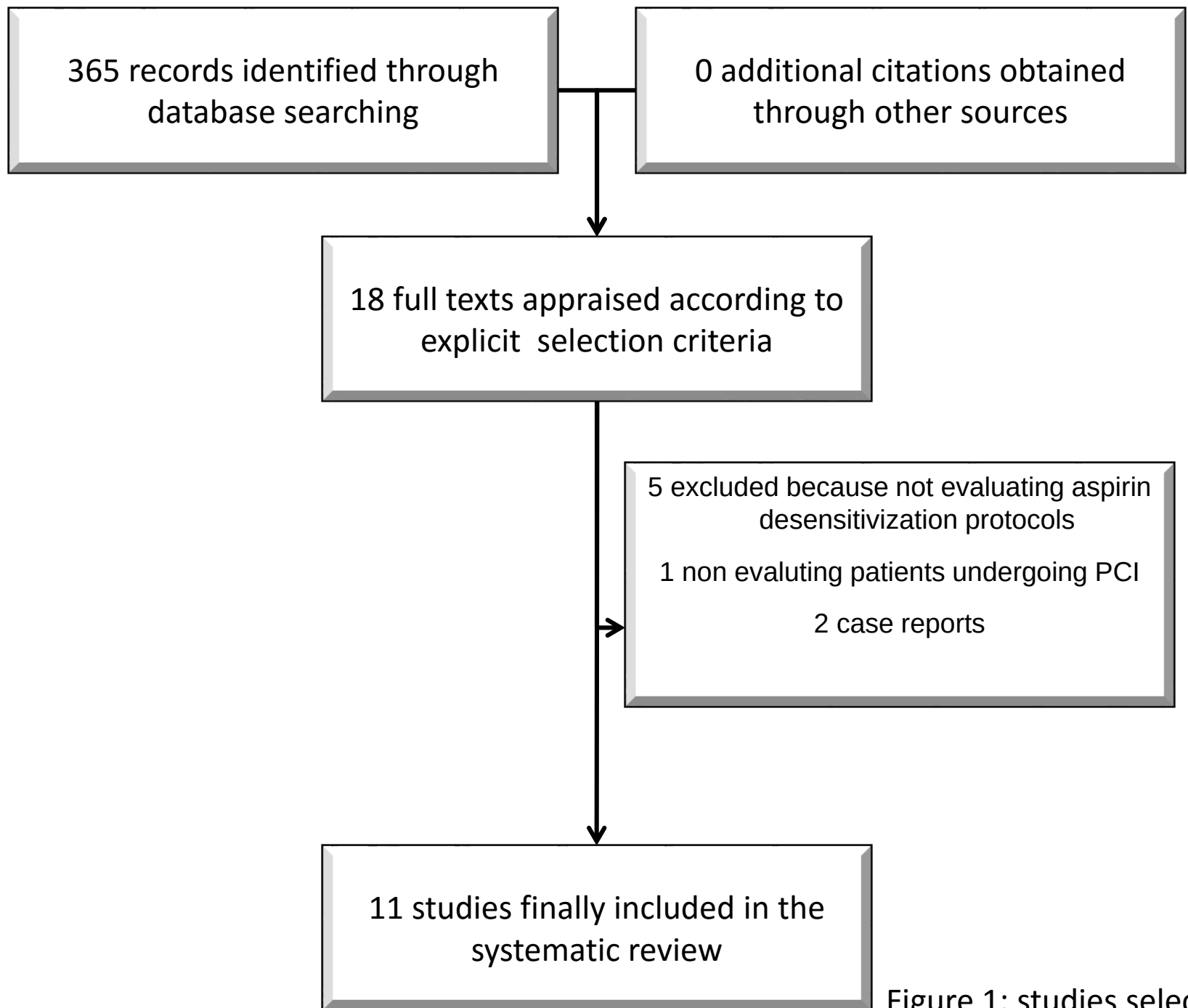
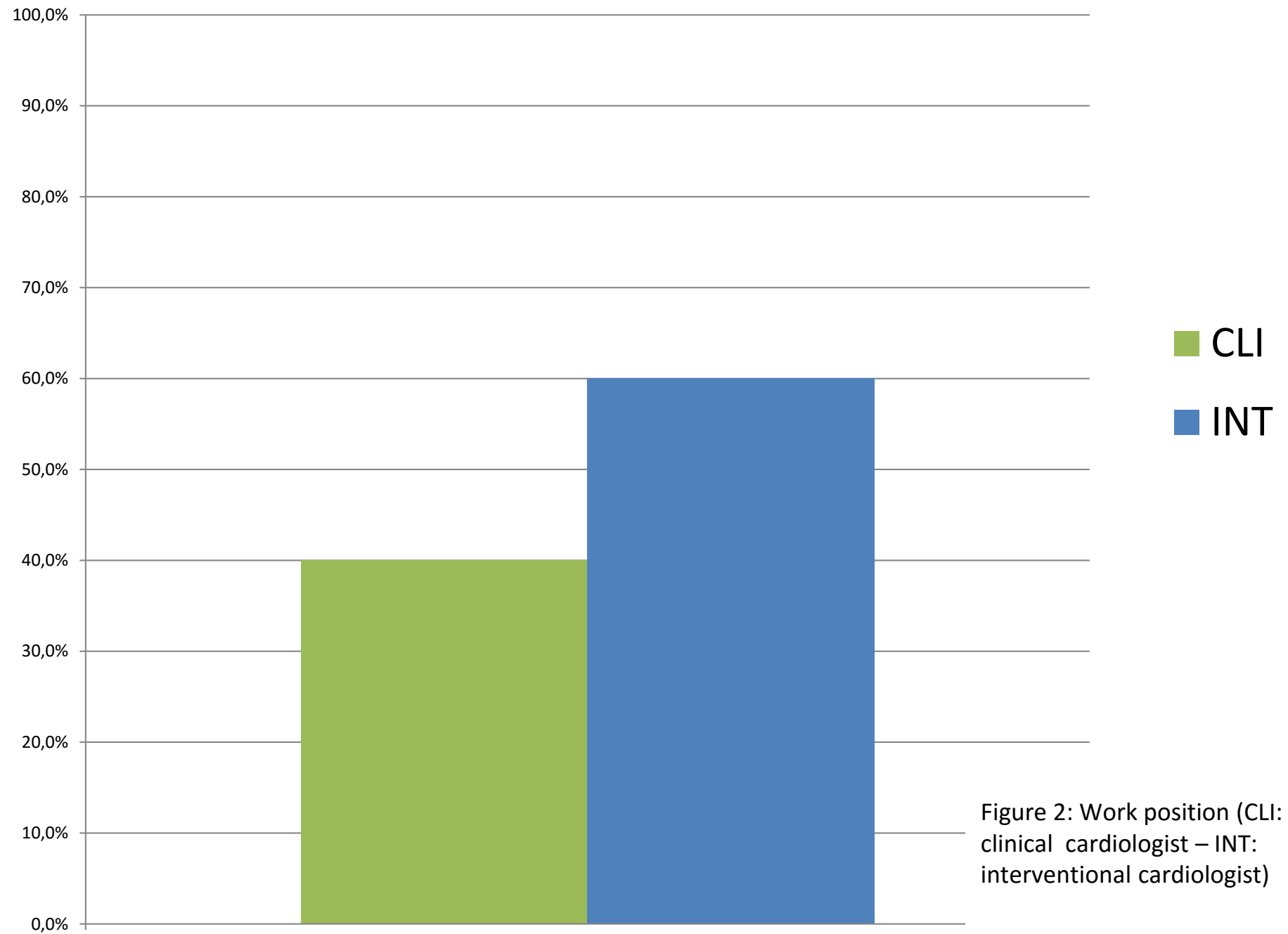
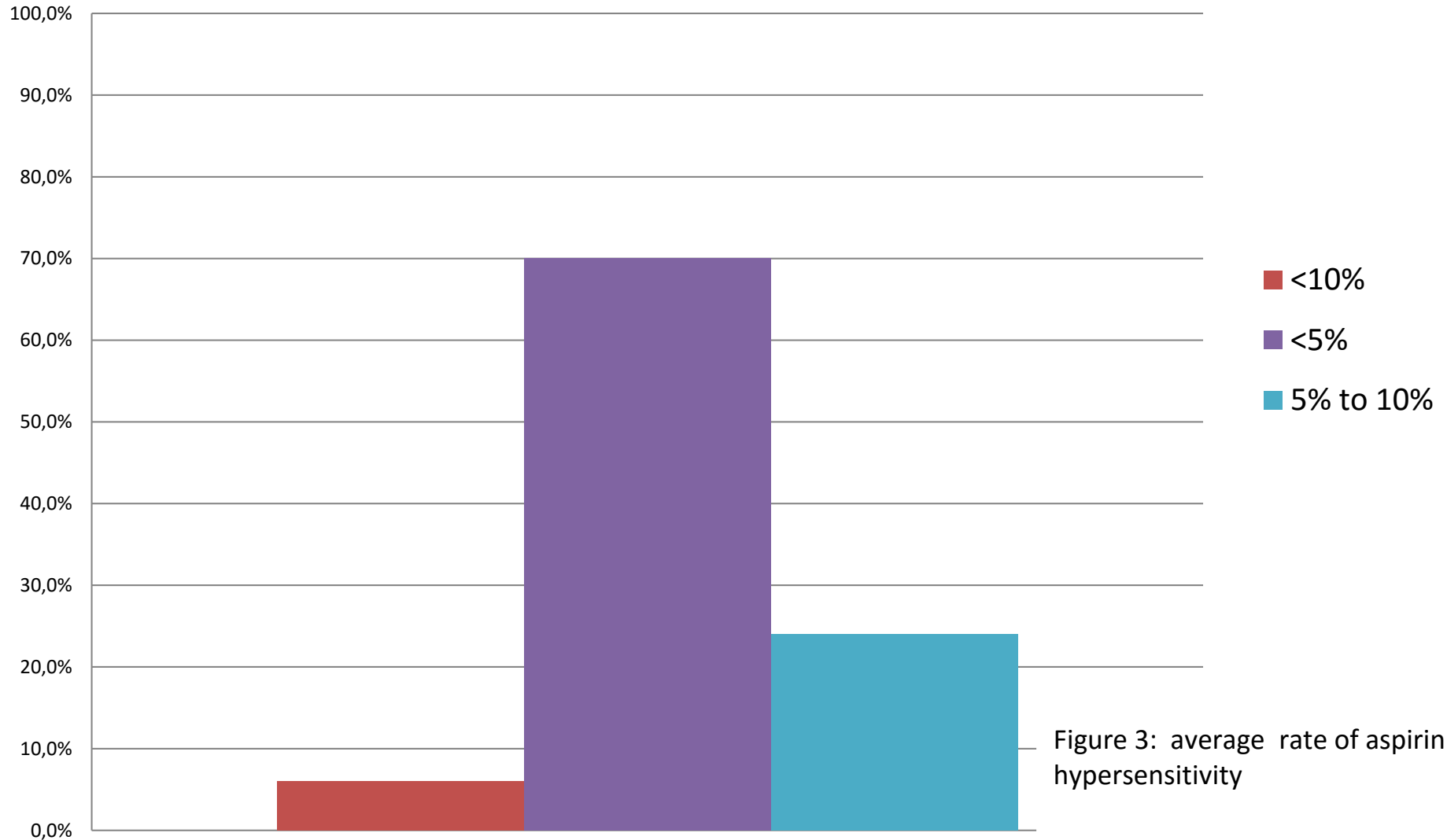


Figure 1: studies selection

Work position



According to your experience how frequent is aspirin hypersensitivity in your cath lab?



What types of reactions do you generally see:

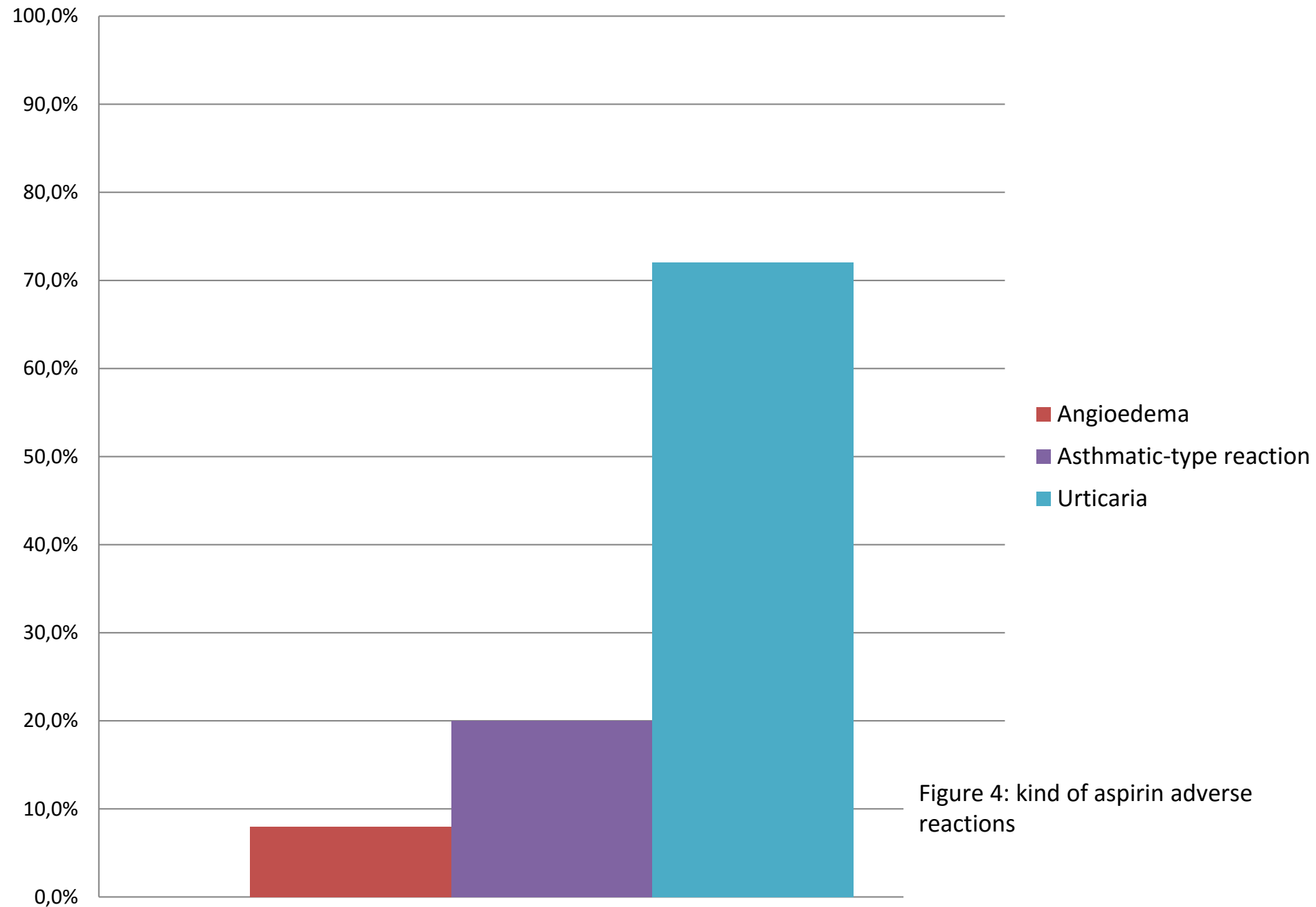


Figure 4: kind of aspirin adverse reactions

How do you commonly manage aspirin hypersensitivity?

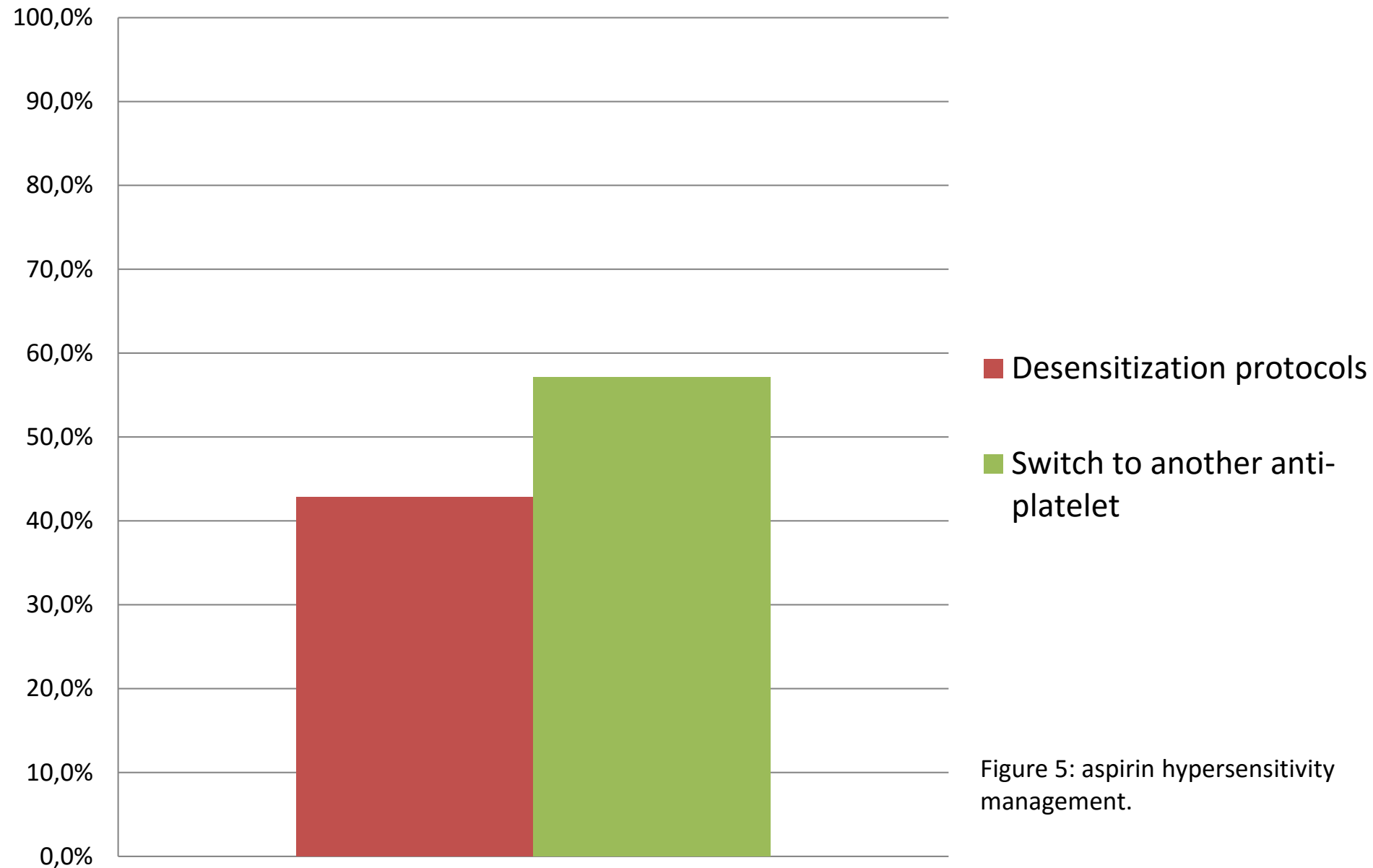


Figure 5: aspirin hypersensitivity management.

If you switch to another anti-aggregant, what is your choice?

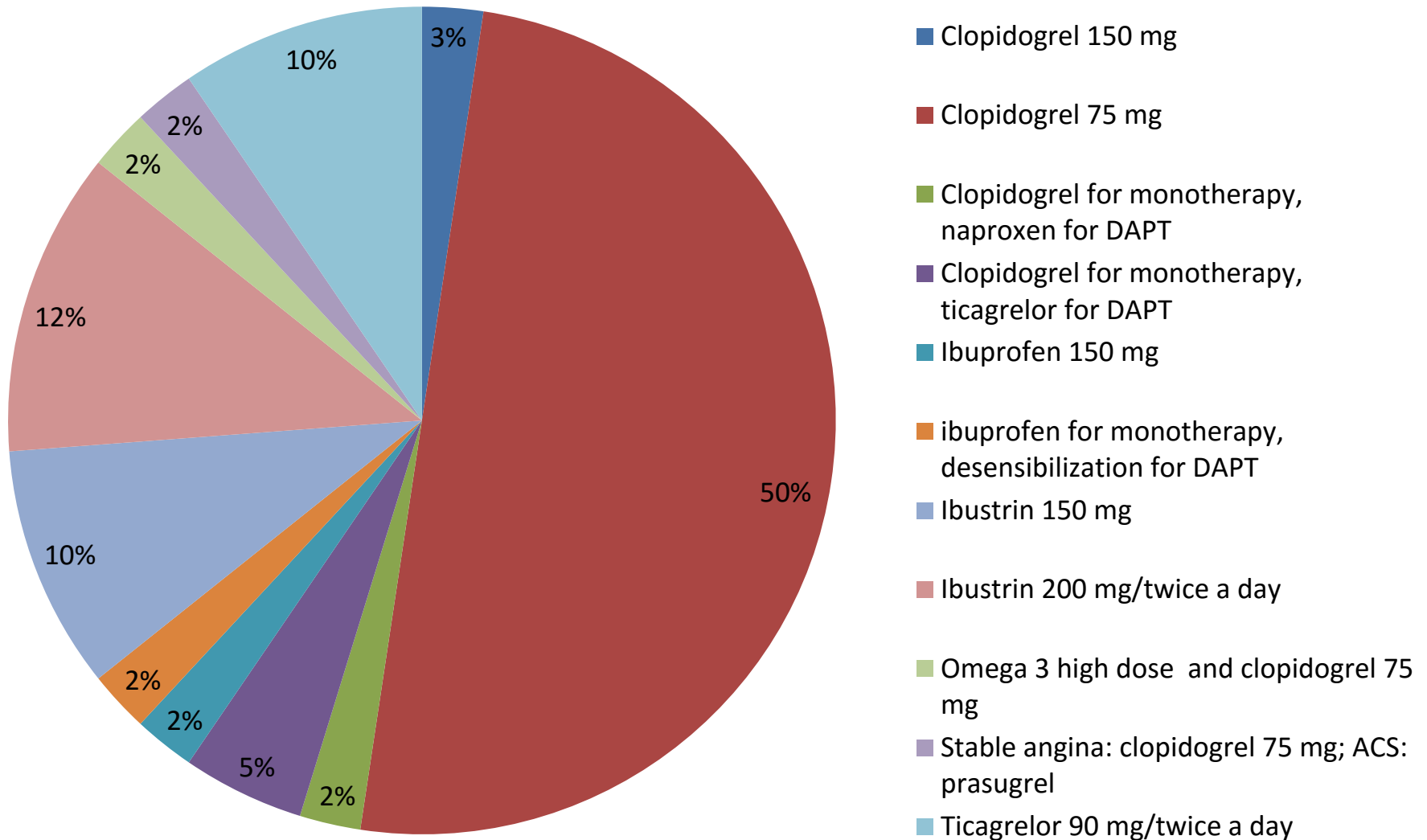
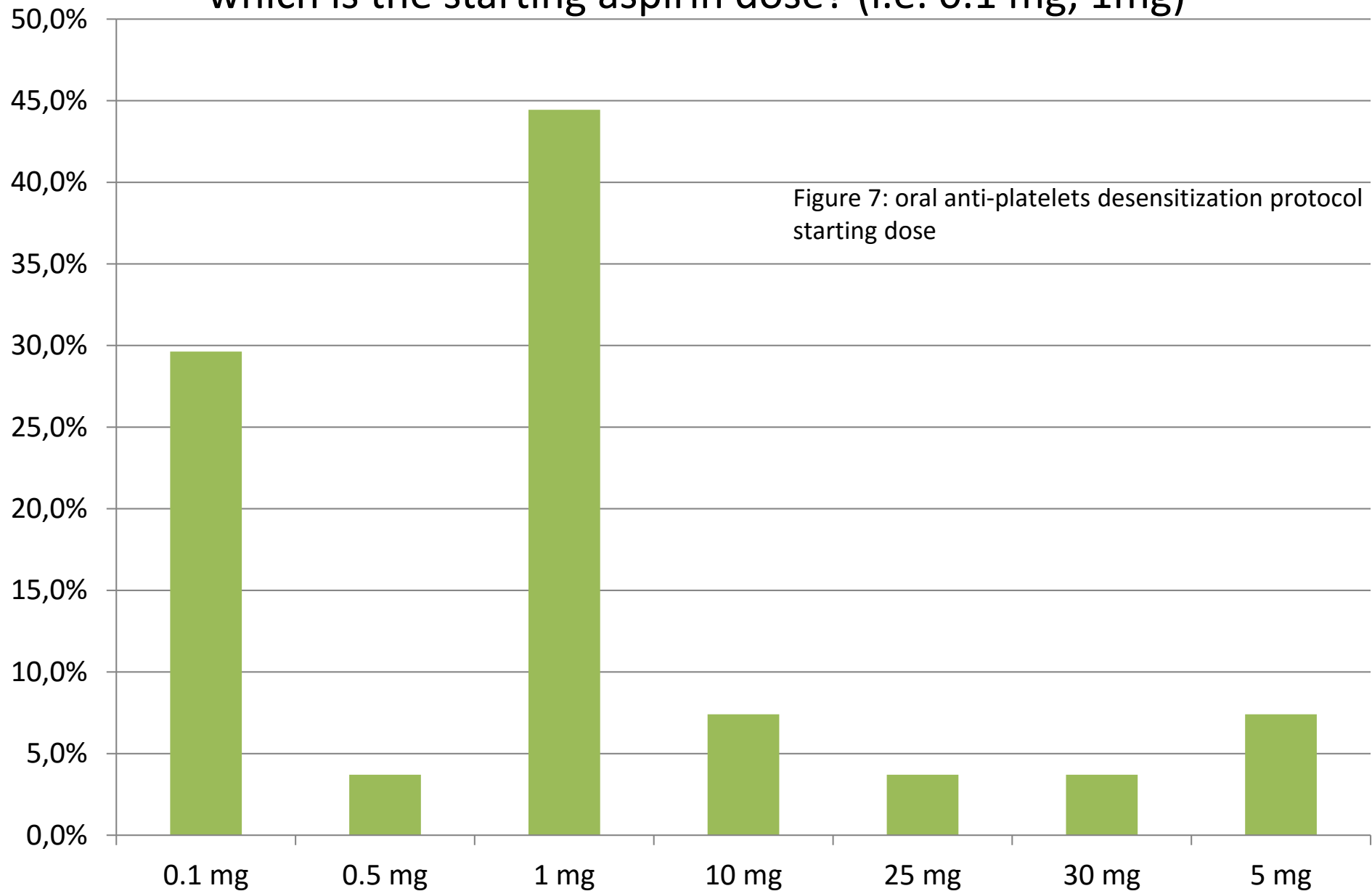
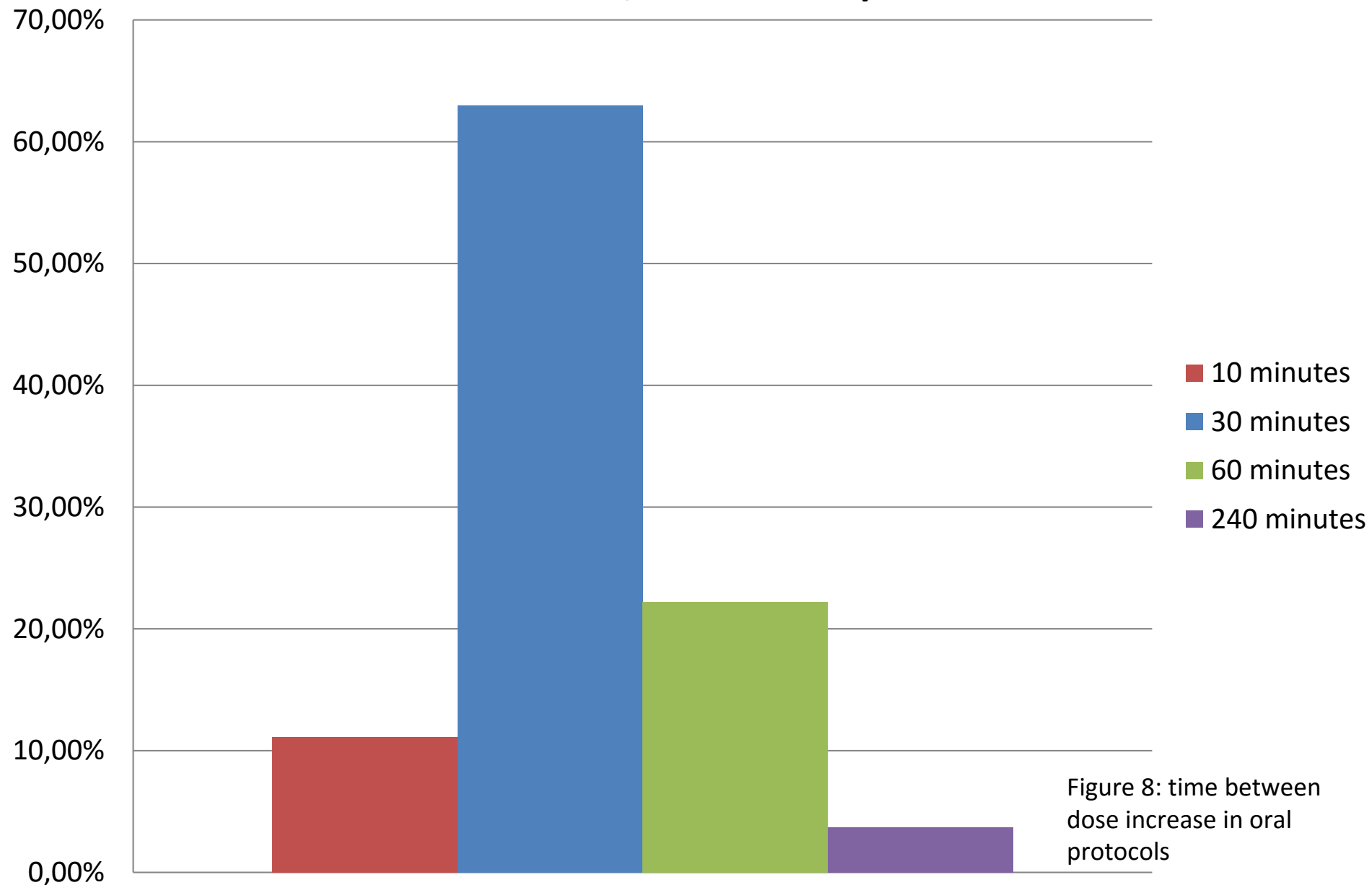


Figure 6: alternative anti-platelets therapy

In case of desensitization protocol with per os aspirin,
which is the starting aspirin dose? (i.e. 0.1 mg, 1mg)

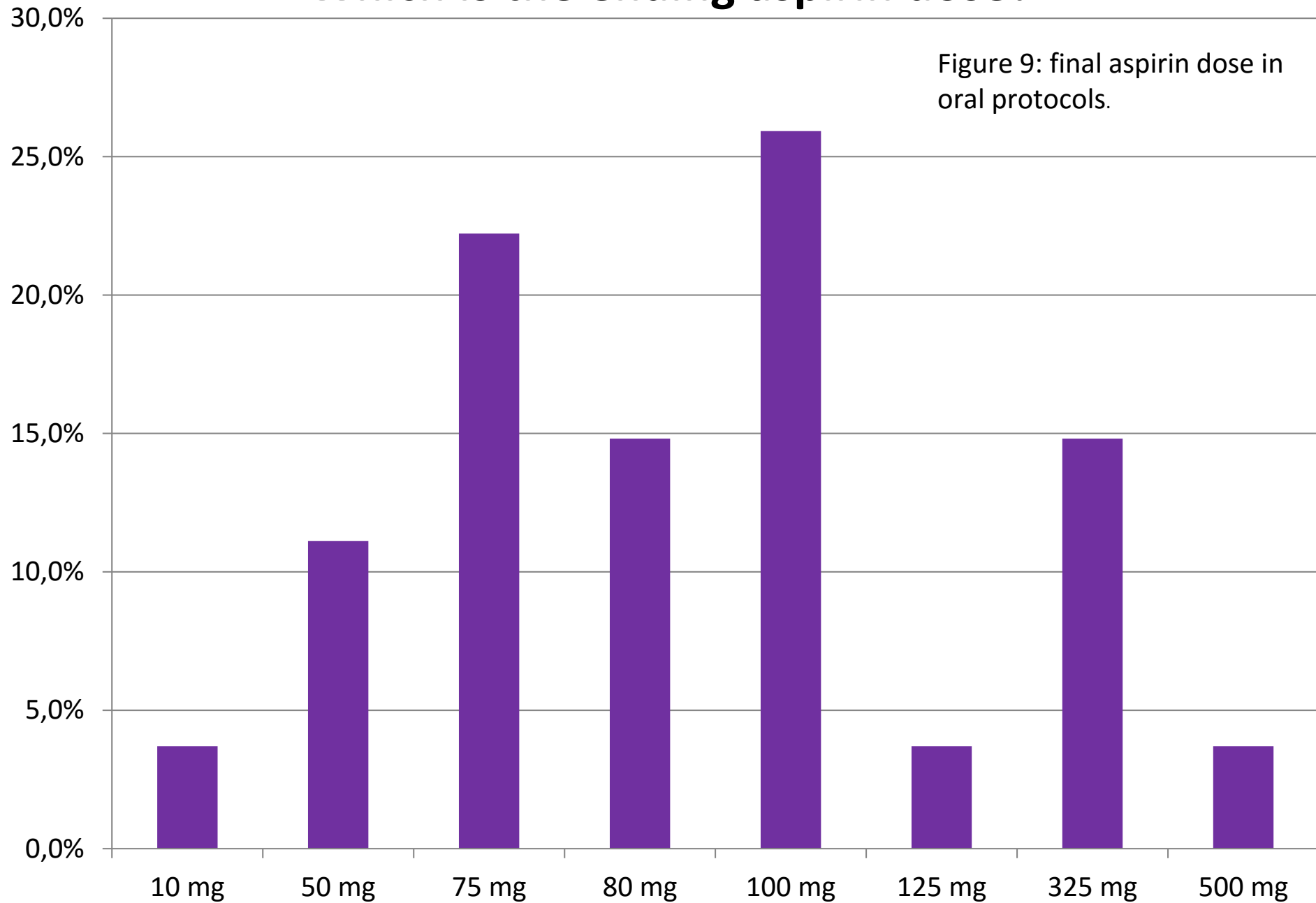


What is the interval between increase the dose (i.e. 10 minutes, 30 minutes)?

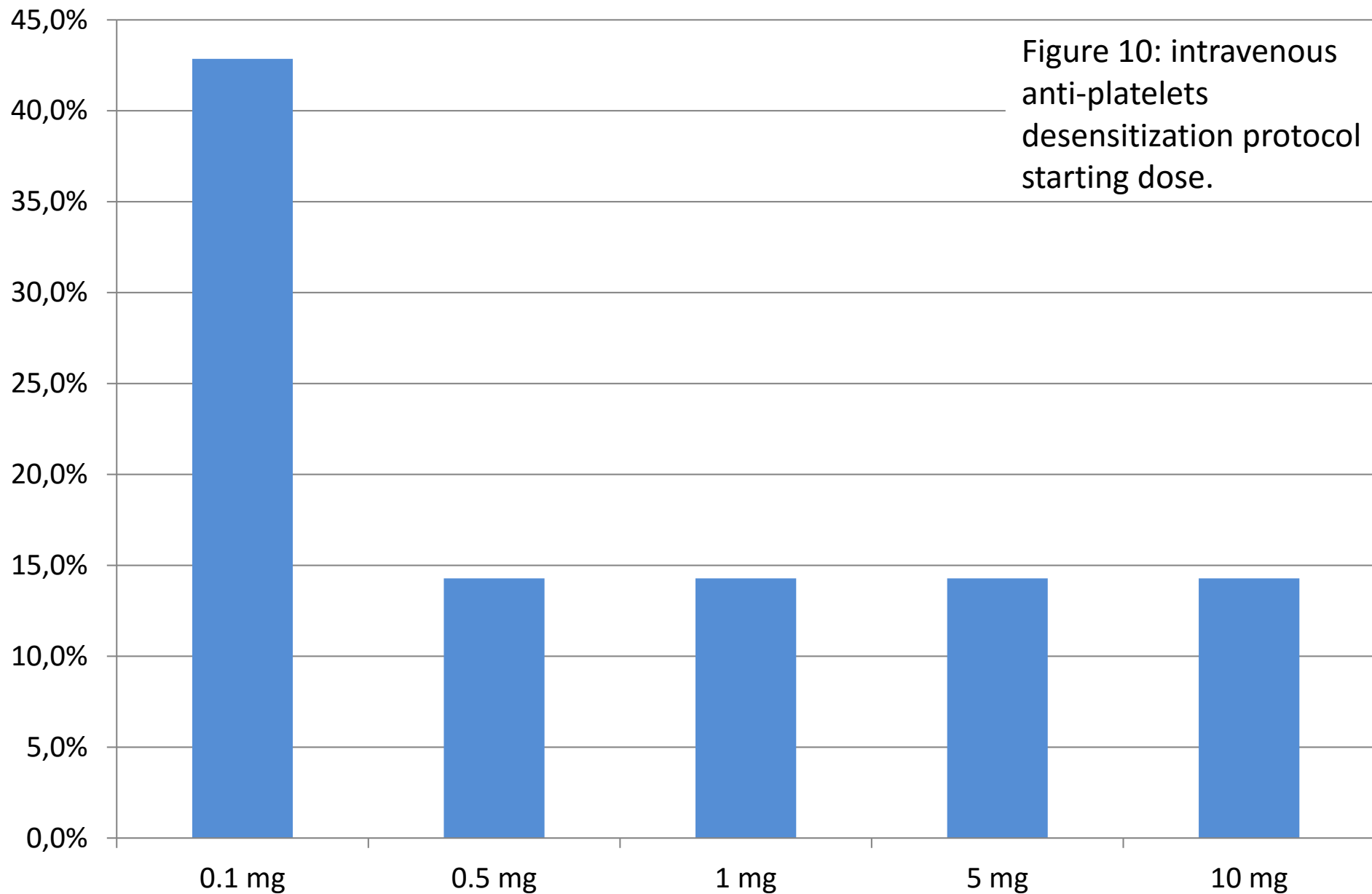


Which is the ending aspirin dose?

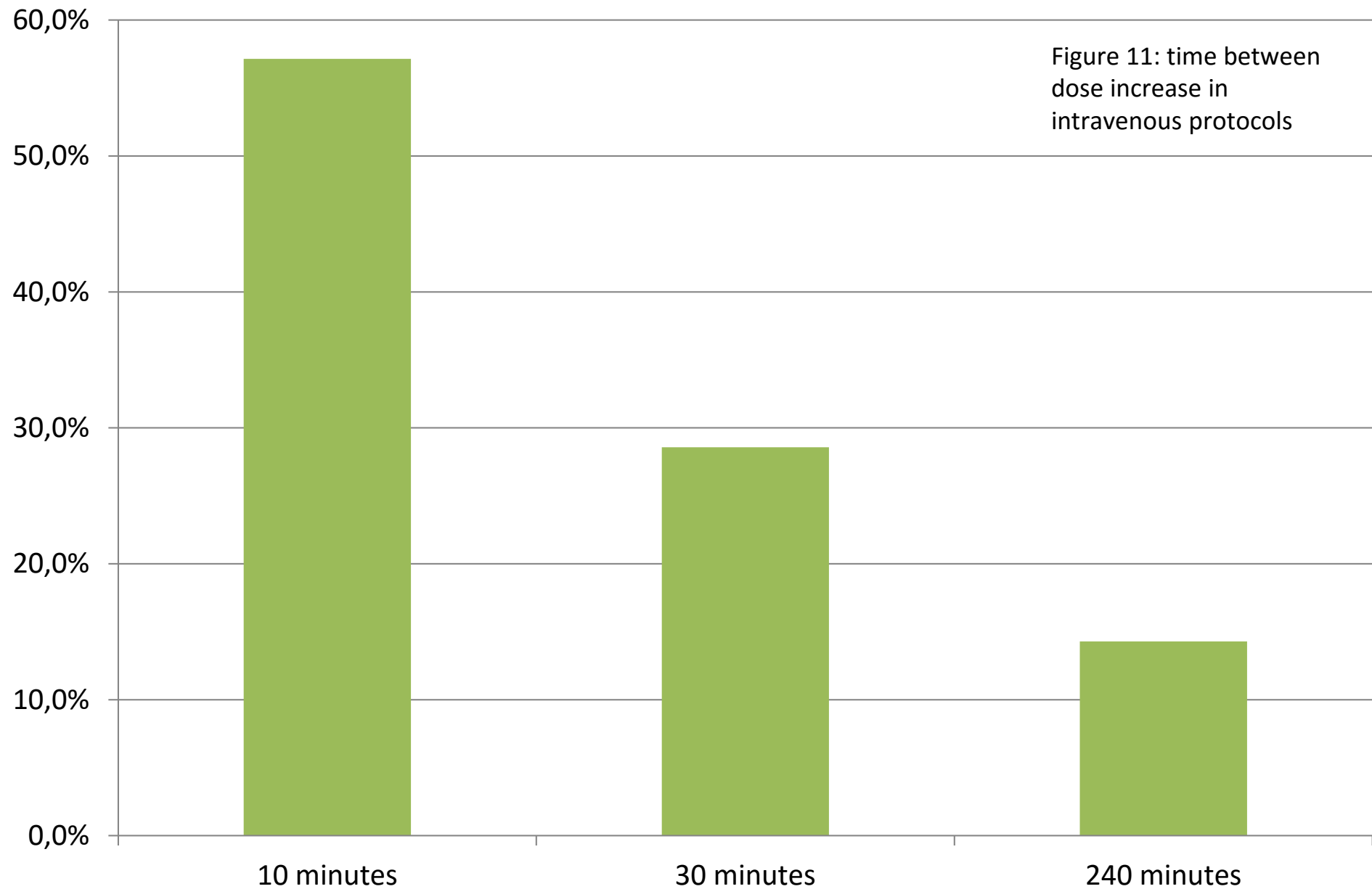
Figure 9: final aspirin dose in oral protocols.



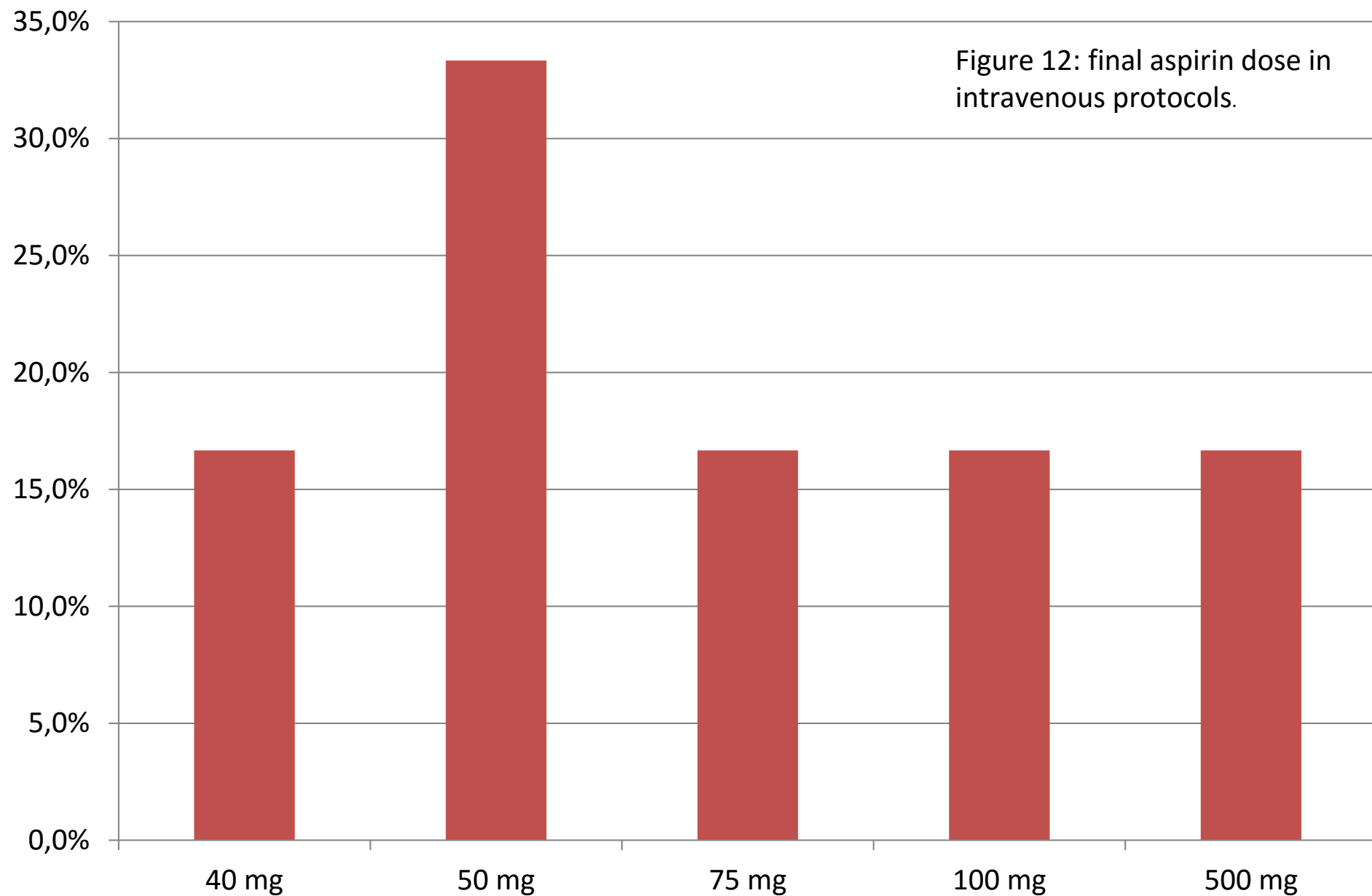
In case of desensitization protocol with endovenous aspirin, which is the starting aspirin dose?



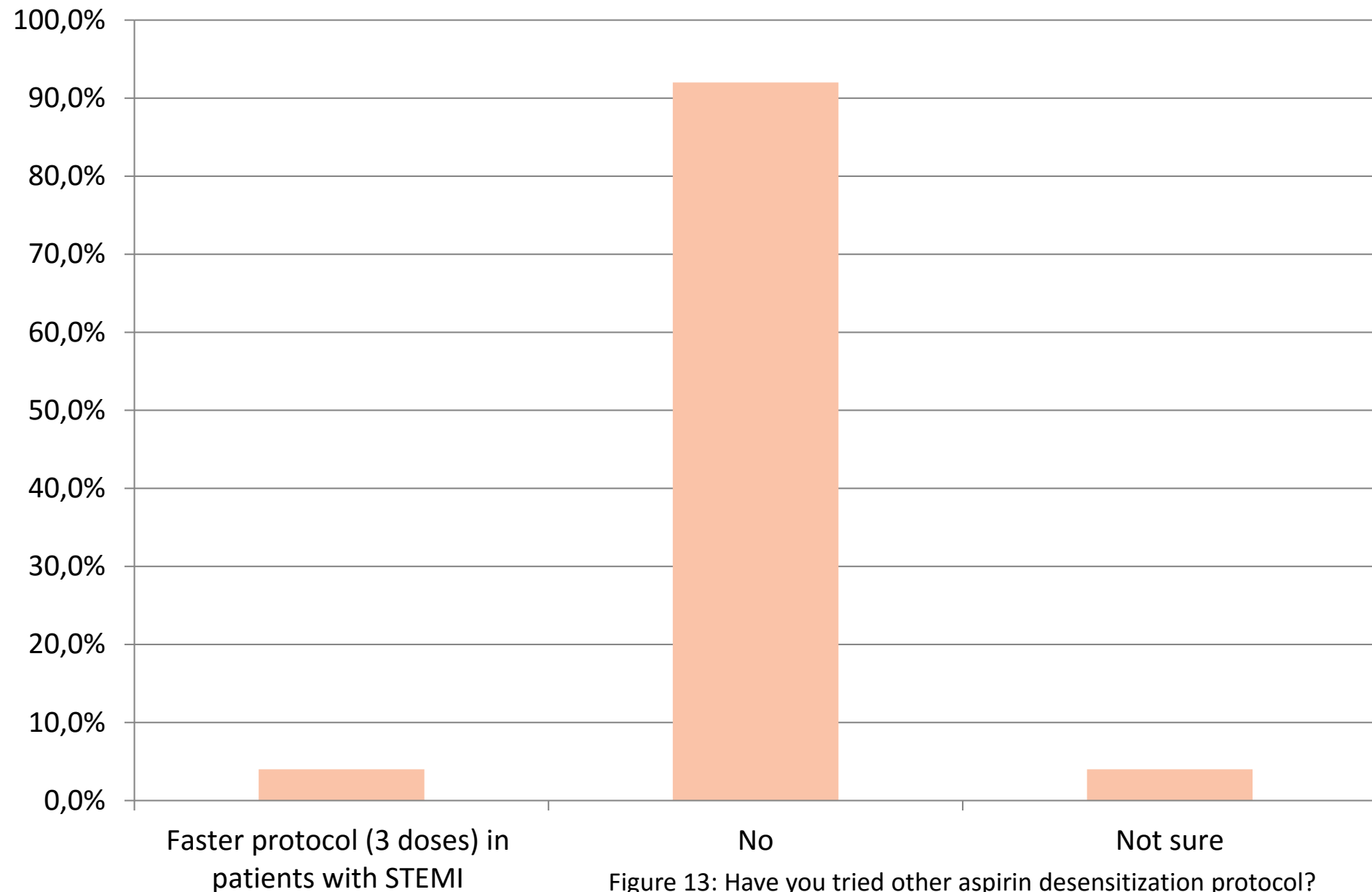
Which is the interval before increase the dose in case of endovenous desensitization?



Which is the ending aspirin dose in case of endovenous desensitization?

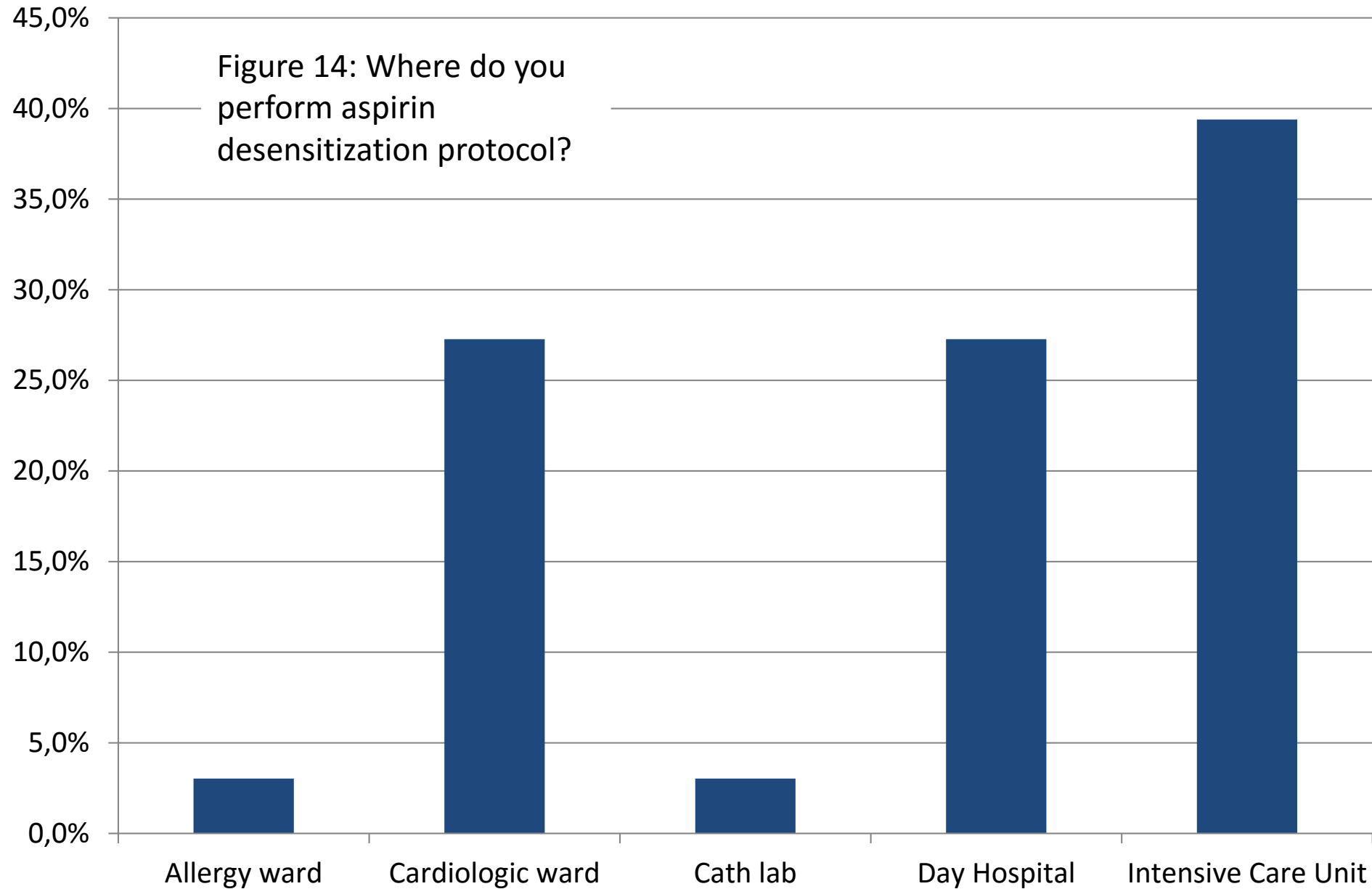


Have you tried other aspirin desensitization protocols prior to the one you use now?

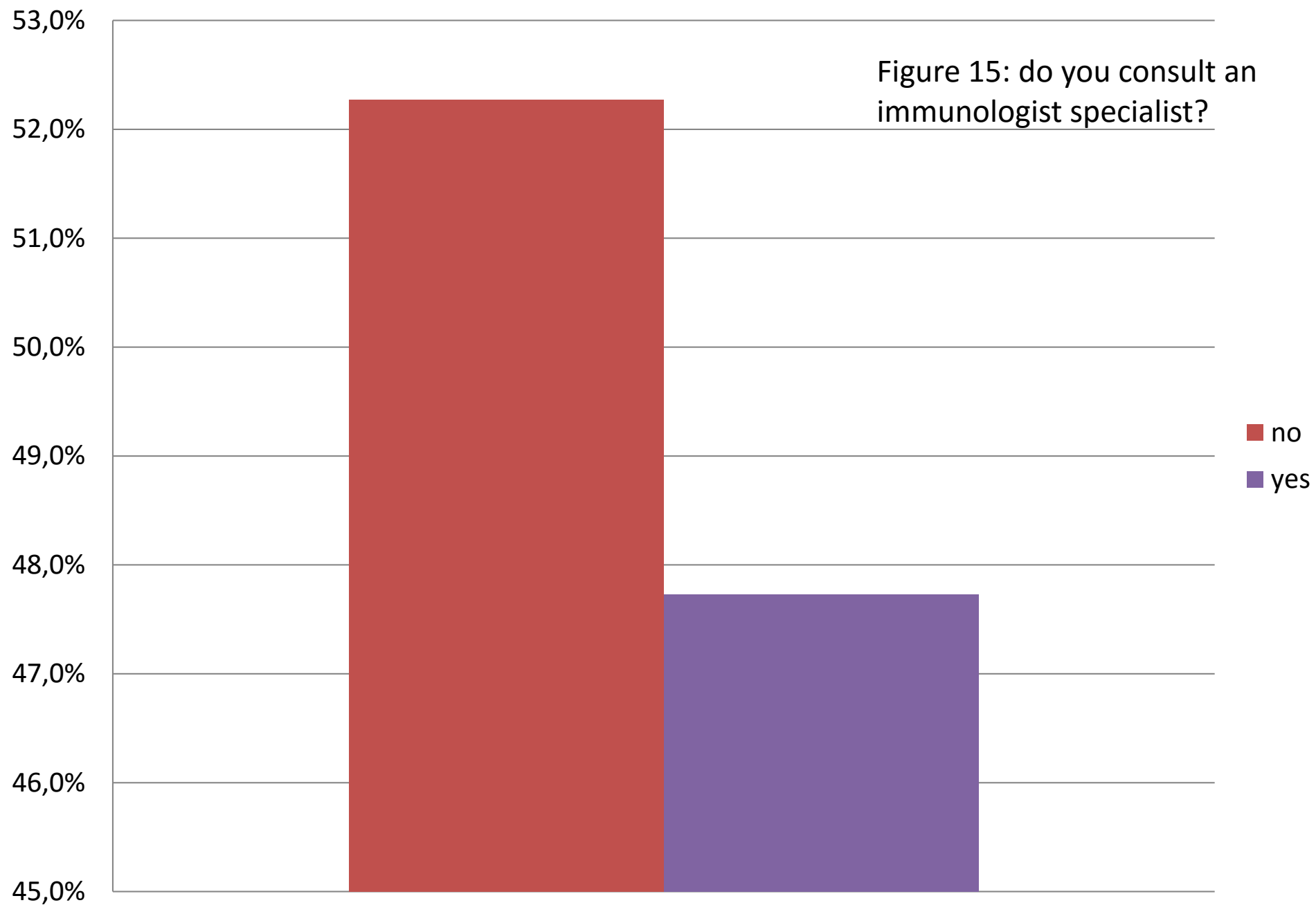


Where do you perform the aspirin desensitization protocol?

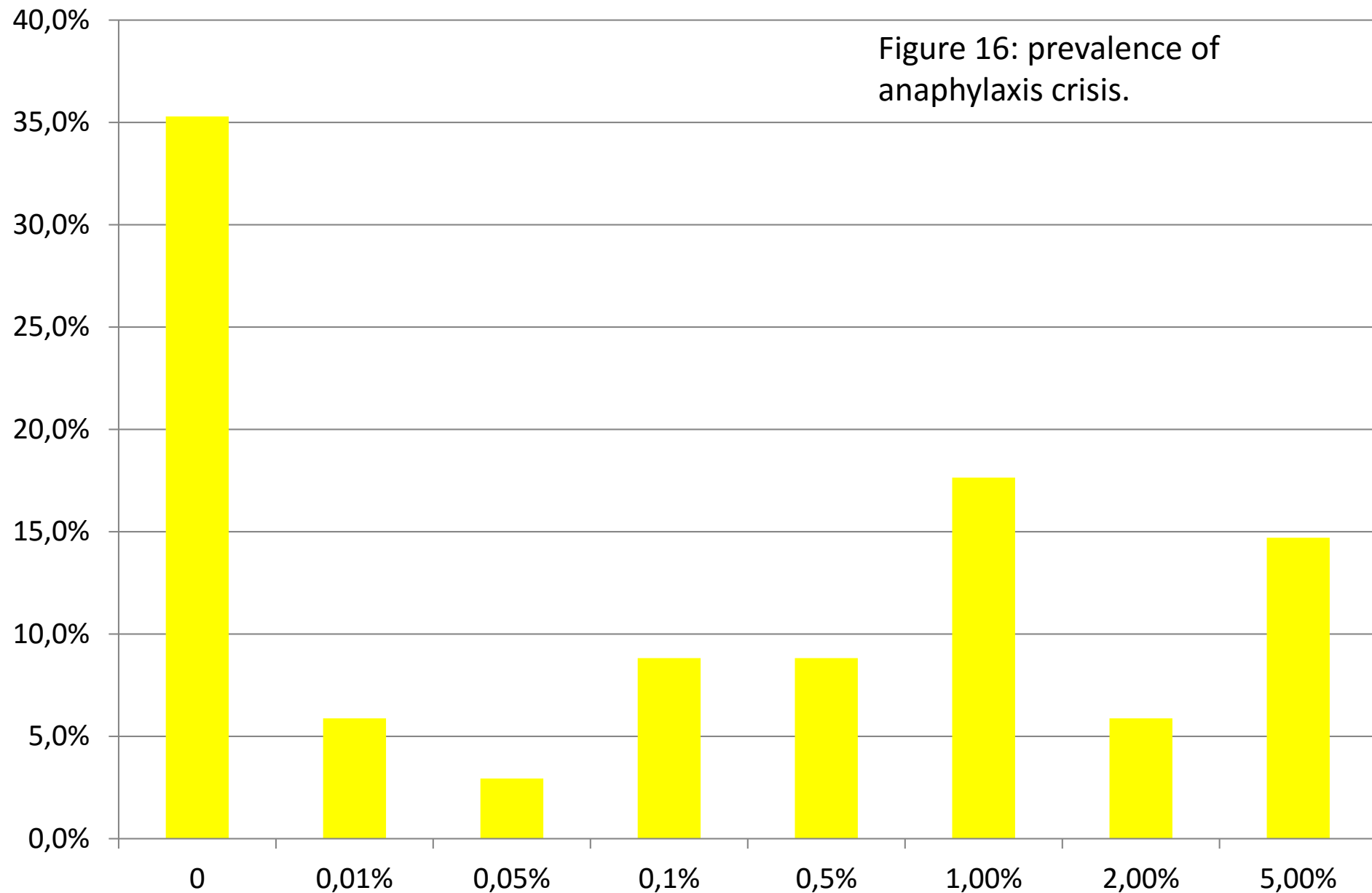
Figure 14: Where do you perform aspirin desensitization protocol?



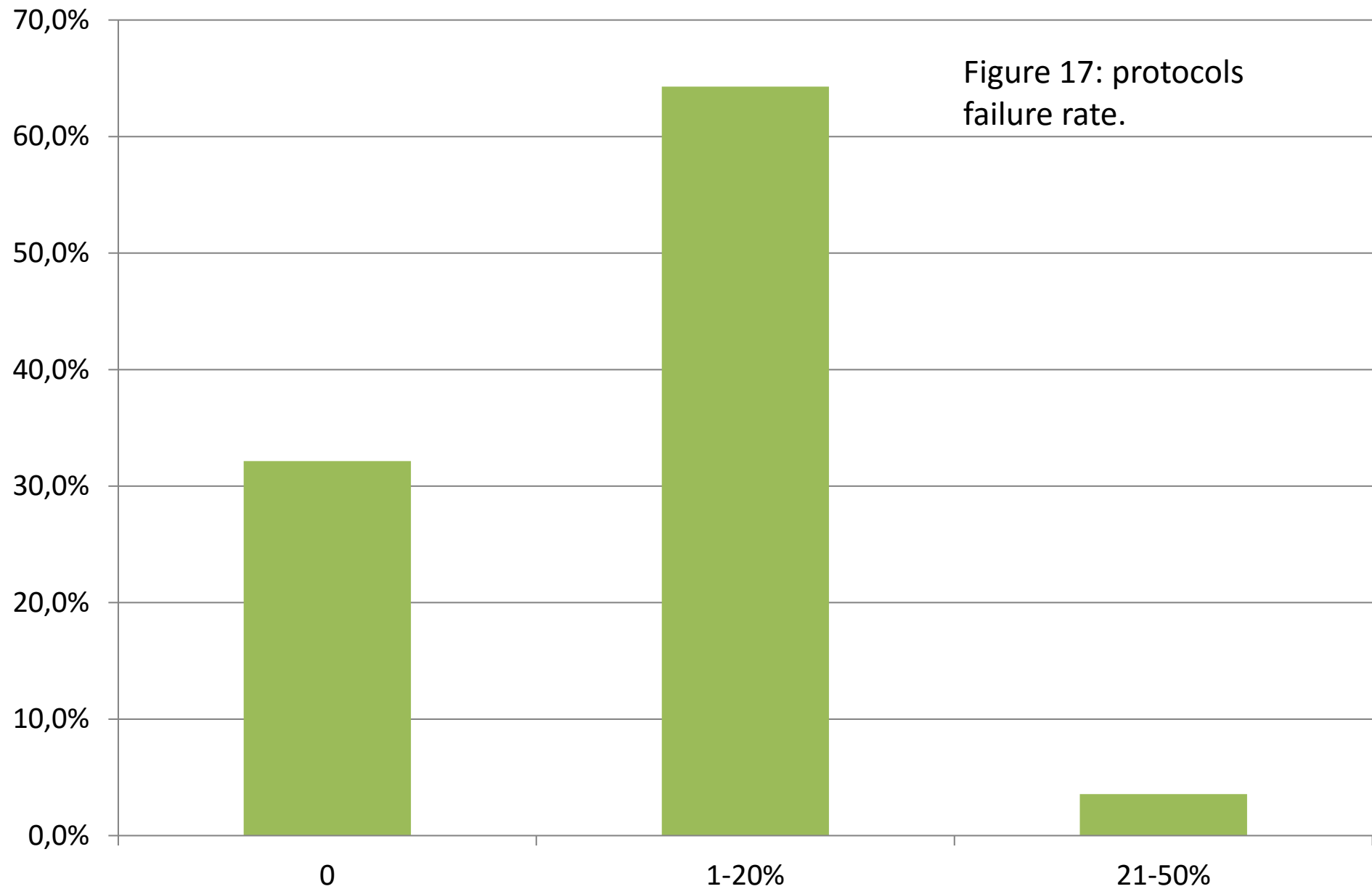
Do you consult your immunologist specialist?



What is the prevalence of anaphylaxis crisis per 100 patients?



How frequently does your protocol fail? (i.e. 2% of the time)



What are the types of reactions (and prevalence if known) that occur upon failure?

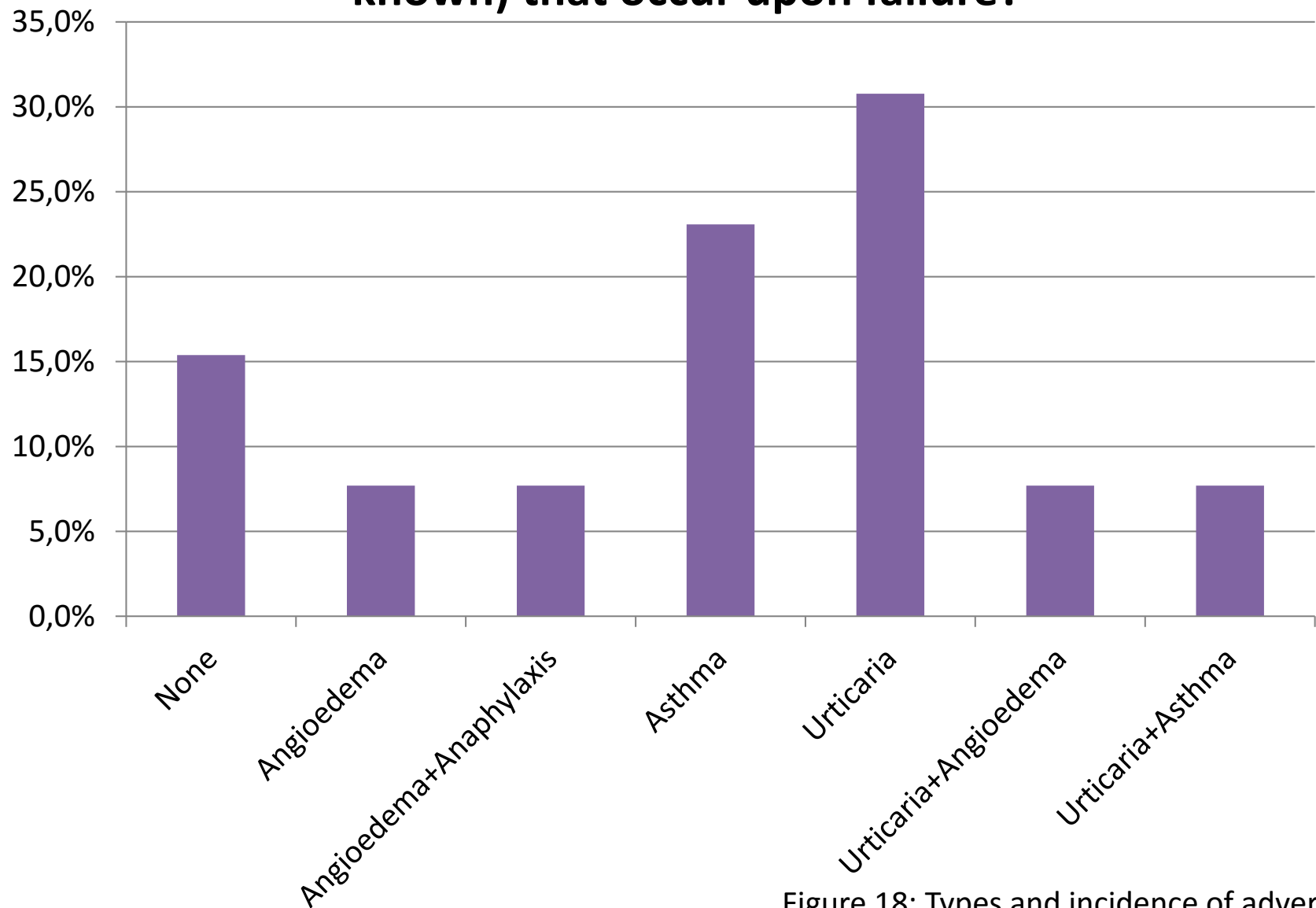
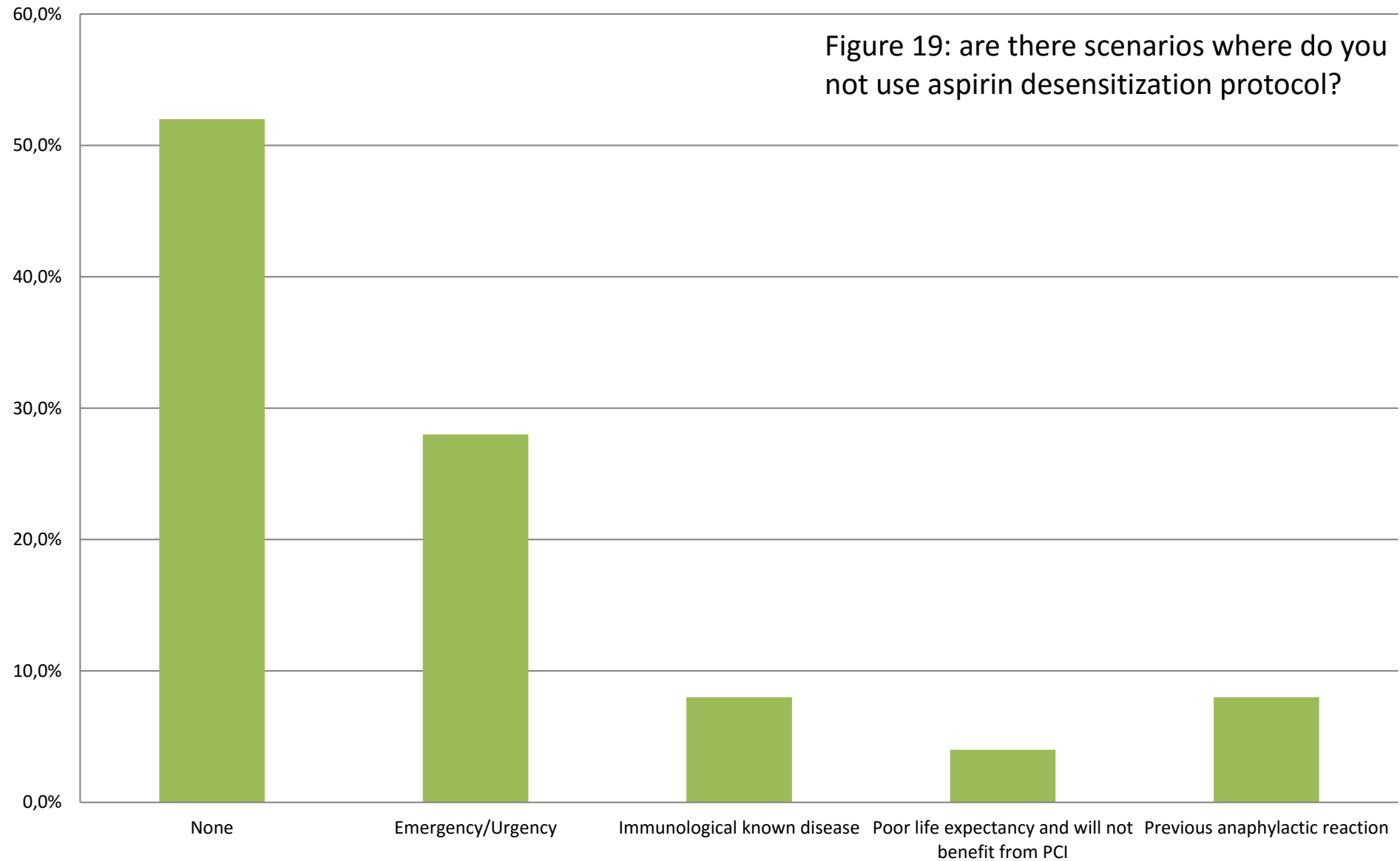


Figure 18: Types and incidence of adverse reactions during desensitization.

Are there scenarios where you do not use aspirin desensitization protocol?



Do you usually schedule patients for a specific follow-up after desensitization?

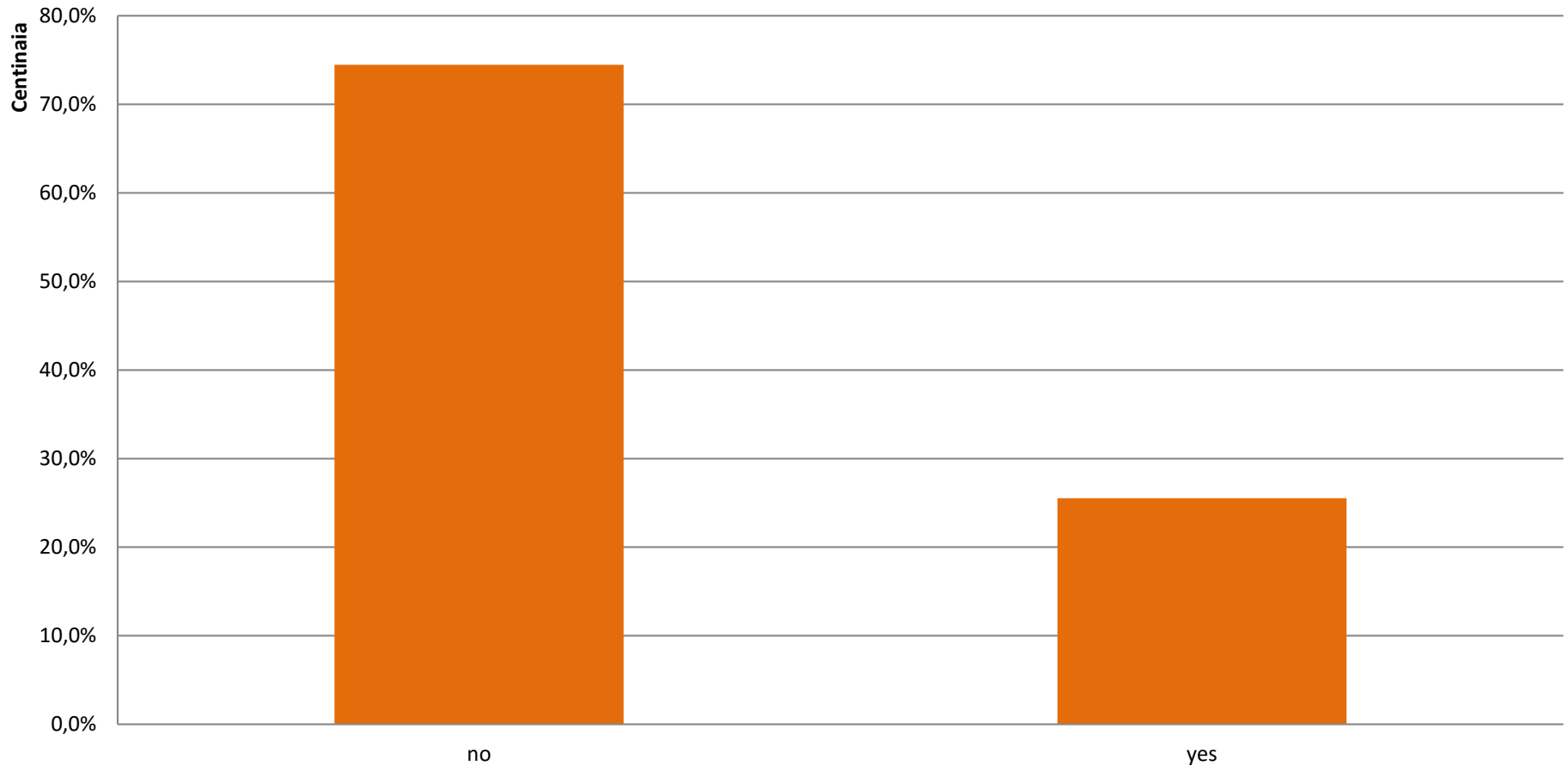
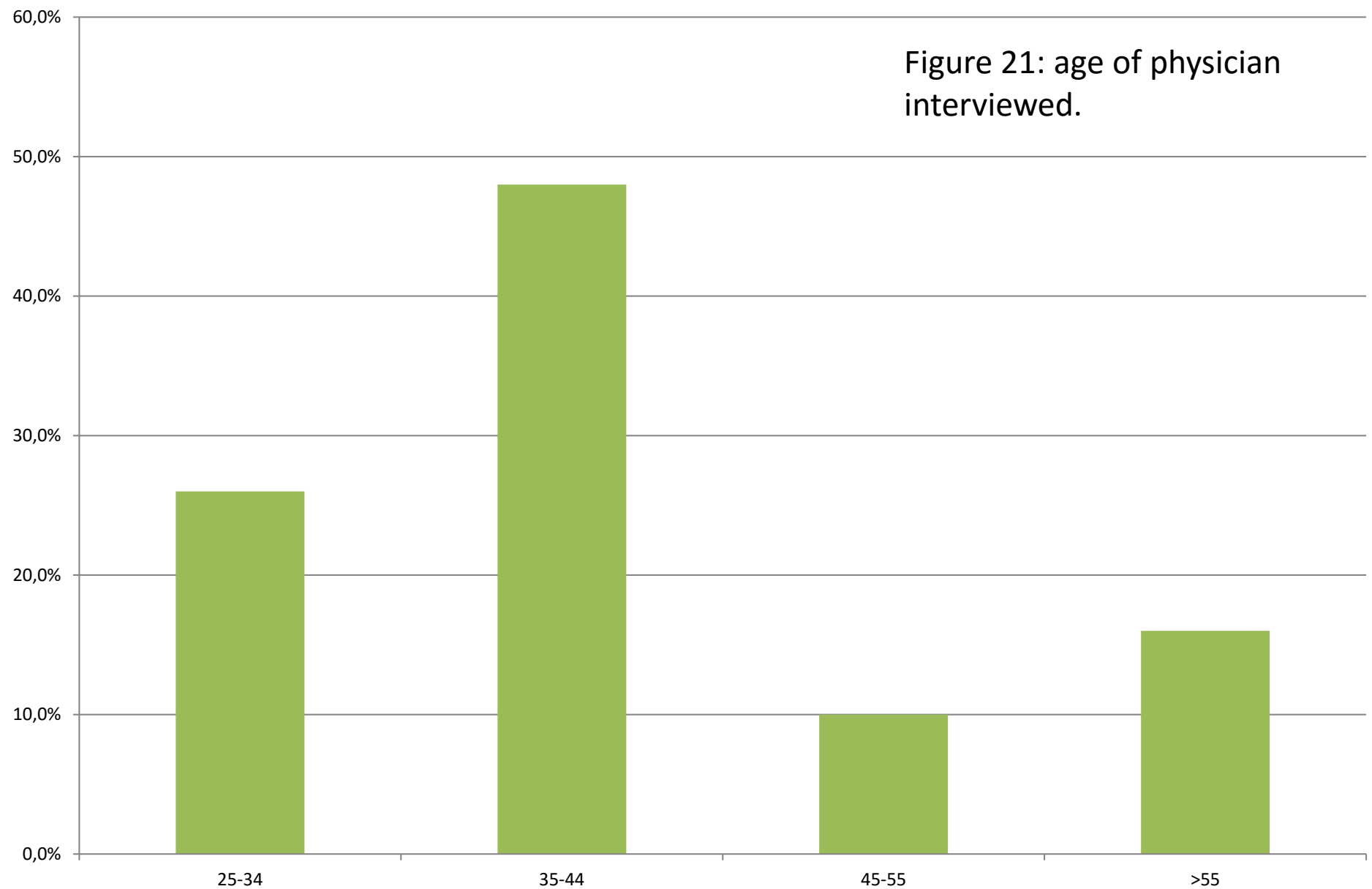


Figure 20: do you usually schedule patients for a specific follow-up after desensitization?

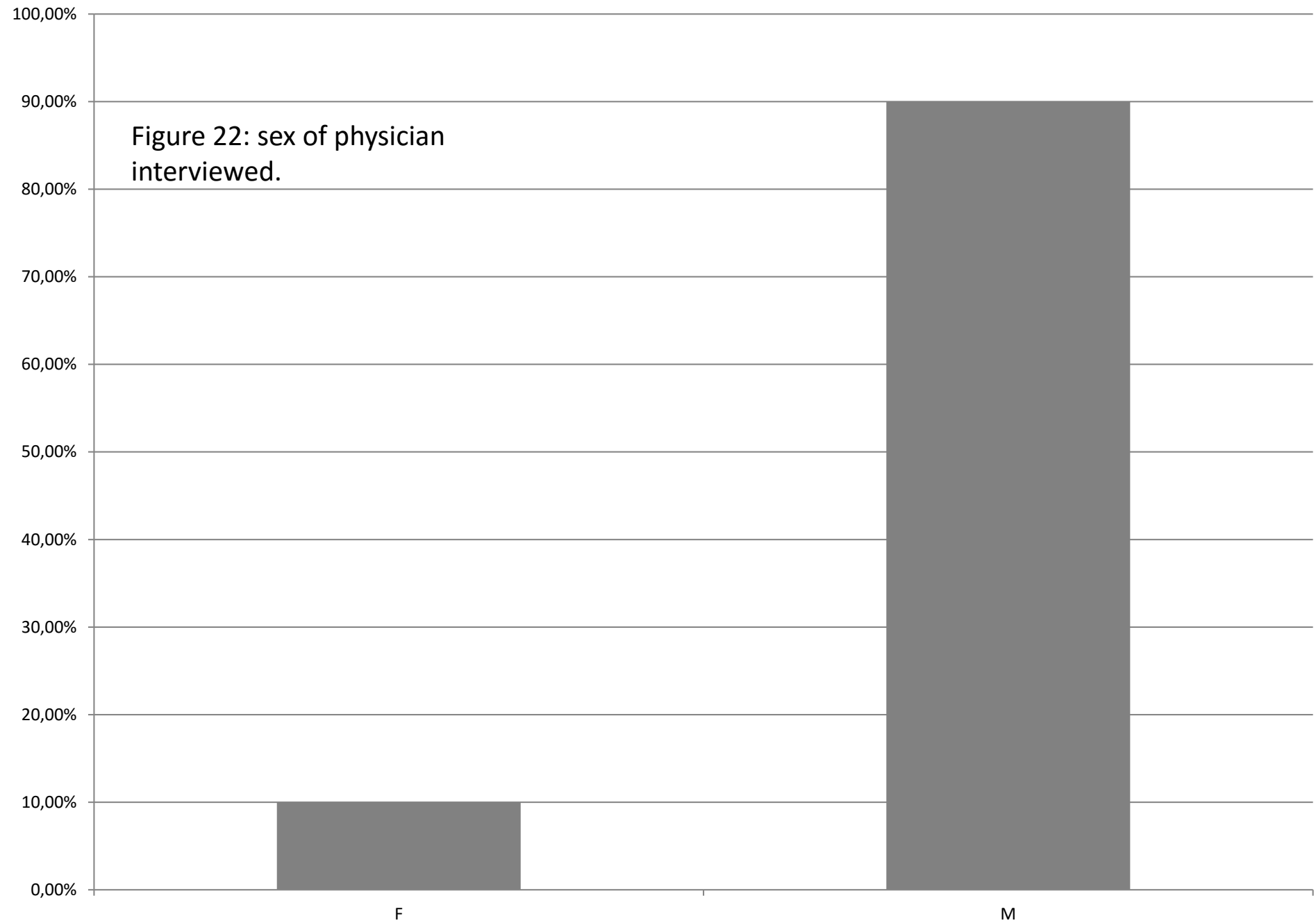
What is your age ?

Figure 21: age of physician interviewed.



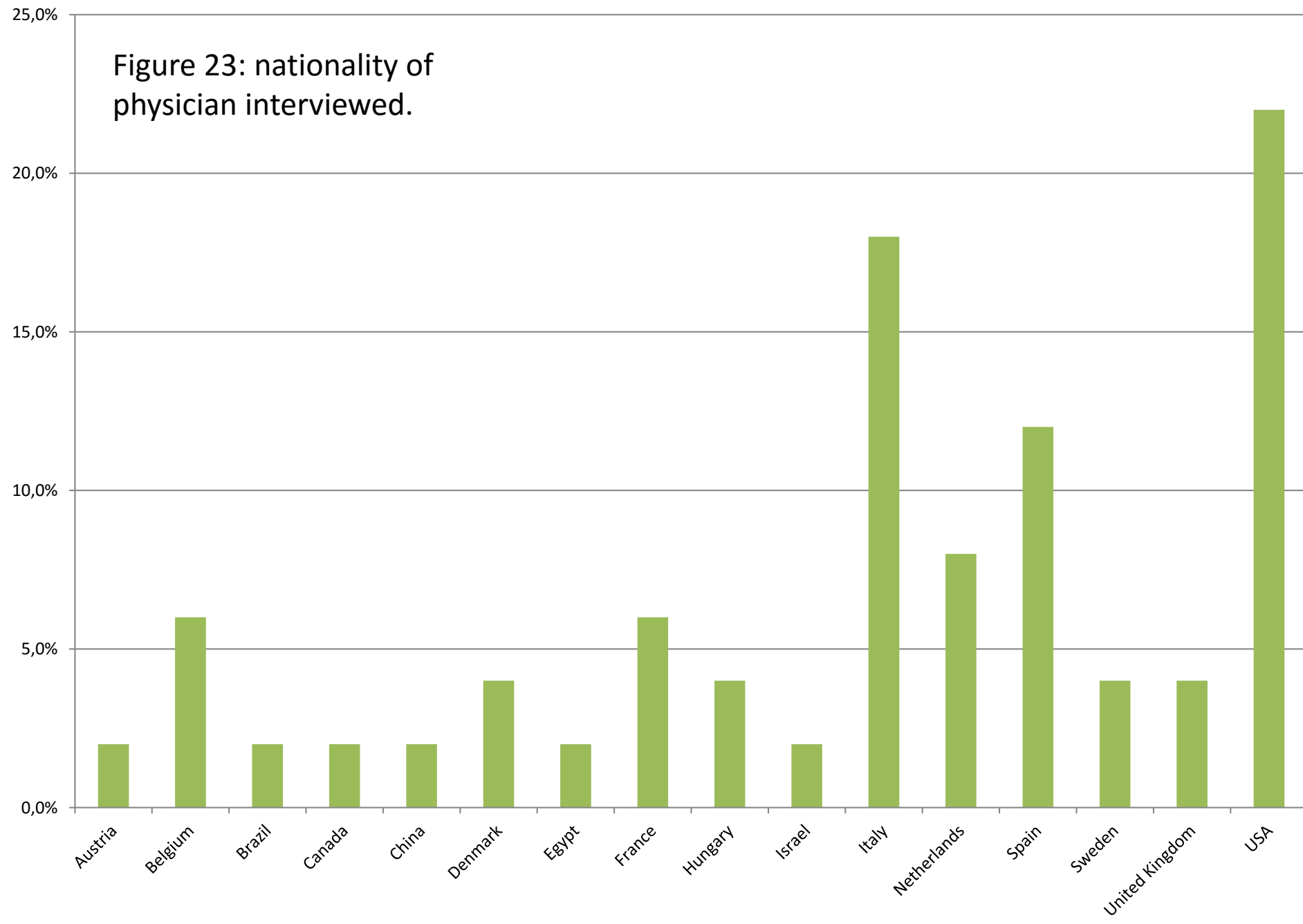
What is your sex?

Figure 22: sex of physician interviewed.



In which country is your Institution?

Figure 23: nationality of physician interviewed.



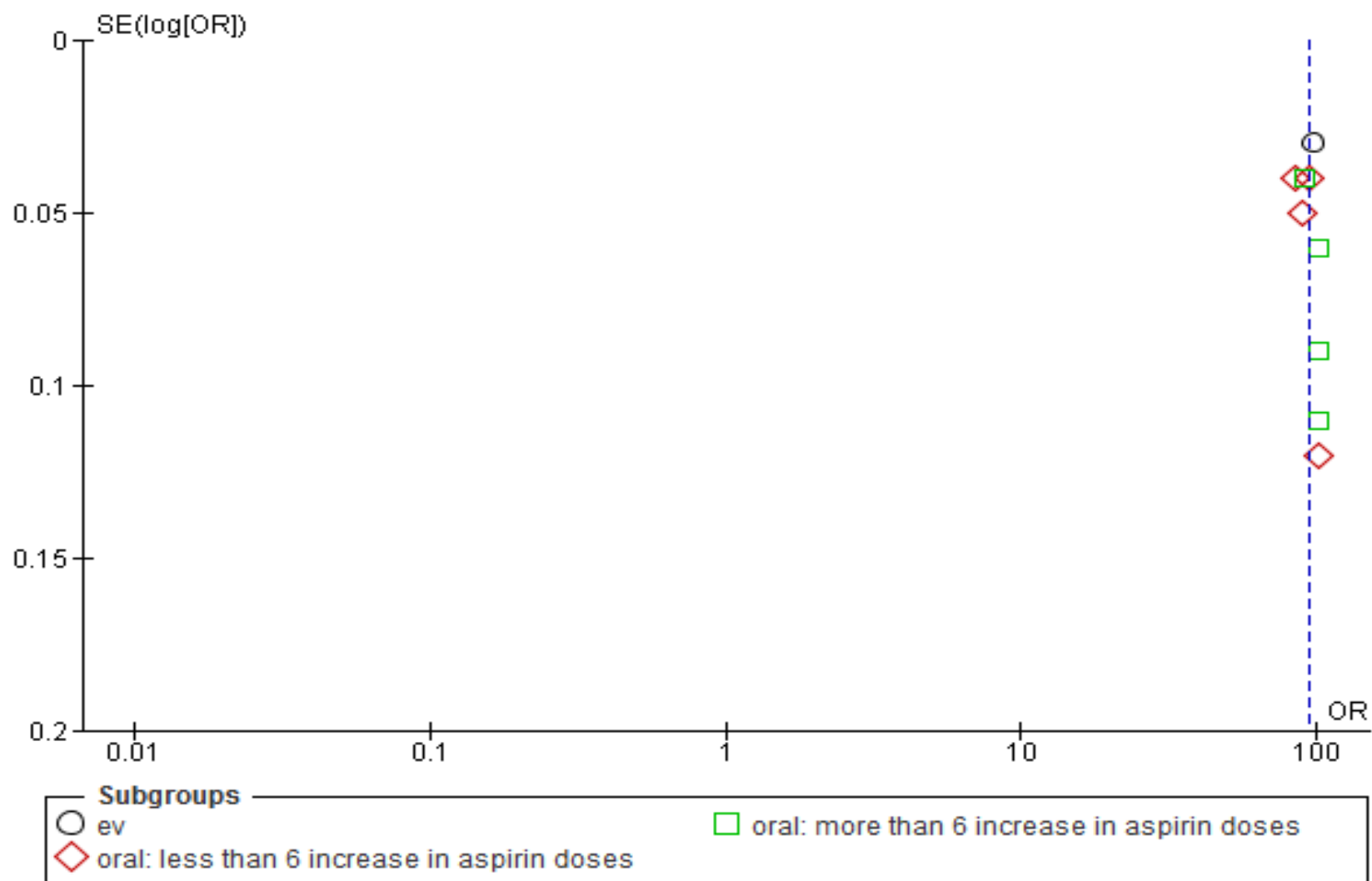


Figure 24. Funnel plot

Aspirin Hypersensitivity and Desensitization Survey's questions

1. Work position
2. According to your experience how frequent is aspirin hypersensitivity out of 1000 patients undergoing catheterism?
3. What type(s) of reactions do you generally see?
4. How do you commonly manage aspirin hypersensitivity?
5. If you switch to another anti-aggregant, what is your choice? (Please detail drug and dose)
6. In case of desensitization protocol with oral administration of aspirin, what is the starting aspirin dose? (i.e. 0.1 mg, 1mg...)
7. In case of oral desensitization, what is the interval between increase the dose (i.e. 10 minutes, 30 minutes...)?
8. In case of oral desensitization, what is the ending aspirin dose?
9. In case of desensitization protocol with endovenous administration of aspirin, what is the starting aspirin dose? (i.e. 0.1 mg, 1mg...)
10. In case of endovenous desensitization, what is the interval between increase the dose (i.e. 10 minutes, 30 minutes...)?
11. In case of endovenous desensitization, what is the ending aspirin dose?
12. Have you tried other aspirin desensitization protocols prior to the one you use now? If so, can you explain the positives and negatives aspects of your past protocol versus the current one?
13. Where do you perform the aspirin desensitization protocol?
14. Do you consult your specialist in allergology?
15. What is the prevalence of anaphylaxis crisis per 100 patients?
16. How frequently does your protocol fail?
17. What are the types of reactions (and prevalence if known) that occur upon failure?
18. Are there scenarios where you do not use your aspirin desensitization protocol?(i.e. immunological known disease, urgency...)
19. Do you usually schedule patients for a specific follow-up after desensitization?
20. What is your age?
21. What is your sex?
22. In which country is your Institution?

Table for Web Appendix. PRISMA statement

Section/Topic	Items	Checklist Item	Page on the article
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3 and page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-	Page 5

		analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6
Risk of bias in studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	Page 6 and page 7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 8 and Figure 1 of the supplemental materials
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8 and tables 1-3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	Page 8 and 9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1-3

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 1-3 and pages 8 and 9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 8 and 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 9 and page 10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	Pages 11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	Page 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 14

*Modified by Moehr D. et al., PLoS Med; 2009.

现有的阿司匹林过敏患者接受经皮冠状动脉介入治疗的用药安全及有效性

一项调查与系统评价

阿司匹林在急性冠脉综合征的治疗中发挥里重要的作用,可显著降低接受经皮冠状动脉介入 (percutaneous coronary intervention, PCI) 治疗患者的冠脉事件再发率,并对支架内血栓形成具有保护性作用。然而,有一些特殊的患者对阿司匹林过敏,在使用阿司匹林后会出现相关的不良反应,如呼吸道疾病恶化、荨麻疹、血管性水肿或过敏反应,这些都是具有停药指针的高危因素,有限的替代用药方案和鲜少的治疗经验,使得临床医生在管理这类患者时困难重重。

为了评估 PCI 患者合并阿司匹林过敏的最佳应对方法,本次研究通过对 Pubmed, Google Scholar 以及 Cochrane 进行系统性搜索,最终入选 11 篇研究 PCI 患者采用阿司匹林脱敏疗法的文章并对其涉及的 283 例患者进行分析研究。在所有研究中,仅 1 项研究进行了静脉脱敏疗法,该研究结果显示静脉脱敏疗法较口服脱敏疗法更高效 (98%),并且不良反应更少。综合各项研究结果发现,采用口服脱敏疗法时,剂量递增次数 < 6 次与 > 6 次疗效没有显著区别 [95.8% (95.4%-96.2%) vs.95.9% (95.2%-96.5%)],但是剂量递增次数 < 6 次时,出现皮疹和血管性水肿的情况更多 [2.6% (1.1%-4.1%) vs.2.6% (1.9%-3.2%)]。

在调查中,共收集到来自欧美的 86 名心脏病专家的回复,94%的专家表示阿司匹林过敏在患者中出现的概率 < 10%,最常见的症状是荨麻疹,其次为哮喘样反应和血管性水肿。令人意外的是,其中 56%的专家仍采用更换治疗方案的方式来管理阿司匹林过敏的患者,如改用氯吡格雷单药治疗或吲哚布芬,仅 42%的被调查专家会采取阿司匹林脱敏疗法。

通过本次研究及调查,我们了解到阿司匹林过敏问题在需要使用阿司匹林的冠脉综合征

患者中确实存在，而现有的阿司匹林脱敏疗法在这类患者需要进行 PCI 支架植入术时是安全有效的，只是仍有过半心脏专家还在通过避不使用阿司匹林的方法来管理这些患者。

Circ Cardiovasc Interv. 2016;9:e002896.