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%]]) or 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
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 antplatelet 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 antplatelet 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 methods14–19 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) du- 

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 genetic inverse-variance weighting, computing risk estimates with 95% confidence intervals. Heterogeneity was evaluated with χ² 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 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.20–22 Finally, 11 studies with 283 patients were included in the final analysis23–31 (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

Bianco et al How to Manage Aspirin Hypersensitivity in the Cath Lab

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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.

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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, angio-
edema 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 differ-
ces 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 desensiti-
zation 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 esca-
lation 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.14

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 out-
cnumbered 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 ther-
apeutic 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 desensitiza-
tion protocol uses an oral scheme, starting with an initial dose
ranging between 0.1 and 1 mg and increasing every 30 min-
utes 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 hos-
pital (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

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**Table**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Incidence</th>
<th>SE</th>
<th>Weight</th>
<th>Incidence (IV, Random, 95% CI)</th>
<th>Incidence (IV, Random, 95% CI)</th>
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<td>1.2.1 ev</td>
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<tr>
<td>De Luca, 135</td>
<td>98.02</td>
<td>11.3%</td>
<td>98.00</td>
<td>[97.96, 98.04]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>11.3%</td>
<td>98.00 [97.96, 98.04]</td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
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<tr>
<td>1.2.2 oral: less than 6 increase in aspirin doses</td>
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<tr>
<td>Cortellini, low risk 1213</td>
<td>97.09</td>
<td>11.0%</td>
<td>97.00</td>
<td>[96.92, 97.18]</td>
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<tr>
<td>Lee, 1226</td>
<td>83.64</td>
<td>4.4%</td>
<td>83.00</td>
<td>[81.75, 84.25]</td>
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<tr>
<td>Rossini, 087</td>
<td>85.39</td>
<td>7.2%</td>
<td>88.00</td>
<td>[88.24, 88.76]</td>
<td></td>
</tr>
<tr>
<td>Silberman, 0520</td>
<td>99.01</td>
<td>11.3%</td>
<td>99.00</td>
<td>[98.96, 99.02]</td>
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<tr>
<td>Vees, 1332</td>
<td>99.01</td>
<td>11.3%</td>
<td>99.00</td>
<td>[98.96, 99.02]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>45.3%</td>
<td>95.83</td>
<td>[95.41, 96.25]</td>
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<tr>
<td>Heterogeneity: Tau² = 0.17; Chi² = 1770.14, df = 4 (P &lt; 0.00001); P = 100%</td>
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<td>Test for overall effect: Z = 447.92 (P &lt; 0.00001)</td>
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<tr>
<td>1.2.3 oral: more than 5 increase in aspirin doses</td>
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<tr>
<td>Christiou, 1330</td>
<td>99.01</td>
<td>11.3%</td>
<td>99.00</td>
<td>[98.96, 99.02]</td>
<td></td>
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<tr>
<td>Cortellini, high risk 1213</td>
<td>90.31</td>
<td>8.3%</td>
<td>90.00</td>
<td>[89.39, 90.61]</td>
<td></td>
</tr>
<tr>
<td>Dalmaz, 0941</td>
<td>99.01</td>
<td>11.3%</td>
<td>99.00</td>
<td>[98.96, 99.02]</td>
<td></td>
</tr>
<tr>
<td>McMillan, 1327</td>
<td>87.03</td>
<td>11.3%</td>
<td>97.00</td>
<td>[96.94, 97.06]</td>
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<tr>
<td>Wong, 0933</td>
<td>81.49</td>
<td>12.9%</td>
<td>81.00</td>
<td>[79.08, 83.02]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>43.4%</td>
<td>95.89</td>
<td>[95.23, 96.54]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.45; Chi² = 5717.56, df = 4 (P &lt; 0.00001); P = 100%</td>
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<tr>
<td>Test for overall effect: Z = 286.65 (P &lt; 0.00001)</td>
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</table>

**Figure 1.** Discharge from hospital with aspirin. CI indicates confidence interval.
How to Manage Aspirin Hypersensitivity in the Cath Lab

The 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. 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. 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.

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. To the best of our knowledge, only 2 studies evaluated alternative therapeutic regimens (indobufen, trapidil, and trifusal) in patients with aspirin hypersensitivity

Table 1. Main Features of Included Studies

<table>
<thead>
<tr>
<th>Endovenous</th>
<th>Oral, with &lt;6 increase in aspirin doses</th>
<th>Oral, with &gt;6 increase in aspirin doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Luca et al6</td>
<td>43</td>
<td>Cortellini et al,13 low risk</td>
</tr>
<tr>
<td>Design</td>
<td>Prospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>Region</td>
<td>Europe</td>
<td>Europe</td>
</tr>
<tr>
<td>Doses, mg</td>
<td>1, 2, 4, 8, 16, 32, 64, 128, 250</td>
<td>10, 15, 25, 20, 50</td>
</tr>
<tr>
<td>Time, h</td>
<td>4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>Other Drugs Before</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Christou et al20</td>
<td>Retrospective</td>
<td>Cortellini et al,13 high risk</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>11</td>
<td>Prospective</td>
</tr>
<tr>
<td>Design</td>
<td>Retrospective</td>
<td>Europe</td>
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<tr>
<td>Region</td>
<td>North America</td>
<td>0.1, 0.3, 1, 3, 10, 20, 40, 81, 162, 325</td>
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<tr>
<td>Doses, mg</td>
<td>0.1, 0.3, 1, 3, 10, 20, 40, 81, 162, 325</td>
<td>3.50</td>
</tr>
<tr>
<td>Time, h</td>
<td>3.50</td>
<td>3.50</td>
</tr>
<tr>
<td>Indication for PCI (%)</td>
<td>Antihistamine</td>
<td></td>
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<tr>
<td>Symptoms of hypersensitivity (%)</td>
<td></td>
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<tr>
<td>PCI indicates percutaneous coronary intervention.</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>11 studies, 283 patients</th>
<th>Value*</th>
</tr>
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<tbody>
<tr>
<td>Prevalence of aspirin allergy (%)</td>
<td>2.0 (1.2–2.7)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>67.0 (62.0–68.0)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>31.0 (25.0–39.0)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>69.0 (67.0–70.0)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>22.0 (20.0–24.0)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>60.0 (52.0–68.0)</td>
</tr>
<tr>
<td>Indication for PCI (%)</td>
<td>44.0 (39.0–47.0)</td>
</tr>
<tr>
<td>Symptoms of hypersensitivity (%)</td>
<td>55.0 (54.0–60.0)</td>
</tr>
<tr>
<td>PCI indicates percutaneous coronary intervention.</td>
<td></td>
</tr>
</tbody>
</table>

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

Table 3. Procedural Features

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Incidence</th>
<th>SE</th>
<th>Weight</th>
<th>Incidence IV, Random, 95% CI</th>
<th>Incidence IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 ev</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Luca, 14</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td>Test for overall effect: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.2 oral: less than 6 increase in aspirin doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortellini, low risk 12 13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Lee, 13 29</td>
<td>3.1</td>
<td>1.5</td>
<td>4.2%</td>
<td>3.10 [0.16, 6.04]</td>
<td></td>
</tr>
<tr>
<td>Rossini, 08 7</td>
<td>2.44</td>
<td>0.9</td>
<td>11.6%</td>
<td>2.44 [0.69, 4.20]</td>
<td></td>
</tr>
<tr>
<td>Silberman, 05 29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Vass, 13 32</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>15.8%</td>
<td>2.61 [1.10, 4.13]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.14, df = 1 (P = 0.71); I^2 = 0%</td>
<td>Test for overall effect: Z = 3.39 (P = 0.0007)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.3 oral: more than 6 increase in aspirin doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Christofori, 11 30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Cortellini, high risk 12 13</td>
<td>2.26</td>
<td>0.9</td>
<td>11.6%</td>
<td>2.26 [0.50, 4.02]</td>
<td></td>
</tr>
<tr>
<td>Dalmau, 09 31</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>McMullan, 13 27</td>
<td>2.61</td>
<td>0.36</td>
<td>72.6%</td>
<td>2.61 [1.90, 3.32]</td>
<td></td>
</tr>
<tr>
<td>Wong, 00 33</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>84.2%</td>
<td>2.56 [1.94, 3.22]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.13, df = 1 (P = 0.72); I^2 = 0%</td>
<td>Test for overall effect: Z = 7.66 (P = 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>2.57 [1.97, 3.17]</td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.28, df = 3 (P = 0.96); I^2 = 0%</td>
<td>Test for overall effect: Z = 0.39 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi^2 = 0.00, df = 1 (P = 0.95), I^2 = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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.33,44 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
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 3.** Rate of angioedema during protocols. CI indicates confidence interval.

**Figure 4.** Alternative antplatelets therapy. DAPT indicates dual antiplatelet therapy.

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

- **Clopidogrel 150 mg**
- **Clopidogrel 75 mg**
- **Clopidogrel for monotherapy, naproxen for DAPT**
- **Clopidogrel for monotherapy, ticagrelor for DAPT**
- **Ibuprofen 150 mg**
- **Ibuprofen for monotherapy, desensitization for DAPT**
- **Ibustrol 150 mg**
- **Ibustrol 200 mg/twice a day**
- **Omega 3 high dose and clopidogrel 75 mg**
- **Stable angina: clopidogrel 75 mg; ACS: prasugrel**
- **Ticagrelor 90 mg/twice a day**
Disclosures

None.

References


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
2. Figure 2: Work position (CLI: clinical cardiologist – INT: interventional cardiologist)
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
365 records identified through database searching

0 additional citations obtained through other sources

18 full texts appraised according to explicit selection criteria

5 excluded because not evaluating aspirin desensitization protocols

1 non evaluating patients undergoing PCI

2 case reports

11 studies finally included in the systematic review

Figure 1: studies selection
Figure 2: Work position (CLI: clinical cardiologist – INT: interventional cardiologist)
According to your experience how frequent is aspirin hypersensitivity in your cath lab?

Figure 3: average rate of aspirin hypersensitivity
What types of reactions do you generally see:

- Angioedema
- Asthmatic-type reaction
- Urticaria

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?

- Clopidogrel 150 mg
- Clopidogrel 75 mg
- Clopidogrel for monotherapy, naproxen for DAPT
- Clopidogrel for monotherapy, ticagrelor for DAPT
- Ibuprofen 150 mg
- Ibuprofen for monotherapy, desensibilization for DAPT
- Ibustrin 150 mg
- Ibustrin 200 mg/twice a day
- Omega 3 high dose and clopidogrel 75 mg
- Stable angina: clopidogrel 75 mg; ACS: prasugrel
- Ticagrelor 90 mg/twice a day

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)

Figure 7: Oral anti-platelets desensitization protocol starting dose
What is the interval between increase the dose (i.e. 10 minutes, 30 minutes)?

Figure 8: time between dose increase in oral protocols
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?

Figure 10: intravenous anti-platelets desensitization protocol starting dose.
Which is the interval before increase the dose in case of endovenous desensitization?

Figure 11: time between dose increase in intravenous protocols
Which is the ending aspirin dose in case of endovenous desensitization?

Figure 12: final aspirin dose in intravenous protocols.
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?

Figure 15: do you consult an immunologist specialist?
What is the prevalence of anaphylaxis crisis per 100 patients?

Figure 16: prevalence of anaphylaxis crisis.
How frequently does your protocol fail? (i.e. 2% of the time)

Figure 17: protocols failure rate.
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?

Figure 19: are there scenarios where do you not use aspirin desensitization protocol?

- None: 50%
- Emergency/Urgency: 20%
- Immunological known disease: 10%
- Poor life expectancy and will not benefit from PCI: 5%
- Previous anaphylactic reaction: 10%
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. immulogical 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>
<thead>
<tr>
<th>Section/Topic</th>
<th>Items</th>
<th>Checklist Item</th>
<th>Page on the article</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>Page 1</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>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.</td>
<td>Page 2</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>Page 3</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>Page 3 and page 4</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>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.</td>
<td>Page 5</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>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.</td>
<td>Page 5</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>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.</td>
<td>Page 5</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>Page 5</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-</td>
<td>Page 5</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>Page 6</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
<td>Page 6</td>
</tr>
<tr>
<td>Risk of bias in studies</td>
<td>12</td>
<td>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.</td>
<td>Page 6</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>Page 6</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
<td>Page 6 and page 7</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>Page 6</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>Page 7</td>
</tr>
</tbody>
</table>

**RESULTS**

<p>| 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 |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Page(s)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>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).</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>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).</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
</tr>
<tr>
<td>FUNDING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>27</td>
<td>Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.</td>
</tr>
</tbody>
</table>

为探究新一代药物洗脱支架 (drug-eluting stents, DES) 对伴有多种动脉粥样硬化继发血栓形成风险 (atherothrombotic risk, ATR) 因素的女性患者的安全性与疗效，研究者汇集了来自 26 个随机试验中的 10449 例女性患者进行研究，并根据患者是否存在糖尿病史、经皮或外科冠状动脉血管重建史、心肌梗死史等 ATR 因素将患者分为高 ATR 组 (5333 例，51%) 以及非高 ATR 组。主要研究终点为心血管不良事件，包括全因死亡、心肌梗死或在 3 年内发生血管重建。

研究结果表明，高 ATR 组患者主要心血管不良事件发生率以及全因死亡率显著高于非高 ATR 组 (15.8% vs. 10.6%; 校正 HR = 1.53; 95% CI 1.34-1.75; p = 0.006)。与早期 DES 相比，应用新一代 DES 的高 ATR 组患者 3 年内主要心血管不良事件发生率显著降低 (校正 HR = 0.69; 95% CI 0.52-0.92)。在高 ATR 组和非高 ATR 组，患者使用新一代 DES 后主要心血管不良事件的获益一致，没有干扰证据 (Pinteraction = 0.14)。界标分析显示，高 ATR 组女性使用不同 DES 支架植入后 1 年内支架内血栓形成率无明显差异，1-3 年内新一代 DES 支架内血栓形成发生率更低。

综上所述，高 ATR 患者使用新一代 DES 可明显获益，在 3 年随访期，新一代 DES 对于非常晚期血栓形成仍有实质性获益。


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着重要的作用，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征的高危因素，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症
患者中确实存在，而现有的阿司匹林脱敏疗法在这些患者需要进行 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免使用阿司匹林的方法来管理这些患者。


**房颤与接受经导管主动脉瓣置换术患者死亡率增高相关**

来自 PARTNER 试验的见解

心房颤动 (atrial fibrillation, AF) 与心房扑动不仅是一种普通的心脏疾病，更与许多心脏手术密切相关，在接受了心脏瓣膜手术和冠状动脉旁路移植术的患者中，房颤更为常见，在所有接受了心脏开胸手术的患者中，有 5% - 40% 的患者会发生房颤。而术前或术后房颤，都可能增加患者的死亡率。

目前已知，术后房颤是导致接受外科主动脉瓣置换术（SAVR）患者死亡的风险因素，而接受了与 SAVR 同样有效，但侵袭性更小的经导管主动脉瓣置换术（TAVR）后发生房颤，是否也会增加患者死亡率的数据还十分有限。本次研究的目的就是要评估房颤对接受经导管主动脉瓣置换术患者临床预后的影响。

在 PARTNER（the Placement of Aortic Transcatheter Valve）实验中，共纳入了 1879 例需接受经导管主动脉瓣置换术的患者，分别在他们入院和出院时进行心电图（ECG）检测。其中 1262 例患者入院 ECG 与出院 ECG 均表现为窦性心律（sinus rhythm，SR），113例患者入院 ECG 为 SR，出院 ECG 为 AF，470 例患者入院 ECG 与出院 ECG 均为 AF。随访发现，ECG 由 SR 转为 AF 组的患者，出院后 30 天全因死亡率最高（各组死亡率不全相同，$p < 0.0001$；14.2% SR/AF vs. 2.6% SR/SR；校正 HR = 3.41；$p = 0.0002$），1 年内全因死亡率增加超过 2 倍（各组死亡率不全相同，$p<0.0001$；35.7% SR/AF vs. 15.8% SR/SR；校正 HR = 2.14；$p < 0.0001$）。入院或出院 ECG 表现为 AF 可作为预测 1 年死亡率的指标（SR/AF 校正 HR = 2.14；AF/AF 校正 HR = 1.88；两组均与 SR/SR 组不同，$p < 0.0001$）。出院 ECG 为 AF 而心室率较低 ( 如：< 9bpm ) 的患者 1 年死亡率也较低 (HR = 0.74；$P = 0.04$)。

经导管主动脉瓣置换术后出院 ECG 表现为 AF，特别是由 SR 转变为 AF 并伴较高心室率的患者与死亡率增高相关。以上数据表明 AF 的不利影响，急需靶向干预以改善经导管主动脉瓣置换术患者的临床预后。