Letters to the Editor

Kounis Syndrome Should Be Considered the Culprit Cause of the Most Feared Stent Thrombosis

In their white paper, Holmes, Jr. et al. (1) do not refer to hypersensitivity coronary syndrome. However, I strongly believe that stent thrombosis (ST) is principally a manifestation of Kounis hypersensitivity coronary syndrome (2), caused by an “antigenic complex” of nickel alloys, polymers, eluted drugs, and possibly concomitant oral antiplatelet drugs and environmental exposures. Thus far, all clinical reports and reported pathologic findings in all patients who have died of ST, and all animal studies and experiments, point toward hypersensitivity inflammation with infiltration of various interrelated and interacting inflammatory cells, including eosinophils, macrophages, T cells, and mast cells. Following are some examples (3–5):

• In patients who developed ST associated with generalized allergic reactions, induced by environmental causes, stents act like magnets attracting inflammatory cells and constitute the area of possible intracoronary mast cell and platelet activation in order to develop ST.
• In the Research on Adverse Drug Events and Reports project, definite ST cases showed peripheral eosinophilia and raised immunoglobulin E titers over 5 times normal, together with eosinophilic thrombus infiltration.
• In serum sickness–like reactions after sirolimus-eluting stent implantation, symptoms did not resolve after the discontinuation of clopidogrel and substitution with ticlopidine, but they resolved with prednisone. However, prednisone abolished symptoms despite aspirin and clopidogrel continuation.
• In occluded biliary stents, pathology revealed infiltration of eosinophils and lymphocytes compatible with nickel allergic reaction.
• In thrombus sections stained with hematoxylin and eosin, neutrophils and eosinophils were associated with stent apposition, suggesting an allergic hypersensitivity reaction.
• In sirolimus-eluting stents, localized coronary hypersensitivity vasculitis and acute myocardial infarction were induced from late ST.
• In patients who received stents and died of multivessel spasm, histologic findings revealed inflammatory cells in the intima and adventitia. Giemsa staining showed few scattered mast cells.

I wonder how many of us have noticed that manufacturers’ information sheets accompanying the new generation of stents state clearly that they are contraindicated for use in patients with hypersensitivity to any stent component.

In conclusion, antigen-free stents should be implanted to avoid catastrophic ST.

Stent Thrombosis
Did Biodegradable Polymers Fail or Are We Too Impatient?

We read with interest the report by Holmes et al. (1), in which the current knowledge about stent thrombosis is revisited, and the possibility that biodegradable polymers improve the long-term safety of drug-eluting stents is mentioned. Durable polymers are associated with persistent arterial wall inflammation and delayed vascular healing, both related to stent thrombosis (2). New biodegradable polymers completely degrade in 6 to 9 months, leaving behind only the bare-metal stent structure.

Apart from the LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) trial (3), many trials have compared biodegradable with durable polymers. We have performed a meta-analysis of 7 randomized trials comparing durable with biodegradable polymers (COSTAR-II [Cobalt Chromium Stent With Antiproliferative for Restenosis II], ISAR-TEST-3 [Intracoronary Stenting and Angiographic Results: Test Efficacy of Rapamycin-Eluting Stents With Different Polymer Coating Strategies], ISAR-TEST-4 [Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents], LEADERS, NOBORI-CORE [A Prospective, Non-Randomized, Multi-Center Comparative Study of Nobori Drug Eluting Stent Systems Versus Cypher Drug Eluting Stent System], NOBORI-I [A Prospective, Randomized, Multi-Centre Comparison of Nobori and Taxus Drug Eluting Stent Systems], and NEVO

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ResElution-I) (3), including more than 7,000 patients, and found no differences in the rate of stent thrombosis during the first year (1.2% vs. 1.2%; odds ratio: 1.01; 95% confidence interval: 0.66 to 1.55; \( p = 0.96 \)) (Fig. 1).

Nevertheless, the potential benefits of biodegradable polymers should be evaluated with longer follow-up. In fact, when we analyzed only late (>1 month) stent thrombosis, a 40% relative risk reduction in the rate of stent thrombosis, although not statistically significant, was found in patients allocated to biodegradable polymer stents (0.27% vs. 0.45%, respectively; odds ratio: 0.68; 95% confidence interval: 0.32 to 1.48; \( p = 0.33 \)).

We believe that biodegradable polymers will contribute to improve the long-term safety of drug-eluting stents, but we will have to wait for evidence from long-term (several years) follow-up in large randomized trials.

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Reply

We appreciate the comments of Dr. Salinas and colleagues regarding our paper (1). The safety of new-generation stents is improving. This may be the result of several factors, one of which may be the use of “biodegradable” polymers; other factors may also be as important, including improved antiplatelet therapy, longer duration of antiplatelet therapy, and improved initial stent placement using high-pressure balloons or guidance with intravascular ultrasound and/or optical computed tomography. Of interest, in the authors’ meta-analysis, there were 43 patients in the biodegradable group and 41 in the permanent polymer group. The numbers are therefore small, although any event is often catastrophic for the individual patient. Given the low incidence of the phenomenon and the changing technology, larger series and longer follow-up will be needed, although challenging. At the present time, a randomized trial with stent thrombosis as the primary end point is unavailable for study.

We also appreciate the comments of Prof. Kounis regarding Kounis syndrome. There are multiple issues involved in stent thrombosis. Some issues relate to the underlying coronary artery disease, some to the specific stent design, including bare-metal versus drug-eluting stents, and for drug-eluting stents in particular the specific polymer and drug or drugs used. In addition, there are issues of compliance with and response to dual-antiplatelet therapy. Findings consistent with hypersensitivity have been seen in some autopsy series, as mentioned by Prof. Kounis, and may play a role. Continuing ongoing experience with polymer-free designs as well as different drugs may help resolve some of the issues. Fortunately, the incidence of this often catastrophic complication is very low; this very fact makes reaching definitive evidence-based conclusions about preventive strategies challenging.

| Figure 1 Effect of Biodegradable Polymer Drug-Eluting Stents on the Risk for Stent Thrombosis During the First Year After Implantation |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Study or Subgroup        | Biodegradable polymer    | Permanent                | Odds Ratio               |
|                         | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | Odds Ratio | M-H, Fixed, 95% CI |
| COSTAR-II                | 6      | 989   | 1      | 686   | 2.8%   | 4.18 [0.50, 34.81] |             |             |
| ISAR-T3-3                | 1      | 202   | 1      | 202   | 2.4%   | 1.00 [0.06, 16.10] |             |             |
| ISAR-TEST-4              | 13     | 1299  | 19     | 1304  | 45.1%  | 0.68 [0.34, 1.39] |             |             |
| LEADERS                  | 22     | 857   | 19     | 650   | 44.7%  | 1.15 [0.62, 2.14] |             |             |
| NOBORI CORE              | 1      | 60    | 0      | 50    | 1.0%   | 2.55 [0.10, 63.89] |             |             |
| NOBORI                  | 0      | 85    | 0      | 35    | Not estimable |             |             |
| RESOLUTION-I            | 0      | 193   | 1     | 187   | 3.7%   | 0.32 [0.01, 9.74] |             |             |
| Total (95% CI)           | 3685   | 3314  | 100.0% |       |       | 1.01 [0.66, 1.55] |             |             |
| Total events             | 43     | 41    |        |       |       |             |             |
| Heterogeneity: \( \chi^2 = 3.87, df = 5 (P = 0.57); \) \( p = 0.00 \) |             |             |
| Test for overall effect: \( Z = 0.05 (P = 0.96) \) |             |             |