study discussed here, Davidson’s study was assessing a non-surgical scenario in which therapeutic doses of oral anticoagulants instead of prophylactic LMWHs were used.

In our trial, roughly 12% of the study population of 1,184 patients, or 144 patients (73 randomized to sugammadex and 71 randomized to usual care), were treated with concomitant LMWH and ASA. There were very few bleeding events in this subgroup, with only four among those that received sugammadex and two in those that received usual care; these numbers are too low to allow for a meaningful comparison of bleeding rates in patients treated with sugammadex versus those treated with usual care. Very few patients were treated with concomitant ASA only (n = 29 total, including 15 in the sugammadex group and 14 in the usual care group); of those patients on ASA only, there were no bleeding events in either the sugammadex or the usual care groups.

Of note, the addition of ASA to LMWH did not increase the bleeding risk among patients who received usual care (4.3% bleeding rate in patients on LMWH compared with 2.8% in patients on LMWH plus ASA who received usual care). Thus, the overall bleeding risk is low in patients receiving LMWH that are randomized to either sugammadex or usual care, and despite the limited experience in this study, it appears that the addition of ASA likely does not confer additional bleeding risk compared with that seen with background LMWH treatment.

As a result, the data of this trial give no reason to interrupt required treatment with ASA in a similar clinical scenario.

Competing Interests
Dr. Rahe-Meyer received research support and speaker’s honoraria from Merck Sharp & Dohme Corp. (Whitehouse Station, New Jersey) and CSL-Behring (Marburg, Germany).

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Reference

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Incidence of Intraoperative Hypersensitivity Reactions: What’s This About?

To the Editor:

Saager et al.1 used a methodology combining electronic search strategies and clinical adjudication to retrospectively determine the incidence of intraoperative hypersensitivity events in one U.S. surgical center. The authors concluded that the overall incidence of anaphylaxis was 1 in 4,583 surgeries, whereas that of hypersensitivity was 1 in 677. However, major methodologic issues should be highlighted, and the results must be debated because no conclusion can be effectively drawn from this study.

First, the claim that “the overall incidence of anaphylaxis was similar to that reported in previous studies but that of hypersensitivity reactions was nearly seven times higher”1 is not accurate because this has not been proved. In addition, it is supposed that hypersensitivity was used to designate immediate hypersensitivity because delayed hypersensitivity does not arise during the periporative period. Thus, six types of criteria were arbitrarily selected to identify potential perioperative hypersensitivity in 178,746 surgeries during the 7-yr study period. The adjudication committee further selected 264 cases of immediate hypersensitivity corresponding to 7% of the study population by 1, 2, 3, or 4 search criteria and subsequently classified these cases according to a modified Ring and Messmer scale. The search criteria included clinical features, biologic measurements, e.g., histamine, tryptase, or IgE (total or specific), and selected preferred terms. Some of these latter should not have been used because they are not consistent with immediate hypersensitivity. Particularly, the first-use syndrome has been described during hemodialysis2; fixed eruption and drug dermatitis belong to cell-mediated hypersensitivity that has a delayed presentation3; and flushing, sensation of foreign body, and laryngospasm or stridor do not belong to perioperative immediate hypersensitivity per se.4 Therefore, it is unclear whether only clinical features related to perioperative immediate hypersensitivity5 were considered for including the 264 cases. In addition, the timing between the introduction of the suspected trigger and the onset of clinical features is lacking. Accordingly, the onset delay is a useful argument in the diagnostic approach of perioperative immediate hypersensitivity, which usually occurs within minutes, even 1 min, of anesthetic induction.4

Second, laboratory tests were performed in only five patients (1.7%) but unfortunately remained undetailed. One should keep in mind that tryptase increase is highly suggestive of mast cell activation as seen in anaphylaxis.4–7 In contrast, total IgE has no indication in the diagnostic approach of perioperative immediate hypersensitivity, whereas the identification of serum IgE to quaternary ammonium provides possible evidence of IgE sensitization but does not prove that a neuromuscular-blocking agent elicited the immediate reaction per se.4–6,8

Third, skin testing was not performed, and thus, none of these 264 cases can be considered to be definitively supported by an appropriate allergologic assessment. The analysis of biologic and skin tests results should always be tied to
a careful and complete review of the clinical history to identify the culprit agent and the pathophysiologic mechanism involved (allergic vs. nonallergic).3–7

Fourth, thus, we respectfully disagree with the authors who claim that “the use of neuromuscular blocking agents was not significantly associated with experiencing hypersensitivity reactions” because this has not been demonstrated. Neuromuscular-blocking agents and antibiotics (e.g., β-lactam drugs) still remain the main triggers involved in cases of perioperative anaphylaxis, whereas latex-induced allergy is now becoming less common.9 Furthermore, only a few cases of anaphylaxis to hetastarch are reported worldwide,6 and this is not consistent with the statement that “high-molecular-weight hetastarch was significantly associated with hypersensitivity reactions.”

In conclusion, the methodology used by Saager et al.3 is not suitable for evaluating perioperative immediate hypersensitivity because none of the 264 cases can be considered to be definitively supported by an appropriate allergologic assessment as recommended by the current guidelines.5–7 In contrast, unfortunately, no conclusion can be drawn from this retrospective study.

Competing Interests
Dr. Dewachter received payment for lectures, communications, and travel fees by MSD France (Courbevoie, France). The other author declares no competing interests.

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In Reply:

Our statement that “the overall incidence of anaphylaxis was similar to that reported in previous studies, but that of hypersensitivity reactions was nearly seven times higher” accurately reflects our results.1 That said, the results of any study need to be interpreted within the context and methodology of the study. As specified in our title and throughout the report, the investigation was restricted to intraoperative hypersensitivity reactions. Because delayed hypersensitivity does not present clinically during the perioperative period, such reactions were not included in our data set. Including delayed reactions would, presumably, increase the incidence we report.

The six search criteria we used to identify possible intraoperative hypersensitivity reactions were not chosen arbitrarily. Instead, as described in the article, they were selected by a Delphi process involving 10 highly experienced board-certified anesthesiologists. All six criteria are clearly related to possible intraoperative hypersensitivity, as recorded in clinical, laboratory, or administrative records. In an effort to capture all possible intraoperative hypersensitivity reactions, we deliberately used broad search criteria, recognizing well that most screened cases would be false positives.

Dewachter and Mouton-Faivre suggest that certain medical key words should not have been used to identify candidate cases for further review. Restricting our search may have eliminated candidate cases that were adjudicated as having hypersensitivity reactions based on other aspects of their records. Therefore, restricting the search could only weaken our study. Most anesthesiologists would agree that flushing, laryngospasm, and stridor are clinical symptoms potentially consequent to intraoperative hypersensitivity reactions and, therefore, should be included in a key word search.

The adjudication committee did not select 264 cases. Instead, members of the committee independently and rigorously adjudicated more than 4,000 individual candidates using all available information in the medical record. The strength of our study was our novel and robust approach to using a large clinical registry to identify rare intraoperative events. As specified in our title and throughout the report, the investigation was restricted to intraoperative hypersensitivity reactions.

Dewachter and Mouton-Faivre criticize our inability to identify elapsed time between administration of suspected triggers and onset of clinical features. Operating room reality precludes accurate identification of elapsed time. Induction