Dabigatran Reversal With Idarucizumab and In-Hospital Mortality in Intracranial Hemorrhage: A Systematic Review of Real-Life Data From Case Reports and Case Series

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Background: Intracranial hemorrhage is a severe and possibly fatal consequence of anticoagulation therapy. Idarucizumab is used in dabigatran-treated patients suffering from intracranial hemorrhage (ICH) to reverse the anticoagulant effect of dabigatran. Systematic review of real-life mortality in these patients is missing.

Objectives: A review of all published dabigatran-related ICH cases treated with idarucizumab was performed. We aimed to estimate in-hospital mortality rate in these patients.

Method: We searched PubMed and Scopus for all published cases of ICH in idarucizumab/dabigatran-treated patients until May 15, 2021. The assessed outcome was in-hospital mortality.

Results: We identified six eligible studies (case series) with 386 patients and 54 single case reports. In-hospital mortality rate was 11.4% in the case series and 9.7% in the case reports.

Conclusions: Our analysis provides clinically relevant quantitative data regarding in-hospital mortality in idarucizumab/dabigatran-treated patients with ICH, which is estimated to be 9.7–11.4%.

Keywords: dabigatran, idarucizumab, reversal agent, intracranial hemorrhage, in-hospital mortality

HIGHLIGHTS

- Intracranial hemorrhage is a serious, life-threatening condition associated with anticoagulation therapy.
- Idarucizumab is a specific reversal agent of dabigatran, which achieves instantaneous reversal of anticoagulation after application.
- Idarucizumab is indicated in dabigatran-treated patients with life-threatening conditions, such as uncontrolled bleeding, or the need for urgent intervention.
Intracranial hemorrhage is a serious, life-threatening condition associated with anticoagulation therapy. Idarucizumab is a specific reversal agent of dabigatran, which achieves instantaneous reversal of anticoagulation after application seemingly without prothrombotic or other serious side effects (1, 2). The use of idarucizumab is indicated in dabigatran-treated patients with life-threatening conditions, such as uncontrolled bleeding, or the need for urgent intervention (2, 3).

Intracranial hemorrhage in dabigatran-treated patients is a rare event, with estimated yearly incidences of 0.1% for the standard dose and 0.12% for the reduced dose (4). Due to very low frequency of intracranial hemorrhage (ICH), consequently, the number of reported cases is limited. The mortality rate in dabigatran-treated patient with ICH in the REVERSal Effects of idarucizumab on Active Dabigatran (REVERSE AD) study, which included only 98 patient with ICH, was 16.4% (2). A small number of patients did not allow for firm conclusions. On the other hand, a relatively high number of reported case series and case reports were published in the following years (1, 2, 5–24).

The aim of this systematic review was to summarize all published cases of dabigatran-treated patients with ICH who were treated with idarucizumab in order to quantitatively evaluate the in-hospital mortality rate.

### Methodology and Statistical Analysis

Patient characteristics and in-hospital mortality were described based on two different prespecified approaches: individual patient data from single case reports and case series that provided individual patient data were pooled together to form a unified group of patients. Case series that provided aggregate data rather than individual patient data were reported separately.

### RESULTS

Among 676 articles identified from the initial literature search, 22 studies were eligible and included in the analysis (1, 2, 5–24) (Supplementary Figure 1). Sixteen studies provided individual patient data of 53 patients with ICH (6–8, 10, 12, 13, 15–24), whereas six case series reported results on, overall, 394 patients (1, 2, 5, 9, 11, 14). Two studies (1, 24) included patient data that have been previously reported (7, 8). In order to avoid any duplication, in this study, we only included the data from the most recent reports (1, 24).

Quality assessment can be found in Supplementary Table 1. Forty-four (11.4%) out of 386 patients in the case series and 4 (9.7%) out of 41 patients in the single case reports died. The characteristics of patients are summarized in Table 1.

Out of 435 patients, individual data (age, sex, traumatic/non-traumatic type of ICH, time to idarucizumab treatment, etc.) were only available for 54, which did not allow us to perform an individual patient characteristic analysis.

### DISCUSSION

Our systematic review of data from published case reports and case series shows an estimated real-life in-hospital mortality of 9.7–11.4% in this patient population. Previous studies have reported the in-hospital mortality rate among warfarin- and direct oral anticoagulant (DOAC)-treated patients with ICH, which ranged from 25 to 33% and from 18 to 27%, respectively (27, 28). In the RE-VERSE AD study, which included dabigatran-treated patients with ICH who received idarucizumab, the described in-hospital mortality was 16.4% (2). This study, which includes data from case series and case reports, summarizes the evidence on the beneficial effect of idarucizumab in patients with ICH treated with dabigatran in order to present real-life quantitative data on in-hospital mortality.

Our review has several limitations. Heterogeneity of the cases (traumatic/non-traumatic, type of ICH: intraparenchymal/subdural hemorrhage) and missing data (age, gender, risk factors, comorbidities, timing of reversal agent application) are the main limitations of this study. Individual data were available for only 54 out of 435 patients, which could limit the assessment of how representative the cohort is. Comparison with patients with ICH who were not treated with idarucizumab would be valuable; however, there are no applicable published real-life data. Finally, we cannot exclude the presence of publication bias, particularly regarding the analysis
of case reports. On the other hand, the strength of the study is consideration of all published cases.

In conclusion, our systematic review of all published cases of dabigatran-related patients with ICH treated with idarucizumab provides a real-life quantitative estimate for real-life in-hospital mortality. This estimate seems to suggest the clinically relevant efficacy and safety of dabigatran reversal in real-life treatment of patients with ICH. However, this needs to be assessed in a propensity-score matched analysis or, ideally, in a prospective study of appropriate size.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

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**AUTHOR CONTRIBUTIONS**

SF and DS: study design, data acquisition, statistical analysis and interpretation, and manuscript preparation. MS and GN: data acquisition, statistical analysis and interpretation, and critical revision of the manuscript. JO: study concept and design, statistical analysis and interpretation, manuscript preparation, and study supervision. All authors contributed to the article and approved the submitted version.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.727403/full#supplementary-material
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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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