Hematoma Expansion Shift Analysis to Assess Acute Intracerebral Hemorrhage Treatments

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Abstract

Objective
Hematoma expansion (HE) is commonly analyzed as a dichotomous outcome in intracerebral hemorrhage (ICH) trials. In this proof-of-concept study, we propose an HE shift analysis model as a method to improve the evaluation of candidate ICH therapies.

Methods
Using data from the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial, we performed HE shift analysis in response to intensive blood pressure lowering by generating polychotomous strata based on previously established HE definitions, percentile/absolute quartiles of hematoma volume change, and quartiles of 24-hour follow-up hematoma volumes. The relationship between blood pressure treatment and HE shift was explored with proportional odds models.

Results
The primary analysis population included 863 patients. In both treatment groups, approximately one-third of patients exhibited no HE. With the use of a trichotomous HE stratification, the highest strata of ≥33% revealed a 5.8% reduction in hematoma growth for those randomized to intensive therapy (adjusted odds ratio [aOR] 0.77, 95% confidence interval [CI] 0.60–0.99). Using percentile quartiles of hematoma volume change, we observed a favorable shift to reduce growth in patients treated with intensive therapy (aOR 0.73, 95% CI 0.57–0.93). Similarly, in a tetrachotomous analysis of 24-hour follow-up hematoma volumes, shifts in the highest stratum (>21.9 mL) were most notable.

Conclusions
Our findings suggest that intensive blood pressure reduction may preferentially mitigate growth in patients at risk of high volume HE. A shift analysis model of HE provides additional insights into the biological effects of a given therapy and may be an additional way to assess hemostatic agents in future studies.

Trial Registration Information
ClinicalTrials.gov Identifier:NCT01176565.
Hematoma expansion (HE) is a determinant of poor outcome in acute intracerebral hemorrhage (ICH) and a compelling target for clinical trials. While hemodynamic and hemostatic therapies appear to mitigate HE,1,2 demonstrating efficacy in phase III trials has proved challenging.3-6

Current assessments of HE as a biomarker outcome include comparisons of central tendency (medians and means) and analysis of fixed dichotomous thresholds.7 However, reducing a continuous variable to a dichotomous outcome risks discarding substantial information on the biological effects of a given therapy and can lead to a reduced ability to detect relationships between a candidate therapy and an outcome of interest.8

Reducing a continuous variable to a polychotomous ordinal outcome may reduce information loss and improve the informativeness of the endpoint regarding treatment effects. For example, a hemostatic agent may reduce HE to a modest degree in all patients, but a dichotomous measure will detect this effect in only the small subset of patients in whom the reduction produces a threshold transition. It is possible that studies using dichotomous HE analysis are missing the true biological effect of therapies targeting HE.

We hypothesize that a more granular assessment of the distributions of hematoma volume change may provide a better assessment of the biological effect of a treatment in question and may support revisiting previous neutral therapeutic options for further study. In this proof-of-concept study, we propose an HE shift analysis model as a strategy for ICH treatment evaluation and illustrate this approach using previously published clinical trial data.

Methods
Participants
Participants were individuals enrolled in the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) trial.6 ATACH-2 was a multicenter, prospective, randomized, controlled trial designed to determine the efficacy of intensive blood pressure reduction in acute ICH. All patients were enrolled within 4.5 hours of symptom onset and received baseline and follow-up imaging at 24 hours via CT. Serial clinical assessments were performed, including a 90-day modified Rankin Scale. Exclusion criteria included clinical presentation >4.5 hours from symptom onset, anticoagulant use, Glasgow Coma Scale score <5 on initial assessment, and baseline hemorrhage volume >60 mL. For this analysis, we excluded patients who underwent emergency craniotomy before 24-hour repeat imaging or who lacked follow-up imaging. To represent a per-protocol analysis, patients who failed to reach their respective blood pressure targets within the first 24 hours after randomization (treatment failures) also were excluded.

Primary Outcome and Exposure
ICH and intraventricular hemorrhage volumes were calculated with volumetric analysis (Analyze Software, Mayo Clinic, Rochester, MN) with manual correction by a central staff blinded to treatment assignment, clinical findings, or the time points of image acquisition. The treatment allocation process of the ATACH-2 trial has been described previously.6 In brief, patients were treated with IV nicardipine and were randomly allocated to intensive (<140 mm Hg systolic blood pressure) or standard (<180 mm Hg systolic blood pressure) treatment arms for a period of 24 hours after randomization.

Analytical Approach
Patients were divided by treatment assignment, and we explored HE shift using the following techniques:

1. Trichotomous HE analyses. We created trichotomous definitions that explored no HE, minimal HE, and significant HE, with significant HE thresholds drawn from prior definitions used in the literature: an absolute intraparenchymal hematoma volume expansion trichotomy (≤0, <6, ≥6 mL), a relative intraparenchymal hematoma volume expansion trichotomy (≤0%, <33%, ≥33%), combined intraparenchymal expansion (≤0, <6 mL or 33%, ≥6 mL or 33%), and combined dual compartment expansion (≤0, <6 mL or 33%, ≥6 mL or 33%, or >0 mL intraventricular hemorrhage expansion)7,9,10 We compared these trichotomous definitions to their conventional dichotomous counterparts via regression models (see below).

2. Polychotomous hematoma volume change analyses. We created 2 analyses defined by quartiles of hematoma volume change: percentile growth and absolute growth. We measured hematoma volume change as the sum change of both intraparenchymal and intraventricular compartments. For absolute growth, the bounds of each shift category were determined by measuring and using the median and 25th/75th percentiles of hematoma volume change for the entire cohort.

3. Tetrachotomous 24-hour follow-up hematoma volume analyses. We created an analysis defined by quartiles of 24-hour follow-up final hematoma volumes. The bounds of each shift category were determined by measuring and using the median and 25th/75th percentiles of baseline hematoma volumes. We measured final hematoma volume at 24 hours after randomization or time of death for those who died before 24 hours.

Glossary

aOR = adjusted odds ratio; ATACH-2 = Antihypertensive Treatment of Acute Cerebral Hemorrhage II; CI = confidence interval; HE = hematoma expansion; ICH = intracerebral hemorrhage; IQR = interquartile range.
volume as the sum total of both intraparenchymal and intraventricular hemorrhage volumes.

A recent analysis showed functional outcome benefit in ATACH-2 patients who were treated within 120 minutes of symptom onset (called ultraearly blood pressure reduction). As a post hoc analysis, we repeated our analysis stratified by ultraearly blood pressure reduction status.

**Statistical Analysis**

We assessed the relationship between blood pressure treatment and stratified HE definitions, hematoma volume change, and 24-hour follow-up hematoma volumes using proportional odds models. Proportional odds assumptions were assessed with the χ² score test. Logistic regression was used to assess the respective definitions in their traditional dichotomous form as a comparison. In all models, we adjusted for baseline intraparenchymal volume and time from symptom onset to treatment initiation, selected a priori, according to previous studies of HE predictors. The Fisher exact test, Mann-Whitney U test, and analysis of variance were used as appropriate to evaluate baseline patient characteristics. We performed all statistical analysis using SPSS version 27.0 (IBM, Armonk, NY) and SAS version 9.4 (SAS Institute Inc, Cary, NC).

**Standard Protocol Approvals, Registrations, and Patient Consents**

Approval by a local ethics standards committee on human experimentation was obtained at all ATACH-2 enrolling sites. All patients provided written consent as per ethics board requirements at each site. Approval to perform this study was received from an ethics standards committee (ClinicalTrials.gov identifier: NCT01176565).

**Data Availability**

Access to the data used in this study can be obtained through a formal proposal to the NIH.

**Results**

**Cohort Characteristics**

The ATACH-2 study enrolled 1,000 patients. Our primary analysis population included 863 patients who met the inclusion criteria. Of the 137 patients excluded, 12 patients had missing imaging, 1 patient lacked treatment allocation, 121 patients did not reach their respective blood pressure targets (treatment failures), and 3 patients were treated with emergent surgery before follow-up imaging (figure 1). Baseline differences in the included and excluded populations are summarized in online-only supplement table 1 (data available from Dryad: doi.org/10.5061/dryad.sn02v6x3z). Patients excluded from this analysis were younger, were more likely to be male, and had higher serum glucose values at baseline. In the primary analysis population, 381 patients were assigned to the intensive therapy arm, and 482 patients were assigned to standard therapy. No major differences between the intensive and standard therapy arms were detected (table 1).

**Trichotomous HE Analysis**

HE shift built on conventional dichotomous definitions is visually represented as stacked horizontal bar graphs in figure 2 and online-only supplement figure 1 (data available from dryad: doi.org/10.5061/dryad.sn02v6x3z). In either treatment arm, approximately a third of patients exhibited no hematoma growth. While the remainder of patients exhibited some degree of growth, significant intraparenchymal expansion (absolute, relative, and combined) was reduced by 5% to 6% in those assigned to the intensive therapy arm. In ordinal regression models, treatment effects were similar in both shift strata and dichotomized definitions (table 2). The proportional odds assumption was met for all stratified definitions in both univariable and multivariable regression models.

**Polychotomous Hematoma Volume Change Analyses**

Three hundred twenty-one patients (37.2%) exhibited hematoma retraction or hematoma stability. Percentile change in hematoma volume is presented in figure 3A, with a 4% reduction of hematoma volume change >75% in patients receiving intensive therapy. An ordinal analysis of percentile hematoma volume change showed a significant between-group difference favoring intensive therapy (adjusted odds ratio [aOR] 0.73, 95% confidence interval [CI] 0.57–0.93, proportional odds assumption met).

Change in hematoma volume had a median of 0.4 mL (interquartile range [IQR] −0.4 to 3.0), yielding the following categories: stratum 1, <−0.5 mL; stratum 2, −0.5 to 0.5 mL; stratum 3, 0.5 to 3 mL; and stratum 4, > 3 mL.
The distribution of absolute hematoma volume change is presented in figure 3B. Intensive therapy was associated with a 5.2% reduction in the proportion of patients in the highest stratum. No significant between-group difference was observed (aOR 1.07, 95% CI 0.84–1.37, proportional odds assumption not met).

### Tetrachotomous 24-Hour Follow-up Hematoma Volume Analyses

Baseline total blood volumes were not normally distributed, with 70% of patients presenting with baseline volumes <20 mL. The median was 12.1 mL (IQR 5.4–21.9 mL). These values, the median and the 25th and 75th quartiles, were used to create hematoma volume strata: stratum 1, \( \leq 5.6 \) mL; stratum 2, 5.6 to 12.1 mL; stratum 3, 12.1 to 21.9 mL; and stratum 4, >21.9 mL.

### Table 1 Patient Characteristics of Primary Analysis Population Stratified by Treatment Assignment (N = 863)

| Characteristics                  | Intensive (n = 381) | Standard (n = 482) | p Value |
|----------------------------------|--------------------|--------------------|---------|
| Age, median (IQR), y             | 62 (54–73)a        | 62 (53–71)b        | 0.17    |
| Sex, n (%)                       | 223 (58.5)         | 301 (62.4)         | 0.24    |
| Medical history, n (%)           |                    |                    |         |
| Hypertension                     | 309/371 (83.3)     | 367/468 (78.4)     | 0.08    |
| Coronary artery disease          | 20/376 (5.3)       | 17/482 (3.5)       | 0.20    |
| Congestive heart failure         | 12/378 (3.2)       | 21/478 (4.4)       | 0.36    |
| Atrial fibrillation              | 16/377 (4.2)       | 16/478 (3.3)       | 0.49    |
| Hypercholesterolemia             | 96/356 (27.0)      | 117/459 (25.5)     | 0.63    |
| Diabetes type II                 | 68/376 (18.1)      | 76/474 (16.0)      | 0.43    |
| Previous stroke/TIA              | 56/379 (14.8)      | 83/480 (17.3)      | 0.32    |
| Smoking status, n (%)            |                    |                    |         |
| Current smoker                   | 85/349 (24.4)      | 133/449 (29.6)     | 0.05    |
| Former smoker                    | 63/349 (18.1)      | 96/449 (21.4)      |         |
| Nonsmoker                        | 201/349 (57.6)     | 220/449 (49.0)     |         |
| Baseline clinical information, median (IQR)  | | | |
| Systolic blood pressure, mm Hg   | 198 (184–214)      | 199 (183–217)      | 0.34    |
| Diastolic blood pressure, mm Hg  | 110 (96–121)       | 109 (98–123)       | 0.83    |
| Glucose, mg/dL                   | 121 (105–148)      | 121 (106–148)      | 0.67    |
| Glasgow Coma Scale score         | 15 (14–15)         | 15 (13–15)         | 0.60    |
| International normalized ratio   | 1.0 (0.9–1.0)      | 1.0 (0.9–1.0)      | 0.43    |
| Partial thromboplastin time, s   | 28 (24–31)         | 28 (25–31)         | 0.90    |
| Platelets, \( \times 10^9 \) cells/mm³ | 214 (177–254) | 213 (180–256) | 0.52    |
| Time to CT, min                  | 84 (60–126)        | 87 (58–130)        | 0.87    |
| Time to randomization, min       | 180 (137–237)      | 186 (137–235)      | 0.89    |
| Imaging                          |                    |                    |         |
| Baseline ICH volume median (IQR), mL | 9.86 (4.89–17.73) | 10.29 (5.16–18.99) | 0.32 |
| IVH presence at baseline, n (%)  | 92 (24.1)          | 133 (27.6)         | 0.25    |
| Baseline IVH volume, mean (SD), mL | 1.90 (5.60)      | 2.63 (6.95)        | 0.07    |

Abbreviations: ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage.

*a Missing 17 values.

*b Missing 23 values.
therapy arm. An ordinal analysis of the 24-hour hematoma follow-up volume distribution did not show a significant between-group difference (aOR 1.04, 95% CI 0.81–1.33, proportional odds assumption not met).

**Post Hoc Analysis**

Three hundred twenty-four patients were treated within 120 minutes of symptom onset and were included in our post hoc analysis. One hundred fifty-six patients were assigned to the intensive therapy arm, and 168 patients were assigned to standard therapy. Relative (33%) intraparenchymal expansion was associated with a 9% reduction in significant HE in the intensive therapy arm (aOR 0.72, 95% CI 0.47–1.07, proportional odds assumption met; figure 5A). Median baseline hemorrhage volume was 13.4 mL (IQR 5.5–23.5 mL). The median hematoma volume change was calculated to be 0.4
Table 2 Treatment Effect Estimates of Trichotomous and Dichotomous Definitions (N = 863)

| Outcome measure | Univariable model | Multivariable modela | p Value | p Value |
|-----------------|------------------|----------------------|---------|---------|
| Trichotomous definitions (ordinal regression)b | Odds ratio (95% CI) | Odds ratio (95% CI) |
| ≤0 mL/<6 mL/≥6 mL | 0.75 (0.58–0.97) | 0.78 (0.60–1.02) | 0.07 | |
| ≤0%/<33%/≥33% | 0.82 (0.65–1.10) | 0.88 (0.69–1.16) | 0.39 | |
| ≤0 mL or <33% or ≥6 mL or 33% | 0.84 (0.67–1.10) | 0.92 (0.71–1.18) | 0.50 | |

Dichotomous definitions (logistic regression)

| ≥6 mL | 0.66 (0.46–0.95) | 0.67 (0.46–0.97) | 0.03 | |
| ≥33% | 0.72 (0.52–0.99) | 0.72 (0.52–0.99) | 0.05 | |
| ≥6 mL or 33% | 0.76 (0.56–1.04) | 0.77 (0.56–1.06) | 0.11 | |
| ≥6 mL or >0 mL IVH | 0.85 (0.63–1.15) | 0.91 (0.66–1.25) | 0.54 | |
| ≥6 mL or 33% or >0 mL IVH | 0.89 (0.67–1.18) | 0.94 (0.71–1.26) | 0.70 | |

Abbreviations: CI = confidence interval; IVH = intraventricular.

a Adjusted for baseline intraparenchymal volume and time to treatment initiation.

b Proportional odds assumption met (via score test).

mL. Because these values were similar to the calculated values of the whole cohort, we elected to use the same strata as above for 24-hour follow-up hematoma volume and hematoma volume change. The distribution of percentile and absolute hematoma volume changes are presented in figure 5B (aOR 0.75, 95% CI 0.50–1.11, proportional odds assumption met) and figure 5C (aOR, 1.35, 95% CI 0.91–2.02, proportional odds assumption not met). The stratified quartiles of 24-hour follow-up hematoma volumes are presented in figure 5D (aOR 0.83, 95% CI 0.56–1.24). Intensive therapy was associated with a 7% reduction in the proportion of patients in the highest stratum. A similar pattern was observed in patients treated after 120 minutes from symptom onset (supplemental figure II; data available from dryad: doi.org/10.5061/dryad.sn02v6x3z).

Discussion

A decade of neutral clinical trials in ICH has led to a sense of nihilism in the medical and research communities and a notion that failed therapeutics should be discarded. Yet, important lessons from prior ICH trials can lead to new approaches in study design14 such as prehospital administration of hemostatic therapy (ClinicalTrials.gov identifier: NCT03496883, NCT03385928) or treatment stratification based on imaging biomarkers.13,15 Likewise, new approaches for evaluating HE are also necessary to better assess candidate therapies and to understand their biological effect on the dynamics of hematoma growth and retraction.

In this study, we propose an HE shift analysis as a way to assess hematoma growth in response to therapy, akin to estimating the effect of therapy in ischemic stroke trials with an ordinal modified Rankin Scale score and horizontally stacked bar graphs (Grotta bars).16-19 This analytical model can improve our understanding of the biological effect of a therapy targeting HE, particularly if that therapy benefits a smaller subgroup of patients who are destined for larger amounts of expansion.

Using this approach, we were able to show that intensive blood pressure reduction in the ATACH-2 study had a greater magnitude of effect in those patients at highest risk of HE. We observed a 5% to 6% reduction in the highest stratum of hematoma volume change and 24-hour follow-up hematoma volumes in the intensive therapy arm (figures 3, A and B and 4), suggesting that those patients with the largest HE may well have received some benefit from the intervention. In contrast to a dichotomous definition for which very little information can be gleaned for patients who experience hematoma growth below the significant threshold, the use of a shift analysis allows us to observe that many patients exhibit lesser degrees of hematoma growth that can also be mitigated by intensive blood pressure therapy. In addition, we observed that the 37.2% of patients with hematoma stability or retraction were distributed equally in both treatment arms, suggesting that roughly a third of patients with acute ICH are unlikely to benefit from intensive blood pressure reduction (figures 2 and 3A). These findings were more pronounced in those patients who were treated within 120 minutes of symptom onset, in
whom the risk of HE is highest (figure 5). It is possible that intensive blood pressure reduction can mitigate the risk of large HE but has a minimal effect on hematomas that are stabilizing and destined for little to no HE. This provides further support for the investigation and application of biomarkers associated with HE in the recruitment of patients for trials, as well as a focus on recruitment within the hyperacute time period.
Figure 5 Post Hoc Analysis

A

Intraparenchymal expansion ≥33% | Ultra-early blood pressure reduction cohort | (n = 324)

- Intensive: 39.1% growth, 41.7% minimal growth, 19.2% no growth or regression
- Standard: 36.3% growth, 35.7% minimal growth, 28.0% no growth or regression

B

Percentile hematoma volume change (THV) | Ultra-early blood pressure reduction cohort | (n = 324)

- Intensive: 40.4% greater than 75%, 35.3% between 50 and 75%, 11.5% between 25 and 50%, 7.7% between 0 and 25%, 3.6% less than 0%
- Standard: 36.3% greater than 75%, 29.2% between 50 and 75%, 15.5% between 25 and 50%, 15.5% between 0 and 25%

C

Absolute hematoma volume change (THV) | Ultra-early blood pressure reduction cohort | (n = 324)

- Intensive: 32.1 mL hematoma growth > 3 mL, 21.8% between 0.5 mL and 3 mL, 19.9% between -0.5 mL and 0.5 mL, 26.3% hematoma retraction > -0.5 mL
- Standard: 23.2 mL hematoma growth > 3 mL, 27.4% between 0.5 mL and 3 mL, 16.7% between -0.5 mL and 0.5 mL, 32.7% hematoma retraction > -0.5 mL

D

24-hour follow-up volumes | Ultra-early blood pressure reduction cohort | (n = 324)

- Intensive: 23.7 mL greater than 21.98 mL, 20.5 mL between 12.13 and 21.98 mL, 22.4 mL between 5.6 and 12.13 mL, 33.3 mL less than or equal to 5.6 mL
- Standard: 22.0 mL greater than 21.98 mL, 20.8 mL between 12.13 and 21.98 mL, 16.7 mL between 5.6 and 12.13 mL, 40.5 mL less than or equal to 5.6 mL

Intraparenchymal expansion ≥33% (A), percentile (B), and absolute (C) hematoma volume change (total hematoma volume [THV]), and 24-hour follow-up volumes (D) for patients with ultraearly blood pressure reduction (treated in <120 minutes from symptom onset).
We explored HE shift strata in multiple ways: using previously established HE dichotomous definitions, quartiles of percentile/absolute hematoma volume change, and quartiles of 24-hour follow-up hematoma volumes. Each method has its merits and potential drawbacks. The use of established dichotomous definitions as stratification criteria is appealing due to their frequent use in prior treatment trials and the ability to incorporate secondary intraventricular hemorrhage expansion.1,6,20,21 However, even the choice of established dichotomous definitions differs between trials; absolute thresholds can underestimate treatment effects in small-volume hemorrhages, while relative thresholds can underestimate effects in large-volume hemorrhages.22,23 In addition, the conversion of a dichotomous definition to a 3-category form offers only a modest amount of new information. Conversely, we were better able to appreciate the biological effects of intensive blood pressure reduction by assessing quartiles of total hematoma volume change after 24 hours. These approaches are data driven, offer increased discriminative ability, and account for the characteristics of the study population because the strata are unique to each individual dataset. In our analysis, we opted to use the median and 25th/75th percentiles as the borders of each shift category because we wanted to select quartiles that were evenly spread across the whole dataset. This approach avoids potential discrepancies between studies due to differences in expansion definitions (e.g., using 6 mL vs 12.5 mL).

Our study has several limitations. Because this is a proof-of-concept study, we used a per-protocol approach and excluded treatment failures and patients with missing imaging or outcome data. In addition, the median intraparenchymal hemorrhage volume of the primary analysis cohort was 10.18 mL (IQR 4.97–18.32 mL); while this is similar to the baseline volumes of other blood pressure treatment trials,2,3,4 it is a mild to moderate ICH cohort and may not represent the full spectrum of severity. Furthermore, we recognize that although developing a new method to analyze a surrogate endpoint can help us better understand the biological effect of a therapy, it may not have any impact on the final clinical outcome itself, and in our analysis, the relationship between shift and outcome was not investigated. In this regard, our intent is not to reinterpret the primary results of the ATACH-2 or other clinical trials. Rather, we believe re-evaluation of therapies using a hematoma shift analysis may shed light on the magnitude of therapeutic effect in specific subpopulations of patients with ICH. This more granular insight into HE supports revisiting previous neutral therapeutic options for further study and can potentially help refine future trial design. Finally, while converting a continuous variable to a polychotomous ordinal outcome improves our assessment of treatment effect, this comes at the cost of some information loss. Additional studies exploring techniques to evaluate the hematoma shift concept as a continuous variable are required.

We applied the technique of HE shift analysis and showed that intensive blood pressure reduction may preferentially mitigate growth in patients at risk of high-volume HE. We suggest that a shift analysis model can be applied to previous clinical trial data to provide additional insights into HE mitigation therapies and to inform patient selection for future trials.

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**Disclosure**
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### Appendix Authors

| Name               | Location                  | Contribution                                      |
|--------------------|----------------------------|---------------------------------------------------|
| Vignan Yogendrakumar, MD, MSc | University of Ottawa, Ontario, Canada | Drafting/Revision of the manuscript for content; study concept or design; analysis or interpretation of data |
| Tim Ramsay, PhD    | University of Ottawa, Ontario, Canada | Drafting/revision of the manuscript for content; study concept or design; analysis or interpretation of data |
| Bijoy K. Menon, MD, MSc | University of Calgary, Alberta, Canada | Study concept or design; analysis or interpretation of data |
| Adnan Qureshi, MD   | University of Missouri, Columbia | Major role in the acquisition of data |
| Jeffrey L. Saver, MD | University of California, Los Angeles | Drafting/revision of the manuscript for content; study concept or design; analysis or interpretation of data |
| Dar Dowlatshahi, MD, PhD | University of Ottawa, Ontario, Canada | Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content |

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