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REVIEW ARTICLE

Evaluating hemostatic thresholds for neuraxial anesthesia in adults with hemorrhagic disorders and tendencies: A scoping review

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Abstract

Neuraxial anesthesia can be complicated by spinal or epidural hematoma and may result in permanent neurologic injury. There is a paucity of literature characterizing this serious complication in patients with congenital and acquired hemorrhagic disorders or tendencies. The objective of this scoping review was to describe the hemostatic laboratory parameters where neuraxial anesthesia has been administered with and without spinal and epidural hematoma in patients with preexisting hemorrhagic disorders and tendencies, including immune thrombocytopenia, gestational thrombocytopenia, thrombocytopenia associated with hypertensive disorders of pregnancy, platelet function disorders, von Willebrand disease, coagulation factor deficiencies, and fibrinogen disorders. A systematic search of Ovid MEDLINE, CINAHL, Embase, Scopus, and Web of Science was performed. Two authors independently reviewed all titles, abstracts, and full texts to determine study eligibility and extract data. Qualitative synthesis of 91 studies revealed significant gaps in our understanding of the risk of spinal and epidural hematoma in patients with hemorrhagic disorders and tendencies, including few studies of males and in nonobstetric settings. Most reviewed articles were small, retrospective studies at high risk for potential bias. With such low-quality data, we were unable to provide any true estimates of the risk of spinal or epidural hematoma for these patients, nor could we attribute any specific hemostatic or laboratory values to increased risk of hematoma. There is a need both for larger and more rigorously designed and reported studies on this subject and for structured, comprehensive recommendations for safe administration and removal of neuraxial anesthesia in patients with hemorrhagic disorders and tendencies.

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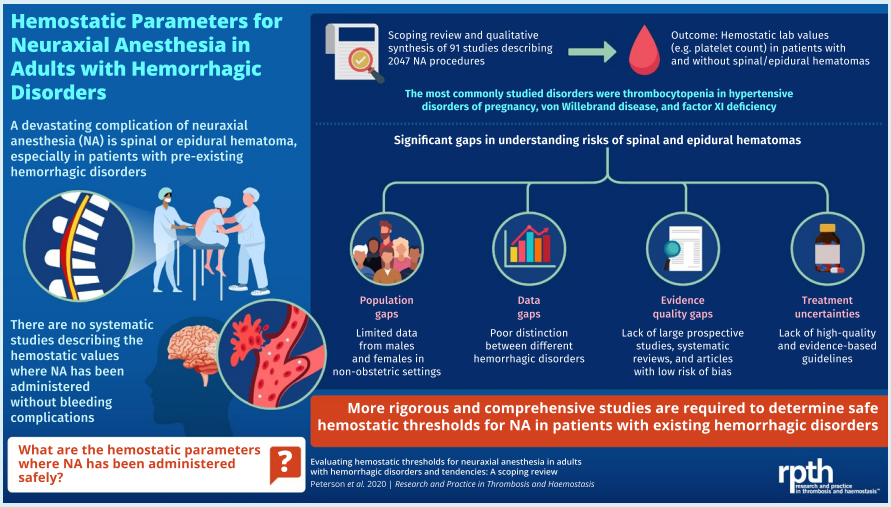

KEYWORDS
anesthesia, blood platelet disorders, epidural, hematologic tests, hematoma, hemorrhagic disorders, spinal

Essentials

- Spinal or epidural hematoma can be a devastating complication of neuraxial anesthesia.
- We review outcomes of 2047 neuraxial anesthetics in patients with hemorrhagic disorders/tendencies.
- Large gaps exist in our understanding of the risk of local hematoma in these patients.
- Current data are insufficient to determine safe hemostatic thresholds for neuraxial anesthesia in this population.

1 | INTRODUCTION

Neuraxial anesthetic techniques, including spinal, epidural, and combined spinal-epidural blocks, are commonly used for acute pain control in surgery and obstetrics.[1] Neuraxial anesthetics may offer patients numerous benefits over general anesthetic, including decreased 30-day mortality, reduced length of stay, and lower risk of venous thromboembolism.[2,3] They may also provide more effective pain control compared to intravenous patient-controlled analgesia.[4] In obstetrics, neuraxial techniques have long been the preferred method of analgesia for labor and delivery, reducing pain more effectively than other methods.[5]

One serious complication of neuraxial anesthesia is spinal or epidural hematoma, which can lead to permanent neurologic injury, including paralysis, sensory loss, or autonomic dysfunction.[1] According to one large retrospective review, the risk of spinal or epidural hematoma following neuraxial blockade is estimated at 2.14 per 100 000 (95% confidence interval, 0.44-6.25 per 100 000) in the population at large.[6] In the general obstetric population, the risk of spinal or epidural hematoma is approximately 0.54 per 100 000.[7] The risk of spinal or epidural hematoma is generally accepted to be higher in patients with bleeding diatheses compared to the general population[8]; however, this conclusion is largely based on anecdotal data rather than empirical evidence.

There is extensive literature describing spinal and epidural hematoma after neuraxial anesthesia in patients receiving antithrombotic therapy[9-12]; however, there is a paucity of literature characterizing this serious bleeding complication in patients with congenital or acquired hemorrhagic disorders/tendencies unrelated to medications. Without a robust body of literature, clinicians are often unable to determine which patients suffering from congenital and acquired hemorrhagic disorders/tendencies can safely receive neuraxial anesthetics.

A review by Choi and Brull[13] described the frequency of hemorrhagic complications after neuraxial anesthesia in patients with immune thrombocytopenia (ITP), von Willebrand disease (VWD) and hemophilia. However, there are no systematic, scoping studies that describe the existing body of literature related to hemorrhagic complications from neuraxial anesthesia in patients with other, less common, hemorrhagic disorders or tendencies. The aim of this scoping review was to describe the hemostatic laboratory parameters where neuraxial anesthesia has been administered with and without spinal or epidural hematoma in patients with single preexisting hemorrhagic disorders/tendencies, including ITP, gestational thrombocytopenia, thrombocytopenia associated with hypertensive disorders of pregnancy, platelet function disorders, VWD, coagulation factor deficiencies, and fibrinogen disorders. While gestational thrombocytopenia does

not confer additional bleeding risk, placing neuraxial anesthesia for a patient with thrombocytopenia of any etiology can be a source of anxiety for patients and healthcare providers alike. Thus, we included gestational thrombocytopenia in this scoping review to help inform the clinical approach to patients affected by this condition.

Ultimately, our objective for this scoping review was to develop an evidence-based framework that may facilitate clinical decision making surrounding neuraxial anesthesia and to identify areas where additional evidence is urgently needed to best support clinical care.

2 | METHODS

This scoping review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.[14] The review's protocol can be found here: https://osf.io/r7qaz/?view_only=fa1088e165cb43a59f1097f0119a56fd.

2.1 | Information sources and searches

A detailed search strategy was developed in collaboration with a medical librarian. Examples of keywords used in the search include "thrombocytopenia," "coagulopathy," "factor deficiency," "bleeding time," "clotting factor assays," "neuraxial anesthesia," "spinal anesthesia," "epidural anesthesia," and their derivatives. The full search strategy is available in Appendix S1. The search was performed in Ovid MEDLINE (1946 to July 10, 2019), CINAHL (inception to July 10, 2019), Embase (1947 to July 10, 2019), Scopus (inception to July 10, 2019), and Web of Science (inception to July 10, 2019). The search was limited to English-language studies only. There were no limits placed on date of publication in order to maximize the repository of data potentially included in the review. Gray literature identified by this search strategy was included. Reference lists of all publications included in full-text review were screened to identify additional sources for inclusion.

2.2 | Study selection

This scoping review included all types of studies, including case reports, case series, observational studies, interventional studies, systematic reviews, meta-analyses, scoping reviews, narrative reviews, guidelines, and editorials. Any individual study with results that had also been reported in a systematic review was excluded to prevent double counting of data.

Titles and abstracts were screened by two reviewers (WP and BT) independently, followed by full-text review. A third reviewer (MS) resolved conflicts through adjudication. Studies were included if patients with a known diagnosis of a single hemorrhagic disorder/tendency received either an epidural, spinal, or combined spinal-epidural anesthetic. In studies that reported hemorrhagic complications, consisting of either spinal or epidural hematoma, the diagnosis must have been confirmed on computed tomography or magnetic resonance imaging for inclusion in the review. Patients with an additional hemorrhagic disorder or other comorbidity predisposing to bleeding (eg, arteriovenous malformation) were excluded because these conditions can independently increase the risk of hematoma. Peripheral nerve blocks and lumbar punctures were also excluded due to their unique risk of complications and indications for use.

After completion of initial title and abstract review, the decision was made to exclude patients with coagulopathy secondary to liver or renal disease, as these patients were too heterogeneous to draw meaningful conclusions from. Thus, we included only patients with ITP, gestational thrombocytopenia, thrombocytopenia associated with hypertensive disorders of pregnancy, platelet function disorders (eg, Glanzmann thrombasthenia), VWD, factor VII deficiency, hemophilia A or B (or carriers), factor XI deficiency, factor XIII deficiency, and fibrinogen disorders.

2.3 | Data collection/charting process/data items

Data were collected using a prepiloted data collection form for each hemorrhagic disorder/tendency. Relevant study characteristics were extracted, including authors, title, publication details and type of study, and whether a full article was available or only an abstract. Available population demographics were collected for all studies, including number of neuraxial procedures, mean age, sex, and bleeding history. The type of surgery or procedure was noted along with relevant details of the neuraxial anesthetic technique and the outcome of the procedure (ie, hematoma or no hematoma).

For case reports and case series, reviewers extracted the last known hemostatic parameter before administration of neuraxial anesthesia, any relevant treatment administered before the anesthetic procedure, and the hemostatic parameter at the time of neuraxial catheter removal. For narrative reviews, systematic reviews, and observational studies, the minimum hemostatic parameter that was reported before an uncomplicated neuraxial anesthetic was recorded. If any study proposed a minimum hemostatic threshold for safe administration of neuraxial anesthesia or removal of the catheter (eg, a guideline statement), this was also recorded. For each included narrative review, data sources with which the reviews generated their recommendations were extracted. Additionally, reviewers were able to clarify any specific details of extracted data in a "notes" section if desired.

2.4 | Synthesis of results

Qualitative synthesis was used to summarize the existing cases, reviews, observational and interventional studies for each hemorrhagic disorder/tendency and report the hemostatic thresholds proposed by guidelines, reviews, and expert opinion papers. Certain

study features were recorded as indicators of potential risk of bias. For review articles, we recorded the proportion that were systematic reviews compared to narrative reviews. Among systematic reviews/meta-analyses, we also noted the proportion analyzing prospective studies. For nonreview studies (ie, observational studies) we identified the presence or absence of three key aspects: prospective design, well-defined population, and measurement of association between the laboratory parameter and risk of hematoma.

3 | RESULTS

We identified 1418 abstracts for review, of which 91 met the criteria for inclusion (Figure 1). Relevant characteristics of these studies are summarized in Table 1. We reviewed 23 case reports/case series, 27 cohort studies, 5 surveys, and 36 review articles. No randomized controlled trials or meta-analyses were identified. Twenty-three percent of articles we reviewed were available only as abstracts. Full results of data extraction can be found in Appendix S2.

Among the studies that reported on neuraxial anesthesia administration in patients with thrombocytopenia, many did not differentiate between disorders. For example, 25 studies did not differentiate between ITP, gestational thrombocytopenia, and hypertensive disorders of pregnancy. In these cases, data were categorized under "thrombocytopenia not otherwise specified."

Results are described in detail below according to hemorrhagic disorder/tendency.

3.1 | Immune thrombocytopenia

Nine studies relating to patients with ITP and neuraxial anesthesia were found[13,15-22] and are presented in Table 2.

Our search yielded two systematic reviews[13,16] and seven narrative reviews.[15,17-22] There were three articles included in the analysis of both systematic reviews, so data were carefully scrutinized to avoid duplicate reporting. One systematic review included data from guidelines and from patients not meeting our inclusion criteria.[13] These data were not extracted and are not reported below.

Within the systematic reviews, one neuraxial procedure was successfully completed at a platelet count <10 × 10^9/L, which was reported in both articles.[13,16] One additional procedure was performed

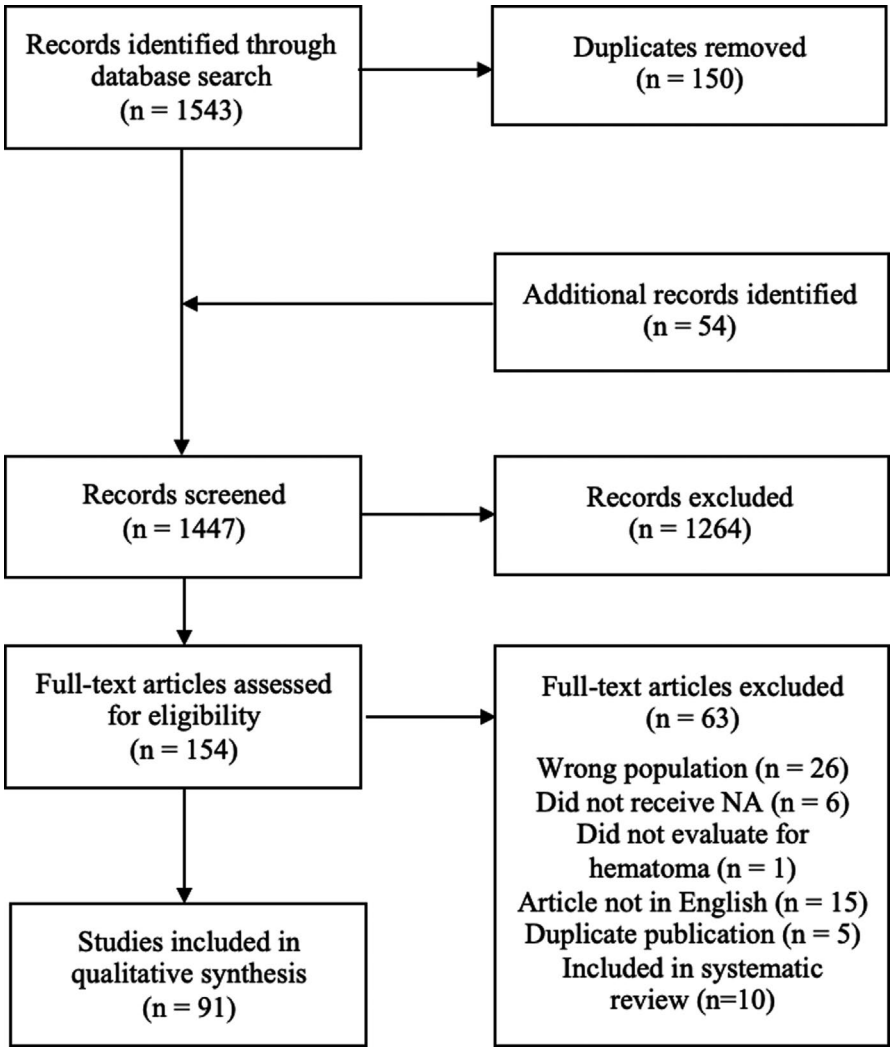

FIGURE 1 PRISMA diagram. NA, neuraxial anesthesia

TABLE 1 Characteristics of included papers

Characteristics	Number of papers	%
Year of publication		
1981-1990	3	3.3
1991-2000	11	12.1
2001-2010	35	38.5
2011-2019 (up to July 2019)	42	46.2
Country of corresponding author		
Canada/United States	39	42.9
Europe	34	37.4
Asia/Middle East	9	9.9
Other	9	9.9
Study design		
Case report/series	23	25.3
Retrospective cohort	24	26.4
Prospective cohort	3	3.3
Questionnaire/survey	5	5.5
Narrative review	34	37.4
Systematic review of retrospective studies	1	1.0
Systematic review of prospective studies	1	1.1
Abstract only	21	23.1
Sample size (n) (when specified)		
1-10.0	25	50.7
11-100	19	38.0
101-200	4	8.0
>200	2	4.0
Type of surgery/procedure		
Obstetric	85	93.4
Orthopedic	1	1.0
Other	5	5.5
Type of neuraxial anesthesia		
Spinal	10	11.0
Epidural	15	16.5
Combined spinal-epidural	5	5.5
Unspecified	61	67.0
Hemorrhagic disorder/tendency		
von Willebrand disease	19	14.7
Immune thrombocytopenia	9	7.0
Gestational thrombocytopenia	3	2.3
Thrombocytopenia associated with hypertensive disorders of pregnancy	29	22.5
Thrombocytopenia not otherwise specified[a]	25	19.4
Platelet function disorders	5	3.9
Hemophilia A (including carriers)	11	8.5
Hemophilia B (including carriers)	8	6.2
Factor VII deficiency	4	3.1
Factor XI deficiency	11	8.5
Factor XIII deficiency	2	1.6
Fibrinogen disorders	3	2.3

[a]Includes studies where etiology of thrombocytopenia is not explicitly stated or not differentiated.

at a platelet count between 10 × 10^9/L and 20 × 10^9/L.[16] The most commonly proposed platelet count threshold for administration of neuraxial anesthesia in patients with immune thrombocytopenia was 50 × 10^9/L,[20-22] with a range of other proposed thresholds from 70 × 10^9/L[15] to 75 × 10^9/L.[19] One narrative review stated that neuraxial anesthesia is generally contraindicated in patients with ITP but did not cite evidence to support this claim.[17] Only one review suggested a threshold for the removal of a neuraxial catheter—a minimum platelet count of 60 × 10^9/L[13]—which was taken directly from the recommendations of a previous study.[23] Most narrative reviews developed their recommendations based on observational studies,[15,17,18] review articles,[15,17-20] or expert opinion.[20,21] There was only one source article that was cited in the recommendations of more than one narrative review.

3.2 | Gestational thrombocytopenia

We extracted data from three studies of women with gestational thrombocytopenia.[17,20,24] A single retrospective cohort study summarized 20 neuraxial procedures—all epidurals—performed at platelet counts as low as 71 × 10^9/L.[24] None resulted in hemorrhagic complications.

Of two narrative reviews, one suggested that neuraxial anesthesia is safe for patients with ITP and gestational thrombocytopenia if the platelet count is >50 × 10^9/L and "stable."[20] The other review article stated that neuraxial anesthesia may be performed in patients with gestational thrombocytopenia "if coagulation tests are normal."[17] Both of these recommendations were based on expert opinion. It is important to highlight that gestational thrombocytopenia is generally considered to be a physiologic condition where, by definition, platelet counts do not fall below 50 × 10^9/L to 80 × 10^9/L and there is no increased bleeding risk or abnormal coagulation status.[25] Thus, the recommendations made by these narrative reviews do not reflect the underlying physiologic nature of the disorder, and their merit in guiding management in this setting is unclear.

No studies recommended a minimum threshold for neuraxial catheter removal.

3.3 | Thrombocytopenia associated with hypertensive disorders of pregnancy

We extracted data from 29 studies of patients with hypertensive disorders of pregnancy, including 12 with preeclampsia,[20,26-36] 2 with eclampsia,[37,38] and 9 with HELLP syndrome (hemolysis,

TABLE 2 Studies with data relevant to use of neuraxial anesthesia in immune thrombocytopenia

Study	Study design	Type of procedure	Type of neuraxial anesthesia	Sample size, No.	Minimum platelet count reported without spinal/epidural hematoma ($\times 10^9$/L)		Minimum safe platelet count threshold proposed ($\times 10_9$/L)	
					Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic	Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic
American College of Obstetricians and Gynecologists (2019)[15]	Narrative review	Obstetric	Epidural	N/A	N/A	N/A	70	N/A
Bailey et al (2019)[16]	Systematic review	Obstetric	Unspecified	166	2	N/A	N/A	N/A
Choi & Brull (2009)[13]	Systematic review	Obstetric	Unspecified	323	2	N/A	N/A	60
Chow et al (2011)[18]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	N/A	Remove as soon as possible
Harrop-Griffiths et al (2013)[20]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	50	N/A
Moen & Irestedt (2008)[17]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	Usually contraindicated	N/A
Myers & Truelove (2011)[19]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	75	N/A
Ozelo et al (2018)[22]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	50	N/A
Pavord (2016)[21]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	50	N/A

N/A, not applicable.

elevated liver enzyme levels, and low platelet levels).[39-47] Six studies reported on multiple hypertensive disorders of pregnancy and did not differentiate between them.[48-53] Of the 29 studies, we reviewed five case reports/case series,[37-39,45,46] six retrospective cohort studies,[40,42-44,47,48] and one prospective cohort study.[36] These studies described 236 neuraxial procedures. We analyzed 19 epidurals,[38-40,48] 28 spinal procedures,[37,45-47] and an additional 189 procedures that did not differentiate between spinal and epidural anesthetics. Some patients were supported with platelet transfusions; however, most authors did not precisely describe which patients received treatment.[42-44] Only Osmanagaoglu[47] published a treatment threshold for platelet transfusion. In this study, all patients with platelet counts <50 × 10^9/L received platelet transfusion before neuraxial anesthetic administration, though platelet counts were not repeated after treatment. Neuraxial anesthesia was administered at platelet counts ranging from 19 × 10^9/L[42] to 99 × 10^9/L[45] without bleeding complications and were removed uneventfully at platelet counts of >100 × 10^9/L in two studies.[43,44] However, three hematomas were reported. In one case, a woman with eclampsia and a platelet count of 71 × 10^9/L experienced a spinal hematoma with neurologic deficits requiring emergent laminectomy.[38] A spinal hematoma developed in a second woman with HELLP syndrome and a platelet count of 91 × 10^9/L.[46] The third local hematoma occurred after epidural analgesia in a woman with HELLP syndrome, a platelet count of 93 × 10^9/L, and a prolonged bleeding time.[48]

Among 15 narrative reviews[20,27-35,41,49-52] and two surveys of anesthesiologists,[26,53] the most commonly proposed minimum platelet count for provision of neuraxial anesthesia was 80 × 10^9/L.[29,31,32,35,41,49,50,52] Overall, proposed thresholds ranged from platelet counts >50 × 10^9/L[36] to >100 × 10^9/L.[33,50,53] Two studies commented on removal of the neuraxial catheter; one stated that removal should occur as soon as possible,[41] and the other recommended removal only if "coagulation status" was normal.[29] Review articles made recommendations based on observational data,[33,41,52] review articles[20,29,30,32,34,41,49,50,52] and/or expert opinion.[20,27-29,31,34,35,41,49,51,52] There was limited overlap in the articles used to generate these recommendations; only three articles were cited more than once.[33,41,52]

3.4 | Thrombocytopenia not otherwise specified

Twenty-five studies reported laboratory thresholds for administration of neuraxial anesthesia in patients with low platelets but did not specify the underlying etiology of thrombocytopenia.[11,23,24,54-75] All but 2 of the 25 studies described women during labor and delivery.[11,62] Studies of pregnant women usually described patients with ITP, gestational thrombocytopenia, or thrombocytopenia associated with hypertensive disorders of pregnancy but did not differentiate between disorders. Some studies may have also described patients with other hemorrhagic disorders that may come with different inherent bleeding risk. Thus, the results of this section must be interpreted with caution.

TABLE 3 Summary of hematomas

Study	Study design	Type of procedure	Type of neuraxial anesthesia	Sample size, N	Hematomas, No.	Platelet count at time of block (×10^9/L)
Lagerkranser (2017)[11]	Narrative review	Nonobstetrics	Unspecified	166	13	<150 (n = 6), <80 (n = 7)
Yuen et al (1999)[38]	Case report	Obstetrics	Epidural	1	1	71
Koyama et al (2010)[46]	Case report	Obstetrics	Spinal	1	1	91
Sibai et al (1986)[48]	Retrospective cohort	Obstetrics	Epidural	16	1	93

A total of 1192 neuraxial procedures were described within 12 retrospective cohort studies,[23,24,66-75] 1 prospective cohort study,[65] and 1 case series.[54] There were 68 epidural anesthetics[24,54,66] and 2 spinal anesthetics.[75] The types of the remaining procedures were not specified. One study analyzed 13 case reports of spinal or epidural hematoma occurring in patients with thrombocytopenia (Table 3); seven of these patients had platelet counts <80 × 10^9/L; however, the author did not report precise platelet counts at the time of bleeding for any case.[11] Neuraxial procedures in the other studies were performed uneventfully at platelet counts ranging from 2 × 10^9/L[62] to 92 × 10^9/L.[24] One study reported a platelet count of 36 × 10^9/L at the time of neuraxial catheter removal.[23]

There were eight narrative reviews[11,58-64] and three surveys of anesthesiologists.[55-57] Platelet count thresholds of 50 × 10^9/L[59,61,62,68,70,74] and 80 × 10^9/L[11,55,57,60,62] were commonly proposed, with some studies suggesting alternate cutoffs of 65 × 10^9/L,[56] 70 × 10^9/L,[63,64,67] and 75 × 10^9/L.[58,72] Only one study commented on neuraxial catheter removal, stating that catheters should be withdrawn as soon as they are no longer needed but only if coagulopathy had been corrected first.[58] Conclusions were made based on data from observational studies,[11,59-61,63,64] review articles,[11,60,63,64] or expert opinion.[58,59,61-64] Only one observational study[59,60] and one review article was cited more than once.[60,63]

3.5 | Platelet function disorders

We extracted data from five studies of patients with platelet function disorders, including Bernard-Soulier syndrome,[76,77] Glanzmann thrombasthenia,[76,77] gray platelet syndrome,[78] and other unspecified disorders.[79,80] Of the five studies, there were three case reports/case series[78-80] that described a total of four neuraxial anesthetic procedures, including one spinal anesthetic,[78] two combined spinal-epidural anesthetics,[80] and one that was of unspecified type.[79] No epidural or spinal hematomas were reported. Only one study reported a hemostatic laboratory parameter tested before administration of neuraxial anesthesia. In this study, a woman with gray platelet syndrome uneventfully received a spinal anesthetic with a platelet count of 112 × 10^9/L.[78]

Among the two narrative reviews identified, one paper warned that neuraxial anesthesia is contraindicated in platelet function disorders,[76] and the other study advised that neuraxial anesthesia should only be considered in mild platelet function disorders where benefit outweighs bleeding risk.[77] Both recommendations were based on expert opinion.

3.6 | Von Willebrand disease

We identified 19 studies relating to neuraxial anesthesia in patients with VWD.[13,17,18,63,64,77,79,81-92] Of the 19 studies, 5 described patients with type 1 VWD,[81,83,84,86,90] and 2 described patients with type 2 VWD,[82,85] while the remainder did not specify the subtype. Studies are summarized in Table 4.

Six case reports/case series,[81-86] one prospective cohort study,[90] and three retrospective cohort studies[79,91,92] were reviewed, which described 134 neuraxial anesthetic procedures without any reported spinal or epidural hematoma. Fifteen epidural procedures,[82-84,92], two spinal anesthetics,[85,86] and one combined spinal-epidural[81] were reviewed. The remaining 116 procedures were performed in studies reporting a mixture of both spinal and epidural anesthetics. All but one neuraxial procedure was performed in the obstetric population.[83] Patients in some studies received treatment with desmopressin or VWF/factor VIII concentrates before administration of neuraxial anesthesia; however, important details were missing from each. Authors either did not specify which patients received treatment[92] or they did not publish a replacement target.[82,83,85,86] Overall, neuraxial anesthesia was performed at VWF levels ranging from 10 IU/dL[13] to 198 IU/dL[83] and factor VIII levels ranging from 38 IU/dL[13] to 249 IU/dL[84] without bleeding complications. Only one study reported VWF and factor VIII levels at time of neuraxial catheter removal: 136 IU/dL and 100 IU/dL, respectively.[83]

Among eight narrative reviews[17,18,63,64,77,87-89] and one systematic review,[13] five studies recommended a VWF and factor VIII threshold of 50 IU/dL for placement of neuraxial anesthetics.[18,63,77,82,89] Three studies stated that neuraxial anesthesia was appropriate if VWF and factor VIII levels were "normalized."[17,64,87] One study suggested that these procedures are contraindicated regardless of VWF and factor

TABLE 4 Studies with data relevant to use of neuraxial anesthesia in von Willebrand disease

Study	Design	Type of procedure	Type of neuraxial anesthesia	Sample size, No.	Type	Minimum VWF activity reported without spinal/epidural hematoma (IU/dL)	
						Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic
Amorde et al (2011)[82]	Case report	Obstetric	Epidural	1	2	N/A	N/A
Breivik et al (2018)[88]	Narrative review	Surgery	Unspecified	N/A	All	N/A	N/A
Cata et al (2009)[85]	Case report	Obstetric	Spinal	1	2	N/A	N/A
Chi et al (2009)[79]	Retrospective cohort	Obstetric	Unspecified	12	1; 2	Type 1 41; Type 2 72	N/A
Choi & Brull (2009)[13]	Systematic review	Obstetric	Unspecified	74	All	10	N/A
Chow et al (2011)[18]	Narrative review	Obstetric	Unspecified	N/A	All	N/A	N/A
Demers et al (2018)[87]	Narrative review	Obstetric	Combined spinal-epidural	N/A	1	N/A	N/A
Hara et al (2009)[83]	Case report	Surgery	Epidural	1	1	198	136
Kailash & Wilkerson (2009)[84]	Case report	Obstetric	Epidural	1	1	99	N/A
Katz & Beilin (2015)[64]	Narrative review	Obstetric	Unspecified	N/A	All	N/A	N/A
Kazi et al (2018)[86]	Case report	Obstetric	Spinal	1	Unspecified	64	N/A
Lipe et al (2011)[89]	Narrative review	Obstetric	Unspecified	N/A	All	N/A	N/A
Malina et. al. (2015)[91]	Retrospective cohort	Obstetric	Unspecified	22	All	N/A	N/A
Moen & Iresedt (2008)[17]	Narrative review	Obstetric	Unspecified	N/A	All	N/A	N/A
Pavord et al (2017)[77]	Narrative review	Obstetric	Unspecified	N/A	All	N/A	N/A
Schuitemaker Requena et al (2010)[81]	Case report	Obstetric	Combined spinal-epidural	1	1	88	N/A
Sood et al (2010)[90]	Prospective cohort	Obstetric	Unspecified	8	1	128	N/A
Thornton & Douglas (2010)[63]	Narrative review	Obstetric	Unspecified	N/A	All	N/A	N/A
Yousuf et al (2017)[92]	Retrospective cohort	Obstetric	Epidural	12	All	N/A	N/A

N/A, not applicable; VWF, von Willebrand factor.

VIII levels, without providing rationale for this recommendation.[88] Recommendations were made with data from observational studies[18,63,64,87] and review articles[18,21,64,87] or were generated from expert opinion.[17,18,21,63,64,88] One observational study was cited in the recommendations of two review articles.[63,64]

3.7 | Factor VII deficiency

Four studies of patients with factor VII deficiency were identified,[77,79,93,94] all of which described obstetric patients receiving neuraxial analgesia for labor and delivery. One case report[93] and two small retrospective cohort studies[79,94] described nine neuraxial procedures, not specifying between spinal and epidural anesthetics. There were no reports of spinal or epidural hematoma. No studies reported the factor VII level before administration of neuraxial analgesia or at the time of catheter removal.

In the single narrative review identified, neuraxial anesthesia was recommended only in mild to moderate factor VII deficiency when "adequate" factor replacement therapy has been provided.[77] Authors did not specify what factor VII level would constitute adequate replacement. These conclusions were made on the basis of expert opinion.

3.8 | Hemophilia A (including carriers)

We extracted data from 11 studies related to hemophilia A and neuraxial anesthesia,[13,18,63,64,77,79,88,95-98] which are summarized in Table 5. These studies included three case reports/case series[95-97]

Minimum factor VIII level reported without spinal/epidural hematoma (IU/dL)		Minimum safe VWF threshold proposed (IU/dL)		Minimum safe factor VIII threshold proposed (IU/dL)	
Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic	Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic	Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic
N/A	N/A	50	N/A	50	N/A
N/A	N/A	Usually contraindicated	N/A	Usually contraindicated	N/A
N/A	N/A	N/A	N/A	N/A	N/A
Type 1 95; Type 2 225	N/A	N/A	N/A	N/A	N/A
38	N/A	N/A	N/A	N/A	N/A
N/A	N/A	50	Remove as soon as possible	50	Remove as soon as possible
N/A	N/A	"Normal" value	If coagulation is "normal"	"Normal" value	If coagulation is "normal"
165	100	N/A	50	N/A	50
249	N/A	N/A	Remove immediately	N/A	Remove immediately
N/A	N/A	"Normal" value	N/A	"Normal" value	N/A
79	N/A	N/A	N/A	N/A	N/A
N/A	N/A	50	N/A	50	N/A
N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	"Normal" value	N/A	"Normal" value	N/A
N/A	N/A	50	N/A	50	N/A
176	N/A	N/A	N/A	N/A	N/A
134	N/A	N/A	N/A	N/A	N/A
N/A	N/A	50	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A

and two retrospective cohort studies.[79,98] In total, 10 neuraxial anesthetic procedures were described in patients with hemophilia A,[96,98] and the remaining 12 procedures were performed for hemophilia A carriers during labor/delivery. A systematic review analyzed an additional 54 neuraxial procedures in patients with hemophilia A or B, which were performed for a variety of indications.[13] These authors did not specify how many patients with hemophilia A received neuraxial anesthesia. In total, there were two epidural anesthetics[95,96] and one spinal anesthetic.[97] The remaining procedures did not specify between spinal or epidural techniques. No epidural or spinal hematomas were reported.

Few studies published factor VIII values before neuraxial anesthesia administration. One case report described uneventful spinal anesthesia for a hemophilia A carrier with a factor VIII level of 76 IU/dL.[97] Another retrospective chart review reported successful neuraxial procedures in 10 female carriers of hemophilia A, the lowest factor level at which anesthesia was placed being 78 IU/dL.[79] Neuraxial procedures were supported by factor VIII replacement in four studies[13,95,96,98]; however, only one repeated a factor VIII level after replacement and before neuraxial anesthesia.[96] Only Skatvold[95] published a factor VIII replacement target; however, the author of this case report did not repeat a factor VIII level after replacement, and it was not clear if their target value of >50 IU/dL was reached. Epidural catheters were removed either as soon as possible after use[79,95] or when factor levels were >50 IU/dL.[13]

Five narrative reviews[18,63,64,77,88] and one systematic review[13] were located. The proposed minimum factor VIII value for insertion of a neuraxial anesthetic was 50 IU/dL in all reviews except one, which suggested that neuraxial blockade was generally

TABLE 5 Studies with data relevant to use of neuraxial anesthesia in hemophilia A

Study	Study design	Type of procedure	Type of neuraxial anesthesia	Sample size, No.	Minimum factor VIII level reported without spinal/epidural hematoma (IU/dL)		Minimum safe factor VIII threshold proposed (IU/dL)	
					Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic	Before administration of neuraxial anesthetic	Before removal of neuraxial anesthetic
Breivik et al (2018)[88]	Narrative review	Surgery	Unspecified	N/A	N/A	N/A	Generally contraindicated	N/A
Chi et al (2009)[79]	Retrospective cohort	Obstetric	Unspecified	10	78	N/A	N/A	Remove immediately
Choi & Brull (2009)[13]	Systematic review	Obstetric & surgery	Unspecified	54	>50	N/A	50	N/A
Chow et al (2011)[18]	Narrative review	Obstetric	Epidural	N/A	N/A	N/A	50	N/A
Eason & Wight (2009)[97]	Case report	Obstetrics	Spinal	1	76	N/A	N/A	N/A
Finzer & Lawrence (2016)[96]	Case report	Surgery	Epidural	1	182	N/A	N/A	N/A
Katz & Beilin (2015)[64]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	50	"Normal" value
Lacalle et al (2015)[98]	Retrospective cohort	Surgery	Unspecified	9	N/A	N/A	N/A	N/A
Pavord et al (2017)[77]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	50	50
Skatvold (2012)[95]	Case report	Obstetric	Epidural	1	N/A	N/A	50	50
Thornton & Douglas (2010)[63]	Narrative review	Obstetric	Unspecified	N/A	N/A	N/A	50	N/A

N/A, not applicable.

contraindicated in patients with hemophilia A irrespective of factor VIII activity level.[88] No evidence was provided to support this recommendation. Three reviews commented on thresholds for removal of epidural catheters, two recommended a factor VIII level of >50 IU/dL,[77,95] and one stated that "normal" factor VIII levels were required.[64] Recommendations were made on the basis of observational data,[18,63,64] review articles,[21,64] or expert opinion.[18,21,63,64,88] There were no duplicate citations.

3.9 | Hemophilia B (including carriers)

Eight studies of hemophilia B and neuraxial anesthesia were revie wed.[13,18,63,64,77,79,88,98] Two retrospective cohort studies described six neuraxial procedures in individuals with hemophilia B and carriers in both obstetric and nonobstetric settings.[79,98] Neither study specified the type of neuraxial anesthesia administered. A systematic review described an additional 54 neuraxial procedures, which were performed on patients with either hemophilia A or B but did not specify how many patients with hemophilia B received neuraxial anesthesia.[13] Only one study published a factor IX level before a neuraxial procedure, reporting a hemophilia B carrier with a factor IX value of 37 IU/dL before obstetric analgesia.[79] Patients in three studies received factor IX replacement[13,79,98]; however, none of the studies published factor IX levels before or after replacement, nor did they provide target values for replacement. No epidural or spinal hematomas were reported.

Among five narrative reviews[18,63,64,77,88] and one systematic review,[13] the almost universally proposed minimum safe factor IX threshold for placement of neuraxial anesthesia was 50 IU/dL. The only study that did not suggest this threshold advised that neuraxial anesthesia was generally contraindicated in this patient population irrespective of factor IX activity level.[88] The authors of this review did not provide any evidence upon which their recommendations were based. Recommendations for catheter removal and the sources of data used were the same as stated above for patients with hemophilia A.

3.10 | Factor XI deficiency

Eleven studies relating to neuraxial anesthesia in patients with factor XI deficiency were identified,[18,64,77,79,94,99-104] including four case reports/case series[99-102] and four retrospective cohort studies.[79,94,103,104] In total, 66 neuraxial procedures were performed, all in women for labor analgesia. There were four combined spinal-epidurals[99,100] and one spinal procedure.[101] The type of neuraxial analgesia was not specified for the remaining procedures. Some women received hemostatic treatment before neuraxial blockade including recombinant factor Xia,[79,99] fresh frozen plasma,[101,102,104] or tranexamic acid.[79,100] Reported data were not comprehensive, as numerous authors did not describe exactly which patients received hemostatic treatment,[79,94,102] and one study[100] did not publish factor XI levels after replacement with recombinant factor XIa. Only O'Connor et al[99] precisely described pre- and posttreatment factor XI levels, though they did not specify their replacement goal. Overall, neuraxial analgesia was placed at factor XI levels ranging from 5 IU/dL[102] to 74 IU/dL.[99] No factor XI values were reported at the time of catheter removal. There were no epidural or spinal hematomas.

Of three narrative reviews,[18,64,77] two provided recommendations regarding administration of neuraxial anesthesia in this population.[64,77] Both stated that bleeding history was the most important factor to consider when deciding to administer neuraxial anesthesia in women with factor XI deficiency. Both reviews advised that any patient with factor XI deficiency and history of excessive bleeding should not receive neuraxial anesthesia. These recommendations were formulated from observational data[64,77] and expert opinion.[77] Two studies were cited more than once.[64,77]

3.11 | Fibrinogen disorders

A total of three studies that described neuraxial anesthesia in patients with fibrinogen disorders were reviewed.[63,77,105] A single case report described a woman with hypofibrinogenemia (prepregnancy fibrinogen antigen 0.40 g/L) who received uneventful epidural analgesia for labor and delivery.[105] However, this report did not provide quantitative or qualitative fibrinogen values at the time of neuraxial administration or removal.

Both of the narrative reviews that were analyzed stated that neuraxial anesthesia should be avoided unless adequate fibrinogen replacement has been confirmed, though neither review provided hemostatic levels that would denote "adequate" replacement.[63,77] There was no discussion of neuraxial catheter removal in either study. One review made recommendations based on data from another review article[63] and the other's recommendations were based on expert opinion.[77]

3.12 | Factor XIII deficiency

We identified two narrative reviews[63,77] on the topic of factor XIII deficiency in obstetric analgesia. One paper stated that neuraxial anesthesia is contraindicated in factor XIII deficiency, a recommendation based on expert opinion.[63] According to the authors of the second study, neuraxial anesthesia should be avoided in patients with severe deficiencies but may be safe if factor XIII levels are adequately replaced.[77] However, these authors did not specify which factor XIII values would constitute "severe deficiency" or "adequate replacement." These recommendations were based on expert opinion. No comments were provided regarding removal of neuraxial anesthesia.

TABLE 6 Identified gaps in the literature by hemorrhagic disorder/tendency

	Identified gaps							
	Population gaps		Data gaps		Evidence quality gaps		Treatment uncertainties	
Hemorrhagic disorder/ tendency	Data from male patients	Data from nonobstetric settings	Greater than 10 studies	Laboratory value before block removal	Large prospective studies	Systematic reviews/ meta-analyses	High-quality guidelines	Concordance among guideline statements
Von Willebrand disease	X	X	-	X	X	X	X	-
Immune thrombocytopenia	X	X	X	X	X	-	X	X
Gestational thrombocytopenia	N/A	N/A	X	X	X	X	X	X
Thrombocytopenia associated with hypertensive disorders of pregnancy	N/A	N/A	-	X	X	X	X	-
Platelet function disorders	X	X	X	X	X	X	X	-
Hemophilia A (including carriers)	X	-	-	X	X	X	X	-
Hemophilia B (including carriers)	X	X	X	-	X	X	X	-
Factor VII deficiency	X	X	X	X	X	X	X	X
Factor XI deficiency	X	X	-	X	X	X	X	X
Factor XIII deficiency	X	X	X	X	X	X	X	-
Fibrinogen disorders	X	X	X	X	X	X	X	-

N/A, not applicable; X, gap present in literature.

3.13 | Potential risk of bias

We analyzed 36 review articles, among which only 5% were systematic reviews. Among the two systematic reviews, only one was a review of prospective studies. Of the 55 nonreview studies, 5% featured a prospective design, 31% had a well-defined population, and 7% included an analysis of association between the laboratory parameter and risk of hematoma.

4 | DISCUSSION

We reviewed 91 studies describing 2047 neuraxial procedures performed on patients with a variety of common and uncommon hemorrhagic disorders and tendencies. Spinal and epidural hematomas were rarely reported, as only 16 cases were described overall (Table 3). Case reports detailed spinal or epidural hematomas in three women with hypertensive disorders of pregnancy and platelet counts between 71 × 10^9/L and 93 × 10^9/L.[38,46,48] Lagerkranser[11] summarized all reports of spinal and epidural hematomas secondary to neuraxial anesthesia from 1994 to 2015. This study described a multitude of personal and procedural factors that increased risk for complications of neuraxial blockade, including 13 cases of local hematoma associated with thrombocytopenia. Six of these cases occurred in patients with platelet counts <150 × 10^9/L, and seven hematomas developed in patients with platelet counts <80 × 10^9/L. However, in this review, we described many uneventful neuraxial procedures performed for individuals with thrombocytopenia at much lower platelet counts. This discrepancy suggests that other, undescribed variables may have contributed to the increased risk of spinal and epidural hematoma in these individuals. These risk factors may include spinal disorders, renal insufficiency, anticoagulant use, and procedural factors, including multiple attempts or use of larger-sized needles.[11] It is also important to consider how the etiology of thrombocytopenia might modify the risk of local hematoma. For example, platelet function is typically thought to be preserved in immune thrombocytopenia but not in platelet function disorders, which may also be associated with a similar degree of thrombocytopenia but an elevated bleeding risk. Finally, risk of local hematoma is also likely moderated by the type of neuraxial anesthesia administered, with epidural anesthesia considered at higher risk for bleeding than spinal anesthesia.[12]

Our study had some important limitations. First, our search strategy was not peer reviewed. Additionally, most studies we reviewed lacked clarity in how authors differentiated related hemorrhagic disorders; thus, data were often challenging to extract into the appropriate category. Diminishing the quality of our data further was the fact that many review papers we analyzed included studies

that were also included individually within our scoping review. Every effort was made to exclude conclusions that were made on the basis of data already presented separately in the scoping review; however, some duplication may still have occurred. Finally, as a large proportion of our data were published in the form of case reports, case series, or very small observational studies, these data are vulnerable to publication bias. This may have skewed our results toward extreme cases and may not accurately reflect hematologic laboratory thresholds that are used more commonly in clinical practice.

As our data revealed, there are many significant gaps in our understanding of the risk of spinal and epidural hematoma in individuals with single preexisting hemorrhagic disorders and tendencies (Table 6). These gaps may be divided into four large categories: population gaps, data gaps, evidence quality gaps, and treatment uncertainties.

The majority of studies we reviewed examined neuraxial analgesia in obstetric populations, resulting in very limited data from men and from women in nonobstetric settings. Since pregnancy induces significant physiologic pro-hemostatic changes, any conclusions developed with data from the obstetric population has limited validity in other settings, such as nonpregnant patients, and should be interpreted with caution.

All of the hemorrhagic disorders/tendencies we examined had gaps in their respective bodies of literature. These gaps were either due to a significant paucity of studies overall or gaps in data presented by individual studies. Thrombocytopenias, including ITP, gestational thrombocytopenia, and thrombocytopenia associated with hypertensive disorders of pregnancy, were the most well-characterized disorders in our review, likely due to the fact that they are among the most prevalent hemorrhagic disorders and tendencies in the general population. The remaining hemorrhagic disorders/tendencies were less robustly described. Gaps in individual studies were often significant, including failure to publish important laboratory values before and after hemostatic replacement and/or before administration of neuraxial anesthesia. Target values for hemostatic replacement were also rarely described. Furthermore, authors often failed to accurately report which patients in a cohort received hemostatic replacement or neuraxial anesthesia. Such significant gaps in presented data introduced a high risk of bias into any conclusions that could be developed from this scoping review.

Evidence quality gaps notably included the overwhelming lack of large prospective studies and systematic reviews of prospective studies. The majority of the articles we reviewed were at high risk for bias, as only a small number featured our indicators for low risk of bias. While there was a higher proportion of observational studies that featured well-described populations, few studies included analysis of the association between hematologic laboratory parameters and risk of hematoma. This high risk of potential bias suggests lower-quality evidence within the body of literature we reviewed and reduced the quality of our potential conclusions.

Finally, treatment uncertainties reflected the universal lack of high-quality guidelines found in our scoping review. Where guidelines were available, concordance among the entire body of reviewed literature was often low and recommendations were rarely evidence based. Furthermore, guidance statements were often vague and recommended that neuraxial anesthesia is safe if replacement is “adequate” or coagulation status is “normal.” Many other guideline statements advised neuraxial anesthesia if the benefits outweighed the risks. These statements leave too much to the discretion of the anesthetic provider and do not add further value over clinical judgment.

With such low-quality data, we found that we were unable to provide any true estimates of the risk of neuraxial anesthesia for individuals with preexisting hemorrhagic disorders/tendencies. Similarly, it was not possible to attribute any specific hemostatic or laboratory values to increased risk of spinal or epidural hematoma based on the small number of hematomas we reviewed. At minimum, data from prospective or high-quality retrospective studies would be required to appreciate the potential for increased hemorrhagic complications of neuraxial anesthesia in individuals with preexisting hemorrhagic disorders and tendencies.

5 | CONCLUSION

In conclusion, this scoping review summarized the scant data describing the use of neuraxial anesthesia in patients with single preexisting hemorrhagic disorders and tendencies. We highlighted areas of particularly limited evidence in male populations and nonobstetric settings. There is a glaring need for larger and more rigorously designed and reported prospective studies on this subject. In particular, there is an urgent need for structured, comprehensive recommendations for safe administration and removal of neuraxial anesthesia for individuals with common and uncommon hemorrhagic disorders and tendencies. Until a more robust and rigorous body of literature can be developed, these recommendations must be based on expert consensus.

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WP, BT, RM, and MF declare no conflicts of interest. MS reports personal fees from Amgen, personal fees from Novartis, outside the submitted work.

AUTHOR CONTRIBUTIONS

WP and MS conceived the article. WP, MF, and MS designed the study. WP and BT screened titles, abstracts, and articles and extracted data. WP performed data analysis and wrote the initial

draft of the article. BT, RM, MF, and MS contributed to critical revision. All authors were responsible for the final approval of the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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