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Real-World Safety and Efficacy of Avatrombopag in Adults with Immune Thrombocytopenia: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This systematic review and meta-analysis aimed to evaluate the risk of thromboembolic events and assess the overall safety and effectiveness of avatrombopag in adult patients with immune thrombocytopenia using real-world evidence.

Methods: A systematic search was conducted following the PRISMA 2020 guidelines. Observational studies (2020–2024) on adults with primary immune thrombocytopenia treated with avatrombopag were included. Primary outcomes were thromboembolic complications and treatment response; secondary outcomes included time to response, treatment discontinuation, and adverse events. Random-effects meta-analyses were performed to synthesise pooled proportions and rates. Risk of bias was assessed using the ROBINS-Version 2 tool.

Results: Fifteen studies were included. The pooled proportion of patients with thromboembolic events was 2.82% (95% confidence interval: 1.61%–4.27%), with an incidence rate of 3.29 per 100 patient-years (95% CI: 1.81–5.08). Response and complete response were achieved by 80.0% and 92.0% of patients, respectively. The median time to response was 11 days, and the discontinuation rate was 18.9%. Adverse events occurred in 4.1% of patients.

Conclusion: In real-world practice, avatrombopag demonstrated high platelet response rates and a low pooled incidence of thrombotic events. These findings add real-world evidence on avatrombopag outcomes in adult immune thrombocytopenia.

1 | Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterised by a low platelet count (PC) leading to purpura and bleeding episodes. It results from immune dysregulation with autoantibody-mediated platelet destruction [1]. ITP is classified as primary, when no underlying cause is identified, or secondary, when associated with factors such as medicines, autoimmune diseases like systemic lupus erythematosus, or infections such as HIV [1]. According to disease duration, it is defined as newly diagnosed (< 3 months), persistent (3–12 months), or chronic (> 12 months). In adults, the incidence ranges from 1.6 to 3.9 per 100 000 person-years, being slightly higher in women and increasing with age [2, 3].

Despite its platelet-destroying nature, patients with ITP are at risk of thrombosis as well as bleeding [4, 5]. Several large-scale population studies have found increased rates of both venous (VTE) and arterial thromboembolism (ATE) when compared with age- and gender-matched healthy individuals. The estimated incidence rate of thrombosis per 100 person-years ranges from 0.41 to 0.67 for VTE and 0.96 to 1.15 for ATE [4]. While these rates may not be considered high in comparison with other conditions, thrombosis remains a clinically significant challenge [4, 5], particularly

in patients with previous vascular events and in elderly populations [5].

Thrombopoietin receptor agonists (TPO-RAs) are a class of drugs used in ITP to induce increased platelet production through the activation of TPO receptors on megakaryocytes [6]. TPO-RAs such as avatrombopag (AVA), eltrombopag, or romiplostim have changed the clinical management of ITP. However, TPO-RAs can also result in adverse effects, including thromboembolic events (TEEs) [7]. It has been a controversial topic, as patients usually have comorbidities that increase their risk of TEEs, such as hypertension, diabetes, smoking, or heart disease [7]. Multiple studies and meta-analyses have assessed whether specific TPO-RAs increase the risk of TEEs, yielding contradictory results. However, the most recent analyses have not demonstrated a statistically significant difference in the incidence of TEEs between groups treated with thrombopoietin receptor agonists (TPO-RAs) and those receiving placebo [8–11]. This lack of association is primarily attributed to limitations in reporting methods and the small sample size or selected casuistry, which hinder the detection of adverse events in clinical trials.

While various TPO-RAs have been extensively studied in routine clinical settings, AVA remains the least investigated, primarily because it is the most recently developed agent in this class. Most existing meta-analyses combine data from randomised clinical trials and observational studies, which limits the ability to draw specific conclusions about AVA. The limited evidence available regarding the risk of thromboembolic events associated with AVA in patients with ITP, along with the predominance of meta-analyses based on randomised clinical trials or combinations of real-world evidence (RWE) and trials [8–18], highlights the need to generate data specifically based on RWE. Furthermore, the inclusion of multiple TPO-RAs in previous studies complicates drawing clear conclusions about the safety and effectiveness of AVA. In this context, the present meta-analysis aims to provide clinical evidence by specifically assessing TEEs and other safety and effectiveness parameters of AVA in patients with ITP, using exclusively real-world data.

2 | Methods

2.1 | Study Design

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [19].

2.2 | Eligibility Criteria

Eligible studies included observational RWE analyses published January 2020 to February 2025 that included adult patients (aged ≥18 years) diagnosed with ITP and treated with AVA. Studies were also required to report a defined follow-up period. Exclusion criteria comprised studies that failed to differentiate adult from paediatric populations, lacked clearly defined follow-up durations, or had been superseded by more recent publications containing updated data sets.

2.3 | Outcomes

The primary outcomes were defined as (1) thromboembolic complications, including the incidence and rate of such events expressed per 100 patient-years, and (2) treatment response, categorised as complete response (CR), defined as achieving a platelet count $\geq 100 \times 10^9$/L on at least one occasion without the need for rescue therapy, and response (R), defined as achieving a platelet count $\geq 50 \times 10^9$/L on at least one occasion without the need for rescue therapy. Secondary outcomes included time to response, treatment discontinuation, and adverse events related to AVA. Those discontinuations due to clinical improvement, in those articles that explicitly mentioned it, were excluded from the analysis.

2.4 | Search Strategy

A systematic literature search was carried out using major biomedical databases, including MEDLINE/PubMed, Embase, Scopus, and Google Scholar. The search strategy was developed following the PICO framework and incorporated relevant MeSH terms and free-text keywords related to AVA, thrombocytopenia, and real-world or observational evidence. The initial strategy was constructed in PubMed and adapted for use in the other databases. This search was complemented by a manual screening to identify studies that might not have been indexed in the selected databases.

Additional sources included the websites of major haematology congresses, namely the American Society of Hematology (ASH), the European Hematology Association (EHA), and the International Society on Thrombosis and Haemostasis (ISTH). The complete search strategy is available in the Supporting Information.

2.5 | Study Selection

Title and abstract screening were conducted independently by two reviewers, followed by full-text assessment of potentially eligible studies. Disagreements were resolved by consensus.

2.6 | Data Extraction

Data extraction was performed using a standardised form developed to collect key variables, including study characteristics, patient demographics, number of TEE, duration of AVA exposure (in patient-years), treatment response (categorised as CR and R), time to response, treatment discontinuation, and adverse events related to AVA. Extraction was carried out independently by two reviewers, with discrepancies resolved through discussion and consensus. Potential overlap of patient cohorts across reports from the same research groups was systematically assessed by comparing data sources, study centers, recruitment periods, and key study descriptors. When overlap was identified or considered plausible, duplicate inclusion was avoided by excluding patients previously described in earlier publications and by retaining the most comprehensive dataset (typically the report with the largest sample size

and/or the most complete outcome reporting) for quantitative synthesis.

2.7 | Risk of Bias Assessment

The quality of the included studies was assessed using the revised version of the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I V2) tool [20] which considers bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results. This tool was designed to evaluate the risk of bias in observational studies where randomisation is not possible, and it provides a structured framework for assessing potential sources of bias across multiple domains [21].

Each study was independently evaluated by two reviewers. The bias in each domain was classified as low, moderate, serious, critical, or no information. These individual assessments informed the overall judgment of the risk of bias for each study [21].

Studies judged to have a low overall risk of bias were considered methodologically comparable with well-conducted randomised controlled trials. A moderate risk of bias indicated that the study was sound for a non-randomised design but did not meet the robustness expected of a randomised trial. Studies with serious or critical risk of bias were those with limitations or methodological flaws likely to impact the credibility of their findings [21].

All discrepancies in risk of bias assessments were resolved through consensus during in-person meetings between the reviewers.

2.8 | Statistical Analysis

Meta-analyses were conducted to synthesize proportions for both effectiveness and safety outcomes using the Freeman–Tukey double-arcsine transformation to stabilize the variance of individual study estimates. Additionally, meta-analyses were used to synthesize medians across studies. A random-effects model was applied for all meta-analyses, and pooled results were reported as percentages or events per 100 patient-years, accompanied by 95% confidence intervals (CIs).

Exposure time to AVA, expressed in patient-years, was estimated based on the median follow-up period reported in each included study. Heterogeneity among studies was assessed using the Q statistic, τ^2, and I^2 indices. In the presence of substantial heterogeneity, Baujat plots were employed to identify potential outliers or influential studies. Forest plots were generated to graphically summarise the pooled estimates.

All statistical analyses were conducted using R version 4.4.1 (The R Foundation for Statistical Computing, Vienna, Austria), employing the meta package (version 8.0-2) [22], metafor package (version 4.8-0) [23] and metamedian package [24].

3 | Results

3.1 | Study Selection and Characteristics

A total of 58 records were identified. A detailed screening process is presented below in the form of a PRISMA flow diagram produced by the tool [25] (Figure S1). Specifically, 26 records were retrieved from MEDLINE/PubMed, Embase, Scopus, and Google Scholar, while 32 additional records were identified through manual searches and hematology congress websites. From the database-derived results, six entries were excluded prior to screening as they corresponded to non-article publications. The remaining 20 records were screened, and all proceeded to full-text assessment. Of these, 14 were excluded for reasons detailed in Figure S1.

All 32 records identified through other sources were assessed in full. Twenty-one were excluded on the following grounds: 13 had been superseded by more recent abstracts or posters reporting updated data sets, two were duplicates across platforms, three did not include ITP patients, two did not involve AVA treatment, and one did not distinguish adult from paediatric cohorts.

Ultimately, 17 publications were identified, corresponding to 15 distinct studies [26–42]. A summary of their characteristics is provided in Table 1.

3.2 | Quality of Study Assessment

The quality of the included studies was assessed using ROBINS-I V2, November 2024 [20]. As shown in Table 2, although most studies showed a low risk of bias in several individual domains, the overall risk of bias was judged to be high in the majority of studies. This was mainly driven by the confounding domain (D1), where most studies were rated as having serious risk of bias, with only two studies and one poster rated as moderate risk. The missing data domain (D5) also contributed to higher risk ratings, with two studies assessed as having serious risk of bias and one rated as critical due to incomplete outcome reporting. Among abstracts and posters, most were rated as having serious risk, with one classified as moderate, consistent with the limited methodological information available in such formats.

A complete summary of bias assessment across all studies and domains is presented in Table 2.

3.3 | Primary Outcomes

3.3.1 | Thromboembolic Complications

Thromboembolic complications were reported in nine real-world studies included in the meta-analysis [27–32, 34, 35, 39]. The pooled proportion of patients who experienced at least one thromboembolic event during treatment with AVA was 2.82% (95% CI: 1.61%–4.27%), with no evidence of heterogeneity across studies ($I^2 = 0.0\%$; $p = 0.4487$), indicating consistency among the findings. When adjusted for exposure

TABLE 1 | Characteristics of included studies.

Study	Country	Design	Data collection period	Number of patients	Endpoints and outcomes
REAL AVA 1.0 (2023) [26]	United States of America	Non-interventional, retrospective cohort study	February 2017 to February 2022	205	DC, CC, TP, outcomes of patients with ITP treated with AVA
AVESPA (2024) [27]	Spain	Nation-wide, multicenter, retrospective study	January 2022 to April 2024	268	R, LOR, R, TTR, RT due to platelet drop or bleeding, WHO grade 2–4 bleeding rate, dose-reduction/suspension of concomitant medications
Al-Samkari H et al. (2021) [28]	United States of America	Multicenter, observational study	July 2019 to December 2020	44	R, median PtC before and after treatment, CIM, RT, AEs
Dranitsaris G et al. (2024) [29]	United States of America	Real-world retrospective observational study	June 2018 to December 2021	44	PC, PtC, AE, RT, HCRU
Lorenzo Vizcaya et al. (2024) [30]	Spain	Observational retrospective study	NA	55	PC
Virk ZM et al. (2023) [31]	United States of America	Multicenter, observational cohort study	July 2019 to February 2023	75	PC, R, BE, AEs
AVAMAD (2024) [32]	Spain	Observational, retrospective, multicenter	July 2022 to May 2023	66	DC, R, RT, AEs, TD
ADOPT (2024) [33, 34]	Croatia, Czech Republic, Germany, Italy, Netherlands, Norway, Spain, Switzerland and United Kingdom	Multicenter, observational, phase 4 study	January 2024 to May 2024	190	CWP3, HRQoL, patient satisfaction, physician satisfaction, TA, AE
Menor Gómez M et al. (2024) [35]	Spain	Observational, retrospective study	January 2023 to February 2024	20	DC, R, RT, AE, TD
Zaja F et al. (2024) [36]	Spain, Italy, Germany, Czech Republic, United Kingdom and Belgium	Non-interventional, retrospective, multi-center study	NA	17	Proportion of patients achieving meaningful PC thresholds and complete response by week 12, 26, 52 and at any time while on AVA post-index; TTR; proportion of patients with a $\geq 50\%$, $\geq 75\%$, and doubled increase in PC from baseline by week 12, 26, and 52 among patients who respond to AVA, DOR, DC, CC, TP, AEs, HCRU
Tomasello R et al. (2023) [37]	Norway	Multicenter, retrospective/ prospective study	NA	14	R, DOR, TTR, AEs

(Continues)

TABLE 1 | (Continued)

Study	Country	Design	Data collection period	Number of patients	Endpoints and outcomes
Cervinek (2023) [38]	Czech Republic	NA	April 2022 to December 2022	20	PC, DH, TP, R, AE
Skopec et al. (2024) [39]	Slovenia, Croatia and Czech Republic	Multicenter, observational study	February 2022 to February 2024	44	R after 8 weeks of AVA treatment (including complete response), RT while undergoing AVA treatment.
Tarantino et al. (2024) [40, 41]	United States of America	Prospective, multi-center, open-label Phase 4 study	NA	61	AEs, SAEs, change of TSQM, PtC post-switch to AVA
REAL AVA 2.0 (2024) [42]	United States of America	Retrospective, multicenter, observational study	July 2019 to June 2024	72	R, R durability, CIM

Abbreviations: AE, adverse event; AVA, avatrombopag; BE, bleeding episodes; C, chronic ITP; CC, clinical characteristics; CIM, concomitant ITP medications; CWP3, Cumulative number of weeks with a PtC $\geq 30\times10^9$/L; CWP5, Cumulative number of weeks with a PtC $\geq 50\times10^9$/L; DC, demographic characteristics; DH, disease history; HRQoL, health-related quality of life; LOR, loss of response; NA, not available; PC, patient's characteristics; PtC, platelet count; R, response; RD/P, recently diagnosed/persistent ITP; RT, rescue therapy; SAEs, serious adverse events; TA, treatment adherence; TD, treatment discontinuation; TSQM, treatment satisfaction questionnaire for medication; TTR, time to response; yr, years.

time, the pooled incidence rate was 3.29 TEEs per 100 patient-years (95% CI: 1.81–5.08), also with no observed heterogeneity ($I^2 = 0.0\%$, $p = 0.6618$), indicating a high level of consistency in the results obtained (Figure 1).

3.3.2 | Treatment Response

Treatment response was assessed in ten studies [26, 28, 30–32, 35, 37–39, 42]. The pooled proportion of patients achieving a CR was 80.03% (95% CI: 72.94–86.35), with moderate heterogeneity across studies ($I^2 = 62.3\%$; $p = 0.0046$). According to the data from nine studies [26–28, 30–32, 35, 37, 42], 91.99% of patients achieved a R, with a 95% confidence interval of 89.25%–94.41%, with low heterogeneity ($I^2 = 11.3\%$; $p = 0.3409$) (Figure 2).

3.4 | Secondary Outcomes

3.4.1 | Time to Response

Time to response was reported in six studies [27, 30, 32, 35, 37, 42]. In four of them, response was defined as achieving a platelet count $\geq 50\times10^9$/L without the need for rescue therapy, while two studies used a threshold of $\geq 30\times10^9$/L. The pooled median time to response was 11.1 days (95% CI: 8.2–13.9), with high heterogeneity observed across studies ($I^2 = 87.7\%$) (Figure 3A).

3.4.2 | Treatment Discontinuation

Treatment discontinuation was reported in twelve studies [26–32, 34, 37, 39, 42]. The overall discontinuation rate was 18.86% (95% CI: 14.46–23.66), with moderate heterogeneity across studies ($I^2 = 66.3\%$; $p = 0.0006$) (Figure 3B).

3.4.3 | Adverse Events Related to AVA

Adverse events related to AVA were reported in four studies [27, 28, 30, 33]. The pooled proportion of patients experiencing at least one adverse event attributed to AVA was 4.05% (95% CI: 1.58–7.43), with moderate heterogeneity across studies ($I^2 = 55.7\%$; $p = 0.0797$). When adjusted for exposure time, the pooled event rate was 4.56 per 100 patient-years (95% CI: 1.47–8.90), also with moderate heterogeneity ($I^2 = 60.1\%$, $p = 0.0569$) (Figure 4).

4 | Discussion

To the best of our knowledge, this is the first RWE meta-analysis specifically focused on evaluating the safety and effectiveness of AVA. While several network meta-analyses have evaluated TPO-RAs within comparative frameworks, primarily based on randomized clinical trials, the present study addresses a complementary question by synthesising real-world evidence for AVA without undertaking cross-agent comparisons.

The analysis describes the pooled incidence of TEEs observed in real-world studies of AVA. Although statistical

TABLE 2 | Risk of bias assessment of included studies.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Complete studies (with abstracts and posters)								
REAL AVA 1.0 (2023) [26]	!	+	+	?	X	+	+	X
AVESPA (2024) [27]	?	+	+	+	+	+	+	?
Al-Samkari H et al. (2022) [28]	!	+	+	?	+	?	+	!
Dranitsaris G et al. (2024) [29]	!	+	+	+	!	+	?	!
Lorenzo Vizcaya et al. (2024) [30]	!	+	+	+	+	+	+	!
Virk ZM et al. (2023) [31]	!	+	+	+	!	!	!	!
AVAMAD (2024) [32]	?	+	+	+	+	+	+	?
Abstracts and posters (without complete studies)								
ADOPT (2024) [33, 34]	!	+	+	?	+	+	+	!
Menor Gómez M et al. (2024) [35]	!	+	+	+	+	+	+	!
Zaja F et al. (2024) [36]	!	+	+	+	+	?	+	!
Tomasello R et al. (2023) [37]	!	+	?	+	+	+	+	!
Cervinek (2023) [38]	!	?	?	?	+	+	+	!
Skopec et al. (2024) [39]	!	+	+	+	+	+	?	!
Tarantino et al. (2024) [40, 41]	?	+	+	+	+	+	+	?
REAL AVA 2.0 (2024) [42]	!	+	+	+	+	+	+	!

Note: + Low risk of bias; ? Moderate risk of bias; ! Serious risk of bias; X Critical risk of bias. Risk of bias assessment for individual studies, performed using the RoBINS-I v.2 tool and categorised by study type. Each column (D1–D7) represents a specific domain of bias assessment, and the "Overall" column indicates the cumulative risk of bias for each study. Domains are: D1, bias due to confounding; D2, bias in the selection of participants into the study; D3, bias in the classification of interventions; D4, bias due to deviations from intended interventions; D5, bias due to missing data; D6, bias in the measurement of outcomes; and D7, bias in the selection of the reported result.

heterogeneity was low for this outcome, such measures should be interpreted cautiously given the inherent clinical and methodological variability across studies. Comparisons with randomized clinical trials were not formally undertaken, and cross-design contrasts should be considered cautiously due to differences in study populations, monitoring intensity, follow-up duration, and event ascertainment.

For contextual purposes, previously published clinical trials have reported TEE incidences within a range that overlaps with the estimates observed in the present synthesis. However, differences in design and reporting standards preclude direct comparison. The pooled thrombotic event estimates from the included real-world studies should therefore be interpreted within the limitations of observational data. Although the pivotal trial by Jurczak et al. reported a higher event rate (9.4%) [43] and also the pooled safety data from four randomised clinical trials indicated an incidence of events of 9% (12.4 events per 100 patient-years) [44], the present results appear notably lower (2.82%; 3.29 events per

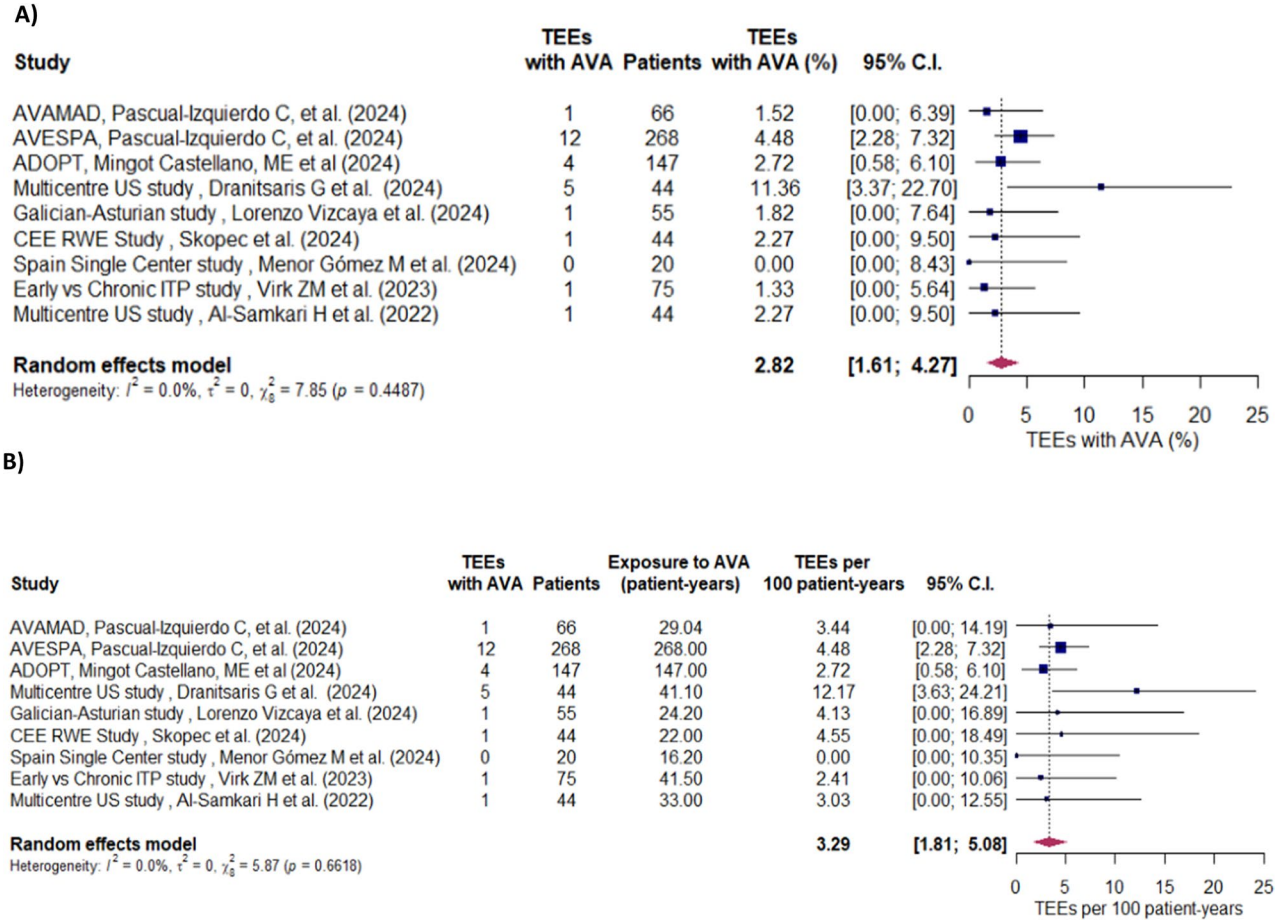

FIGURE 1 | Thromboembolic complications in patients treated with AVA. (A) Pooled proportion of patients who experienced thromboembolic events with AVA, expressed as percentage. (B) Pooled rate of thromboembolic events per 100 patient-years for patients treated with AVA. AVA, avatrombopag; CI, confidence interval; TEE, thromboembolic event.

100 patient-years; 95% CI: 1.61%–4.27%, and 1.81–5.08, respectively). Similarly, Dong et al.'s meta-analysis of randomised clinical trials reported a TEE incidence of 3.2% for AVA (95% CI: 0.0–7.6), which is consistent with our findings with real-world data [10]. Interpretation of the pooled thrombotic event estimates should consider the observational design of the included studies. Cross-design comparisons with clinical trials warrant caution, as differences in study populations, follow-up duration, and event definitions or ascertainment may contribute to variations across settings. Although the study by Dranitsaris et al. [29] reported a comparatively higher event rate, it was retained in the meta-analysis to preserve transparency; inclusion of this study did not materially alter the overall pooled estimate.

With respect to effectiveness, high rates of platelet response were observed across the included real-world studies. AVA real-world studies indicated approximately 92% of patients achieving a R and 80% reaching CR. Moderate statistical heterogeneity was present for complete response ($I^2 = 62.3\%$), whereas overall response rates demonstrated low statistical heterogeneity ($I^2 = 11.3\%$). These findings are broadly compatible with response rates reported in clinical trials, where platelet responses $\geq 50 \times 10^9$/L by day 28 were achieved in 84.4% of AVA-treated patients, compared with 0% in the placebo group ($p < 0.0001$) [45], and day-8 platelet responses $\geq 50 \times 10^9$/L were observed in 65.6% of AVA-treated patients [43]. In long-term assessments, R and CR rates exceeded 80% at month 6 [45], comparable with the present estimates despite variability in definitions and timing. Taken together, the results describe high level of concordance with clinical trials, and a consistent response outcomes across heterogeneous real-world clinical settings.

Considerable variability was observed in time to response across studies, likely driven by differing platelet thresholds used to define effectiveness. Two studies applied a cut-off of $\geq 30 \times 10^9$/L, a threshold that, although lower than the more commonly used $\geq 50 \times 10^9$/L, reflects the standardised definition according to current terminology [46, 47]. In this context, response is defined as a platelet count $\geq 30 \times 10^9$/L and at least doubling of the baseline platelet count, with the additional criterion of the absence of bleeding [46, 47]. Including these studies, despite contributing to the observed heterogeneity, highlights that AVA enables patients to achieve adequate platelet counts within a relatively short period. Although the specific timing of the first post-treatment assessment was not reported in these studies, considering the day-8 responses

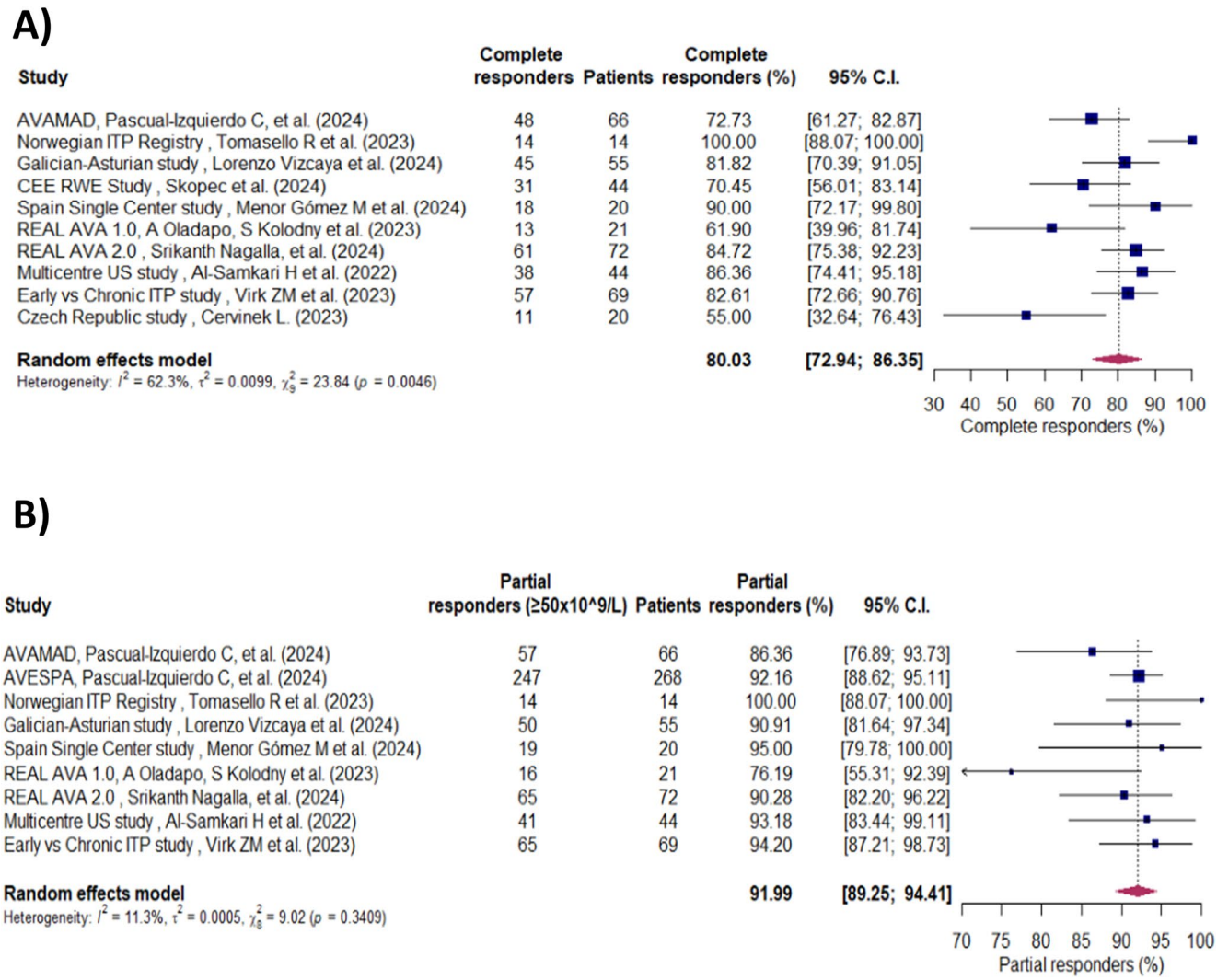

FIGURE 2 | Complete responders and responders to AVA. (A) Proportion of patients achieving a complete response (platelet count $\geq 100 \times 10^9$/L without the need for rescue therapy). (B) Pooled proportion of patients achieving a response (platelet count $\geq 50 \times 10^9$/L without the need for rescue therapy). AVA, avatrombopag; CI, confidence interval.

observed in pivotal trials (platelet responses $\geq 50 \times 10^9$/L in 65.6% of AVA-treated patients), it is likely that platelet increases occurred earlier than the median of 11 days observed in this analysis.

The pooled rate of treatment discontinuation observed across the included real-world studies was 18.86% (95% CI: 14.46–23.66) in a large aggregated cohort of over 1000 patients. In contrast with randomised trials, where discontinuation reached 31.3% during the core study period [43], the observed rates in real-world practice are lower, despite a longer follow-up in some series. This suggests a high degree of treatment persistence and therapeutic stability in routine practice. It should also be noted that discontinuations due to clinical improvement were excluded from the present analysis, and in some series ambiguity in classification may have influenced estimates.

Beyond effectiveness outcomes, adverse events attributed to AVA were reported infrequently across the included real-world studies, both in absolute terms (4.05%; 95% CI: 1.58–7.43) and per 100 patient-years (4.56; 95% CI: 1.47–8.90). These rates are substantially lower than those reported in randomised trials, where the pooled incidence reached 66.4% and 117.5 events per 100 patient-years [44], despite the present analysis comprising a considerably larger population. The inability to standardise adverse event reporting limited the identification of the most frequent events across studies. Among those studies that provided such information, headache was the most commonly cited, followed by fatigue and gastrointestinal discomfort [27, 29, 32, 35, 40]. Overall, the available data describe the adverse events reported in routine clinical practice settings. Nevertheless, it should be acknowledged that, due to the inherent limitations of real-world studies, adverse events are often under-reported, which may contribute to the lower incidence observed.

This study has limitations inherent to its observational design and reliance on real-world data. A methodological concern was the serious overall risk of bias observed in most studies, primarily due to confounding factors (Domain 1). This was expected given the retrospective nature of the included studies, where

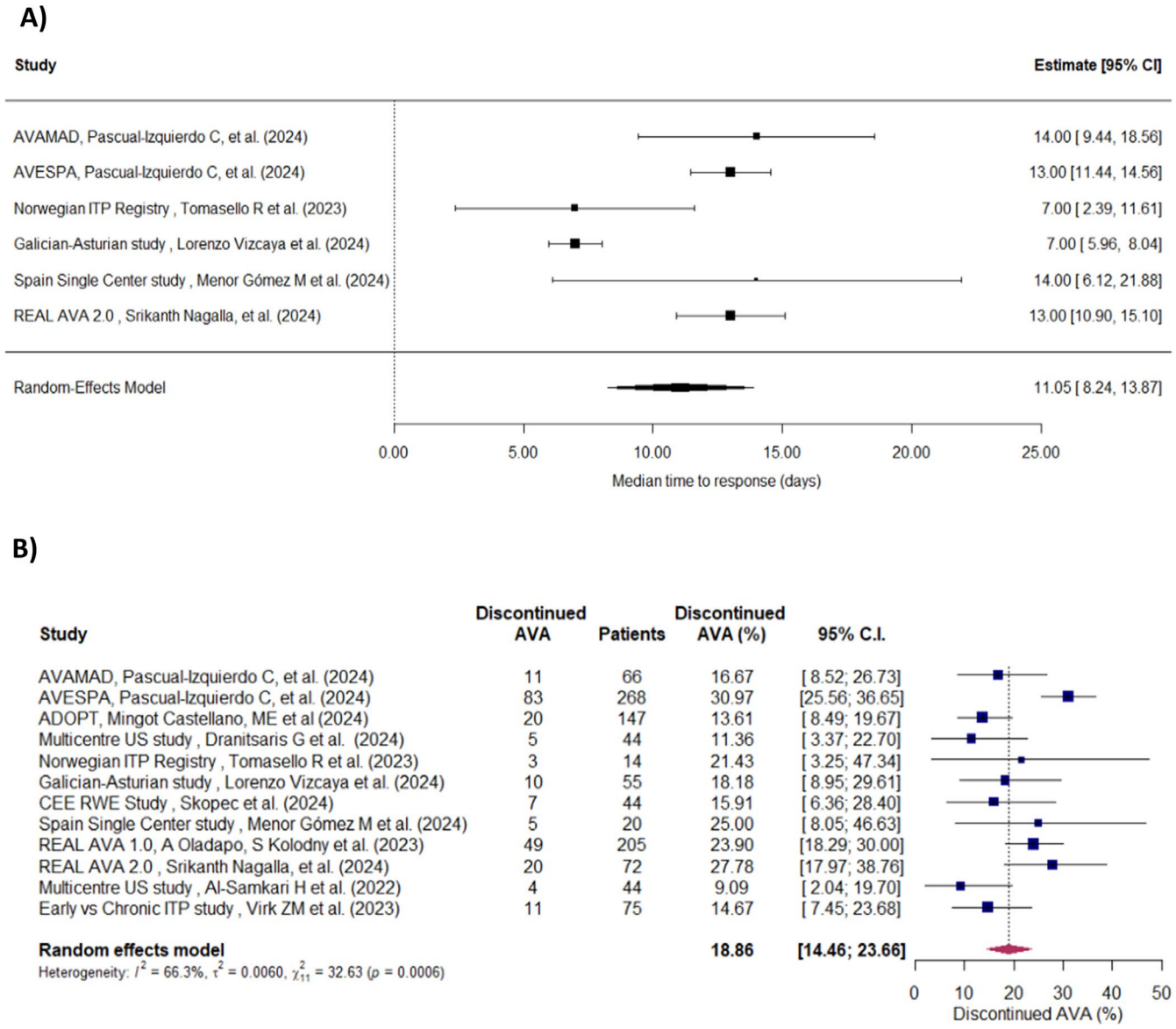

FIGURE 3 | Analysis of time to response and treatment discontinuation for AVA. (A) Time to response, defined as a platelet count $\geq 50\times10^9$/L (or $\geq 30\times10^9$/L for the Norwegian and Galician-Asturian studies) on at least one measurement without requirement for rescue therapy. (B) Rate of treatment discontinuation due to adverse events, lack of efficacy, or unknown causes. AVA, avatrombopag; CI, confidence interval; ITP, immune thrombocytopenia; RWE, real-world evidence.

baseline information is frequently incomplete. Key thrombotic risk determinants were inconsistently reported across studies, limiting the interpretation of thrombotic safety outcomes and introducing the possibility of residual confounding. Furthermore, prior exposure to other TPO-RAs, including treatment switching, was variably reported across studies and may have contributed to between-study heterogeneity in both effectiveness and safety outcomes. Importantly, this review was specifically designed to synthesise real-world evidence on AVA and did not aim to compare outcomes with other TPO-RAs. Accordingly, the study selection and data extraction were not structured to support unbiased cross-agent comparisons or treatment-selection recommendations, and such analyses would require a dedicated comparative framework. Although the risk of bias across the remaining ROBINS-I domains was generally low to moderate, the retrospective nature of the included studies and reliance on medical records limited the standardisation of key variables across reports. In addition, inconsistent reporting of patient-level characteristics and outcomes precluded subgroup analyses and restricted a more granular evaluation of adverse events. These limitations should be carefully considered when interpreting the findings. Notwithstanding these constraints, strengths of this meta-analysis include the large aggregated sample size, the focused synthesis of real-world evidence on AVA, and the structured risk-of-bias performed using the ROBINS-I framework.

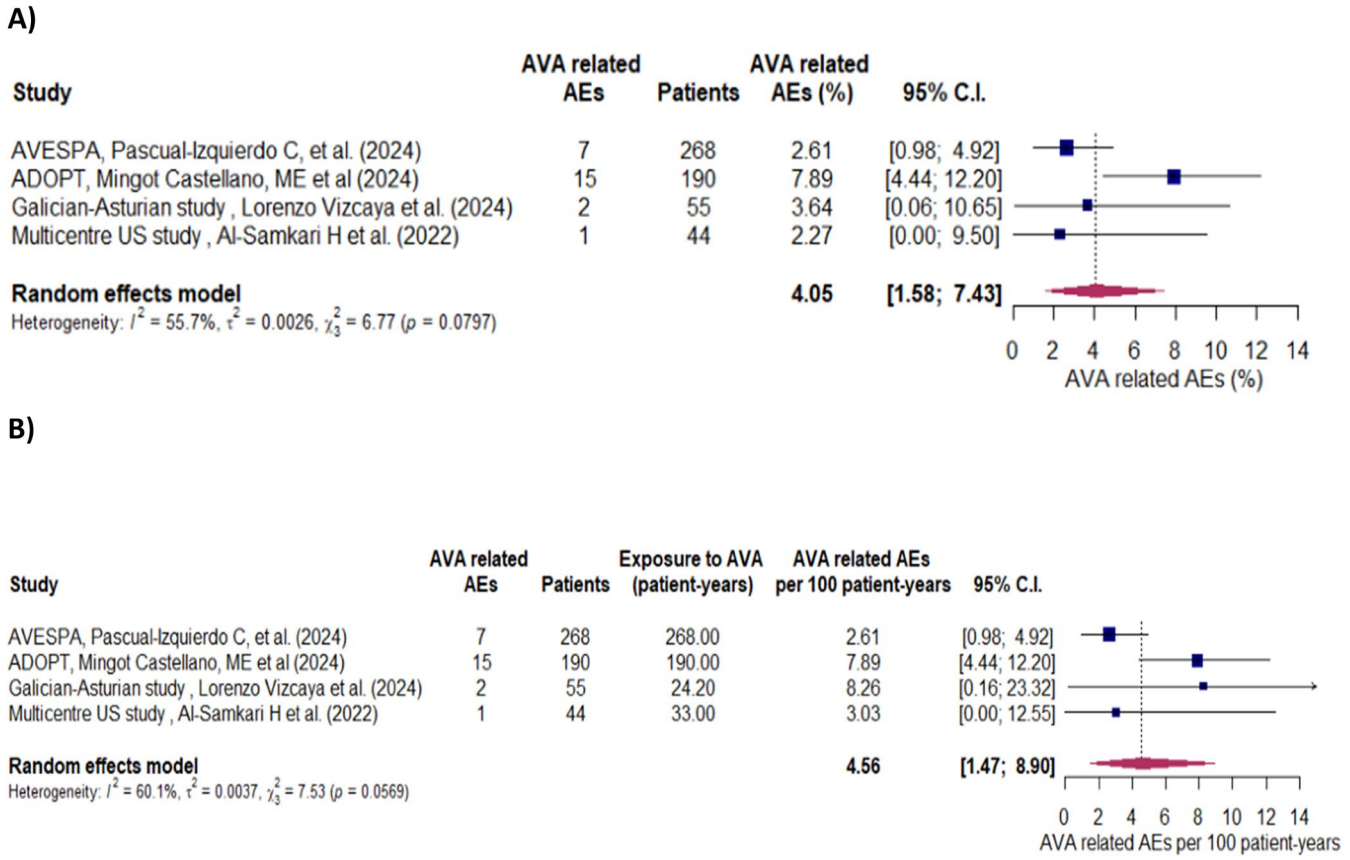

FIGURE 4 | Analysis of AVA-related adverse events. (A) Overall proportion of AVA-related AEs, expressed as a percentage of patients. (B) Rate of AVA-related AEs per 100 patient-years of exposure. AEs, adverse events; AVA, avatrombopag; CI, confidence interval.

5 | Conclusions

In summary, this meta-analysis provides the most comprehensive synthesis of AVA use in real-world clinical settings for ITP. These findings suggest that, within the included real-world studies, AVA was associated with a relatively low pooled incidence of TEE, high rates of complete and partial platelet responses, and a manageable tolerability profile across a clinically heterogeneous population. Although variability in study design and reporting limited full harmonisation of certain variables, the consistency of results and the absence of high risk of bias in most methodological domains support the robustness of the evidence. These findings should be interpreted within the context of observational real-world data and differences in study design compared with randomized clinical trials. Rather than establishing comparative advantage, the present results provide additional real-world information regarding thrombotic events and treatment response with AVA in heterogeneous clinical populations. Overall, this analysis contributes complementary real-world evidence to the existing literature, describing outcomes observed in routine clinical practice without implying comparative conclusions across therapeutic agents.

Author Contributions

M.L.L. contributed to the conception and design of the study, analysis and interpretation of the data, and drafting of the manuscript. D.V. contributed to the conception and design of the study, analysis and interpretation of the data, and drafting of the manuscript.

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Conflicts of Interest

M.L.L. has received consultancy fees from Amgen, Novartis, Grifols, Argenx, Sanofi, and Sobi. D.V. has received consultancy fees from Agios, Amgen, Bristol Myers Squibb/Celgene, Gilead, Grifols, Janssen, Jazz, Novartis, Sanofi, Sobi, Pfizer, and Takeda.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Study selection diagram.