Standard of care with or without caplacizumab in adults with immune thrombotic thrombocytopenic purpura: A systematic review and meta-analysis
SUPPLEMENTARY MATERIAL

Table of Contents

S1: Search Strategy

Search Terms

- Caplacizumab
- Caplivi
- Caplacizumab-yhdp
- ALX-0081
- Thrombotic Thrombocytopenic Purpura
- Thrombocytopenic Purpura, Thrombotic
- Purpura, Thrombotic Thrombopenic
- Thrombopenic Purpura, Thrombotic
- Thrombotic Thrombopenic Purpura
- Moschcowitz Disease
- Moschkowitz Disease
- Schulman-Upshaw Syndrome
- Schulman Upshaw Syndrome
- Upshaw-Schulman Syndrome
- Upshaw Schulman Syndrome
- Upshaw Factor, Deficiency of
- Idiopathic thrombotic thrombocytopenic purpura
- Acquired Thrombotic thrombocytopenic purpura
- Microangiopathic hemolytic anemia
- Thrombotic microangiopathy

Search Query **KEY:** **Pubmed** **Embase** **Cochrane** **Scopus**
((Caplacizumab) OR (Cablivi) OR ("caplacizumab-yhdp") OR ("ALX-0081")) AND (("Thrombotic thrombocytopenia purpura") OR ("Thrombocytopenic Purpura, Thrombotic") OR ("Purpura, Thrombotic Thrombopenic") OR ("Thrombopenic Purpura, Thrombotic") OR ("Thrombotic Thrombopenic Purpura") OR ("Moschcowitz Disease") OR ("Moschkowitz Disease") OR ("Schulman-Upshaw Syndrome") OR ("Schulman Upshaw Syndrome") OR ("Upshaw-Schulman Syndrome") OR ("Upshaw Schulman Syndrome") OR ("Upshaw Factor, Deficiency of") OR ("Idiopathic thrombotic thrombocytopenic purpura") OR ("acquired Thrombotic thrombocytopenic purpura") OR ("Microangiopathic hemolytic anemia") OR ("Thrombotic microangiopathy")) AND (("2000/01/01"[Date - Publication] : "2021/07/19"[Date - Publication]))
(caplacizumab OR cablivi OR 'caplacizumab-yhdp' OR 'alx-0081') AND ('thrombotic thrombocytopenia purpura' OR 'thrombocytopenic purpura, thrombotic' OR 'purpura, thrombotic thrombopenic' OR 'thrombopenic purpura, thrombotic' OR 'thrombotic thrombopenic purpura' OR 'moschcowitz disease' OR 'moschkowitz disease' OR 'schulman-upshaw syndrome' OR 'schulman upshaw syndrome' OR 'upshaw-schulman syndrome' OR 'upshaw schulman syndrome' OR 'upshaw factor, deficiency of' OR 'idiopathic thrombotic thrombocytopenic purpura' OR 'acquired thrombotic thrombocytopenic purpura' OR 'microangiopathic hemolytic anemia' OR 'thrombotic microangiopathy') AND [1-1-2000]/sd NOT [20-7-2021]/sd
((caplacizumab OR cablivi OR 'caplacizumab-yhdp' OR 'alx-0081') AND ('thrombotic thrombocytopenia purpura' OR 'thrombocytopenic purpura, thrombotic' OR 'purpura, thrombotic thrombopenic' OR 'thrombopenic purpura, thrombotic' OR 'thrombotic thrombopenic purpura' OR 'moschcowitz disease' OR 'moschkowitz disease' OR 'schulman-upshaw syndrome' OR 'schulman upshaw syndrome' OR 'upshaw-schulman syndrome' OR 'upshaw schulman syndrome' OR 'upshaw factor, deficiency of' OR 'idiopathic thrombotic thrombocytopenic purpura' OR 'acquired thrombotic thrombocytopenic purpura' OR 'microangiopathic hemolytic anemia' OR 'thrombotic microangiopathy')
ALL (((caplacizumab) OR (cablivi) OR ("caplacizumab-yhdp") OR ("ALX-0081")) AND (("Thrombotic thrombocytopenia purpura") OR ("Thrombocytopenic Purpura, Thrombotic") OR ("Purpura, Thrombotic Thrombopenic") OR ("Thrombopenic Purpura, Thrombotic") OR ("Thrombotic Thrombopenic Purpura") OR ("Moschcowitz Disease") OR ("Moschkowitz Disease") OR ("Schulman-Upshaw Syndrome") OR ("Schulman Upshaw Syndrome") OR ("Upshaw-Schulman Syndrome") OR ("Upshaw Schulman Syndrome") OR ("Upshaw Factor, Deficiency of") OR ("Idiopathic thrombotic thrombocytopenic purpura") OR ("acquired Thrombotic thrombocytopenic purpura") OR ("Microangiopathic hemolytic anemia") OR ("Thrombotic microangiopathy")))

S2: Characteristics of Included Studies

eTable 2A: Inclusion and exclusion criteria of included studies

Study Name (Year)	Inclusion Criteria	How was iTTP diagnosed/defined?	Exclusion Criteria	Primary Outcome
HERCULES (2019)	Adults ≥ 18 years with a clinical diagnosis of iTTP and ≥1 TPE treatment prior to randomization. Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized and hysterectomized women) must have a negative pregnancy test and must agree to use a generally accepted adequate contraceptive method from screening until at least 2 months after last dosing. Subjects have provided informed consent prior to initiation of any study specific activity/procedure.	The presence of both thrombocytopenia and microangiopathic hemolytic anemia with schistocytes seen on blood smear.	Suspected thrombotic microangiopathies that were not associated with TTP, such as hemolytic uremic syndrome or congenital TTP. Additionally: Platelet count ≥ 100k/µL; serum creatinine > 200µmol/L in case platelet count is > 30k/µL (to exclude possible cases of atypical Hemolytic Uremic Syndrome); known other causes of thrombocytopenia; congenital TTP known at the time of study entry; pregnancy or breast0feeding; clinical significant active bleeding or high risk of bleeding (excluding thrombocytopenia); known chronic treatment with anticoagulant that cannot be stopped safely; malignant arterial hypertension; clinical condition other than that associated with TTP, with life expectancy < 6 months; known sensitivity to the active product or excipient of the study drug; participation in another interventional trial with an investigational treatment; considered, by the investigator, to be unsuitable for trial participation for any reason	Time to response: from the 1st IV admin of caplacizumab or placebo to normalization of the platelet count (>150k/µL) followed by TPE discontinuation within 5 days
TITAN (2016)	Adults ≥ 18 years or adolescents 12-18 years with a clinical diagnosis of acquired TTP and platelet count ≤100 k/µL without active bleeding and	Not defined	Platelet count > 100k/µL; active infection or sepsis (pressor requirement or positive blood cultures); clinical evidence of	Time to response: normalization of the platelet count (≥ 150k/µL, confirmed on repeating testing at 48

	requiring TPE (1 TPE prior to randomization was allowed). Additionally: willing to accept contraception, accessible for follow-up, obtained signed and dated consent form prior to randomization.		infection with E. Coli 0157 or related organism; history of APLS; diagnosis of DIC; pregnant or breast feeding; history of stem cell or bone marrow transplantation-associated thrombotic microangiopathy; congenital TTP; active bleeding or high-risk of bleeding; uncontrolled arterial hypertension; chronic treatment with anticoagulant that could not be stopped safely; malignancy with life expectancy < 3 months; bone marrow carcinosis; severe renal or liver impairment; severe or life threatening clinical condition other than TTP that would impair participation in the trial; subjects who cannot comply with study protocol requirements and procedures.	hours) and an LDH that was < twice the upper limit of normal
France (2021)	All patients with a clinical diagnosis of iTTP treated with the combination of daily TPE + steroids + caplacizumab compared to a historical cohort of iTTP patients managed with TPE + steroids +/- salvage rituximab.	The clinical diagnosis of iTTP was considered in patients with features of thrombotic microangiopathy and a French score of 1 or 2. The French score was calculated in patients with features of thrombotic microangiopathy and no associated condition (cancer, chemotherapy, pregnancy, transplantation, severe disseminated intravascular coagulopathy). A French score of 2 (platelet count < 30 k/µL and serum creatinine < 200 µmol/L [2.27 mg/dL]) was highly suggestive of iTTP. Patients with only 1 of these 2 measures were considered having probable iTTP, and daily TPE with corticosteroids and caplacizumab was immediately started; rituximab was started only after iTTP diagnosis was confirmed (ie, if ADAMTS13 activity was ,10%). The final diagnosis	Patients with a French score of 0 (platelet count ≥ 30k/µL and serum creatinine ≥ 200 µmol/L [2.27 mg/dL]) were considered having an alternative diagnosis (e.g. HUS) and were not considered eligible for this study. Patients were also excluded if they had iTTP but died before receiving any treatment, did not receive caplacizumab during the prospective part of the study (intervention arm), received caplacizumab as salvage therapy, or whose caplacizumab was stopped by day 3 due to consideration of an alternate diagnosis.	Prevalence of a composite of death and/or refractoriness within 30 days since diagnosis.

		of iTTP was confirmed in patients with a severe acquired ADAMTS-13 deficiency (<10% of activity with anti-ADAMTS13 antibodies ≥ 15 U/mL).		
UK (2021)	Patients of any age, who had received ≥1 dose of caplacizumab through the patient free drug access scheme, following a confirmed diagnosis of acute TTP.	ADAMTS13 < 10 IU/dL	None	Primary outcome not explicitly stated; outcomes examined included serological markers of organ injury, platelet count recovery, TPE requirement, TTP recurrences, bleeding/thromboembolic com plications, and mortality.
Barcelona* (2020)	Not described (abstract only)	Not described (abstract only)	Not described (abstract only)	Time to complete response: two consecutive days with platelets ≥ 150k/μL
Legend: APLS = antiphospholipid antibody syndrome; DIC = disseminated intravascular coagulation; iTTP = immune thrombotic thrombocytopenic pupura; TPE = therapeutic plasma exchange *abstract only				

eTable 2B: Additional baseline characteristics not reported in Table 1

Study Name (Year)	Mean (SD) body mass index	Platelet count per µL at presentation: median (range)	LDH (U per L) at presentation: median (range)	Serum creatinine (µmol/L): median (range)
HERCULES (2019)	30 (18-53)¤	24,000 (3,000 - 119,000)	449 (120-2525)	77 (35–717)
	30 (19-59) ¤	25,000 (9,000 - 133,000)	403 (151-3343)	82 (52–482)
TITAN (2016)	28.7 (9.1)	21,000 (2,000 - 70,000)	1277 (240-3874)	Not reported
	29.3 (6.7)	28,000 (5,000 - 84,000)	1270 (247-4703)	Not reported
France (2021)	27.2 (23-32) ¤	12,000 (10,000-20,000)	5.1 (4.0-6.5) †	92 (71 -120)
	27 (23-32) ¤	12,000 (8,000-23,000)	3.7 (2.4-5.6) †	86 (68-133)
UK (2021)	Not reported	13,000 (9,000-21,000)	Not reported	90 (71-135); elevated in 35 (41%) patients
	Not reported	10,000 (6,000-20,000)	Not reported	elevated in 10 (26%) patients
Barcelona* (2020)	Not reported	16,000 (8,000-21,000)	Not reported	84 (65-99)
	Not reported	12,000 (7,000-18,000)	Not reported	75 (72-121)

TPE = therapeutic plasma exchange
*Abstract only
† expressed as multiple of normal
¤ Median (interquartile range)

eTable 2C: Details of treatments received

Study Name (Year)	Treatment assignment	Average time of caplacizumab initiation	Duration of caplacizumab	No. (%) receiving concomitant steroids	No. (%) receiving concomitant rituximab	No. (%) receiving other immunosupp-ression§	No. (%) receiving other TTP tx (splenectomy, IVIG, etc.)
HERCULES (2019)	Caplacizu-mab + SOC	Unclear†	Mean 35 (range 1 to 65) days	69 (96)	28 (39)	12 (17) §	7 (10)
	SOC	n/a	n/a	71 (97)	35 (48)	3 (4) §	6 (8)
TITAN (2016)	Caplacizu-mab + SOC	Before or after 1st TPE¤	Mean 38 (range 3-77 days) days	32 (89)	2 (6)	Not reported	Not reported
	SOC	n/a	n/a	36 (92)	9 (23)	Not reported	Not reported
France (2021)	Caplacizu-mab + SOC	Median 0 [same day as TPE] (range 0-4) days‡	Median 33 (range 29-38) days	88 (98)	90 (100)	0 (0)	0 (0)
	SOC	n/a	n/a	166 (92)	123 (68)	8 (0.04)	2 (0.01)
UK (2021)	Caplacizu-mab + SOC	Mean 2 (IQR 1-3) days after TPE initiation	Median 32 (IQR 22-47) days	84 (99)	84 (99)	33 (39)	Not reported
	SOC	n/a	n/a	Not reported	34 (87)	Not reported	Not reported
Barcelona* (2020)	Caplacizu-mab + SOC	3 days	Median 39 (IQR 33-39 days)	9 (100)	2 (22)¥	0 (0)	0 (0)
	SOC	n/a	n/a	9 (100)	8 (89)¥	4 (44) §	0 (0)

All patients across the studies received therapeutic plasma exchange (and inferred in the Barcelona study).
SOC = standard of carer; TPE = therapeutic plasma exchange
*Abstract only
†The study reports "patients received an intravenous loading dose of caplacizumab (10 mg) or placebo before the start of the first plasma exchange after randomization."
‡In 47 of 90 patients, caplacizumab was started on the same day as TPE (day 0); in the remaining patients, it was started on day 1 (24 patients), day 2 (8 patients), day 3 (6 patients), or day 4 (5 patients).
¤A total of 69 patients had not undergone a plasma-exchange session before enrollment.
¥ The rate of patients receiving concomitant rituximab was unclear: "There was 1 exacerbation before initiation of caplacizumab and 1 relapse. Both cases were treated with rituximab." (It is unclear if only these 2 patients received rituximab in the caplacizumab arm). "In the control group …we observed 4 refractory cases (1 aTTP-related death), 3 exacerbations and 1 relapse; rituximab was necessary in 8 patients" (similarly, it is unclear if only these 8 patients received rituximab in the control arm).
§ In the HERCULES study this included mycophenolate motefil, hydroxychloroquine, bortezomib, cyclophosphamide, and cyclosporine. In the Barcelona study, this was specifically 3rd line vincristine.

eTable 2D: Definition of major bleeding

HERCULES: definition not reported, but major bleeding events described.
"These [bleeding] events were mild or moderate in severity in a majority of patients and were severe in 3 patients in the caplacizumab group (epistaxis, gingival bleeding, and upper gastrointestinal hemorrhage in 1 patient each) and in 1 patient in the placebo group (hemorrhagic transformation stroke)." (p. 342 last paragraph before discussion)

TITAN: definition not reported, but major bleeding events described.
"Serious bleeding-related adverse events were report- ed in 2 patients in each study group: subarachnoid and retinal hemorrhage and metrorrhagia in the caplacizumab group and cerebral hemorrhage and hematuria in the placebo group."

The French and UK studies used the International Society on Thrombosis and Haemostasis definition for major bleeding in non-surgical patients (Journal of Thrombosis and Haemostasis. 2005;3(4):692-694).

The Barcelona study did not report their definition of major bleeding, and only described all adverse events as "mild."

S3: Risk-of-bias of the included studies

eTable 3A: Methodological quality of the included randomized controlled trials

Study Name	HERCULES	TITAN
Method of randomization	*Adequate (low risk of bias)*[†]	*Adequate (low risk of bias)*[‡]
Method of allocation concealment	*Adequate (low risk of bias)* Trial group assignments remained concealed even to those who switched to open-label treatment.	*Adequate (low risk of bias)* Although concealment of the allocation from participants was not explicitly stated, it was presumed based on the description of the randomization process and description of "single-blinded study"
Deviations from intended interventions	*Some concerns* The study is described as a "single-blinded study" but the investigators do not explicitly state who was blinded or what the blinding and unblinding procedures were. It is presumed that only participants were blinded to the treatment group assignment.	*Some concerns* This study is described as a "single-blinded study" but the investigators do not explicitly state who was blinded or what the blinding and unblinding procedures were. It is presumed that only participants were blinded to the treatment group

		assignment. The authors report that site investigators were aware of the treatment assignment.
Measurement and reporting of the outcome	*Some concerns* Both the unadjusted (Kaplan-Meier analysis and stratified log rank test) and adjusted (Cox proportional-hazards regression model) were reportedly performed – according to the protocol – to assess time to platelet count recovery, but only the former was reported. The question of which of these methods is superior is highly controversial, but we note 'some concerns' given selective reporting.	*Some concerns* Refractory TTP was measured per the protocol but not explicitly stated. The only reference to this outcome was in a description of all-cause mortality, where one of the deaths in the placebo arm was attributed to severe, refractory TTP. Additionally, there is no composite endpoint of "thrombosis" reported. Deep venous thrombosis and pulmonary embolism are reported separately, and it is unclear how many individual patients these events represent
Missing outcome data and loss to follow up	*Well described (low risk of bias)* 1 patient withdrew consent before receiving the 1st dose of caplacizumab; 13 patients who received caplacizumab discontinued; 0 withdrew from control group; 13 patients who received placebo discontinued	*Well described (low-risk of bias)* In the caplacizumab arm: 7 discontinued the treatment early, 32 completed 1 month follow-up, 22 completed 12 month follow-up. In the control arm: 8 discontinued the treatment earlry, 31 completed 1-month follow up; 21 completed 12-month follow-up.
Contamination	*Well described (low risk of bias)* Patients with disease recurrence during the treatment period were switched to open-label caplacizumab.	*Not reported* The authors do not report patients switching therapy.
Blinding of outcome assessment	*Adequate (low risk of bias)* An independent adjudication committee whose members were unaware of the trial-group assignments reviewed all potential major thromboembolic events and assessed the relatedness of deaths to TTP.	*Unclear risk of bias* The authors do not report blinding of outcome assessors.
Intention to treat analysis	*Performed*	*Performed*
Overall	***Low risk of bias***	***Low risk of bias***

We used the Cochrane risk-of-bias tool for randomized trials (RoB-2) to assess the methodological quality of the HERCULES and TITAN trials. RoB-2 is structured to appraise the risk-of-bias across multiple domains, focusing on different aspects of trial design, conduct, and reporting. Within each domain, the assessor answers "signaling questions" that algorithmically generate risk-of-bias ('high-risk', 'low-risk,' or 'some concerns') for each outcome of interest. Here, we present the study-level risk of bias for each domain; for domains where risk-of-bias varied across outcomes, we report the highest risk-of-bias.

† Baseline characteristics were generally well balanced between the treatment groups, except there were more patients with recurrent TTP at presentation in the caplacizumab arm (vs more initial episodes in the control arm)

‡ "The proportion of patients who received rituximab during daily plasma exchange differed significantly between the two groups (P<0.05). The imbalance may have been a site effect, since one site used rituximab as part of the standard of care starting on day 2 of daily plasma exchange, and this site recruited seven patients, five of whom were randomly assigned to the placebo group." However, since all other factors were generally well balanced between the experimental and control groups, we assessed the randomization process as adequate.

eTable 3B: Methodological quality of the included observational studies

Study Name	France	UK	Barcelona
Selection			
Representativeness of the exposed cohort	somewhat representative of the average iTTP demographic in the community ❋	somewhat representative of the average iTTP demographic in the community ❋	somewhat representative of the average iTTP demographic in the community ❋
Selection of the non-exposed cohort	drawn from the same community as the exposed cohort ❋	drawn from the same community as the exposed cohort ❋	drawn from the same community as the exposed cohort ❋
Ascertainment of exposure	Secure record (e.g., medical record) ❋	Secure record (e.g., medical record) ❋	Secure record (e.g., medical record) ❋
Outcomes of interest not present at study start	Yes ❋	Yes ❋	Yes ❋
Comparability of cohorts based on design or analysis	Study neither controls for severity of illness (the most important factor) nor co-intervention (2nd most important factor)	Study neither controls for severity of illness (the most important factor) nor co-intervention (2nd most important factor)	Study neither controls for severity of illness (the most important factor) nor co-intervention (2nd most important factor)
Outcome			
Assessment of outcome	Through record linkage ❋	Reference to secure records (e.g., medical records) ❋	No description.
Adequacy of length of follow up	Median follow-up of 107 days adequate for all outcomes. ❋	Median follow-up of 80 days adequate for all outcomes.❋	Median follow-up of 6 months adequate for all outcomes.❋
Cohort follow-up adequacy	Not described†	Not described†	Not described†
Total # stars	Selection: ❋❋❋❋ Comparability: 0 Outcome: ❋❋	Selection: ❋❋❋❋ Comparability: 0 Outcome: ❋❋	Selection ❋❋❋❋ Comparability: 0 Outcome: ❋
Qualitative assessment	*Some concerns*	*Several concerns*	*Some concerns*

	No matching between prospectively followed cohort and historical controls. Confounders not addressed nor controlled for. No mention of missing data or loss to follow-up.	No matching between prospectively followed cohort and historical controls. Confounders not addressed nor controlled for. Time to normalization of platelet count was reported only among the patients who achieved normalization (81 of 85 patients), which is potentially misleading. Baseline characteristics and co-interventions not reported for control group in the same level of detail as the intervention group; not all outcomes reported for both groups (TTP exacerbation or relapse); all-cause mortality not reported; refractory TTP measured (stated in methods) but not explicitly reported. Control cohort not published but drawn from same registry. Unclear numbers lost to follow-up. Anonymized outcome data was submitted by centers for outcomes.	This study was reported only in abstract form and its report not peer-reviewed. There was no matching between the experimental group with historical controls. Confounders not addressed nor controlled for. Does not report all-cause mortality. No description of how outcomes were recorded-assume electronic health record review. No statement of missing data or loss to follow-up.

The Newcastle-Ottawa Scale (NOS) was developed to assess the quality of nonrandomized, comparative studies; we used the NOS for cohort studies. Assessors use a "star system" to judge studies on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. Two authors independently assessed the methodological quality of the non-randomized studies included in this review and evaluated study-level selection and comparability domains and the cohort follow-up adequacy (outcome domain). The two authors appraised the assessment and adequacy of follow up for each outcome of interest; here, we report the average across all outcomes. We denote whether a star was given with ❋. A study can be awarded a maximum of one star for each item within the selection and outcome categories (4 and 3 stars for each domain maximum, respectively); a maximum of two stars can be given for the comparability domain. We also report a hybrid of each author's qualitative assessment of these non-randomized studies.

† No mention of missing data or loss to follow-up

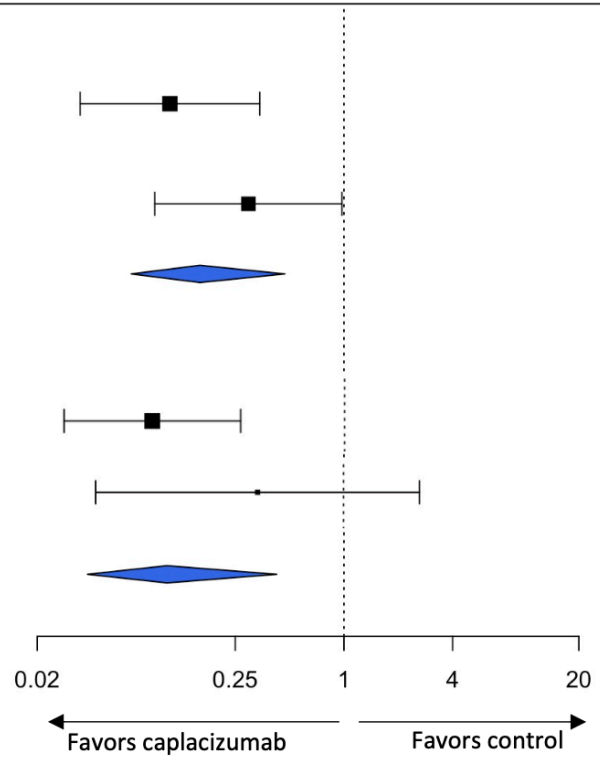
S4: Primary meta-analysis and forest plots of secondary outcomes

S4.1: Binary Outcomes

We present the outcomes reported in each individual trial as well as meta-analysis according to study design. Control refers to standard of care alone without caplacizumab (refer to Supplement S2 “eTable 2C: Details of treatments received”). Event rates refer to the number of patients with the event of interest.

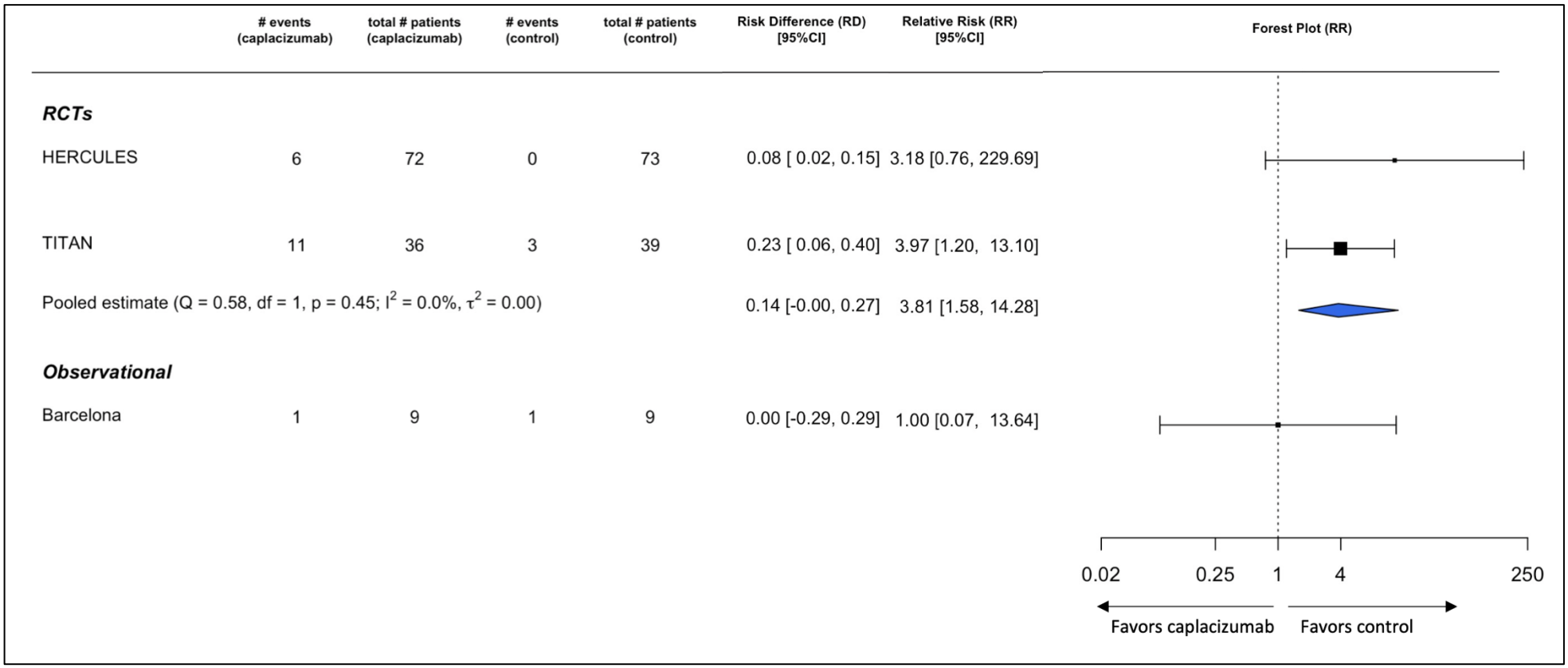
eFigure 4A: TTP exacerbation

	# events (caplacizumab)	total # patients (caplacizumab)	# events (control)	total # patients (control)	Risk Difference (RD) [95%CI]	Relative Risk (RR) [95%CI]
RCTs						
HERCULES	3	72	28	73	-0.34 [-0.46, -0.22]	0.11 [0.03, 0.34]
TITAN	3	36	11	39	-0.20 [-0.37, -0.03]	0.30 [0.09, 0.97]
Pooled estimate (Q = 1.41, df = 1, p = 0.24; I^2 = 28.9%, τ^2 = 0.14)					-0.29 [-0.42, -0.14]	0.16 [0.07, 0.47]
Observational						
France	3	90	70	180	-0.36 [-0.44, -0.28]	0.09 [0.03, 0.26]
Barcelona	1	9	3	9	-0.22 [-0.59, 0.15]	0.33 [0.04, 2.63]
Pooled estimate (Q = 1.28, df = 1, p = 0.26; I^2 = 21.8%, τ^2 = 0.20)					-0.35 [-0.43, -0.27]	0.10 [0.04, 0.42]



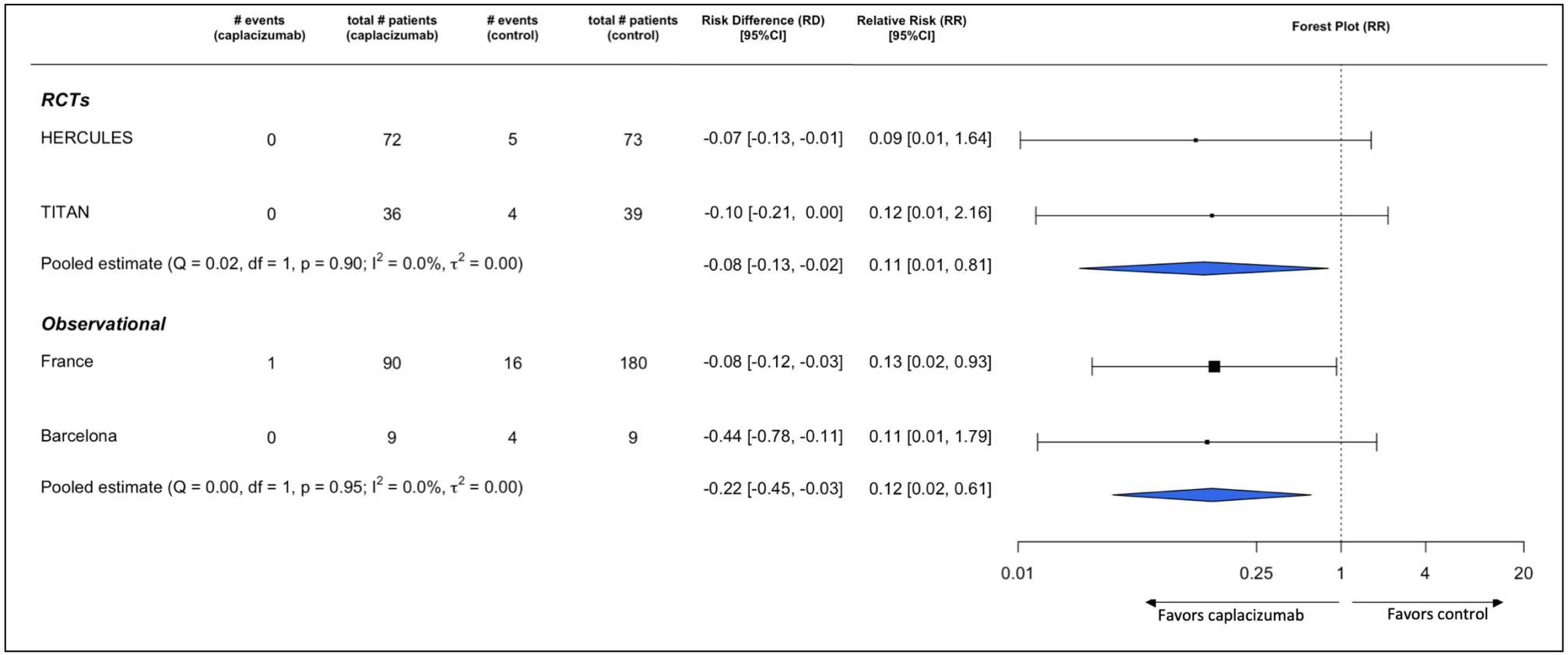
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 4B: TTP relapse



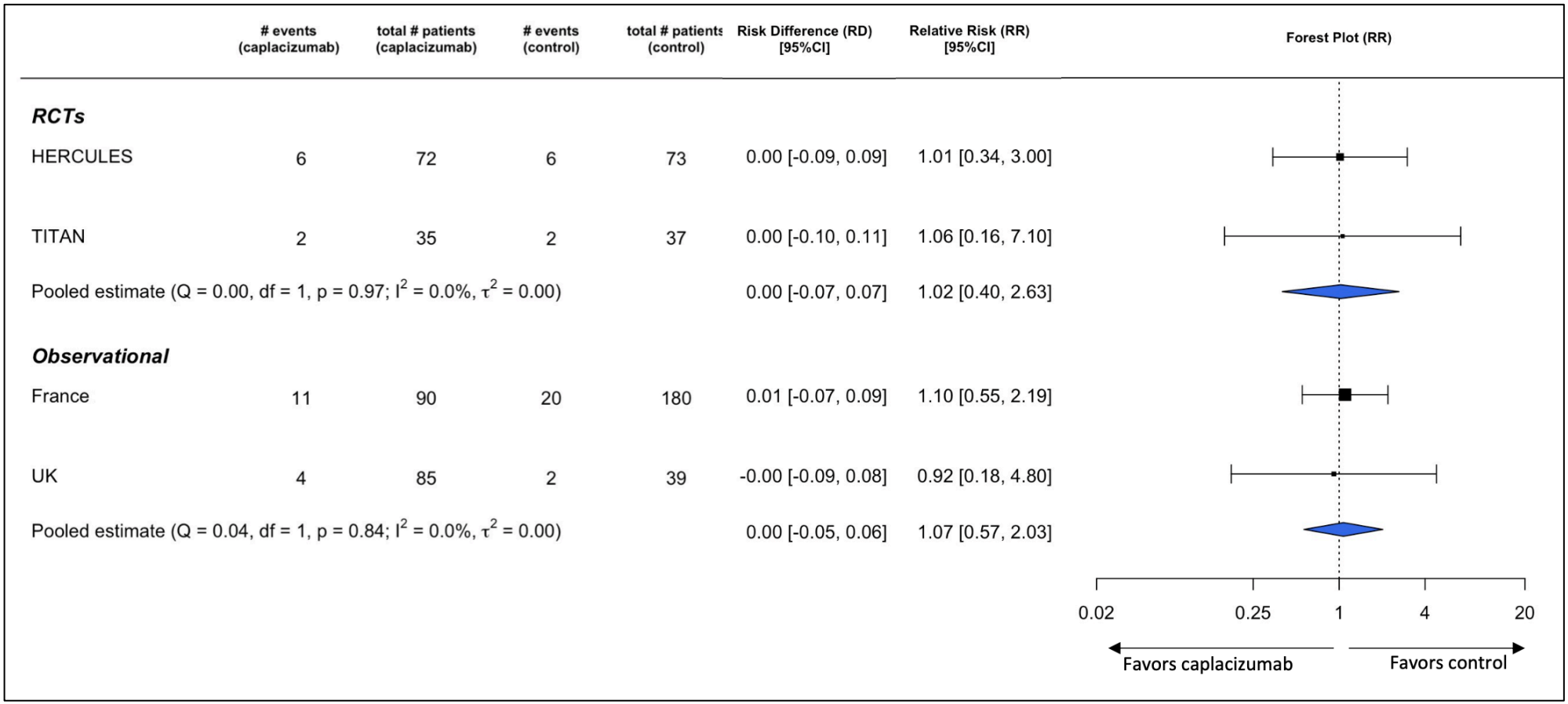
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 4C: Refractory TTP



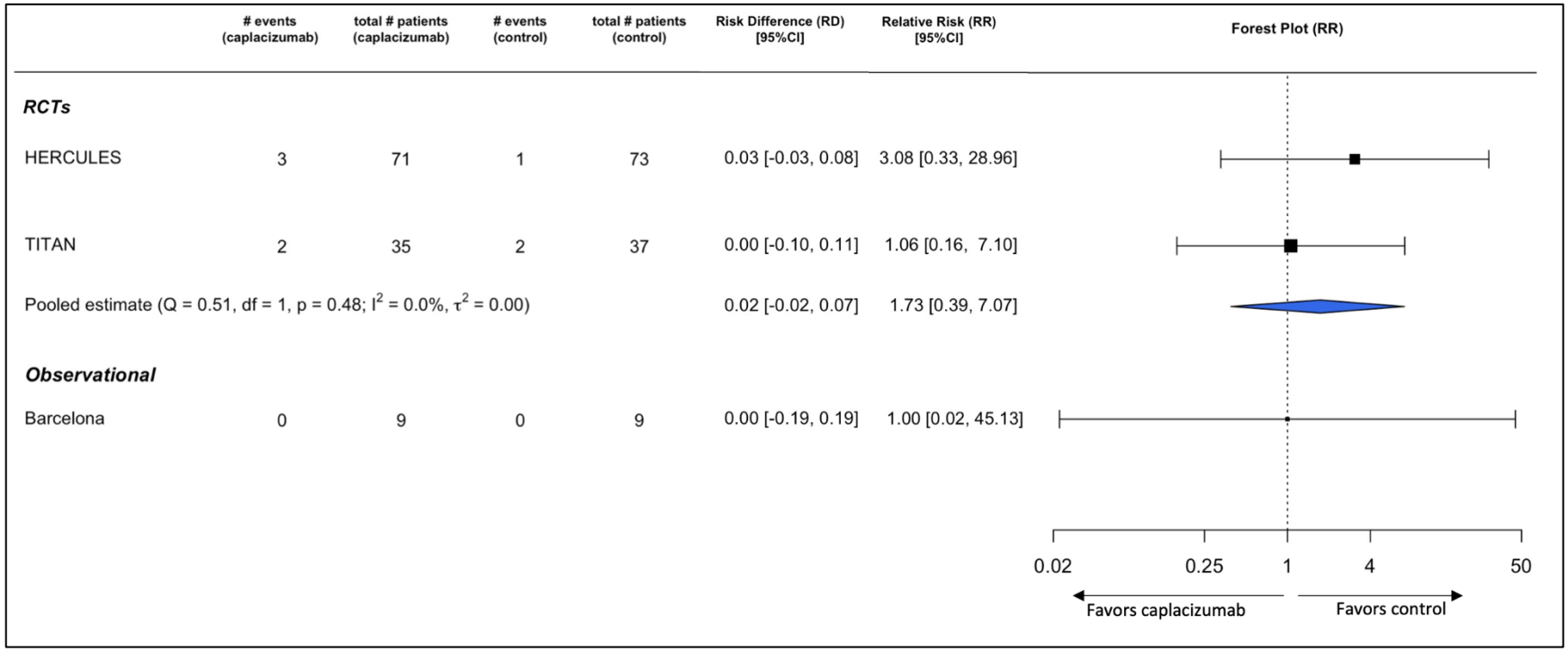
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 4D: Thrombosis



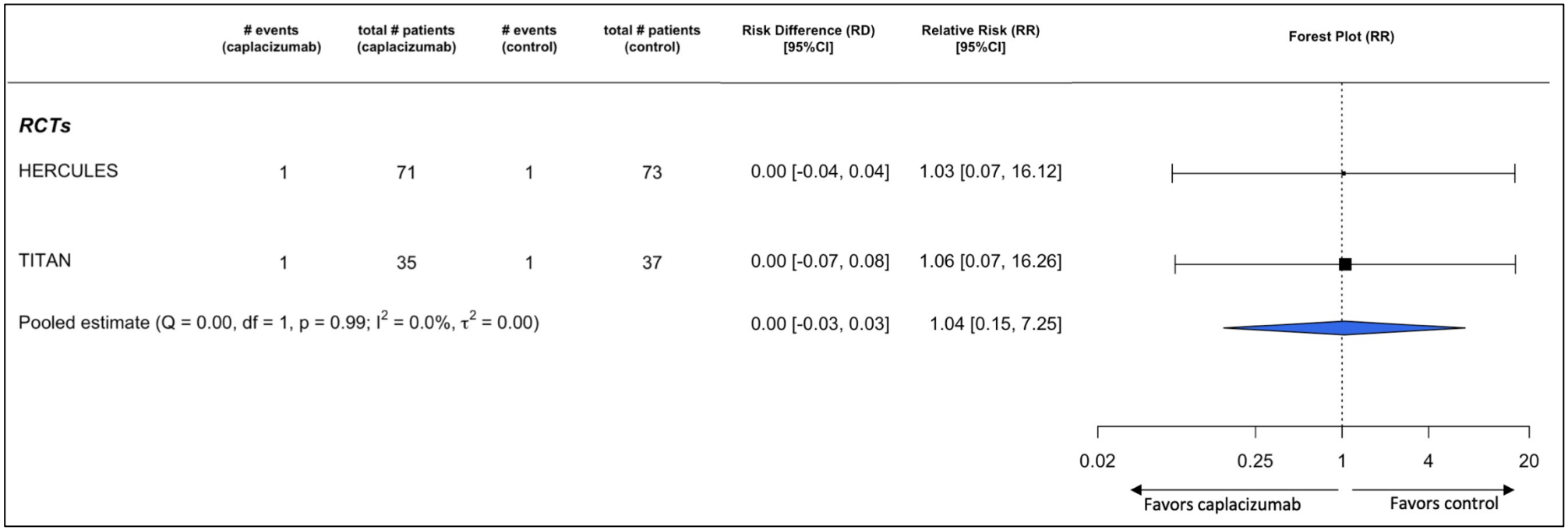
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 4E: Major bleeding



Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 4F: Intracranial bleeding



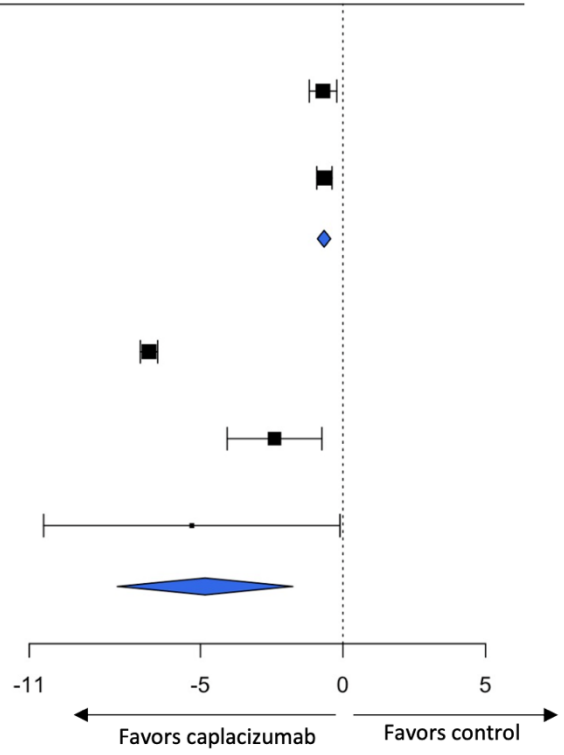
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

S4.2: Continuous Outcomes

We present the outcomes reported in each individual trial as well as meta-analysis according to study design. Control refers to standard of care alone without caplacizumab (refer to Supplement S2 “eTable 2C: Details of treatments received”). As few trials reported means and no trials reported standard deviation (SD), we calculated mean (SD) to generated pooled estimates using the methods described in the main text. We denote reported mean with § to differentiate from calculated mean. We calculated standard deviations from the available aggregate data (ranges or interquartile ranges for all outcomes in all studies, except for time to response in TITAN [where we used 95% CI of the associated median]).

eFigure 4G: Time to normalization of the platelet count (days)

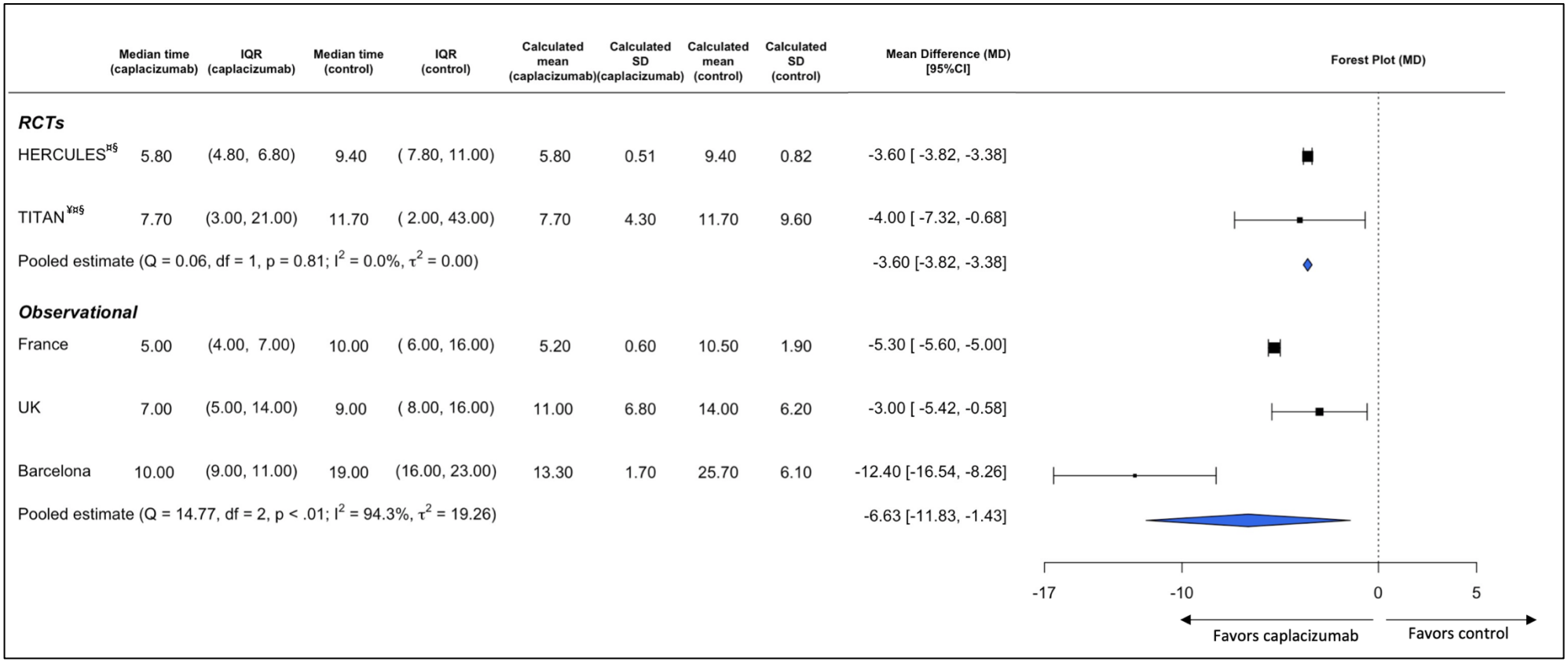
	Median time (caplacizumab)	IQR (caplacizumab)	Median time (control)	IQR (control)	Calculated mean (caplacizumab)	Calculated SD (caplacizumab)	Calculated mean (control)	Calculated SD (control)	Mean Difference (MD) [95%CI]
RCTs									
HERCULES[†]	2.69	(1.74, 2.95)	2.88	(1.94, 4.50)	3.40	0.90	4.10	1.90	-0.70 [-1.18, -0.22]
TITAN[†‡]	3.00	(2.70, 4.30)	4.60	(3.00, 5.90)	0.80	0.41	1.45	0.74	-0.65 [-0.92, -0.38]
Pooled estimate (Q = 0.03, df = 1, p = 0.86; I^2 = 0.0%, τ^2 = 0.00)									-0.66 [-0.90, -0.43]
Observational									
France	5.00	(4.00, 6.00)	12.00	(6.00, 17.00)	5.00	0.40	11.80	2.00	-6.80 [-7.10, -6.50]
UK	4.00	(3.00, 8.00)	6.00	(4.00, 10.00)	6.30	3.80	8.70	4.60	-2.40 [-4.06, -0.74]
Barcelona	4.00	(3.00, 4.00)	6.00	(5.00, 14.00)	5.00	0.90	10.30	7.90	-5.30 [-10.49, -0.11]
Pooled estimate (Q = 26.25, df = 2, p < .01; I^2 = 89.5%, τ^2 = 5.76)									-4.84 [-7.91, -1.76]



Legend: IQR=interquartile range; TTP=thrombotic thrombocytopenic purpura; RCT=Randomized Controlled Trials; SD=standard deviation

† Median (95% confidence interval)
‡ Since time to platelet count recovery was not reported for the entire cohort in the TITAN trial, we used the aggregate data reported for the subgroup of patients who had a baseline ADAMTS13 < 10% (n=58).

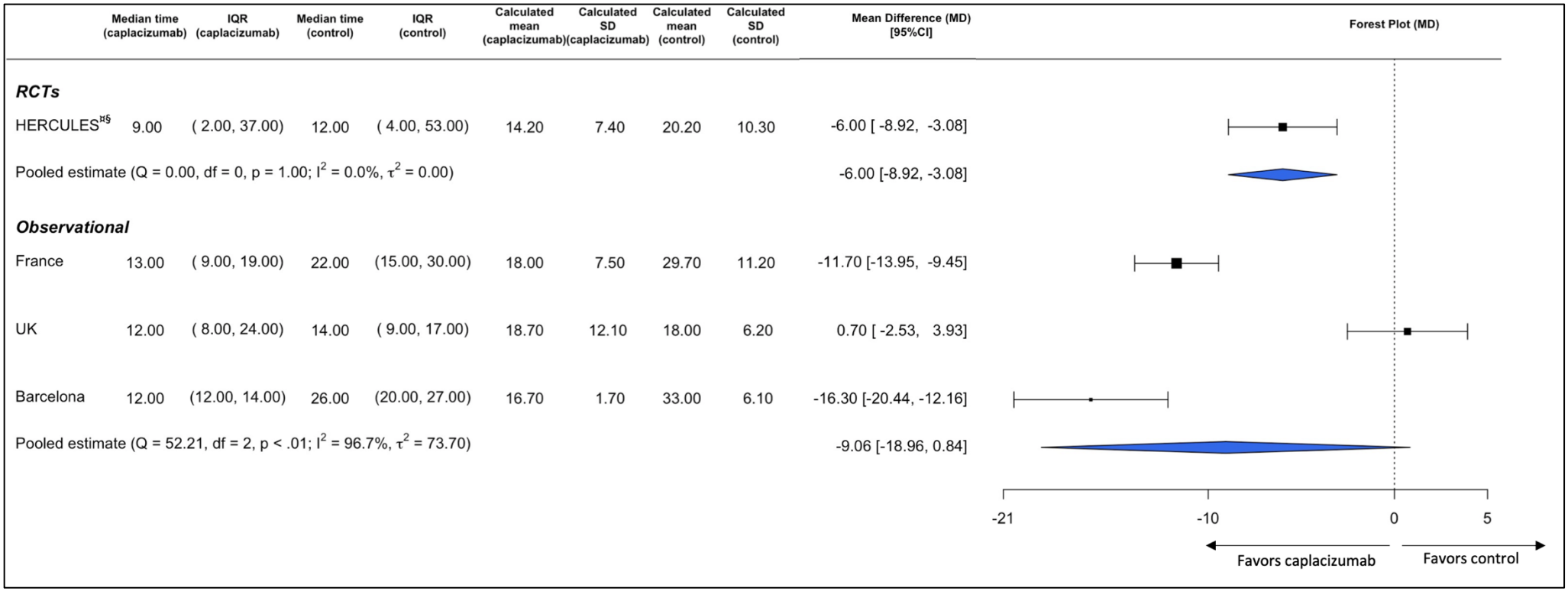
eFigure 4H: Duration of plasma exchange (days)



Legend: IQR=interquartile range; TTP=thrombotic thrombocytopenic purpura; RCT=Randomized Controlled Trials; SD=standard deviation

¤ IQR not reported, full range reported instead.
¥ Median not reported, mean reported instead.
§ Reported mean (rather than calculated mean).

eFigure 4*l*: Hospital length of stay (days)



Legend: IQR=interquartile range; TTP=thrombotic thrombocytopenic purpura; RCT=Randomized Controlled Trials; SD=standard deviation

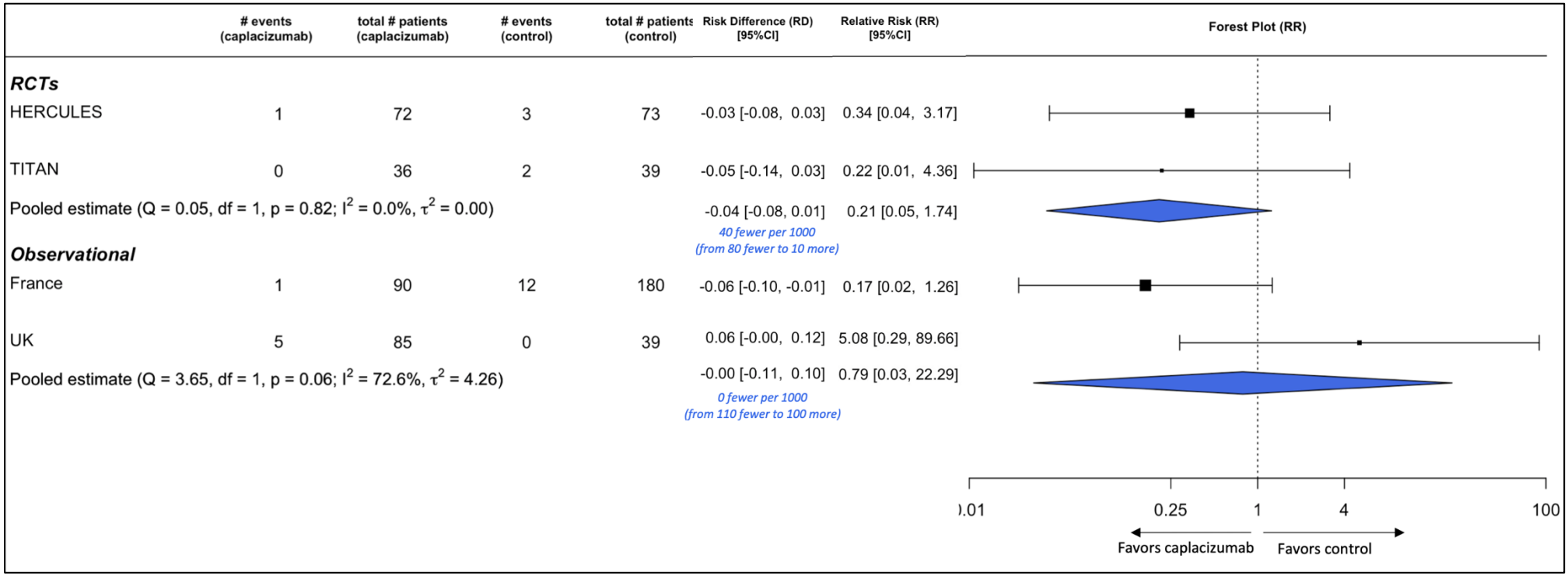
¤ IQR not reported, full range reported instead.
§ Reported mean (rather than calculated mean).

S5: Sensitivity meta-analysis and forest plots: peer-reviewed publications only

The following outcomes were analyzed only among studies published as peer-reviewed research articles, and excludes the results of the Barcelona study (an abstract-only publication). We did not perform a sensitivity analysis of the outcomes "thrombosis" and "intracranial bleeding" because they were not reported in the Barcelona study and the analysis did not change with focusing on peer-reviewed-only publications.

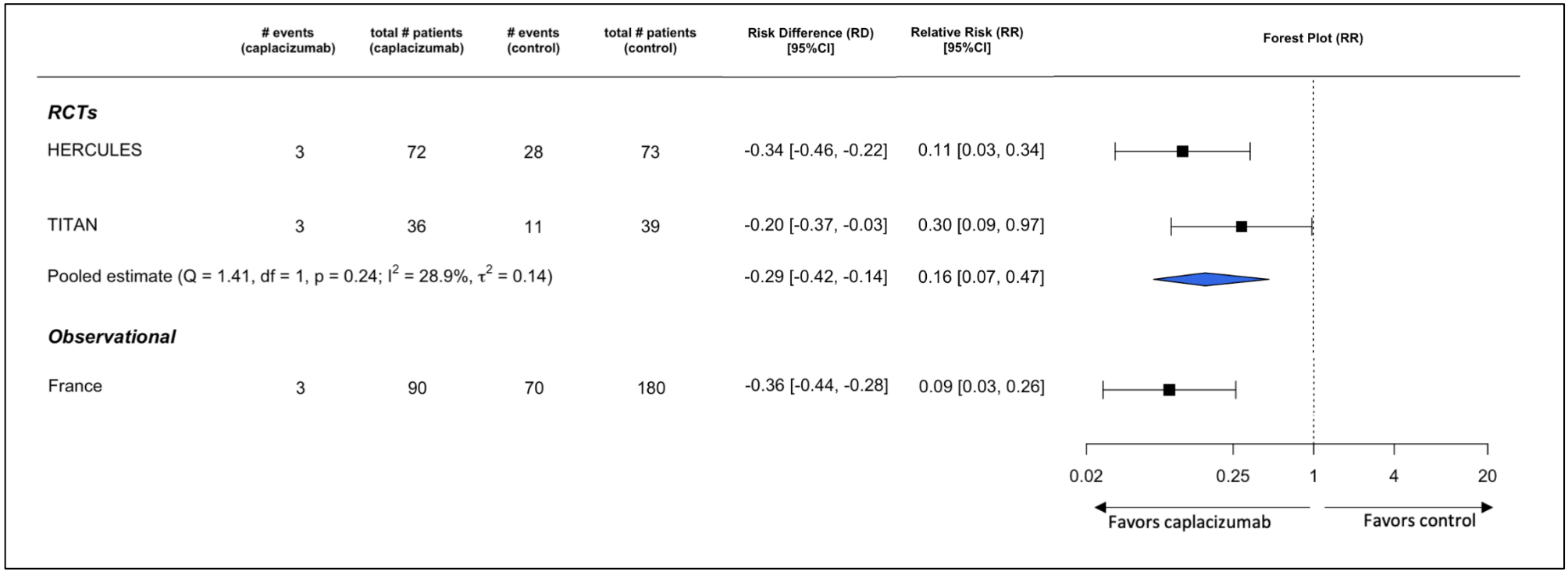
S5.1: Binary Outcomes

eFigure 5A: All-cause mortality



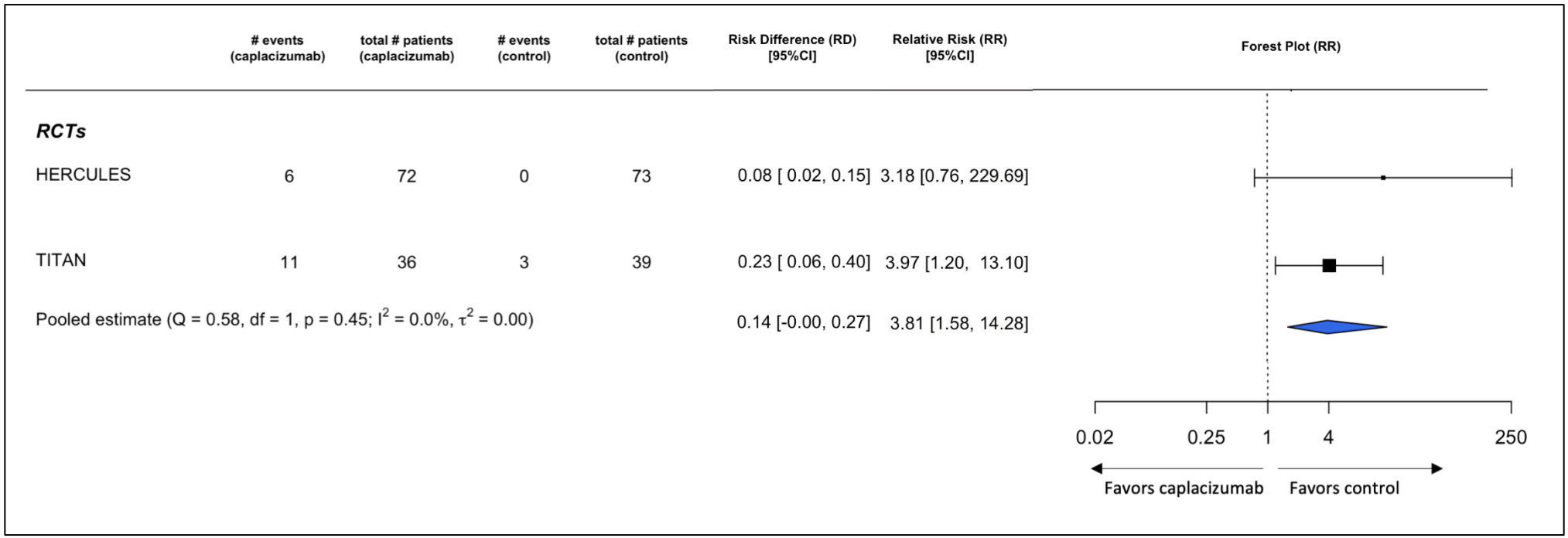
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk; SD=standard deviation

eFigure 5B: TTP exacerbation



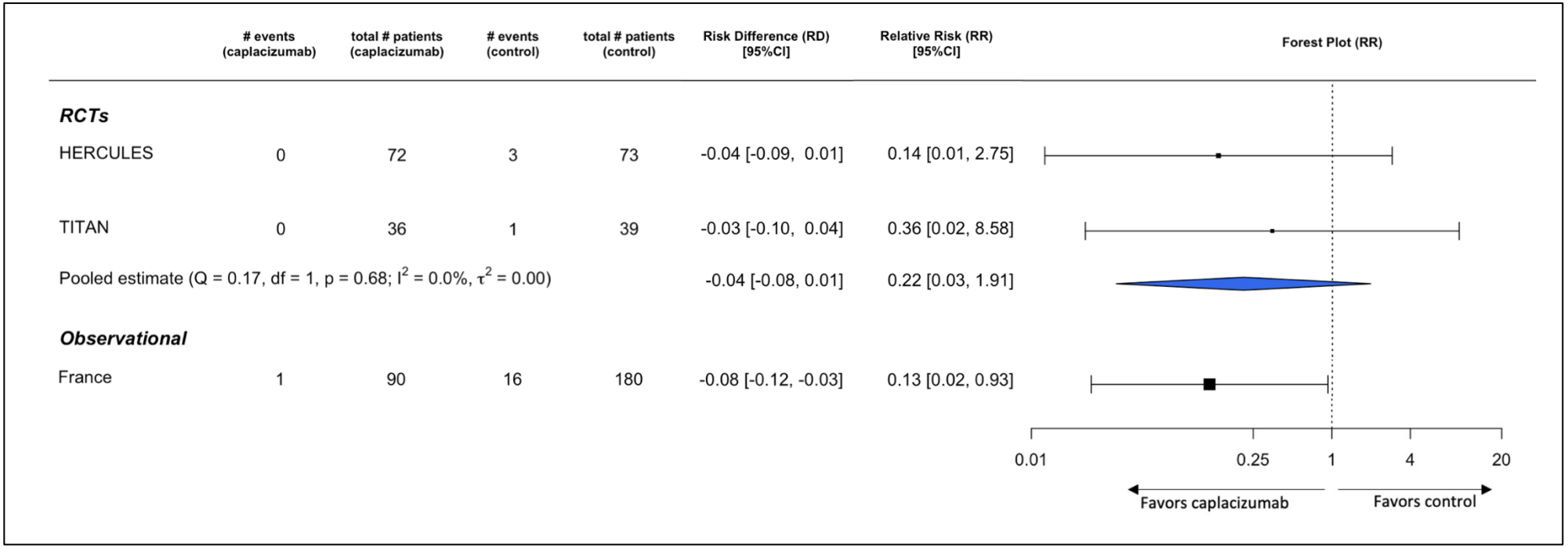
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 5C: TTP relapse



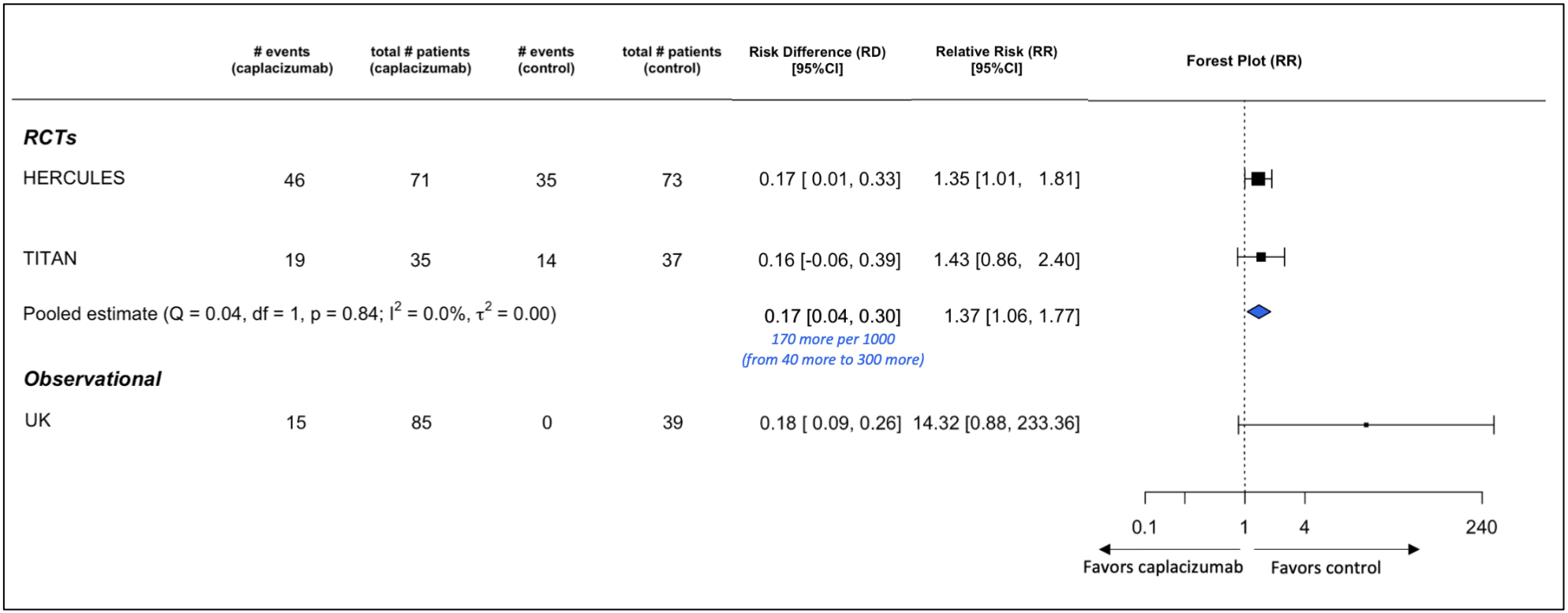
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 5D: Refractory TTP



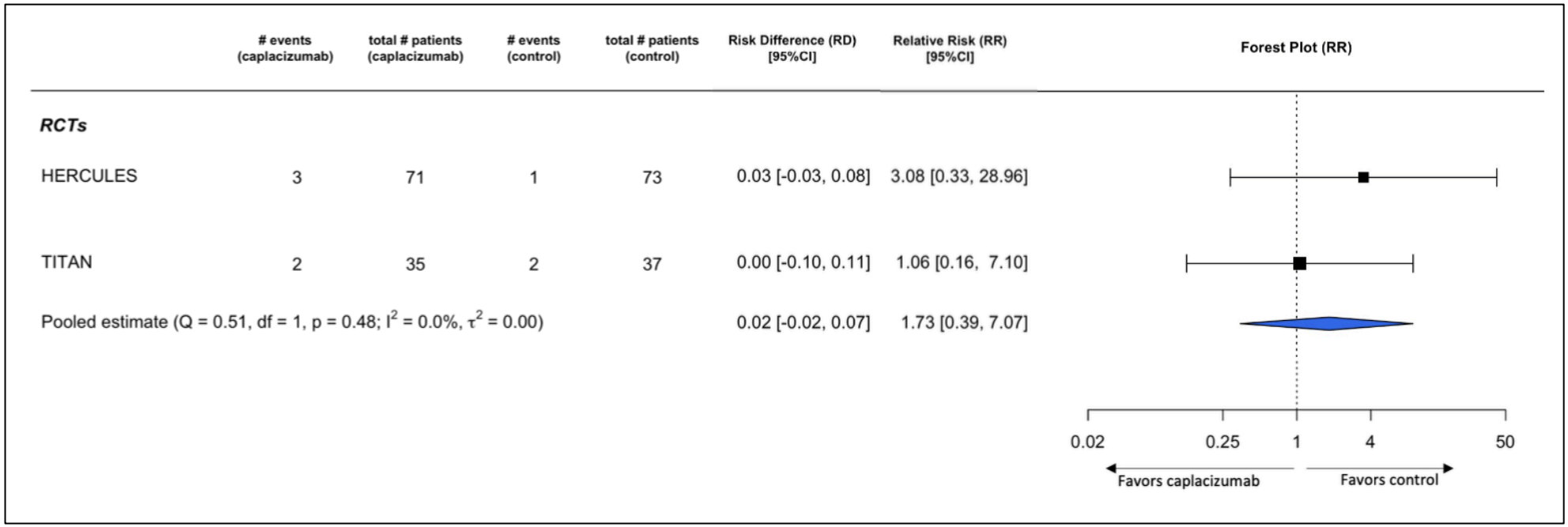
Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

eFigure 5E: Any treatment-emergent bleeding



Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk; SD=standard deviation

eFigure 5F: Major bleeding

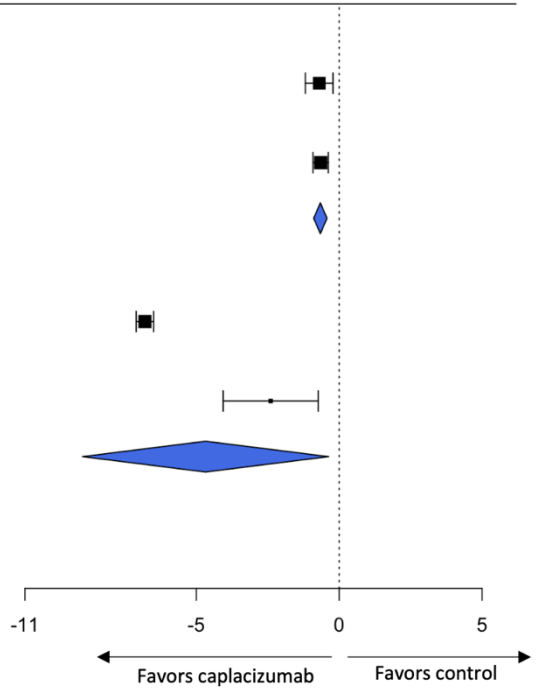


Legend: CI=Confidence Interval; RCT=Randomized Controlled Trials; RR=relative risk

S5.2: Continuous Outcomes

eFigure 5G: Time to normalization of the platelet count (days)

	Median time (caplacizumab)	IQR (caplacizumab)	Median time (control)	IQR (control)	Calculated mean (caplacizumab)	Calculated SD (caplacizumab)	Calculated mean (control)	Calculated SD (control)	Mean Difference (MD) [95%CI]
RCTs									
HERCULES†	2.69	(1.74, 2.95)	2.88	(1.94, 4.50)	3.40	0.90	4.10	1.90	-0.70 [-1.18, -0.22]
TITAN†‡	3.00	(2.70, 4.30)	4.60	(3.00, 5.90)	0.80	0.41	1.45	0.74	-0.65 [-0.92, -0.38]
Pooled estimate (Q = 0.03, df = 1, p = 0.86; I^2 = 0.0%, τ^2 = 0.00)									-0.66 [-0.90, -0.43]
Observational									
France	5.00	(4.00, 6.00)	12.00	(6.00, 17.00)	5.00	0.40	11.80	2.00	-6.80 [-7.10, -6.50]
UK	4.00	(3.00, 8.00)	6.00	(4.00, 10.00)	6.30	3.80	8.70	4.60	-2.40 [-4.06, -0.74]
Pooled estimate (Q = 25.99, df = 1, p < .01; I^2 = 96.2%, τ^2 = 9.31)									-4.68 [-8.99, -0.37]

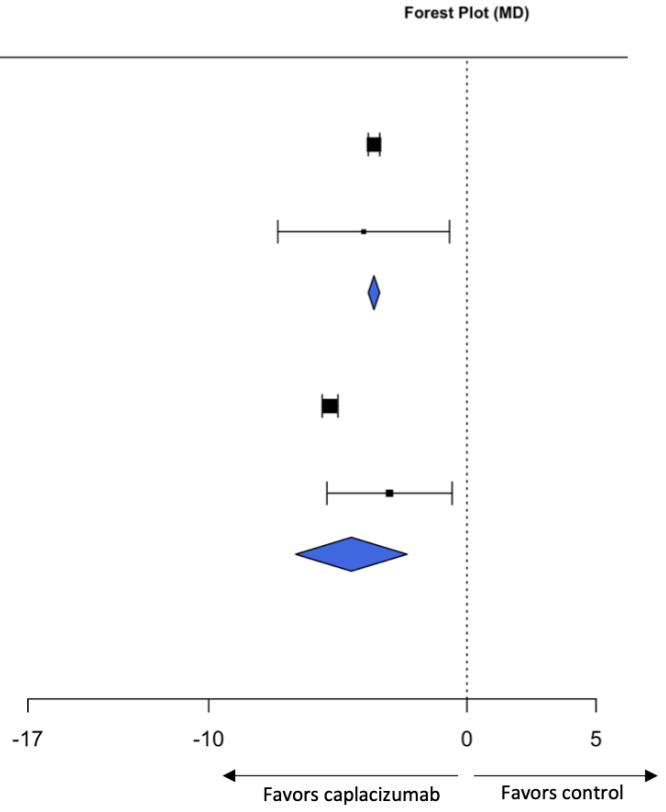


Legend: IQR=interquartile range; TTP=thrombotic thrombocytopenic purpura; RCT=Randomized Controlled Trials; SD=standard deviation

† Median (95% confidence interval)
‡ Since time to platelet count recovery was not reported for the entire cohort in the TITAN trial, we used the aggregate data reported for the subgroup of patients who had a baseline ADAMTS13 < 10% (n=58).

eFigure 5H: Duration of plasma exchange (days)

	Median time (caplacizumab)	IQR (caplacizumab)	Median time (control)	IQR (control)	Calculated mean (caplacizumab)	Calculated SD (caplacizumab)	Calculated mean (control)	Calculated SD (control)	Mean Difference (MD) [95%CI]
RCTs									
HERCULES[¤§]	5.80	(4.80, 6.80)	9.40	(7.80, 11.00)	5.80	0.51	9.40	0.82	-3.60 [-3.82, -3.38]
TITAN[¥¤§]	7.70	(3.00, 21.00)	11.70	(2.00, 43.00)	7.70	4.30	11.70	9.60	-4.00 [-7.32, -0.68]
Pooled estimate (Q = 0.06, df = 1, p = 0.81; I^2 = 0.0%, τ^2 = 0.00)									-3.60 [-3.82, -3.38]
Observational									
France	5.00	(4.00, 7.00)	10.00	(6.00, 16.00)	5.20	0.60	10.50	1.90	-5.30 [-5.60, -5.00]
UK	7.00	(5.00, 14.00)	9.00	(8.00, 16.00)	11.00	6.80	14.00	6.20	-3.00 [-5.42, -0.58]
Pooled estimate (Q = 3.40, df = 1, p = 0.07; I^2 = 70.6%, τ^2 = 1.87)									-4.48 [-6.64, -2.32]

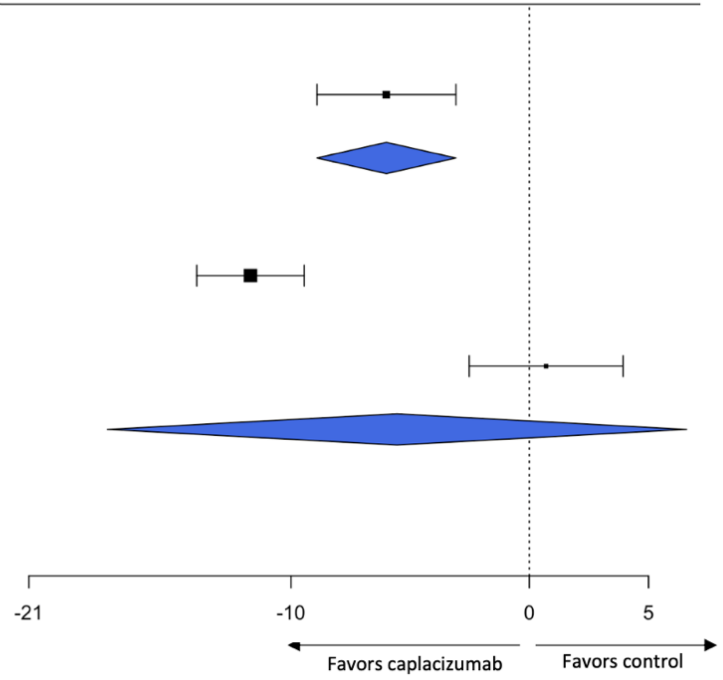


Legend: IQR=interquartile range; TTP=thrombotic thrombocytopenic purpura; RCT=Randomized Controlled Trials; SD=standard deviation

¤ IQR not reported, full range reported instead.
¥ Median not reported, mean reported instead.
§ Reported mean (rather than calculated mean).

eFigure 5*I*: Hospital length of stay (days)

	Median time (caplacizumab)	IQR (caplacizumab)	Median time (control)	IQR (control)	Calculated mean (caplacizumab)	Calculated SD (caplacizumab)	Calculated mean (control)	Calculated SD (control)	Mean Difference (MD) [95%CI]
RCTs									
HERCULES[¤§]	9.00	(2.00, 37.00)	12.00	(4.00, 53.00)	14.20	7.40	20.20	10.30	-6.00 [-8.92, -3.08]
Pooled estimate (Q = 0.00, df = 0, p = 1.00; I^2 = 0.0%, τ^2 = 0.00)									-6.00 [-8.92, -3.08]
Observational									
France	13.00	(9.00, 19.00)	22.00	(15.00, 30.00)	18.00	7.50	29.70	11.20	-11.70 [-13.95, -9.45]
UK	12.00	(8.00, 24.00)	14.00	(9.00, 17.00)	18.70	12.10	18.00	6.20	0.70 [-2.53, 3.93]
Pooled estimate (Q = 38.15, df = 1, p < .01; I^2 = 97.4%, τ^2 = 74.86)									-5.56 [-17.71, 6.60]



Legend: IQR=interquartile range; TTP=thrombotic thrombocytopenic purpura; RCT=Randomized Controlled Trials; SD=standard deviation

¤ IQR not reported, full range reported instead.
§ Reported mean (rather than calculated mean).