# Benign Hematology: Clotting, Bleeding and More

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# Disclosures

- Research- Bayer, NovoNordisk, Octapharma, Genentech/Roche, Sangamo, Takeda
- Advisory Boards- Argenx, Bayer, BioMarin, CSL-Behring, Freeline, Genentech/Roche, Grifols, NovoNordisk, Octapharma, Pfizer, Takeda, Principia, Rigel, Spark
- DSMB- NIH, Dimension, Revo, Octapharma
- Stock- Not applicable
- Employment – Not applicable
- Speakers' Bureau – Not applicable

# Topics

- Advances in Immune Thrombocytopenic Purpura (ITP)
- ITP and COVID-19
- COVID-19 and coagulation
- Cancer and Thrombosis
- Hemophilia and Gene therapy
- New reversal strategy for direct acting oral anticoagulants (DOACs)

# Treatment of Newly Diagnosed ITP

## ASH 2019

Suggests treatment instead of observation for platelet count <30K

”…may be a subset of patients for whom observation may be appropriate”

Suggests hospital admission over outpatient management for platelet count <20K *at diagnosis*

## International Consensus Report (ICR) 2019

Suggests treatment instead of observation for platelet count <20K

Patient considerations weigh heavily in treatment decisions

Suggests hospital admission over outpatient management for platelet count <20K *at diagnosis*

**Both highlight patients >60 are a high risk group more likely to experience major bleeding**

Provan D et al. *Blood Adv*. 2019;22:3780-3817;
Neunert C et al. *Blood Adv*. 2019;23:3829-3866.

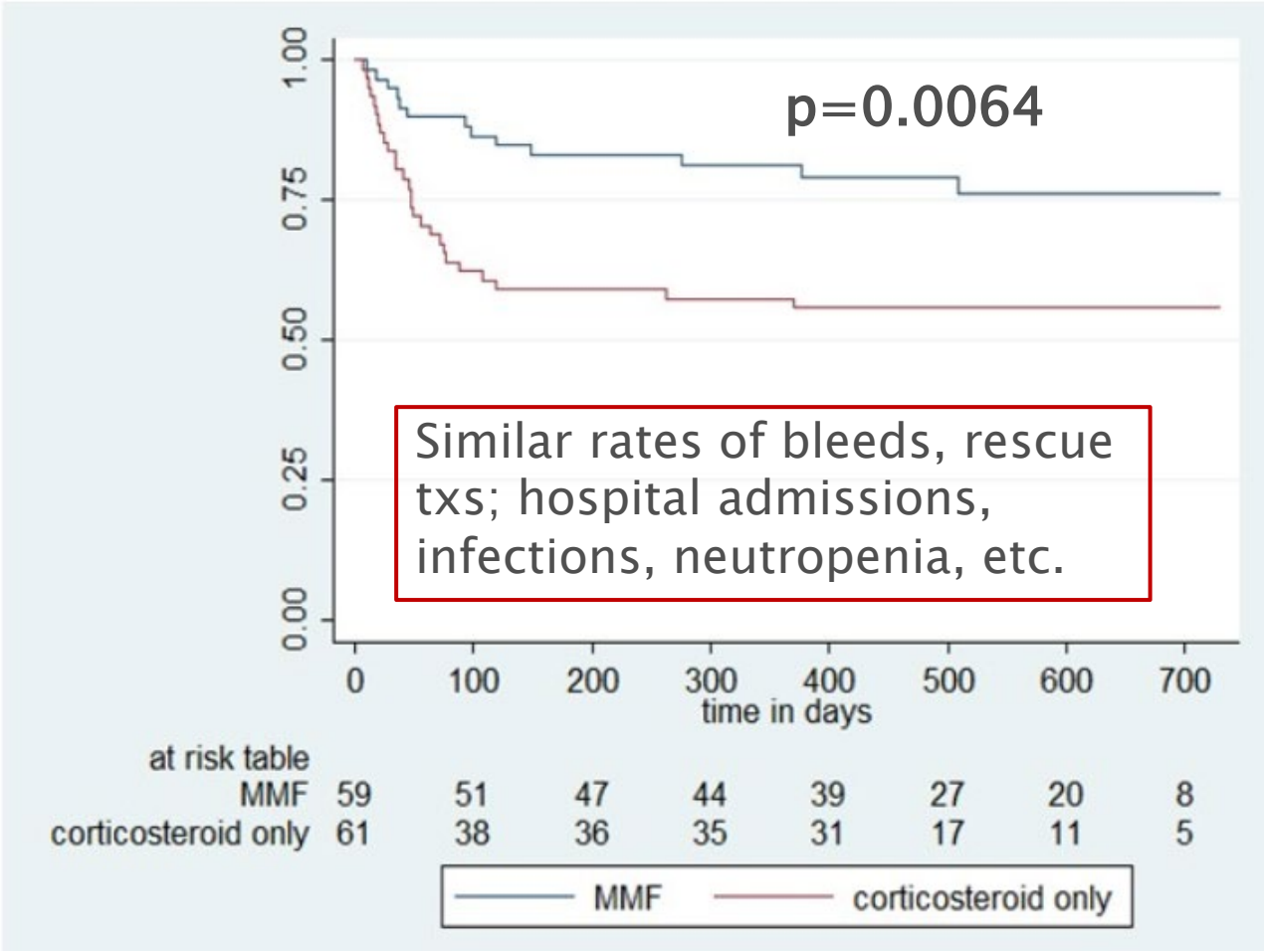
# Upfront Management

- No reliable way to predict response to therapy in advance
- Both guidelines recommend corticosteroids as the front-line treatment of choice for newly diagnosed ITP
- Goal: decrease risk of bleeding, NOT normalize platelet count
- Balance risk of side effects, likelihood of benefit, cost, route of administration, insurance, patient preferences and values
- **Both guidelines place value on avoidance of prolonged courses (>2-3 weeks with taper) of corticosteroids given side effects**
- Consider transition to second line therapy

Provan D et al. *Blood Adv*. 2019;22:3780-3817;
Neunert C et al. *Blood Adv*. 2019;23:3829-3866.

# A Multicentre Randomised Trial of First Line Treatment Pathways for Newly Diagnosed Immune Thrombocytopenia: Standard Steroid Treatment Versus Combined Steroid and Mycophenolate. the Flight Trial

**Figure 1: Kaplan Meier graph showing the proportion of patients without treatment failure**




Similar rates of bleeds, rescue txs; hospital admissions, infections, neutropenia, etc.

First randomized trial using MMF to treat ITP; good efficacy and tolerability, even with the inclusion of elderly patients (27.5% were >70 years, 15.8% >75 years)

Corticosteroid only:1 mg/kg/d prednisolone x 4d; 40 mg/d x 2 wk; 20 mg/d x 2 wk; 10 mg/d x 2 wk; 5 mg/d x 2 wks; 5 mg qod x 2 wk; then stop
MMF: 500 mg bid x 2 wk; 750 mg bid x 2 wks; 1g bid x 2 wk for 6 mos, if tolerated; if CR, taper to lowest dose to maintain plts >100K;

Fewer tx failures: MMF+CS vs CS: 22% vs 44%, aHR=0.41 [0.21, 0.80], p=0.0064

When secondary ITP was excluded: aHR 0.37 [0.19, 0.71] p=0.0029)

Bradbury CA ,et al. ASH Annual Meeting 2020. Abstract LBA-2.

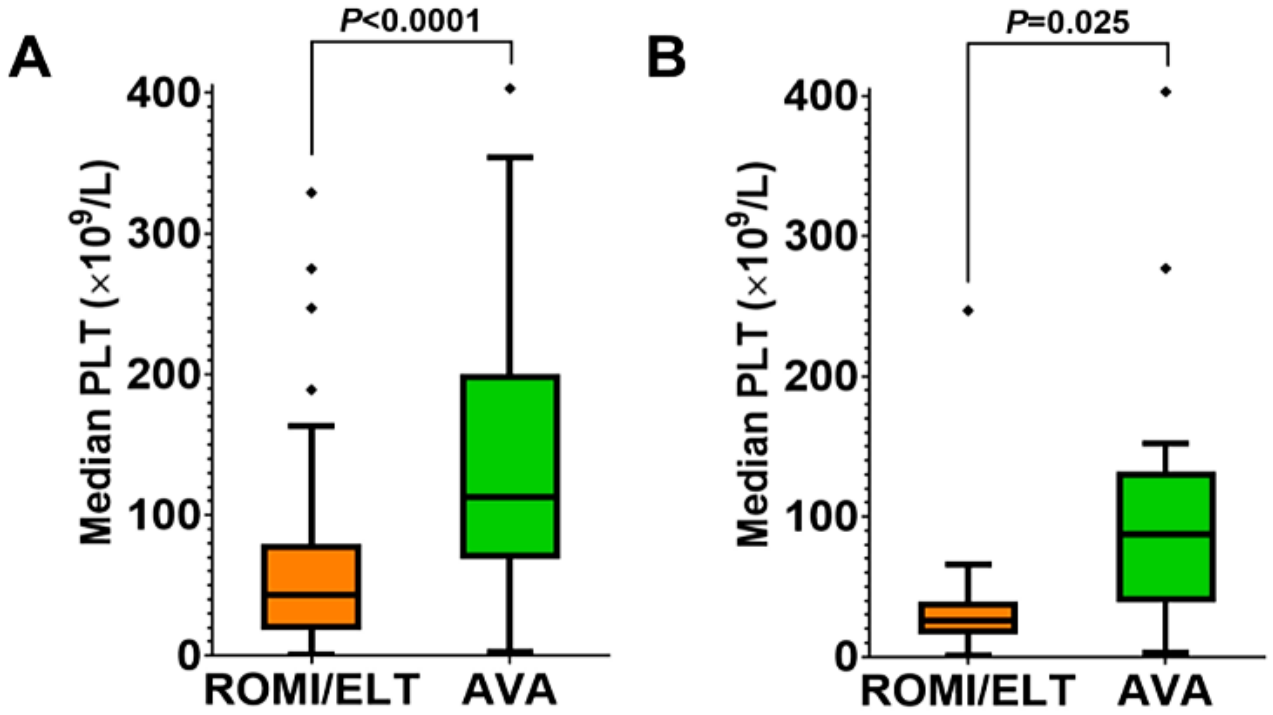
# Second-line Therapies

| | Class/therapy | Agents |
|---|---|---|
| | Splenectomy | |
| | Anti-CD20 antibody | Rituximab |
| | TPO-RAs | Eltrombopag, romiplostim, avatrombopag |
| | Syk inhibition | Fostamatinib |
| | Immunosuppressants | Azathioprine, MMF, danazol, cyclosporine, cyclophosphamide, vinca alkaloids, dapsone |
| Investigational | FcRn inhibition | Rozanolixizumab, efgartigmod |
| | BTK inhibitor | PRN1008 |
| | Hypomethylation | Low-dose decitabine |

- No head-to-head trials exist comparing one second line therapy to another
- Limited clinical predictors and/or molecular biomarkers to guide treatment decisions

# Are the TPO-RA agents interchangeable?

*Rates of platelet response following switch to avatrombopag in the absence of rescue therapy (counts were disqualified if <8 weeks from receipt of rescue corticosteroids or <4 weeks from IVIG).*



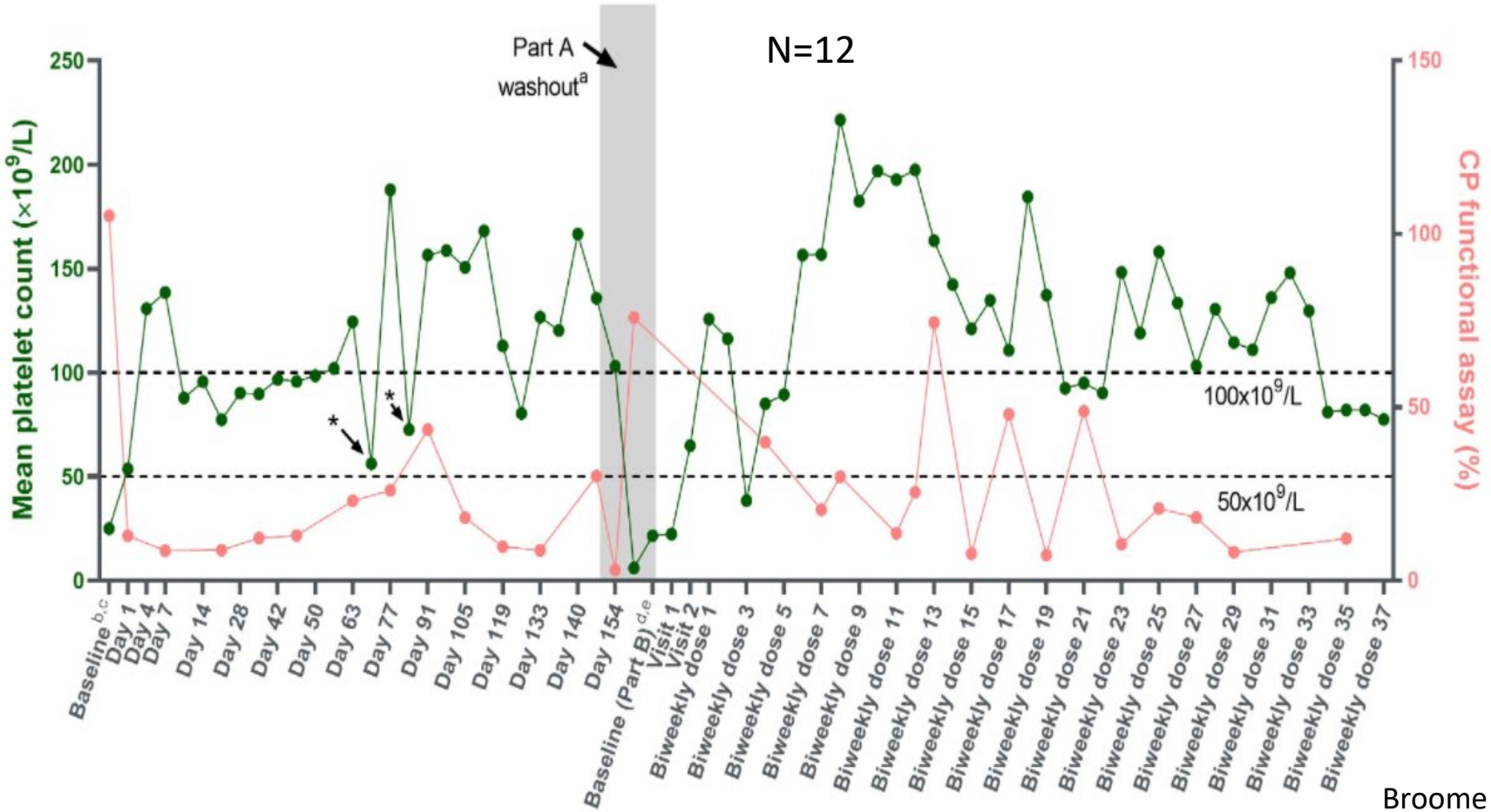

*Median platelet counts for each patient prior to switch (during treatment with romiplostim or eltrombopag) vs. following the switch to avatrombopag. For each patient, the median platelet count is the median of the most recent 3 platelet counts measured while receiving that agent. (A) All patients (N=45). (B) Patients switched due to ineffectiveness of romiplostim or eltrombopag (N=14). One patient with median Plt 585×109/L on avatrombopag omitted from both graphs to preserve graph resolution.*

**Conclusions:** In a heavily-pretreated chronic ITP population, Avatrombopag (AVA) was effective following therapy with romiplostim (ROM) or Eltrombopag (ELT), with high response rates even in patients with inadequate response to a prior TPO-RA

*Al-Samkari H et al. Res Pract Thromb Haemost*. 2021; 5 (Suppl 1). https://abstracts.isth.org/abstract/switching-from-eltrombopag-or-romiplostim-to-avatrombopag-in-immune-thrombocytopenia-a-multicenter-study-of-u-s-itp-referral-centers/. Accessed July 30, 2021.

# Long-Term Safety and Efficacy of Sutimlimab in Patients with Chronic Immune Thrombocytopenia

Figure 1. Mean platelet counts (×$10^9$/L) and CP activity over time in patients receiving sutimlimab




**INHIBITION OF CLASSICAL COMPLEMENT PATHWAY (CP)**

With humanized monoclonal AB selectively blocks activation of the CP by binding to C1s

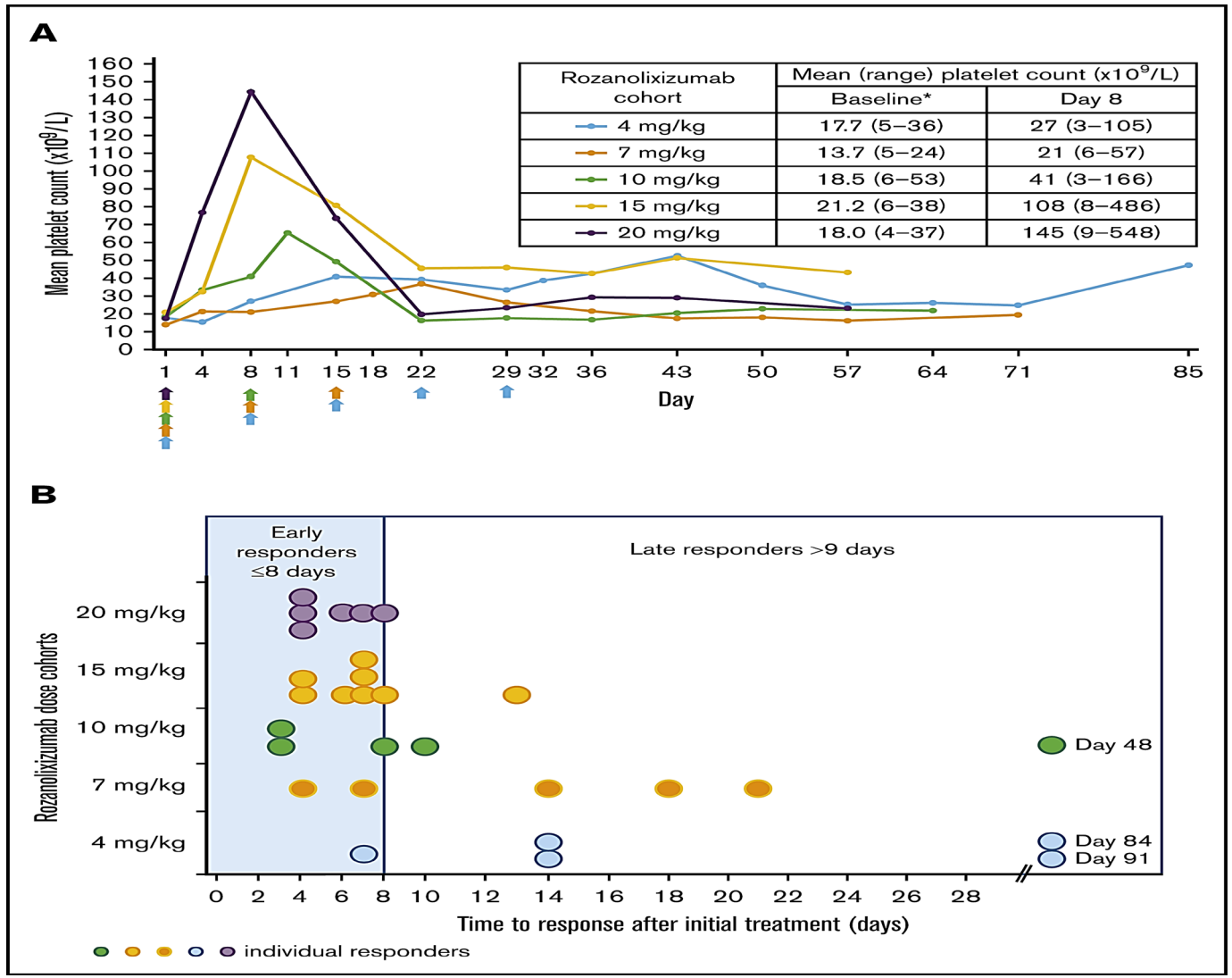
Eight patients insufficiently responded to rituximab and 9 had insufficient response to TPO-RAs

Plt responses correlate with changes in CP activity, consistent with CP inhibition.

>1 pathophysiologic etiology for heterogeneity of ITP

Broome CM, et al. ASH Annual Meeting 2020. Abstract 23.

# Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia

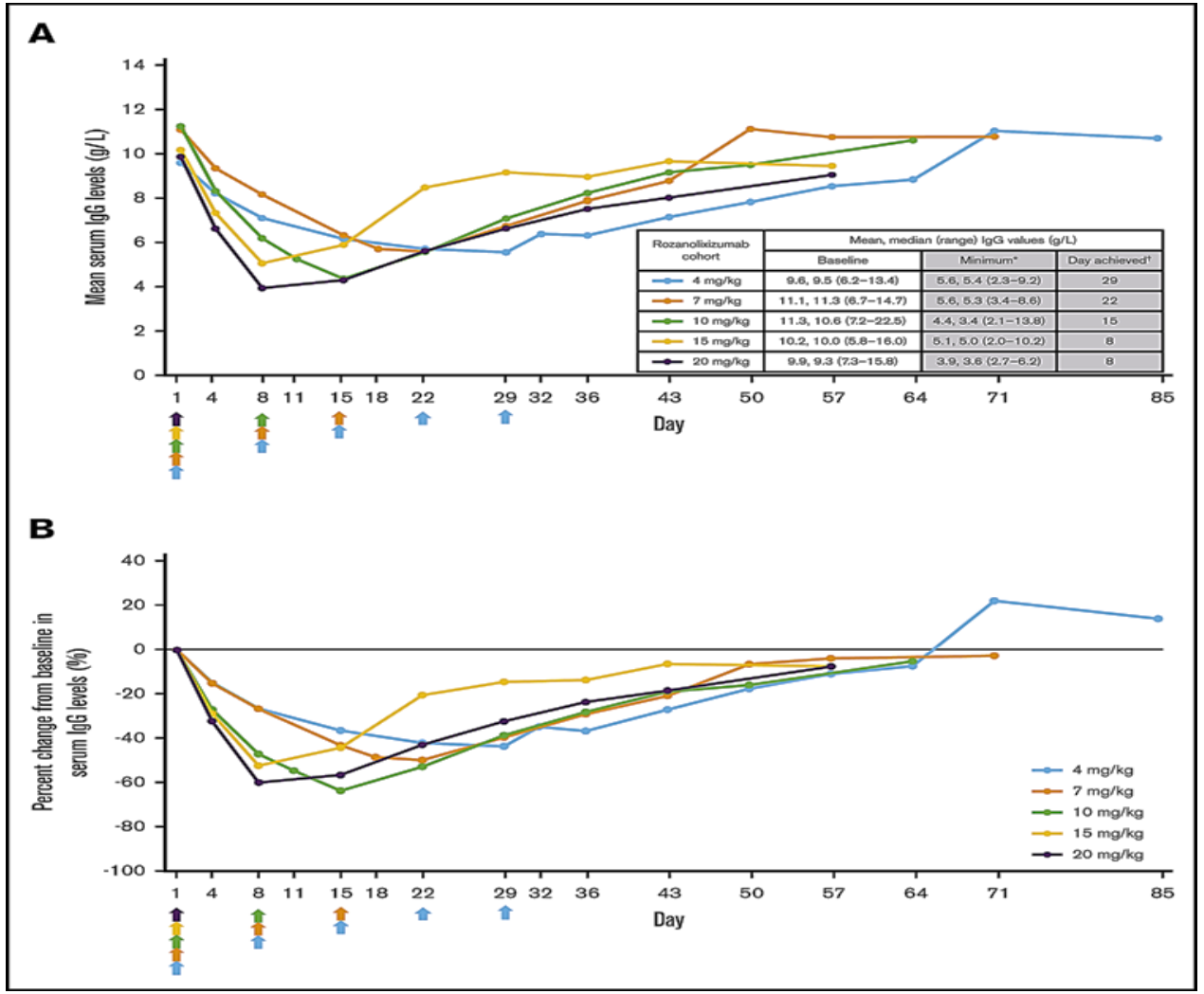



Rapid platelet rise is dose responsive

*Robak T et al. Blood Adv* (2020) 4 (17): 4136–4146.
https://doi.org/10.1182/bloodadvances.2020002003

# Phase 2 multiple-dose study of an FcRn inhibitor, rozanolixizumab, in patients with primary immune thrombocytopenia

**Long recovery period for IgG levels: What are the implications?**




*Robak T et al. Blood Adv* (2020) 4 (17): 4136–4146. https://doi.org/10.1182/bloodadvances.2020002003

# Oral Rilzabrutinib, a Bruton Tyrosine Kinase Inhibitor, Showed Clinically Active and Durable Platelet Responses and Was Well-Tolerated in Patients with Heavily Pretreated Immune Thrombocytopenia

*Table. Platelet Response in ITP Patients Initiating Rilzabrutinib 400 mg BID*

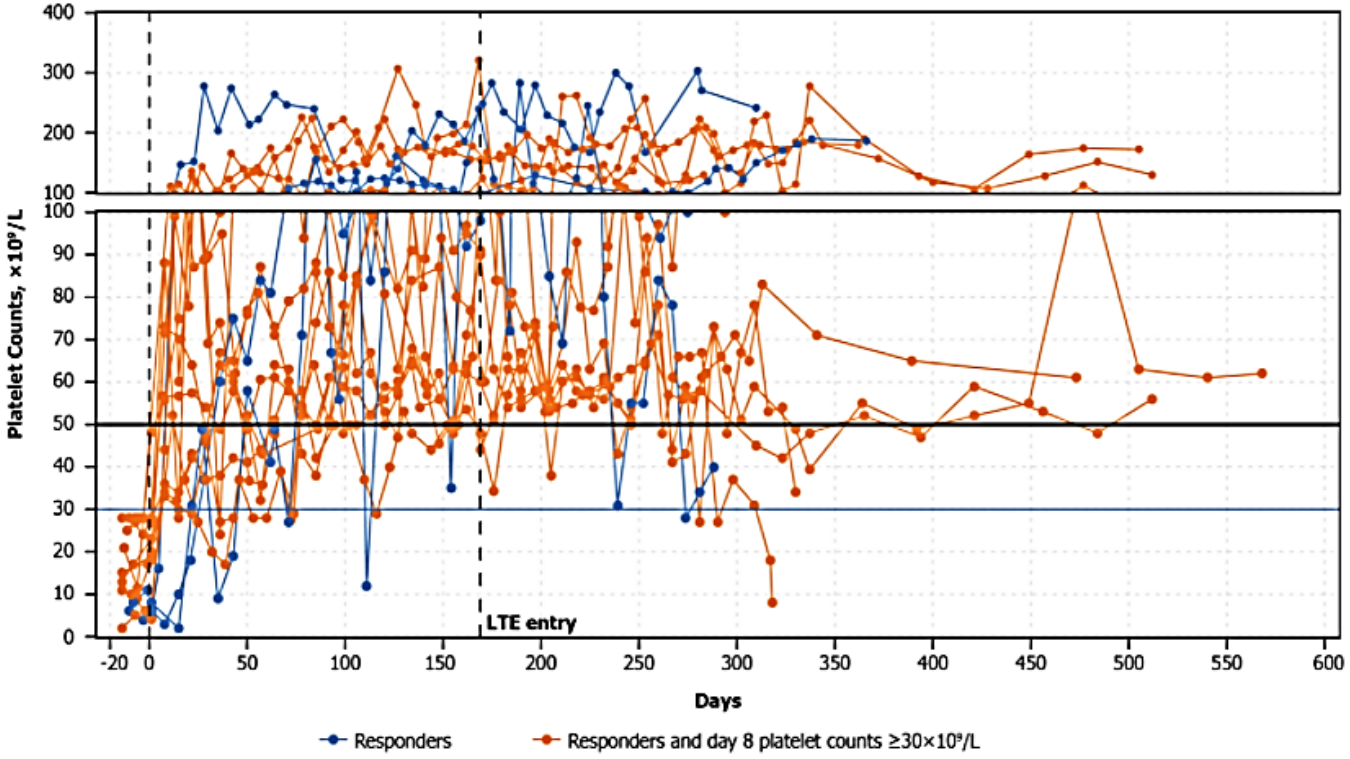



*Figure. Individual platelet counts over time in LTE responding patients receiving rilzabrutinib (n = 14), including patients with day 8 platelet counts ≥30×10^9/L*

**Table. Primary Endpoint Platelet Counts for Patients Initiating Rilzabrutinib 400 mg BID Were Achieved Independent of Prior Therapy**

| Patients Initiating Rilzabrutinib 400 mg BID, n/n (%) | Platelet Counts 2 Consecutive ≥50×10⁹/L (primary endpoint) | |
|---|---|---|
| All patients | 14/32 (44) | |
| Prior splenectomy | 3/9 (33) | |
| Any prior therapy | Responded to Prior | No Prior Response |
| TPO-RA | 3/11 (27) | 5/13 (38) |
| Rituximab | 2/5 (40) | 2/11 (18) |
| Fostamatinib | 2/4 (50) | 1/2 (50) |

Data cut-off: 05May2020. TPO-RA, thrombopoietin receptor agonist.

*Kuter DJ et al. Res Pract Thromb Haemost*. 2021; 5 (Suppl 1). https://abstracts.isth.org/abstract/phase-i-ii-ongoing-study-of-rilzabrutinib-an-oral-bruton-tyrosine-kinase-inhibitor-in-immune-thrombocytopenia-extended-follow-up-and-long-term-analyses-with-optimal-dose/. Accessed July 30, 2021.

# ITP Secondary to COVID-19: A Comprehensive Review of Reported Cases

**(as of 2/28/2021)**

| Demographics | |
|---|---|
| **Cases** | **n (% of cohort)** |
| Adult, new diagnosis | 51 (81%) |
| Adult, relapse | 7 (11.1%) |
| Pediatric, new diagnosis | 5 (7.9%) |
| Pediatric, relapse | 0 (0.0%) |
| Total | 63 (100%) |
| **Age at diagnosis (years)** | 53.5 ± 22 |
| **Sex** | **n (% of cohort)** |
| Male | 29 (46%) |
| Female | 30 (47.6%) |
| Not reported | 4 (6.3%) |
| **Comborbid conditions at time of diagnosis** | **n (% of cohort)** |
| Autoimmune disease | 8 (12.7%) |
| Cancer | 5 (7.9%) |
| Thrombosis | 4 (6.3%) |
| Pregnancy | 2 (3.2%) |

| Presentation | |
|---|---|
| **Bleeding symptoms** | **n (% of cohort)** |
| Petechiae | 20 (31.7%) |
| Purpura | 15 (23.8%) |
| Epistaxis | 14 (22.2%) |
| Gingival bleeding | 12 (19%) |
| Ecchymoses | 7 (11.1%) |
| Oral hemorrhagic bullae | 7 (11.1%) |
| Hematuria | 4 (6.3%) |
| Intracranial hemorrhage | 3 (4.8%) |
| Venipuncture site bleeding | 2 (3.2%) |
| **Platelet count nadir (cells/µL)** | 12,600 ± 20,200 |
| **COVID-19 symptoms** | **n (% of cohort)** |
| Experienced symptoms | 56 (88.9%) |
| Symptomatic at time of diagnosis | 16 (28.6%) |
| Post-symptomatic at time of diagnosis | 8 (14.2%) |
| Unclear timing of symptoms and diagnosis | 32 (57.1%) |
| Never symptomatic | 5 (7.9%) |
| Not reported | 2 (3.2%) |
| **Time from symptom onset to diagnosis (days)** | 12.8 ± 8.1 |

| Management | | |
|---|---|---|
| **Treatment** | **n** | **Rate of Complete Response** |
| Steroids, IVIG, TPO-RA | 4 | 100.0% |
| IVIG, TPO-RA | 6 | 83.3% |
| Steroids | 13 | 77.0% |
| Steroids, IVIG | 20 | 56.0% |
| IVIG | 13 | 53.8% |
| Regimen including TPO-RA | 10 | 90.0% |
| Regimen including steroids | 37 | 70.2% |
| Regimen including IVIG | 44 | 63.6% |
| **Complications of therapy** | **n** | **% of cohort** |
| Thrombocytosis | 1 | 1.6% |
| Acute heart failure secondary to volume overload | 1 | 1.6% |
| Hyperglycemia | 1 | 1.6% |
| Constitutional symptoms | 1 | 1.6% |

| Outcomes | |
|---|---|
| **Outcomes** | **n (% of cohort)** |
| Response | |
| Complete | 41 (65%) |
| Partial | 20 (32.7%) |
| Major bleeding | 7 (11.1%) |
| Mortality | |
| Due to complications of ITP | 1 (1.6%) |
| Due to complications of COVID-19 | 1 (1.6%) |
| **Level of care** | **n (% of cohort)** |
| Inpatient | 39 (61.9%) |
| ICU | 8 (12.7%) |
| Outpatient | 2 (3.2%) |
| Not specified | 17 (27%) |

Table 1. Patient demographics and clinical presentations.

*Berger B et al. Res Pract Thromb Haemost*. 2021; 5 (Suppl 1). https://abstracts.isth.org/abstract/itp-secondary-to-covid-19-a-comprehensive-review-of-reported-cases/. Accessed July 30, 2021.

# Incidence of and Risk Factors for Venous Thromboembolism (VTE) Among Hospitalized Patients with Cancer and COVID-19: Report from the COVID-19 and Cancer Consortium (CCC19) Registry

- VTE risk in patients with both cancer and COVID-19 infection remains unknown
- The COVID-19 and Cancer Consortium: an international retrospective cohort study to investigate the clinical course and complications of COVID-19 among adults with active or previous history of cancer
- The overall incidence of in hospital VTE and PE was 9.3% and 5.2%, respectively. Corresponding estimates were 13.4% and 7.9% among the ICU subgroup

- Non-ICU/not on anti-cancer therapy: 4.5% VTE incidence
- Either ICU or recent anti-cancer therapy: 11.0% VTE
- ICU/recent anti-cancer therapy: 16.7% VTE

Li A, et al. ASH Annual Meeting 2020. Abstract 204.

# Incidence of and Risk Factors for Venous Thromboembolism Among Hospitalized Patients with Cancer and COVID-19: Report from the COVID-19 and Cancer Consortium (CCC19) Registry

**Table 1. VTE incidence and risk factors among hospitalized patients with cancer and COVID-19**

| | Overall (N) | Number of VTE (%) | OR (95% CI) | Number of PE (%) | OR (95% CI) |
|---|---|---|---|---|---|
| **All hospitalized patients** | 1629 | 152 (9.3%) | | 85 (5.2%) | |
| **ICU admission** | | | | | |
| No | 947 | 62 (6.5%) | Reference | 33 (3.5%) | Reference |
| Yes | 530 | 71 (13.4%) | 2.21 (1.54-3.17) | 42 (7.9%) | 2.44 (1.53-3.92) |
| *Unknown or missing* | *152* | *19* | | *10* | |
| **Recent anti-cancer therapy within last 3 months** | | | | | |
| No | 836 | 55 (6.6%) | Reference | 28 (3.3%) | Reference |
| Yes | 641 | 83 (12.9%) | 2.11 (1.48-3.03) | 49 (7.6%) | 2.35 (1.48-3.8) |
| *Unknown or missing* | 152 | 14 | | 8 | |
| **Cancer status** | | | | | |
| Remission/no evidence of disease | 718 | 43 (6.0%) | Reference | 24 (3.3%) | Reference |
| Active, stable/responding | 412 | 38 (9.2%) | 1.59 (1.01-2.51) | 22 (5.3%) | 1.71 (0.95-3.07) |
| Active, progressing | 244 | 36 (14.8%) | 2.72 (1.69-4.34) | 18 (7.4%) | 2.44 (1.3-4.53) |
| *Unknown or missing* | 255 | 35 | | 21 | |
| **Cancer subtype VTE risk group** | | | | | |
| low-risk VTE malignancy* | 674 | 55 (8.2%) | Reference | 35 (5.2%) | Reference |
| High-risk VTE malignancy* | 380 | 48 (12.6%) | 1.63 (1.08-2.45) | 25 (6.6%) | 1.3 (0.76-2.18) |
| Very high-risk VTE malignancy* | 47 | 9 (19.1%) | 2.67 (1.16-5.58) | 5 (10.6%) | 2.15 (0.71-5.34) |
| Other solid tumor malignancy | 283 | 21 (7.4%) | 0.9 (0.52-1.5) | 9 (3.2%) | 0.58 (0.26-1.18) |
| Other hematologic maligancy | 245 | 19 (7.8%) | 0.95 (0.54-1.6) | 11 (4.5%) | 0.83 (0.4-1.61) |
| **Pre-admission anticoagulant use** | | | | | |
| No | 1202 | 110 (9.2%) | Reference | 68 (5.7%) | Reference |
| Yes | 306 | 24 (7.8%) | 0.84 (0.52-1.32) | 8 (2.6%) | 0.43 (0.19-0.86) |
| *Unknown or missing* | 121 | 18 | | 9 | |
| **Pre-admission antiplatelet use** | | | | | |
| No | 977 | 100 (10.2%) | Reference | 57 (5.8%) | Reference |
| Yes | 530 | 35 (6.6%) | 0.62 (0.41-0.92) | 20 (3.8%) | 0.61 (0.36-1.01) |
| *Unknown or missing* | 122 | 17 | | 8 | |

* Low-risk: breast, prostate, colorectal, head and neck
* High-risk: lung, ovarian, kidney, bladder, testicular, lymphoma
* Very high-risk: pancreas, stomach, esophageal
** Multivariable adjustment was not performed in the present analysis

Li A, et al. ASH Annual Meeting 2020. Abstract 204.

# Thromboembolic Outcomes of Hospitalized COVID-19 Patients in the 90-Day Post-Discharge Period: Early Data from the Northwell CORE-19 Registry

**Prospective Study**

*Table 1: Population characteristics and post-discharge outcomes*

| | |
|---|---|
| **Population characteristics (N = 4100)** | |
| Age (Mean (SD)) | 61.0 (17.0) |
| Male (N (%)) | 2243 (54.7) |
| **Post-discharge outcomes N (%)** | |
| Rehospitalization | 527 (12.85) |
| ***Venous thromboembolism*** | 99 (2.41) |
| Deep vein thrombosis | 46 (1.12) |
| Pulmonary embolism | 40 (0.98) |
| Superficial vein thrombosis | 8 (0.20) |
| Splanchnic vein thrombosis | 1 (0.02) |
| Other vein thrombosis | 4 (0.10) |
| ***Arterial thromboembolism*** | 45 (1.10) |
| Stroke | 14 (0.34) |
| Myocardial Infarction | 15 (0.37) |
| Major adverse limb event | 11 (0.27) |
| Systemic Embolism | 5 (0.12) |
| ***Major Bleeding*** | 66 (1.61) |
| ***All-Cause Mortality*** | 176 (4.29) |

- Stipulated the use of post-discharge low-molecular weight heparin, direct oral anticoagulants, or baby aspirin in hospitalized COVID-19 patients with high thrombotic risk features.
- All-cause mortality rate=4.29%
- Overall thromboembolic rate =3.51%
  - 2.41% VTE/1.10% ATE
- Major bleeding rate=1.61%
- Rehospitalization rate=12.85%
- Of patients with either DVT or PE post-discharge: 13.43% died
- Importance of post-discharge surveillance and extended thromboprophylaxis

Giannis D, et al. ASH Annual Meeting 2020. Abstract 443.

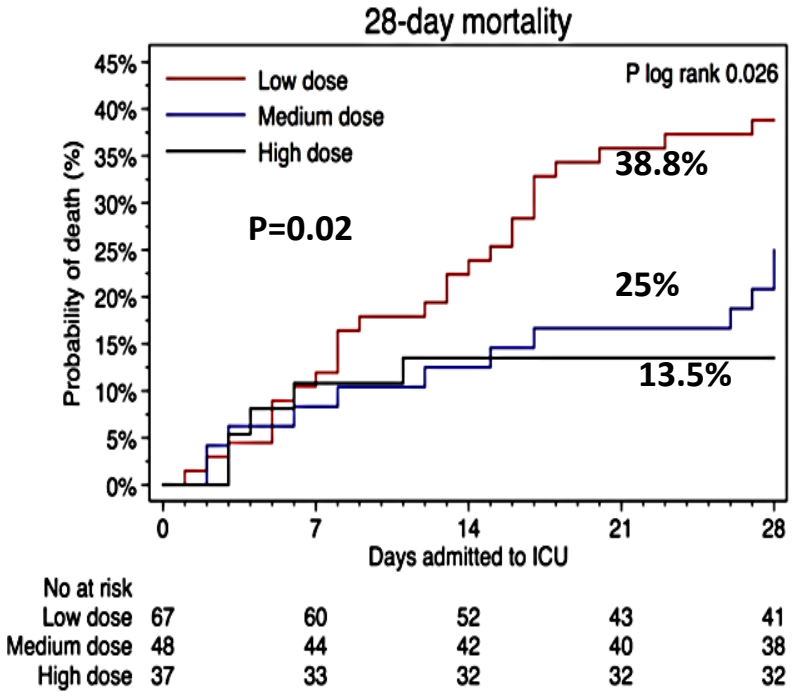
# ASH Guidelines on Use of Anticoagulation in Patients with COVID-19- Updated on July 8, 2021

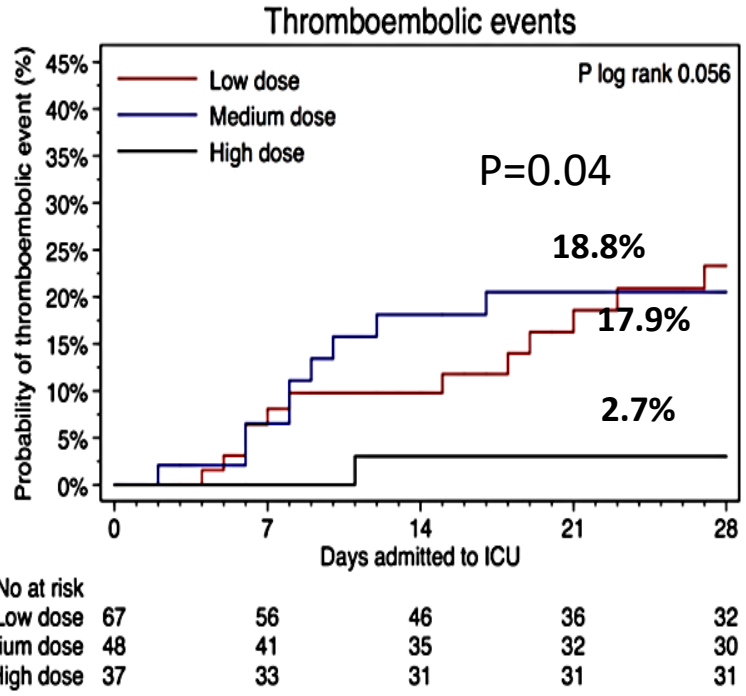
- ***suggest*** **not using anticoagulant outpatient thromboprophylaxis in patients with COVID-19 who are being discharged from the hospital and who do not have suspected or confirmed VTE or another indication for anticoagulation (conditional recommendation based on very low certainty in the evidence about effects)**

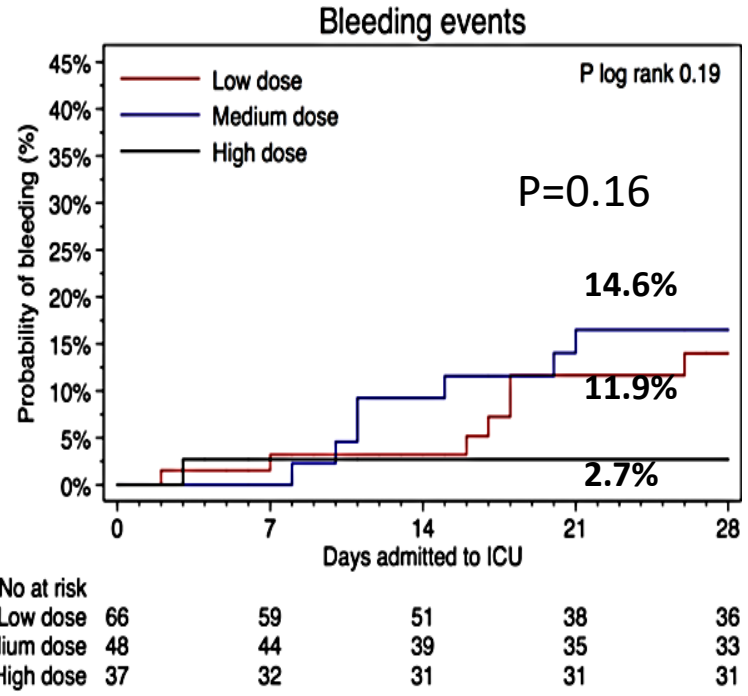
https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines/venous-thromboembolism-guidelines/ash-guidelines-on-use-of-anticoagulation-in-patients-with-covid-19#rec3

# Dosing of LMWH thromboprophylaxis and mortality in critically ill COVID-19 patients

*jonmarker S et al. Crit Care* **24,** 653 (2020). https://doi.org/10.1186/s13054-020-03375-7



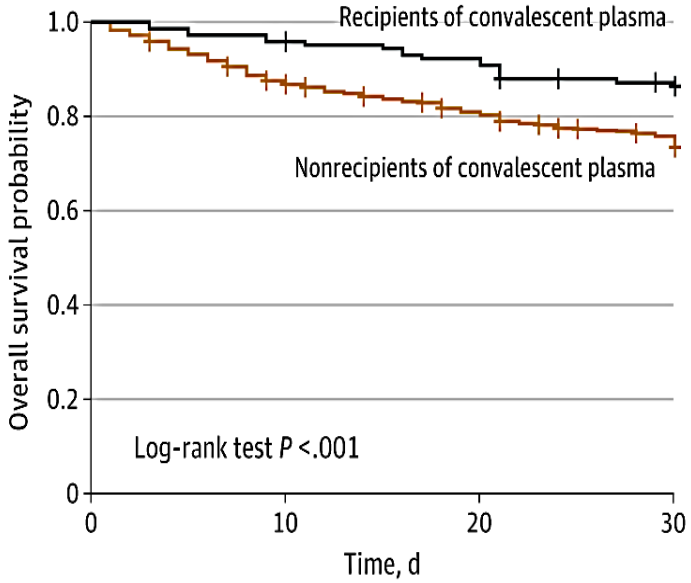

-152 patients: 67 received low-, 48 medium-, and 37 high-dose LMWH thromboprophylaxis

- Mortality: high-dose = 13.5%; medium dose = 25.0%; low dose = 38.8%, $p = 0.02$.
- Hazard Ratio of death: High dose = 0.33 (95% confidence intervals 0.13–0.87) compared to low dose
  Medium dose = 0.88 (95% confidence intervals 0.43–1.83) compared to low dose

# Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19

Thompson MA et al. JAMA Oncol. Published online June 17, 2021. doi:10.1001/jamaoncol.2021.1799

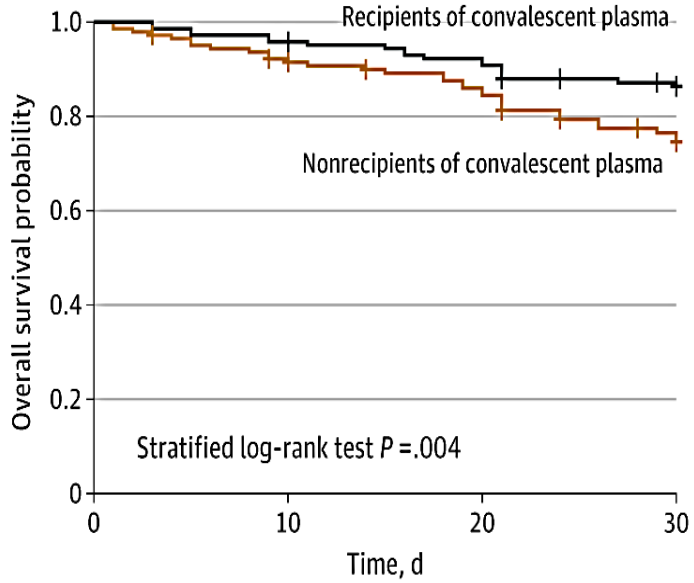
**A** Overall comparison




No. at risk

| | | | | |
|---|---|---|---|---|
| Nonrecipients of convalescent plasma | 823 | 702 | 613 | 507 |
| Recipients of convalescent plasma | 143 | 137 | 129 | 108 |

**B** Propensity score-matched comparison




No. at risk

| | | | | |
|---|---|---|---|---|
| Nonrecipients of convalescent plasma | 143 | 128 | 109 | 79 |
| Recipients of convalescent plasma | 143 | 137 | 129 | 108 |

**Overall Survival Rates Among Recipients vs Nonrecipients of Convalescent Plasma**

# Biomarkers of Haemostasis and Occurrence of Venous Thromboembolism Are Associated with Disease Progression and Poor Prognosis in Patients with Pancreatic Cancer

**Figure 1:** Overall survival according to levels of D-dimer, PAI-1 and sP-selectin, dichotomized at the 75th percentile of distribution. PAI-1 indicates plasminogen activator inhibitor type 1; and sP-selectin soluble P-selectin.

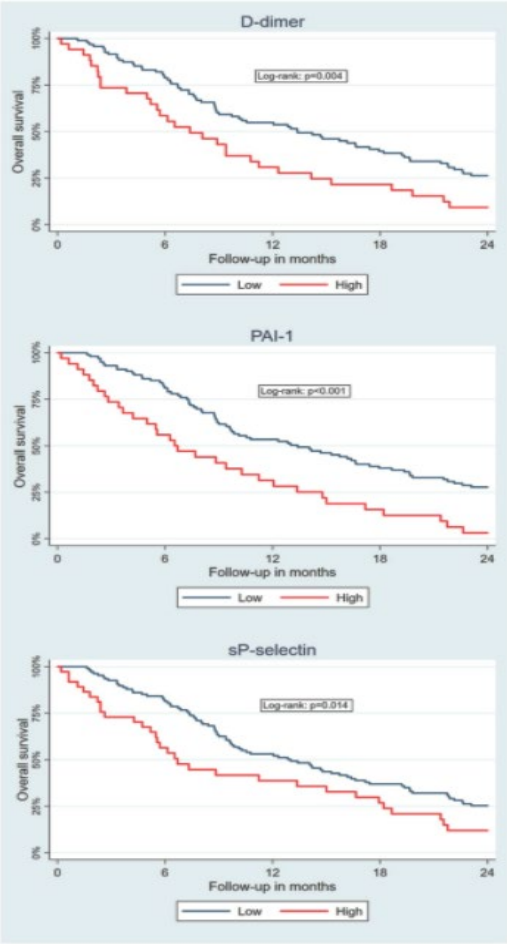
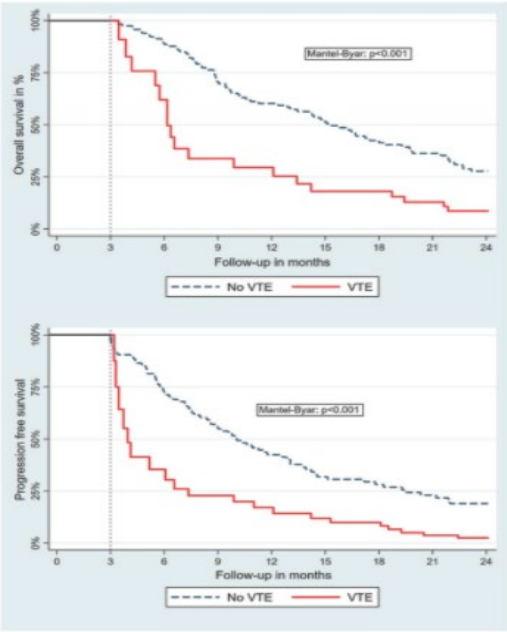


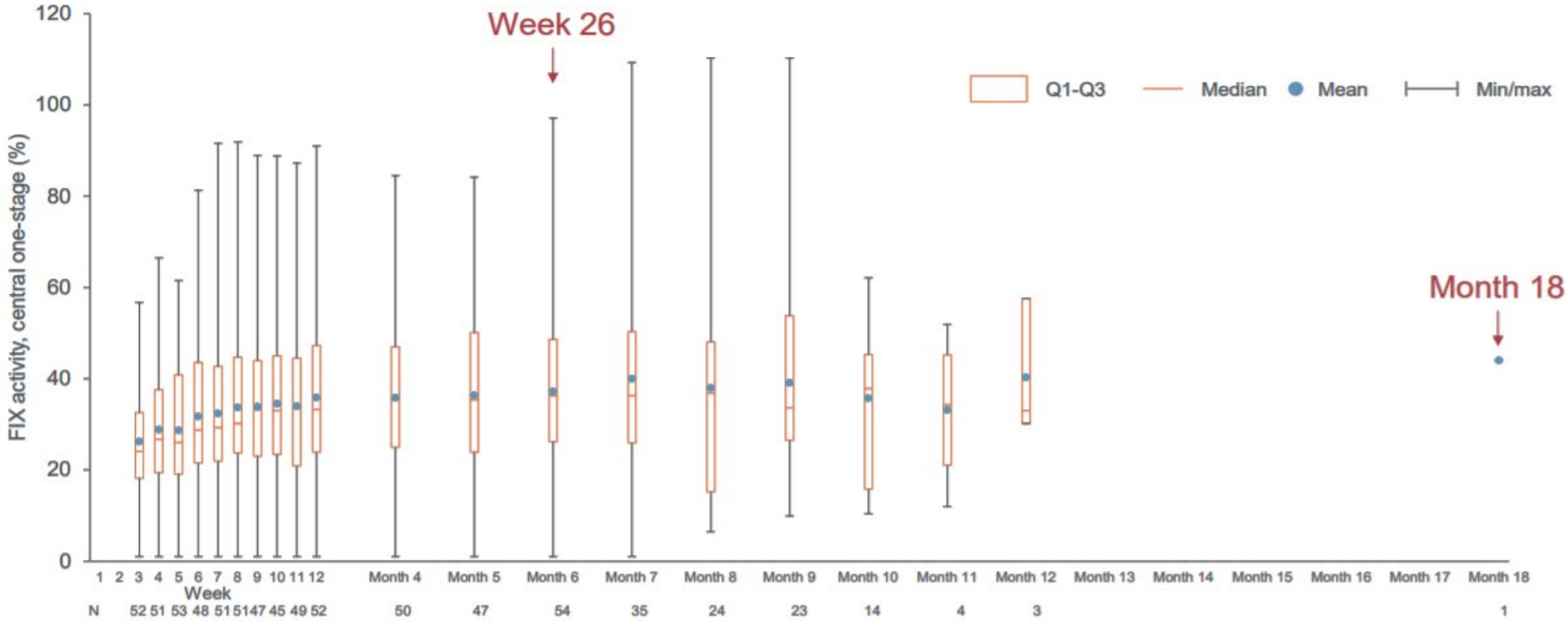

**Figure 2:** Landmark analysis of overall survival (OS) and progression free survival (PFS) according to the occurrence of VTE. OS indicates overall survival; PFS progression free survival, and VTE; venous thromboembolism.




Moik F, et al. ASH Annual Meeting 2020. Abstract 515.

# First Data from the Phase 3 HOPE-B Gene Therapy Trial: Efficacy and Safety of Etranacogene Dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in Adults with Severe or Moderate-Severe Hemophilia B Treated Irrespective of Pre-Existing Anti-Capsid Neutralizing Antibodies

## Overview of FIX activity[a]: Beyond 26 weeks




[a]Uncontaminated central laboratory data (the visit did not occur within 10 days of exogeneous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value. Baseline factor IX was imputed based on subject's historical hemophilia B severity documented on the case record form. If the patient had documented severe factor IX deficiency (FIX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level ≥1% and ≤ 2%), their baseline factor IX activity level was imputed as 2%.
SD, standard deviation.

9

**N=54 of whom 43 responded**

**Mean FIX at 26 wks near normal**

**No immuno-suppression needed**

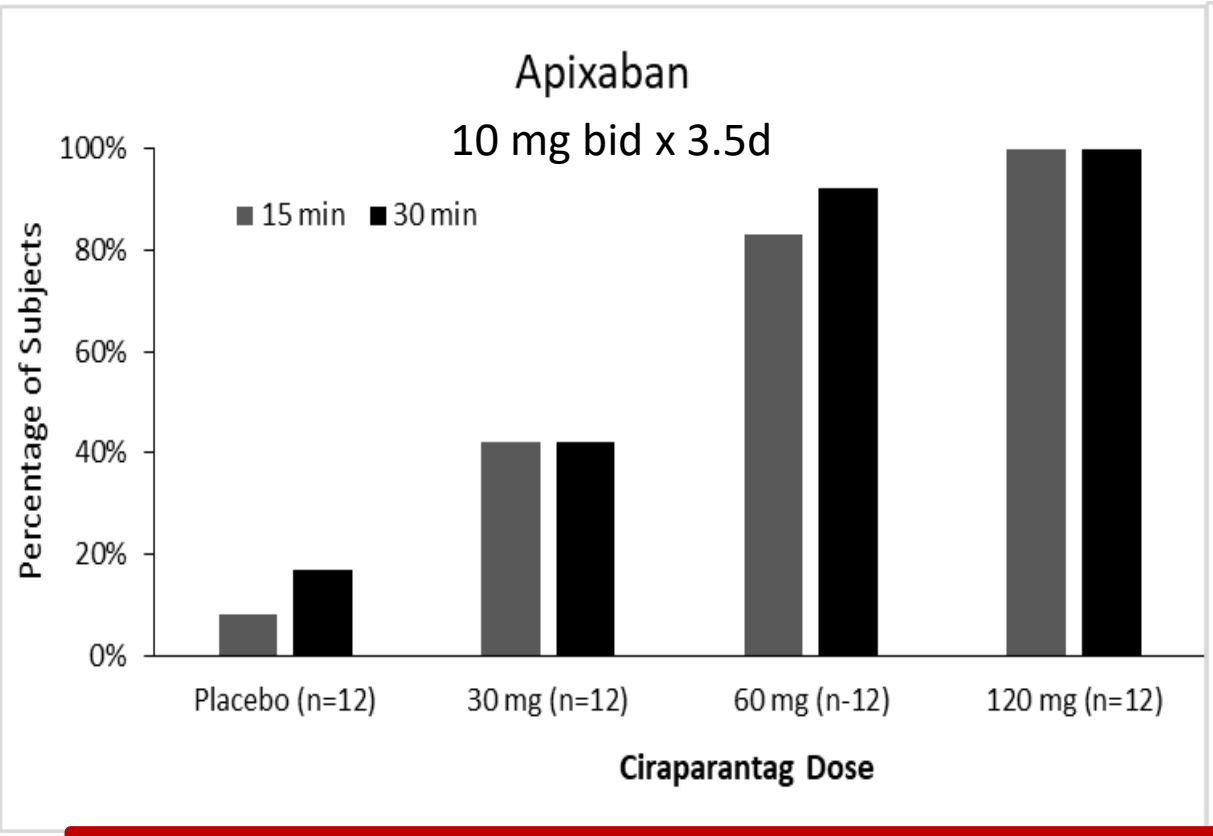
**Neutralizing AAV5 Abs not excluded**

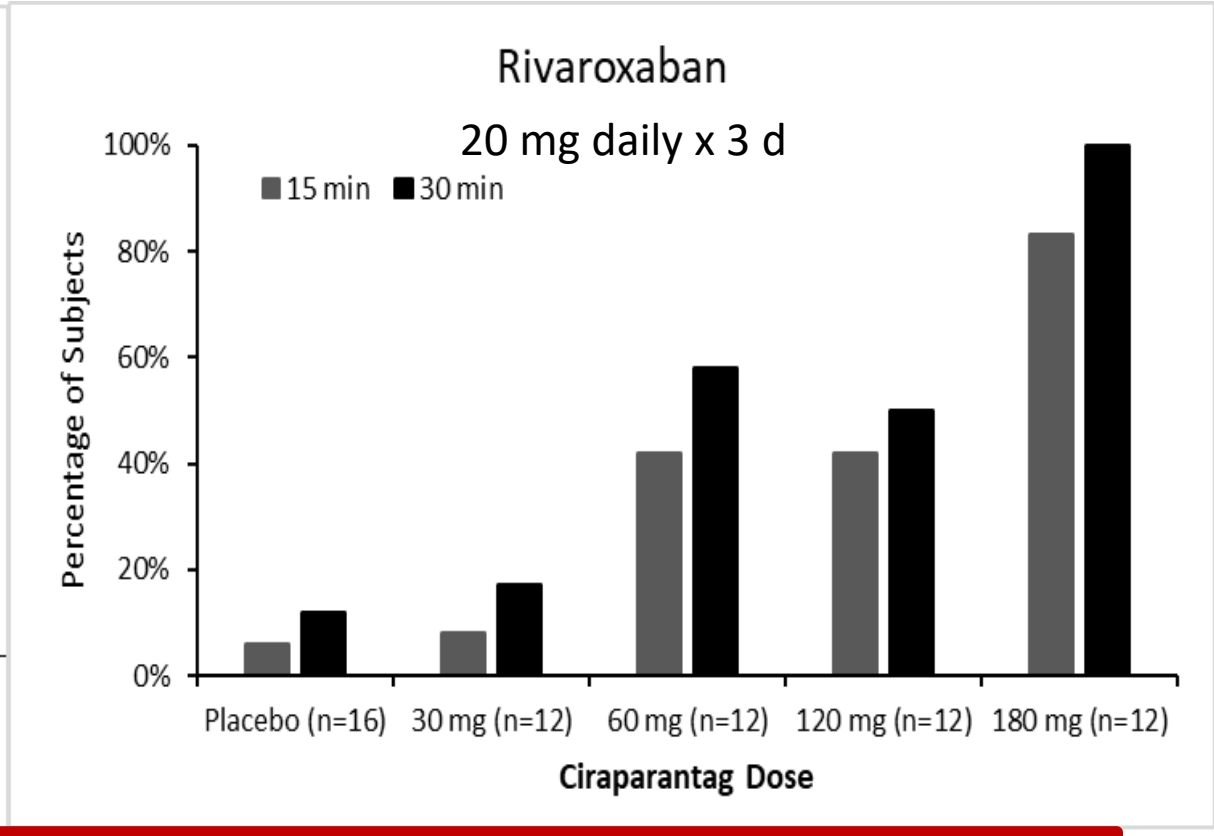
**Few bleeding events; no prophy FIX**

Pipe SW, et al. ASH Annual Meeting 2020. Abstract LBA-6.

# Reversal of Anticoagulation By Ciraparantag: Time to Onset and Duration of Effect

**Proportion of subjects with WBCT reversed to within 10% above baseline at 15 minutes and 30 minutes after dosing**

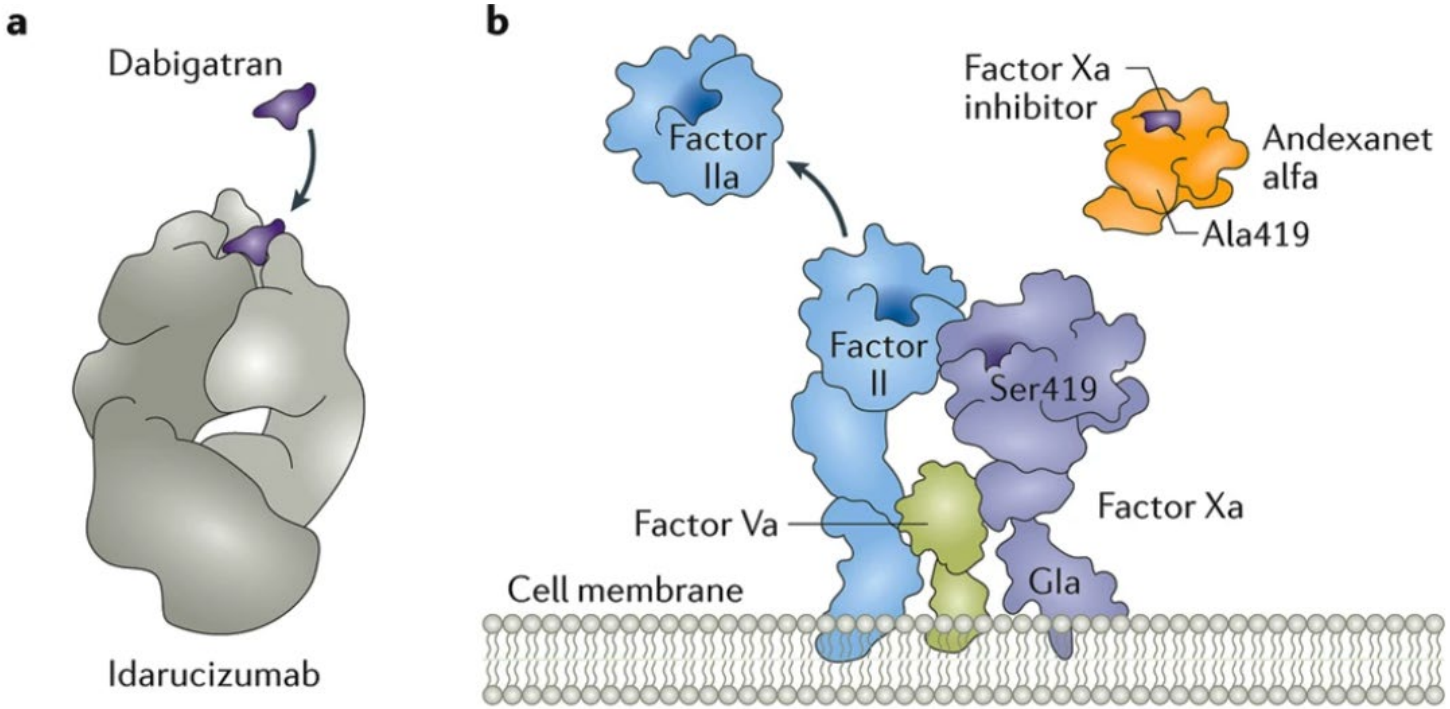



Phase II dose finding study in healthy subjects; Reversal persisted for over 24 hrs

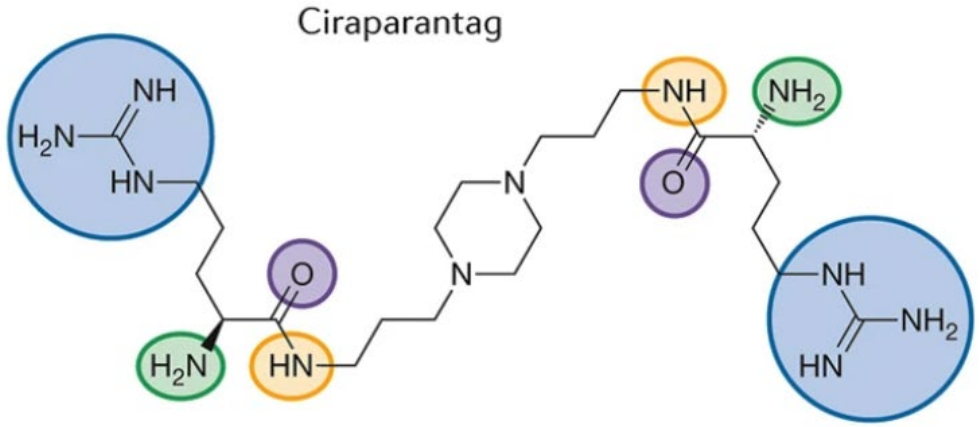
Ansell J, et al. ASH Annual Meeting 2020. Abstract 238.

# Reversal Agents for Non-Vitamin K Antagonist Oral Anticoagulants




c

| Drug | Binding sites |
|---|---|
| Apixaban | ● ● |
| Dabigatran | ● ● ● |
| Edoxaban | ● ● |
| Fondaparinux | ● ● ● |
| Rivaroxaban | ● ● ● |
| UFH or LMWH | ● ● ● |




Levy J, et al. *Nat Rev Cardiol.* 2018;15: 273–281.