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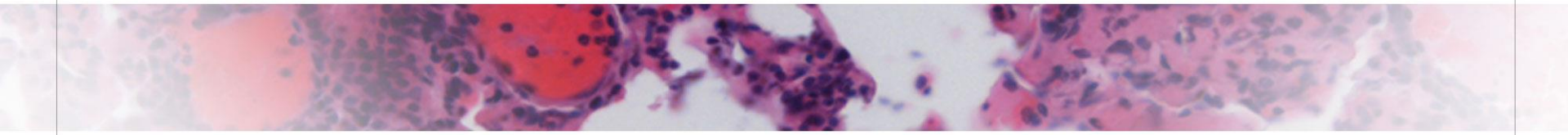

Risk of Hemorrhage in Patients with Polycythemia Vera Exposed to Aspirin in Combination with Anticoagulants: Results of a Prospective, Multicenter, Observational Cohort Study (REVEAL)

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Background

- Polycythemia vera (PV) is associated with an increased risk of thrombosis and major hemorrhage[1]
- Aspirin (ASA) is recommended for primary thromboprophylaxis in patients with PV[2]
- ASA is often continued with an anticoagulant after an acute thrombotic event in patients with PV

[1] Tefferi A. et al. *Blood Cancer J*. 2018 Jan 10;8(1):3. [2] NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative Neoplasms. Version 2.2019. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed November 13, 2019.

Objective

- To assess the rate of hemorrhage with concomitant antiplatelet and anticoagulant therapy in patients with PV

Methods

- The REVEAL study is a prospective, noninterventional, observational study of patients with PV conducted at 204 sites in the United States
- Post-enrollment hemorrhagic events were graded according to CTCAE by treating physicians

CTCAE, Common Terminology Criteria for Adverse Events.

Methods (cont'd)

- Hemorrhagic event rates were estimated according to subgroups (anticoagulant only, ASA only, ASA + anticoagulant, neither)
- A Cox proportional hazards model was used to assess the association between the risk of hemorrhage and platelet levels and the use of an anticoagulant and/or ASA
- Analyses were conducted for all hemorrhagic events and for severe (CTCAE grade 3 or 4) events

ASA, aspirin; CTCAE, Common Terminology Criteria for Adverse Events.

Common Terminology Criteria for Adverse Events (CTCAE)

- Gastrointestinal
  - Grade 3: Transfusion or endoscopic/operative procedure indicated
  - Grade 4: Life threatening; urgent intervention indicated
- Intracranial hemorrhage
  - Grade 3: Ventriculostomy, ICP monitoring, or operative intervention indicated
  - Grade 4: Life threatening; urgent intervention indicated

CTCAE version 4.0; ICP, intracranial pressure.

Patient Characteristics at Enrollment

- 2510 patients were enrolled in REVEAL and included in this analysis

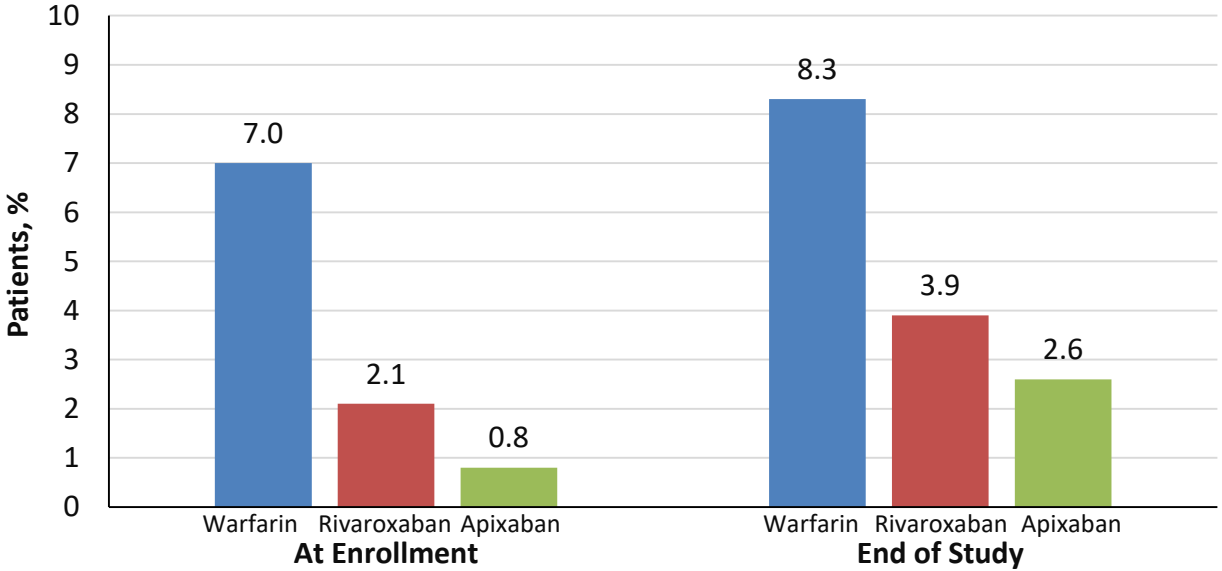
Table. Patient Characteristics at the Time of Enrollment

Characteristic	N=2510
Median (range) age, y	67 (22–95)
Women, n (%)	1150 (45.8)
Median (range) disease duration, y	4.0 (0.0–56.3)
History of hypertension, n (%)	1405 (56.0)
History of hemorrhagic events, n (%)	164 (6.5)
History of thrombotic events, n (%) Arterial Venous	500 (19.9) 223 (9.3) 300 (12.0)
Treatments at enrollment, n (%) ASA only Anticoagulant only Anticoagulant + ASA Neither	 1492 (59.4) 181 (7.2) 101 (4.0) 736 (29.3)

ASA, aspirin.

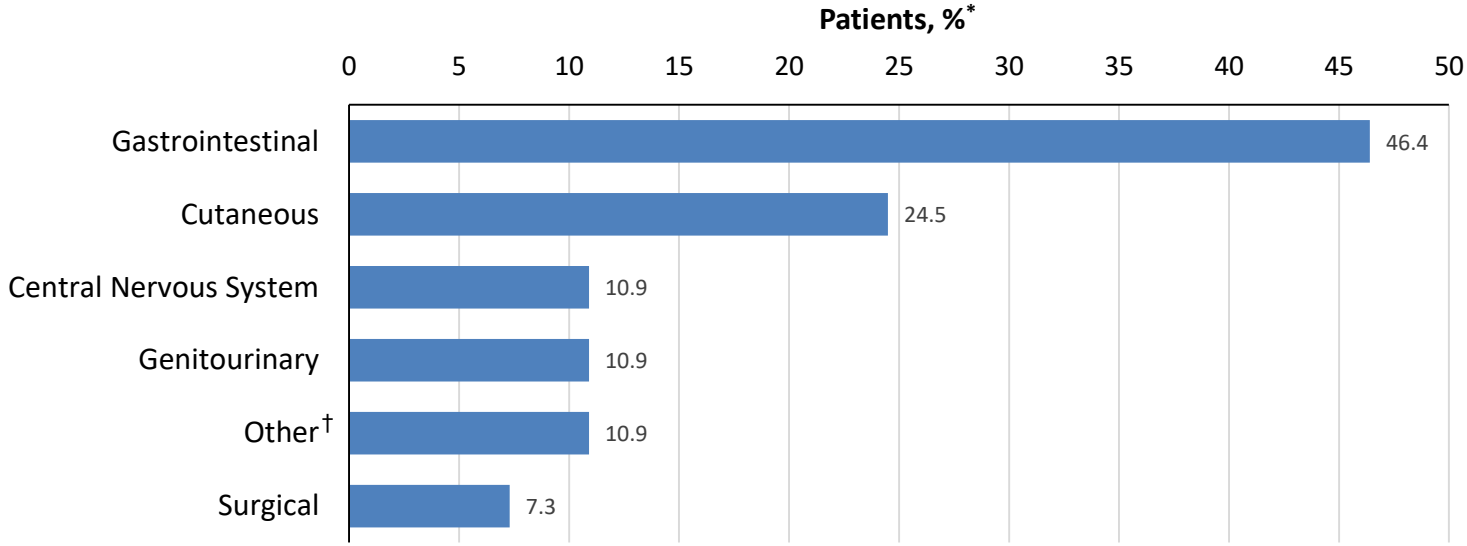
Anticoagulants

- At enrollment and at the end of the study, the 3 most commonly prescribed anticoagulants were warfarin, rivaroxaban, and apixaban



All-Grade Hemorrhagic Events

- 110 patients (4.4%) experienced hemorrhagic events over a median (range) of 2.3 (0–3.6) years



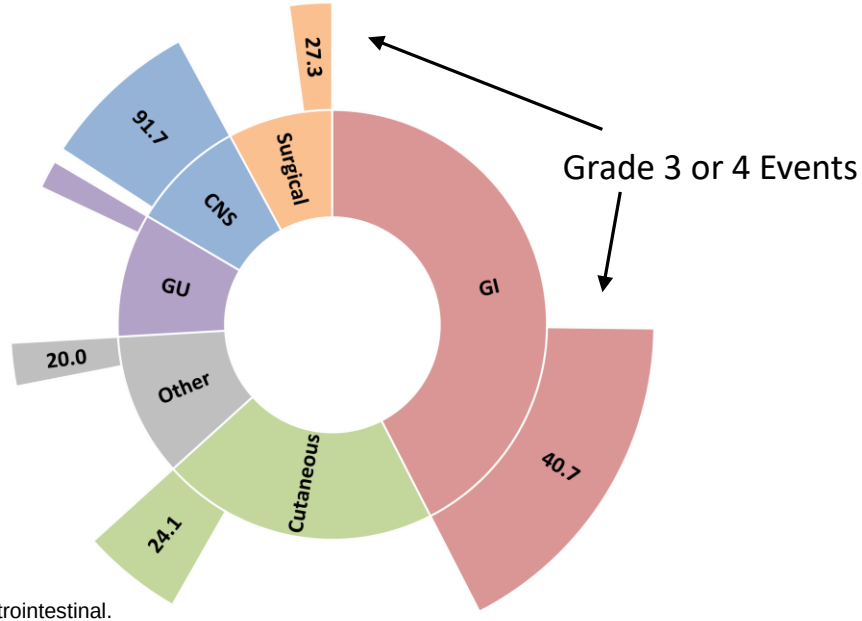
* Not mutually exclusive. † "Other" included the following sites: eye, joint, mouth, retroperitoneum, tongue, and uterus.

Severe (Grade 3 or 4) Hemorrhagic Events

- 46 patients (1.8%) developed ≥1 severe hemorrhage, most commonly:
  - Gastrointestinal (23/46, 50%)
  - Central nervous system (11/46, 23.9%)
- 38 (82.6%) severe hemorrhagic events required hospitalization

Hemorrhagic Events and Severity

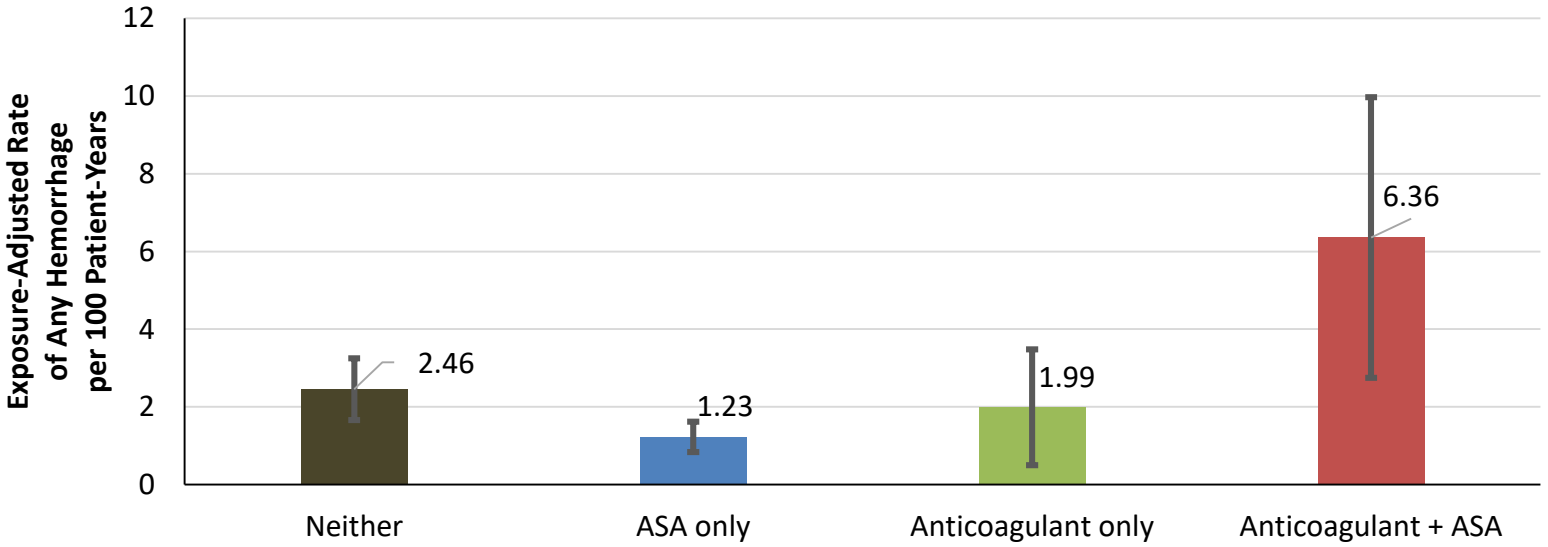
- The majority of CNS events (11/12, 91.7%) and a considerable proportion of GI events (24/59, 40.7%) were severe (CTCAE grade 3 or 4)
  - Fatal events (7)
    - GI (2)
    - Subdural hemorrhage (2)
    - Subdural hematoma (1)
    - Cerebral hemorrhage (1)
    - Hemorrhagic stroke (1)



CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal.

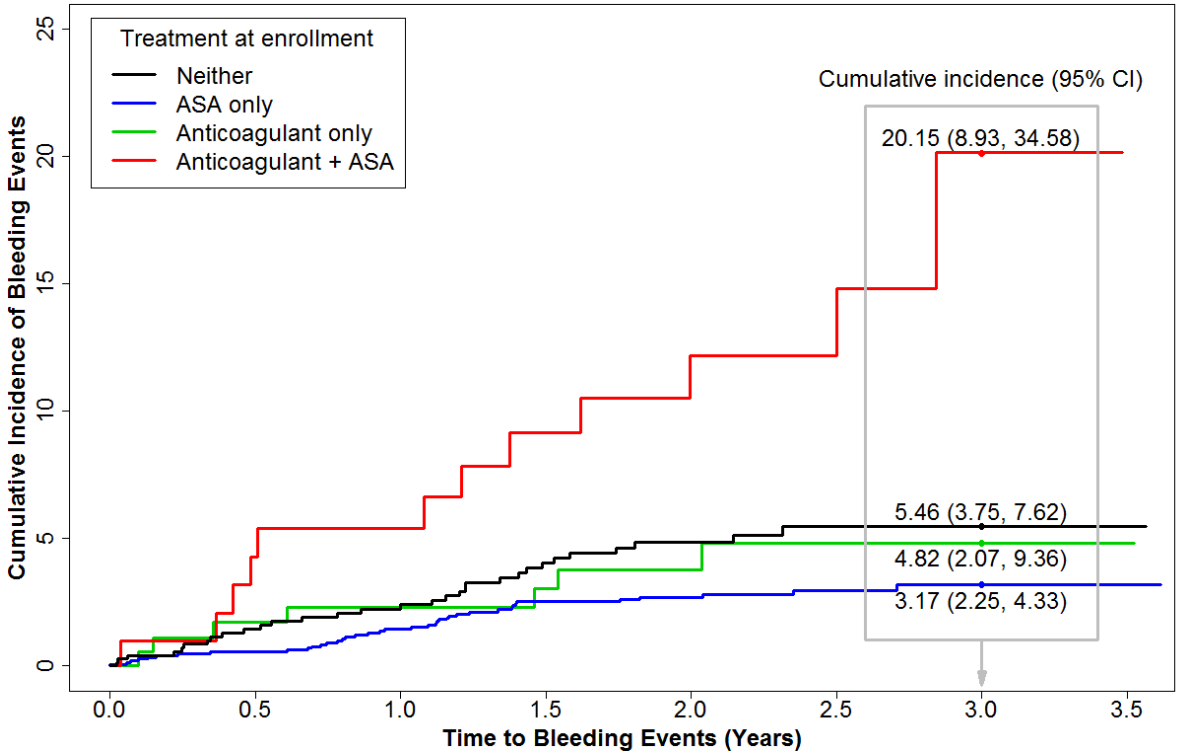
Rates of Hemorrhagic Events

- The rate of hemorrhage was highest in the group of patients receiving an anticoagulant + ASA



Error bars represent 95% confidence intervals. Exposure was assessed from enrollment to the earliest of first bleeding event, treatment change, disenrollment, death, or data cut. ASA, aspirin.

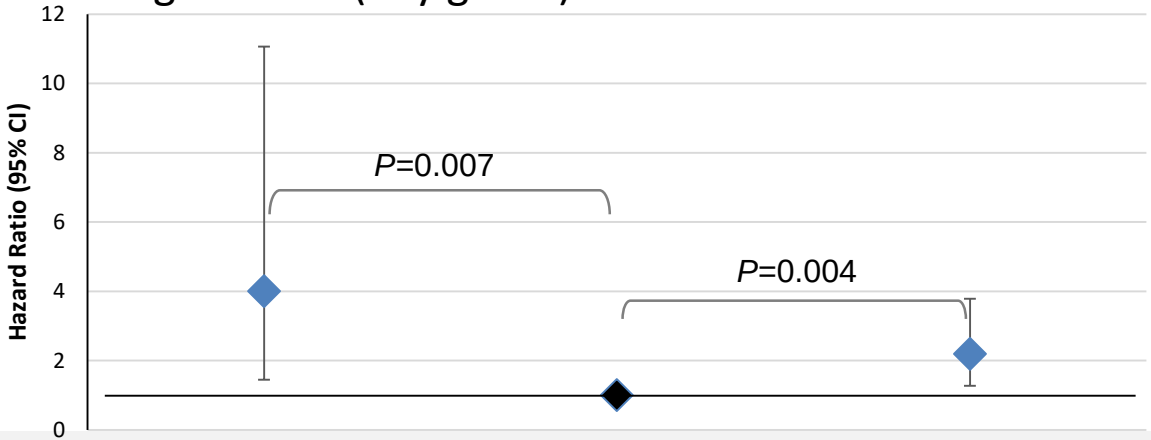
Cumulative Incidence of Hemorrhagic Events



Time to earliest of first bleeding event, treatment change, disenrollment, death, or data cut was modeled.
ASA, aspirin.

Extremes of Platelets Associated with Hemorrhage

- High platelets or low platelets were associated with an increased risk of a hemorrhagic event* (any grade)

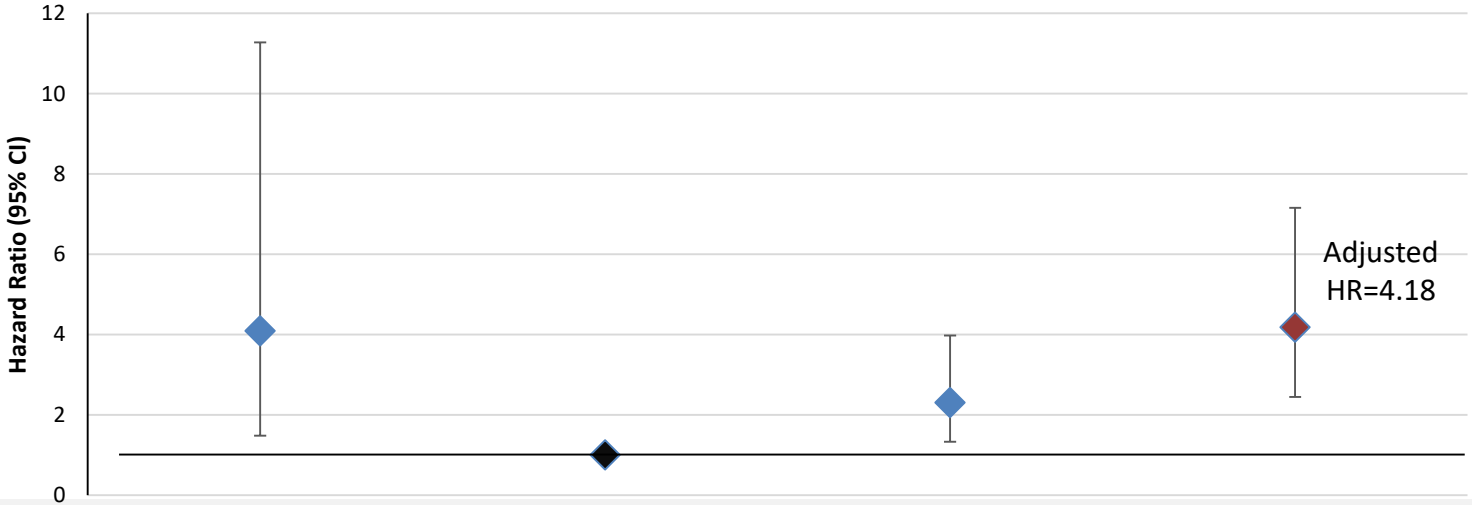


	Low Platelets (<100 ×10^9/L)	Normal Platelets (100–600 ×10^9/L)	High Platelets (>600 ×10^9/L)
Platelet exposure†	44.9 years	3643.4 years	395.2 years

* Platelet categories were modeled as time-dependent covariates, adjusting for age, sex, disease duration, and history of bleeding prior to enrollment in a Cox proportional hazards model; time was censored at death, date of discontinuation, or last visit. † Patient years; error bars represent 95% confidence intervals.

Anticoagulant + ASA Associated with Hemorrhage

- Risk of hemorrhage with anticoagulant + ASA was independent of platelet count*



Platelet exposure†	44.9 years	3643.4 years	395.2 years	

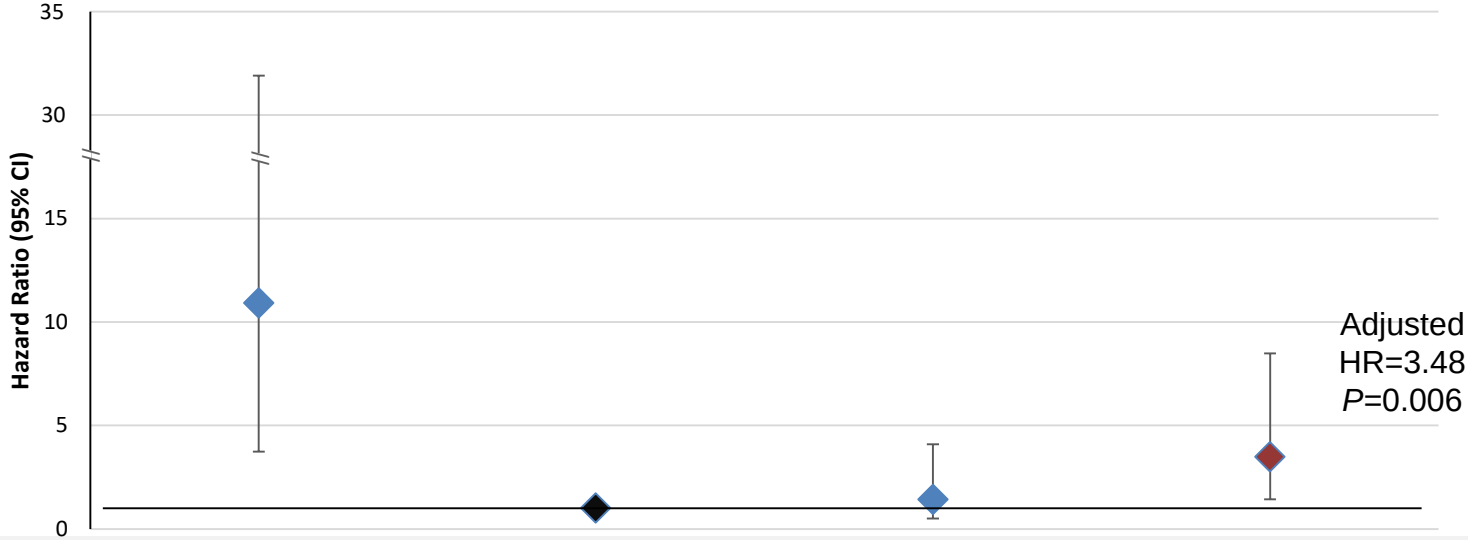
* Platelet categories and anticoagulant + ASA use were modeled as time-dependent covariates, adjusting for age, sex, disease duration, and history of bleeding prior to enrollment in a Cox proportional hazards model; time was censored at death, date of discontinuation, or last visit. † Patient years; error bars represent 95% confidence intervals.
ASA, aspirin; HR, hazard ratio.

Risk of Severe Hemorrhage

Group	Hazard Ratio (95% CI)	*P* value
None	Ref	--
ASA only	0.74 (0.31, 1.76)	0.50
Anticoagulant only	2.23 (0.76, 6.52)	0.14
Anticoagulant + ASA	3.31 (1.13, 9.68)	0.03

No treatment, ASA alone, anticoagulant alone, and ASA + anticoagulant use were modeled as a 4-level time-dependent covariate, adjusting for age, sex, disease duration, history of bleeding prior to enrollment, and platelet levels in a Cox proportional hazards model; time was censored at death, date of discontinuation, or last visit.
ASA, aspirin.

Risk of **Severe** Hemorrhage with Anticoagulant + ASA Independent of Platelet Count

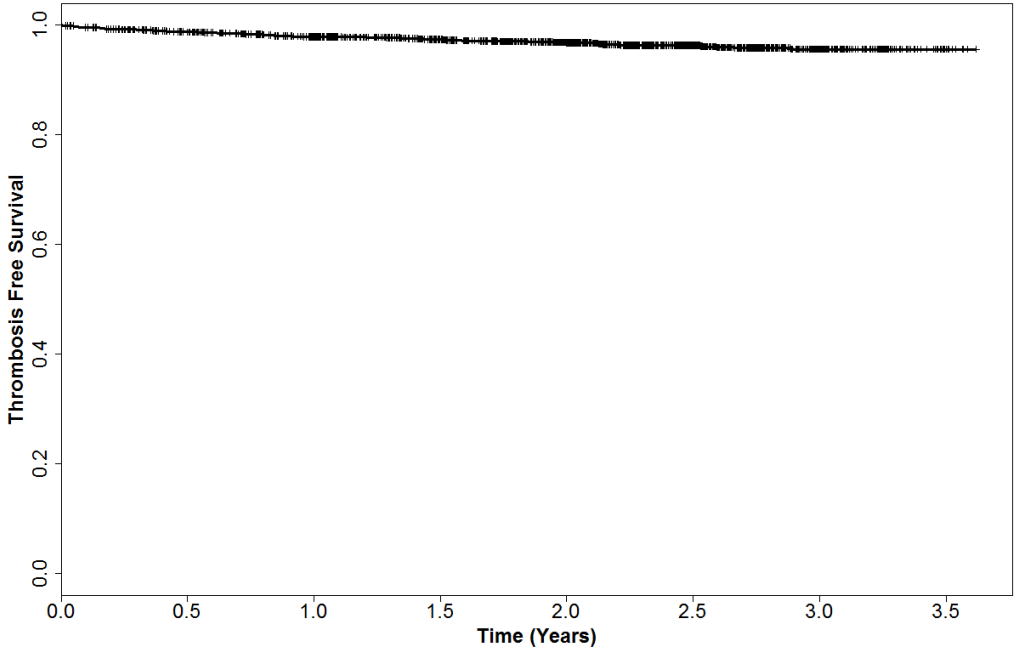


	Low Platelets (<100 × 10^9/L)	Normal Platelets (100–600 × 10^9/L)	High Platelets (>600 × 10^9/L)	Anticoagulant + ASA
Platelet exposure*	44.9 years	3643.4 years	395.2 years	

Platelet categories and anticoagulant + ASA use were modeled as time-dependent covariates, adjusting for age, sex, disease duration, and history of bleeding prior to enrollment in a Cox proportional hazards model; time was censored at death, date of discontinuation, or last visit. * Patient years; error bars represent 95% confidence intervals.
ASA, aspirin.

Rate of Thrombotic Events

- The rate of thrombotic events was too low to draw conclusions about the relative efficacy of anticoagulation versus anticoagulant + ASA



ASA, aspirin.

Conclusions

- In a large prospective cohort of patients with PV, the combination of an anticoagulant with ASA was associated with an increased risk of bleeding compared with ASA alone
- Extremes of platelet count were also associated with increased risk of bleeding (all grades)
- Based on the observed 3-fold increased risk of severe hemorrhage associated with the combination of an anticoagulant and ASA, caution is advised when continuing an antiplatelet agent with an anticoagulant in patients with PV

ASA, aspirin; PV, polycythemia vera.

Acknowledgments

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- The REVEAL study was sponsored by Incyte Corporation