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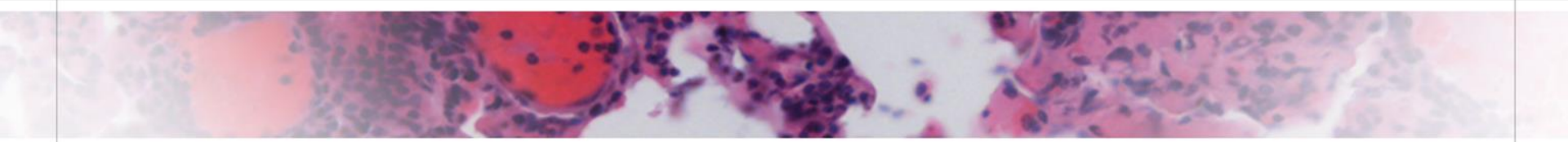
Abstract 484



Mortality and Causes of Death of Patients With Polycythemia Vera: Analysis of the REVEAL Prospective, Observational Study

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Background and Objective

- Polycythemia vera (PV) is a chronic myeloproliferative neoplasm marked by clonal stem cell proliferation, leading to increased risk for thrombosis, disease transformation, and reduced survival[1]
- Median survival from PV diagnosis is estimated to be about 20 years[2]
- However, survival in patients with PV has most often been evaluated retrospectively; as a result, granularity with respect to causes of death is often lacking
- The multicenter, noninterventional, **P**rospective Obs**e**rvational Study of Patients with Polycythemia **Ve**ra in US Clinic**al** Practices (REVEAL)[3] followed patients with PV treated in 227 community and academic practices in the United States
- This analysis of final data from REVEAL evaluates the characteristics of deceased patients, survival by risk, and causes of death over the course of the study

1. Stein BL, et al. *J Clin Oncol.* 2015;33:3953–3960. **2.** Alvarez-Larrán A, et al. *Blood.* 2012;119:1363–1369. **3.** ClinicalTrials.gov ID: NCT02252159.

Methods

- Patients enrolled in REVEAL between July 2014 and August 2016 were followed up for clinical characteristics and symptoms data during usual-care visits until death, consent withdrawal, or study end (36 months from the date of last patient enrollment)
- This analysis included all enrolled patients
  - Patients ≥60 years of age and/or with TE history at enrollment were classified as high risk per modified ELN criteria[1]
  - Patients were categorized according to whether they had “died” or remained “alive” over the course of the study
    - Causes of death were provided by site physicians; patients categorized as “alive” were censored at the last known study visit date (for those lost to follow-up) or at study completion
- Statistical analysis
  - Descriptive statistics were used to summarize demographics, characteristics before death, and causes of death
  - Continuous and categorical variables were compared using *t* tests and chi-square tests, respectively
  - Kaplan-Meier methods were used to summarize survival data
  - Time-specific survival probabilities were compared using tests of proportions
  - Association between survival and TEs was assessed using a Cox proportional hazards model

ELN, European LeukemiaNet; TE, thrombotic event.

1. Tefferi A, et al. *Blood.* 2013;122:1395–1398.

Results – Patient Characteristics

Characteristic	Died (N = 244)	Alive (N = 2266)*	Total (N = 2510)
Mean (SD) age, years			
At diagnosis	**68.5 (11.4)**	**60.2 (13.1)†**	61.0 (13.2)
At enrollment	74.5 (10.1)	65.4 (12.2)	66.3 (12.3)
At death	77.1 (10.3)	—	—
Sex, n (%)			
Men	131 (53.7)	1229 (54.2)	1360 (54.2)
Women	113 (46.3)	1037 (45.8)	1150 (45.8)
Mean (SD) disease duration, years			
From diagnosis to enrollment	6.5 (5.7)	5.7 (6.2)	5.8 (6.1)
At death	8.6 (5.8)	—	—
Duration of follow-up, mean (SD), weeks	110.3 (58.0)	179.4 (56.1)	172.7 (59.9)

- Patients who had died were significantly older at diagnosis

*Data were censored at the date of the last known study visit (for those lost to follow-up) or study completion. †$P < 0.001$ for patients who had died vs those alive.
SD, standard deviation.

Results – Patient Characteristics

Characteristic	Died (N = 244)	Alive (N = 2266)*	Total (N = 2510)
Risk at diagnosis, n (%)			
Low	44 (18.0)	926 (40.9)	970 (38.6)
High	**200 (82.0)**	**1340 (59.1)†**	1540 (61.4)
Age ≥60 years only	159 (65.2)	1041 (45.9)	1200 (47.8)
TE only	13 (5.3)	131 (5.8)	144 (5.7)
Age ≥60 years + TE	26 (10.7)	158 (7.0)	184 (7.3)
Missing	2 (0.8)	10 (0.4)	12 (0.5)

- Compared with patients who were alive, significantly more patients who died during the study were categorized as high risk at diagnosis, primarily due to age ≥60 years only

*Data were censored at the date of the last known study visit (for those lost to follow-up) or study completion. †$P < 0.001$ for patients who had died vs those alive.

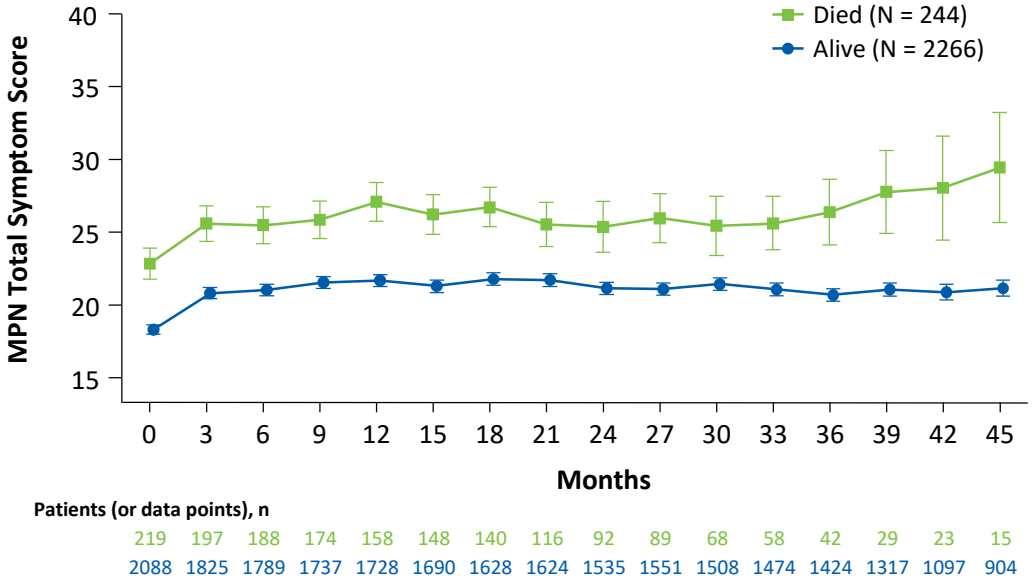
Results – Mean MPN-SAF at Enrollment

Symptom	Died (N = 244)	Alive (N = 2266)*	Total (N = 2510)
Fatigue	**4.2**	**3.4**[†]	3.5
Early satiety	**3.5**	**2.5**[†]	2.6
Abdominal discomfort	**2.0**	**1.4**[†]	1.4
Inactivity	**3.5**	**2.4**[†]	2.5
Bone pain	**1.9**	**1.5**[†]	1.5
Unintentional weight loss	**1.5**	**0.8**[†]	0.8
Problems with concentration	2.4	2.0	2.0
Night sweats	1.5	1.7	1.7
Itching (pruritus)	2.1	2.4	2.3
Fever (>37.8°C or 100°F)	0.3	0.2	0.2
Mean MPN-SAF TSS	**22.8**	**18.3**[†]	**18.7**
TSS ≥20, n (%)[‡]	110 (50.2)	814 (39.0)	924 (40.1)

- Patients who died during the study had significantly higher symptom burden at enrollment vs patients who were alive

*Data were censored at the date of the last known study visit (for those lost to follow-up) or study completion. [†]$P < 0.001$ for patients who had died vs those alive. [‡]The difference between proportions of patients with TSS ≥20 who had died vs those who were alive was not statistically significant.
MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; TSS, Total Symptom Score.

Results – MPN-SAF TSS Over Time



- Differences in TSS between “died” vs “alive” cohorts were driven by fatigue, early satiety, inactivity, difficulty concentrating, and unintentional weight loss

MPN, myeloproliferative neoplasm.

Results – Comorbidities at Enrollment and During Follow-up

Comorbidity*	Died (N = 244)	Alive (N = 2266)†	Total (N = 2510)
Vascular disorders	**176 (72.1)**	**1412 (62.3)‡**	1588 (63.3)
Respiratory, thoracic, and mediastinal disorders	**136 (55.7)**	**757 (33.4)‡**	893 (35.6)
Neoplasms benign, malignant, and unspecified (inc. cysts and polyps)	**116 (47.5)**	**503 (22.2)‡**	619 (24.7)
Gastrointestinal disorders	**110 (45.1)**	**806 (35.6)‡**	916 (36.5)
Cardiac disorders	**100 (41.0)**	**275 (12.1)‡**	375 (14.9)
Infections and infestations	**100 (41.0)**	**597 (26.3)‡**	697 (27.8)
Injury, poisoning, and procedural complications	**63 (25.8)**	**333 (14.7)‡**	396 (15.8)
General disorders and administration-site conditions	155 (63.5)	1348 (59.5)	1503 (59.9)
Nervous system disorders	131 (53.7)	1215 (53.6)	1346 (53.6)
Skin and subcutaneous tissue disorders	117 (48.0)	1169 (51.6)	1286 (51.2)
Musculoskeletal and connective tissue disorders	103 (42.2)	1039 (45.9)	1142 (45.5)
Metabolism and nutrition disorders	99 (40.6)	784 (34.6)	883 (35.2)
Psychiatric disorders	79 (32.4)	599 (26.4)	678 (27.0)
Investigations	68 (27.9)	565 (24.9)	633 (25.2)

*Comorbidities (MedDRA System Organ Class) occurring in ≥25% of patients who had died in descending order of frequency (grouped by comorbidities significantly different [$P < 0.001$]‡ and not significantly different between died vs alive cohorts). †Data were censored at the date of the last known study visit (for those lost to follow-up) or study completion.
MedDRA, Medical Dictionary for Regulatory Activities.

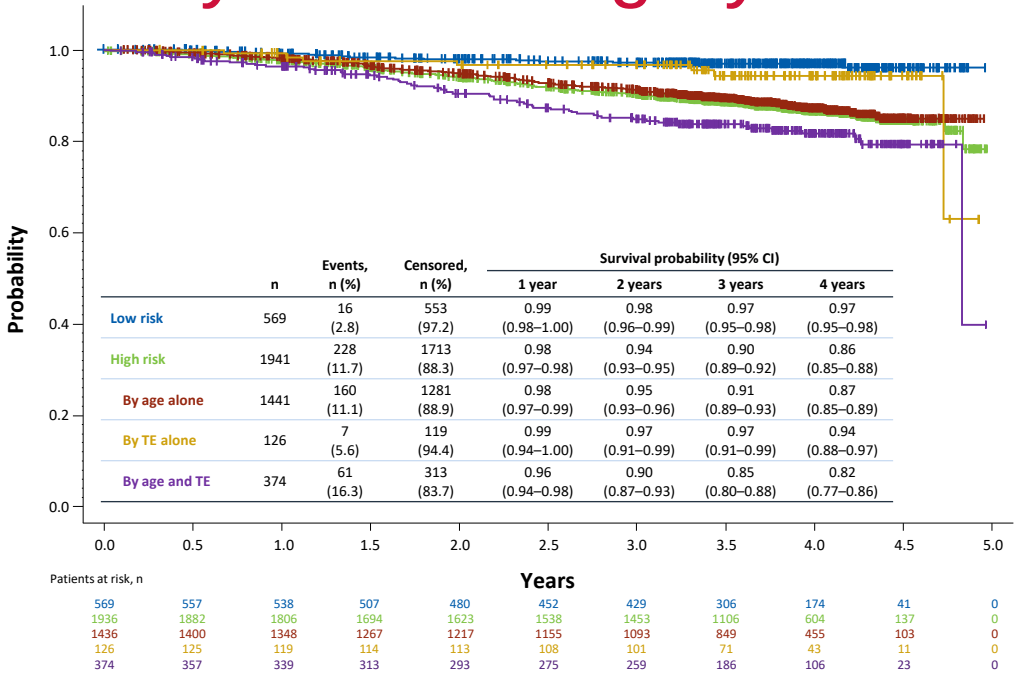
Results – Characteristics of Patients Who Died During Follow-up

Characteristics, n/N (%)	Total (N = 2510)
≥1 elevated HCT value* occurring ≤6 months before death	59/190 (31.1)
≥1 elevated WBC count† occurring ≤6 months before death	110/190 (57.9)
≥1 elevated platelet count‡ occurring ≤6 months before death	70/ 90 (36.8)
≥1 elevated WBC and platelet count occurring ≤6 months before death	52/189 (27.5)
>60 years of age before death	230/244 (94.3)
TE before death (at any time)§	85/244 (34.8)
TEs occurring ≤6 months before death	15/244 (6.1)
>60 years of age and TE before death	81/244 (33.2)

- A history of TEs prior to enrollment¶ and TEs occurring during the study period‖ were both significantly associated with overall survival

*HCT value >45% vs ≤45%. †WBC count >11 x 10^9/L vs ≤11 x 10^9/L. ‡Platelet count >600 x 10^9/L vs ≤600 x 10^9/L. § TEs were documented as an adverse event and may not include TEs that caused death. ¶HR 1.34 [95% CI 1.00-1.78]; *P* = 0.0484; ‖HR 2.85 [95% CI 1.88-4.31]; *P* < 0.001.
CI, confidence interval; HCT, hematocrit; HR, hazard ratio; WBC, white blood cell.

Results – OS by Risk Category at Enrollment

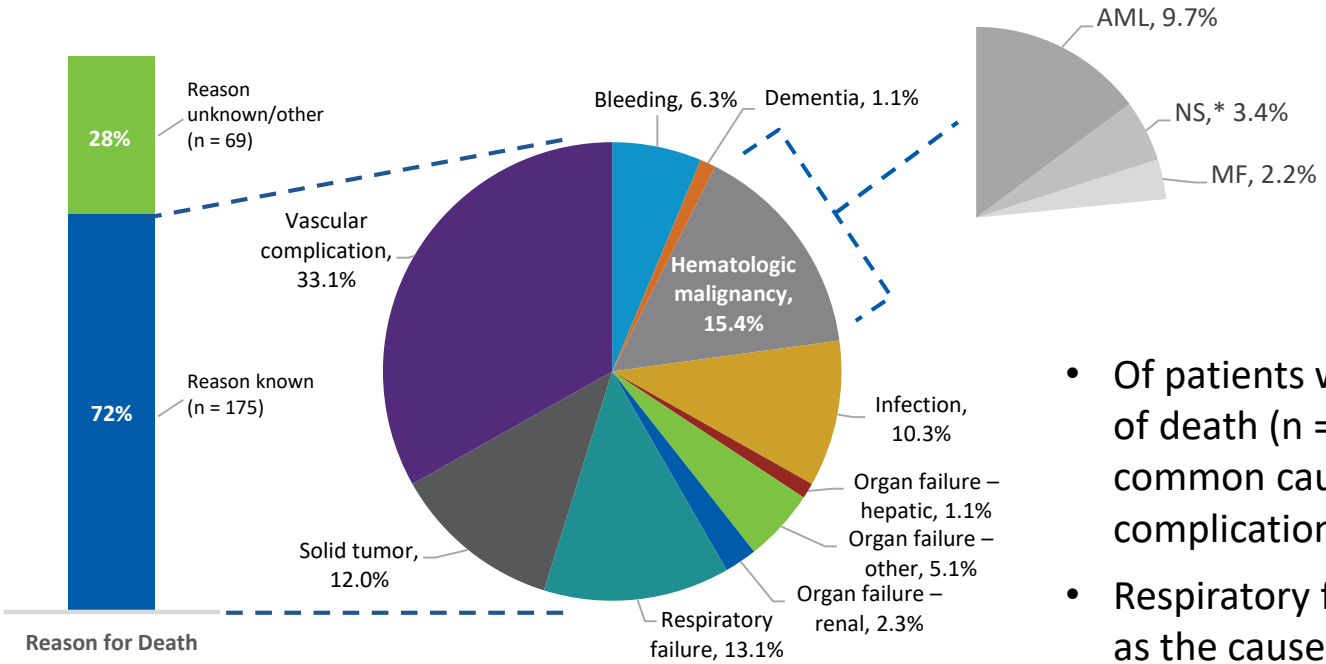


	n	Events, n (%)	Censored, n (%)	Survival probability (95% CI) 1 year	2 years	3 years	4 years
Low risk	569	16 (2.8)	553 (97.2)	0.99 (0.98–1.00)	0.98 (0.96–0.99)	0.97 (0.95–0.98)	0.97 (0.95–0.98)
High risk	1941	228 (11.7)	1713 (88.3)	0.98 (0.97–0.98)	0.94 (0.93–0.95)	0.90 (0.89–0.92)	0.86 (0.85–0.88)
By age alone	1441	160 (11.1)	1281 (88.9)	0.98 (0.97–0.99)	0.95 (0.93–0.96)	0.91 (0.89–0.93)	0.87 (0.85–0.89)
By TE alone	126	7 (5.6)	119 (94.4)	0.99 (0.94–1.00)	0.97 (0.91–0.99)	0.97 (0.91–0.99)	0.94 (0.88–0.97)
By age and TE	374	61 (16.3)	313 (83.7)	0.96 (0.94–0.98)	0.90 (0.87–0.93)	0.85 (0.80–0.88)	0.82 (0.77–0.86)

- The survival probability at 4 years was significantly lower for high- vs low-risk patients (86% vs 97%; $P < 0.001$)

OS, overall survival; TE, thrombotic event.

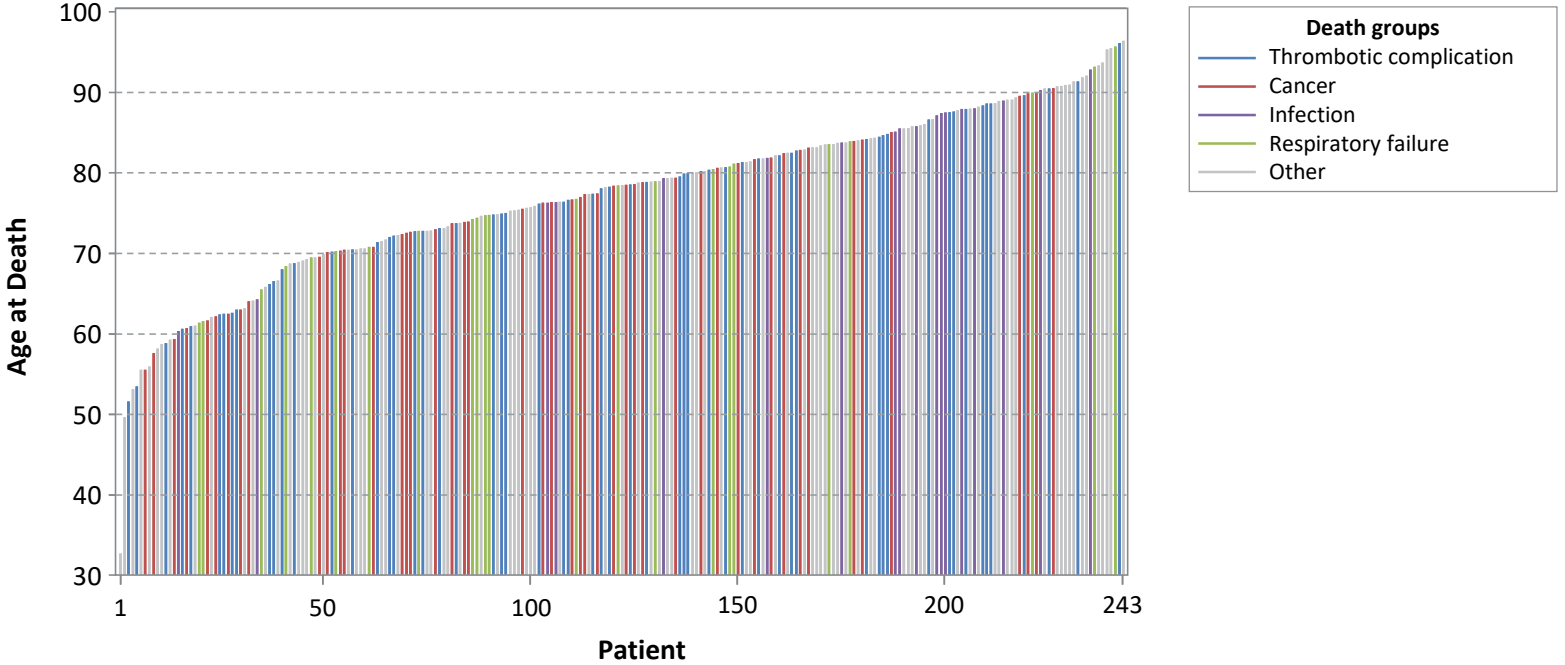
Results – Causes of Death



- Of patients with known cause of death (n = 175), the most common cause was vascular complications (33.1%)
- Respiratory failure was reported as the cause of death in 13.1%

*Physicians indicated progression but did not provide details.
AML, acute myeloid leukemia; MF, myelofibrosis; NS, not specified.

Results – Age at Death by Cause of Death



- There were diverse causes of death, regardless of age

Conclusions

- In this analysis from REVEAL, the largest prospective and contemporary cohort of patients with PV in the United States, the estimated 4-year mortality rate was >10%, a finding that is surprising given the mean age at enrollment was only approximately 66 years
- Compared with patients who were alive at study completion, patients who had died had higher-risk disease and higher rates of comorbid conditions
- Approximately one-third of the deaths were due to vascular complications; in the 6 months prior to death, more than a quarter of patients had elevated HCT or uncontrolled myeloproliferation
- The high rate of respiratory disorders observed in the deceased population, both as comorbidities and causes of death, has not been well characterized in other PV mortality studies and warrants further investigation of whether some patients may have undiagnosed pulmonary hypertension

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Disclosures

Stein: Advisory board participation – *Pharmaessentia, Constellation Pharmaceuticals; Kartos (educational content presented on one occasion for the Professor series PV); Incyte (REVEAL steering committee)*

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