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High incidence of venous thromboembolism after autologous stem cell transplantation in multiple myeloma

Running head

High VTE rate following HDT/ASCT for MM

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Data-sharing statement:

The data that support the findings of this study are not openly available and are available from the corresponding author upon reasonable request.

Multiple myeloma (MM) is associated with an increased risk of venous thromboembolism (VTE).¹ Recommendations regarding thromboprophylaxis are based on the absolute thrombotic risk as estimated by scores such as the IMPEDE-VTE.² However, these models and prevention strategies have primarily focused on the first six months after diagnosis.

In fit patients younger than 70 years, induction therapy, typically incorporating an immunomodulatory drug (IMiD), is followed by high-dose therapy and autologous stem cell transplantation (HDT/ASCT).³ Although this period does not fall in the first six months, it may also be associated with a high VTE risk due to the presence of a central venous catheter (CVC), systemic inflammation, immobilization, and recent IMiD use.^{4,5} Few data are available on the risk of VTE and arterial thrombosis (AT) during hospitalization for HDT/ASCT and in the subsequent post-transplant period. Furthermore, validated risk scores for this setting are lacking, and thromboprophylaxis is not routinely administered during hospitalization or in the post-transplant period.⁶⁻⁸ We hypothesized that the post-transplant period is also associated with a high thrombotic risk. The primary aim of this study was to determine the real-world incidence of VTE during hospitalization for HDT/ASCT and within 100 days and 1 year following transplantation. The secondary aim was to evaluate the applicability of the IMPEDE-VTE score in this setting and to determine the incidence of AT.

This retrospective cohort study included patients with MM treated with consolidative HDT/ASCT as first-line therapy between 2006 and 2022 at the University Medical Centre Groningen (UMCG), irrespective of previous anticoagulation use or history of thrombosis. Patients with a plasma cell dyscrasia other than MM and those with a planned transfer to another hospital (shared care) were excluded. All patients provided

informed consent and the Institutional Review Board of the UMCG approved the use of the data for research purposes (reference number M23.315360).

VTE (pulmonary embolism (PE), deep venous thrombosis (DVT), and catheter-related thrombosis (CRT)) and AT events were collected over a one-year period starting from transplantation. Death within one year of HDT/ASCT was considered a competing risk unless it was attributable to thrombosis. VTE events were classified as hospitalization-related if they occurred during hospitalization or within 14 days of discharge.

All variables required for the IMPEDE-VTE score were collected. Patients with IMPEDE-VTE scores of ≤ 3 , 4–7 and ≥ 8 were classified as low, intermediate, and high-risk, respectively.² To explore the applicability of the IMPEDE-VTE score, the cumulative VTE incidence with death as competing risk was calculated per category and compared using Gray's test for the first 100 days post-transplant. A Cox regression and receiver operating characteristic (ROC) curve analyses were performed, and the area under the curve (AUC) was reported as the C-statistic. We performed post-hoc analyses of the intermediate IMPEDE-VTE score category subdivided as low-intermediate (4-5 points) and high-intermediate (6-7 points). Explorative univariable analyses were performed to identify variables, selected based on the validated Padua-score, that could improve the IMPEDE-VTE model in this transplant-setting.⁹

Between 2006 and 2022, a total of 501 patients were treated with HDT/ASCT. Patient characteristics are shown in Table 1. One year of follow-up was available for 93% of patients. The median hospitalization time from transplantation was 16 days.

The absolute hospitalization-related VTE risk was 3.6% (19 events in 18 patients: 13 CRT, 1 proximal DVT, 2 distal DVT, 3 PE). One patient experienced both CRT and PE as separate events. VTE occurred at platelet counts of $<20 \times 10^9/L$ in 8 patients (44%),

between 20–50 x 10⁹/L in 2 patients (11%), and after platelet recovery (>50 x 10⁹/L) in 8 patients (44%). Seventy-two percent of hospitalization-related VTE events were CRTs.

After the hospitalization-related period, but within the first 100 days post-transplant, an additional 5 patients experienced a VTE: 1 CRT, 2 PE, and 2 distal DVTs. In total, the cumulative 100-day incidence of VTE with death as competing risk was 4.6% (95% CI 3.0–6.7).

Beyond 100 days up to one year post-transplant, only 3 events occurred (2 PE and 1 distal DVT). The cumulative 1-year incidence of VTE with death as competing risk was 5.2% (95% CI 3.5–7.4) (Figure 1). Of all 26 patients with VTE, 9 patients (35%) had a prior history of VTE; of these, 5 were receiving anticoagulation (1 prophylactic and 4 therapeutic dose) at the time of admission for transplantation. Eight events were not related to hospitalization (1 CRT, 3 distal DVT, 4 PE).

The IMPEDE-VTE score could be calculated for 492 patients (98%) (Table S1). The median IMPEDE-VTE score was 5 (IQR 4-5). Low-, intermediate- and high-risk scores were present in 3%, 84% and 13% of patients, respectively. The 100-day VTE cumulative incidences stratified by low-, intermediate- and high-risk were 3.1% (95% CI 0.6–9.6), 4.2% (95% CI 2.5–6.5) and 21% (95% CI 6.3–41.6), respectively (Figure 2A), with a statistically significant Gray's test ($p = 0.002$). In the univariate Cox proportional hazards model, patients with high-risk had a significantly higher 100-day VTE HR (HR 7.58, 95% CI 1.39–41.39; $p = 0.02$), whereas patients with intermediate-risk had a higher VTE HR albeit not significant (HR 1.35, 95% CI 0.31–5.83; $p = 0.69$). The AUC for the IMPEDE-VTE score was 0.58.

Previous VTE was the factor that most clearly differentiated the groups: 95% of patients with a high score had a history of VTE, whereas only 20% and 0% of patients

with an intermediate- and low-risk, respectively, had a history of VTE. Only VTE-history was associated with a significantly higher VTE risk in the explorative univariable analyses (Table S2).

In the post-hoc analysis of the intermediate group, the 340 patients with low-intermediate (4–5 points) and the 68 patients with high-intermediate (6–7 points) scores had a cumulative 100-day VTE incidence of 3.5% (95% CI 1.9–5.9) and 7.4% (95% CI 2.7–15.2), respectively (Figure 2B).

Five patients experienced an AT event (2 myocardial infarctions and 3 ischemic strokes) in the first year post-transplant. The cumulative 1-year incidence of AT with death as competing risk was 1.0% (95% CI 0.4–2.2) (Figure S1).

In conclusion, the 1-year post-transplant cumulative incidence of VTE and AT in patients with MM was 5.2% and 1.0%, respectively. Most VTE events were hospitalization-related (absolute risk 3.6%) and predominantly consisted of CRTs. Patients classified as high-risk by the IMPEDE-VTE score had a 100-day cumulative VTE incidence of 21%. In a post-hoc analysis, a cumulative incidence of 7.4% in the high-intermediate group was observed.

Previous studies reported a VTE incidence of 3.5% in the immediate post-transplant period and a CRT incidence of 2.5% at 100 days post-transplant in patients with MM.^{10,11} Similarly, in our cohort, most VTEs occurred within the first 100 days. However, a higher proportion of non-CRT events occurred after discharge compared with previous studies.

Patients with a high IMPEDE-VTE score were at substantially increased risk for VTE after HDT/ASCT. However, the model had a low predictive value as most included variables showed little distinctive value. Consequently, the majority of patients had an intermediate score. By dividing this into a low-intermediate and high-intermediate

subgroup, a relevant but small risk difference could be identified. Furthermore, in the univariable analyses, a higher comorbidity index, age >65 and body mass index ≥ 25 were associated with an unexpected lower VTE risk. The above explains why the performance of the IMPEDE-VTE was low. Unfortunately, explorative analyses did not identify new predictors to optimize the model.

In this study, 56% of hospitalization-related VTEs occurred after the platelet count exceeded $20 \times 10^9/L$. Limited evidence suggests that starting thromboprophylaxis may be feasible in selected high-risk patients with platelet counts between $20\text{--}50 \times 10^9/L$, although safety remains uncertain with hemorrhage as major concern.^{12,13} Therefore, identification of patients with a high risk of thrombosis in the post-transplant period is important and should be further investigated.

The majority of the observed VTE events were CRTs (54%) and hospitalization-related (69%). Therefore, duration of hospitalization, and type and duration of CVC use are probably important determinants of the absolute VTE risk.⁶ Kreuziger et al.¹⁴ report a higher CRT risk with specific CVC types, bigger diameters, and a left-sided insertion. As the variation of CVCs used in our cohort was limited, it could not be analyzed. Recent research has shown strong advantages of outpatient HDT/ASCT¹⁵, possibly reducing the risk of VTE through lower infection rates, shorter CVC time, and enhanced patient mobility.

Our study has several strengths. We provide a comprehensive description of the type and timing of VTE and the related circumstances in a large cohort of patients based on real-world data. This study has a limitation due to its retrospective design, with limited data on in-hospital thromboprophylaxis, and bleeding complications. Moreover, the limited number of events constrained analyses.

We highlight an increased thrombotic risk during the first 100 days post-transplant, particularly for CRT. Patients with a high IMPEDE-VTE score were at increased risk of VTE. However, the model had limited discriminatory power. These findings suggest that patients with MM experience an under-recognized period of increased thrombotic risk, warranting improved preventive strategies based on optimized risk stratification.

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Tables:

Table 1. Cohort description.

	<i>All</i>	(%)	<i>No VTE</i>	(%)	<i>VTE</i>	(%)
	<i>patients</i>					
Total	501	100%	475	95%	26	5%
Age at transplant						
Median (IQR)	61	(54–65)	61.0	(54–64)	60.5	(57–65)
Sex						
Male	314	63%	295	62%	19	73%
ISS						
1	132	26%	127	27%	5	19%
2	165	33%	151	32%	14	54%
3	121	24%	116	24%	5	19%
Missing	83	17%	81	17%	2	8%
Induction						
IMiDs	287	57%	272	57%	15	58%
Other	214	43%	203	43%	11	42%
Response after induction						
CR or better	160	32%	154	33%	6	23%
No CR	341	68%	321	68%	20	77%
HCT-CI						
0-2	318	63%	302	64%	16	62%
3-4	139	28%	132	28%	7	27%
≥ 5	44	9%	41	9%	3	12%
WHO performance status						
0	185	37%	178	37%	7	27%
≥1	232	46%	219	46%	13	50%
Missing	84	17%	78	16%	6	23%
IMPEDE-VTE						
Low (0-3)	19	4%	17	4%	2	8%
Intermediate (4-7)	408	81%	388	82%	20	77%
High (>7)	65	13%	61	13%	4	15%
Missing	9	2%	9	2%	0	0%
VTE-History						
Yes	101	20%	92	19%	9	35%
BMI						
≥25 (kg/m ²)	285	57%	275	58%	10	38%
Missing	7	1%	7	1%	0	0
Anticoagulation (at hospitalization)						
None	344	69%	325	68%	19	73%
Prophylactic	76	15%	73	15%	3	12%
Therapeutic	81	16%	77	16%	4	15%
Hospitalization length*						
In days, median (IQR)	16	(14–20)	16	(14–20)	16.5	(14–24.3)
CVC length of stay						
In days, median (IQR)	19	(17–21)	20.4	(17–21)	18	(15.8–19)
Infections						
≥ 1 infection in 100 days	297	59%	281	59%	16	62%
Maintenance						
Any	269	54%	253	53%	16	62%

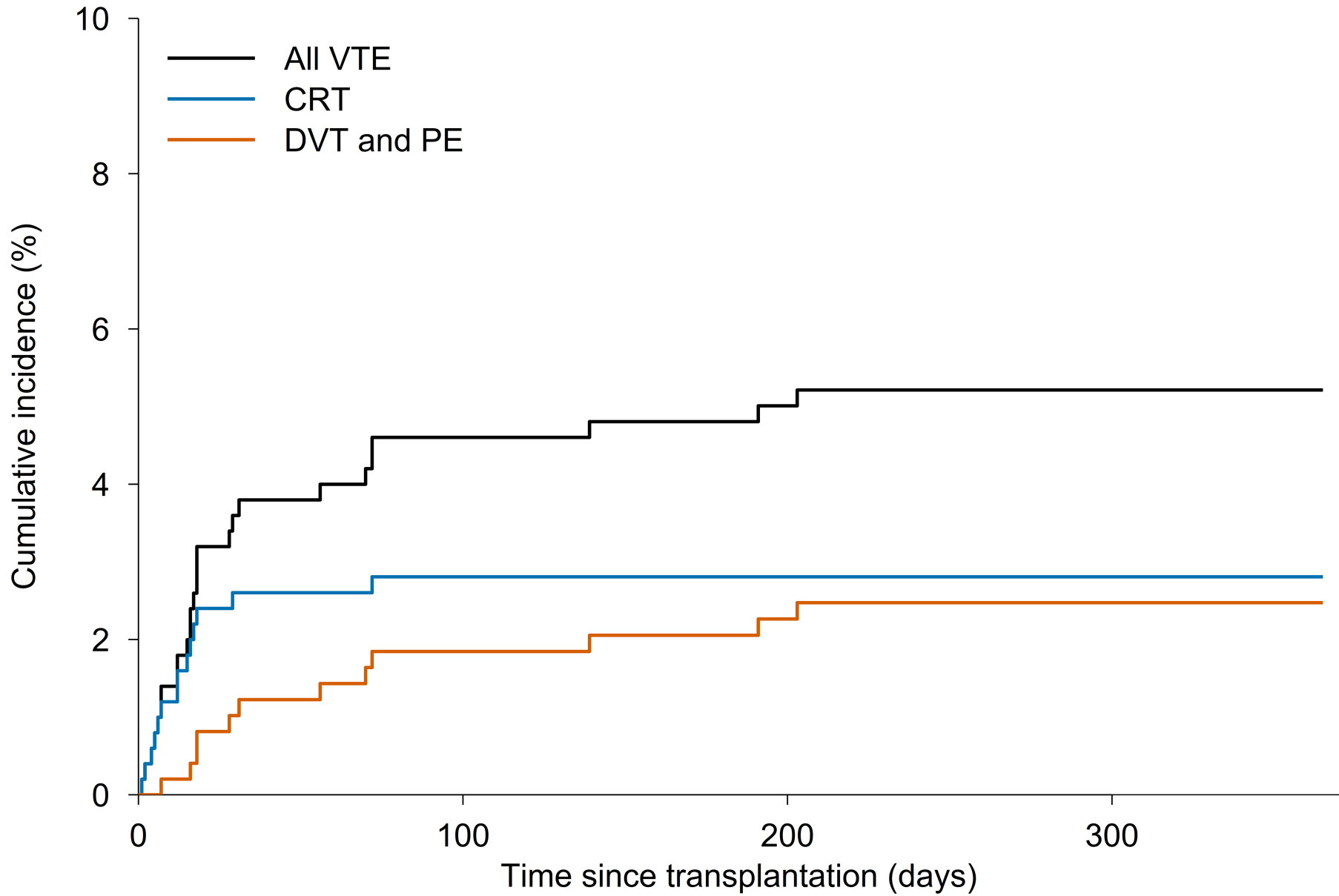
<i>Len</i>	198	40%	184	39%	14	54%
<i>Missing</i>	18	4%	16	3%	2	8%

*From transplantation. Abbreviations: AT: arterial thrombosis; BMI: body mass index; CR: complete response; CVC: central venous catheter; HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index adjusted for age; IMiDs: immunomodulatory drugs; IQR: interquartile range; ISS: international staging system; Len: lenalidomide; VTE: venous thromboembolism; WHO: World Health Organization.

Figure legends:

Figure 1. Cumulative incidence of venous thrombosis with death as competing risk. Abbreviations: CRT: catheter-related thrombosis; DVT: deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism.

Figure 2. Cumulative incidence of venous thrombosis with death as competing risk stratified per IMPEDE-VTE score category. Panel A displays venous thrombosis incidence stratified per low-, intermediate- and high-risk. Panel B displays venous thrombosis incidence additionally stratified as low-intermediate and high-intermediate risk. Abbreviations: H-interm.: high-intermediate; Interm.: intermediate; L-interm.: low-intermediate.

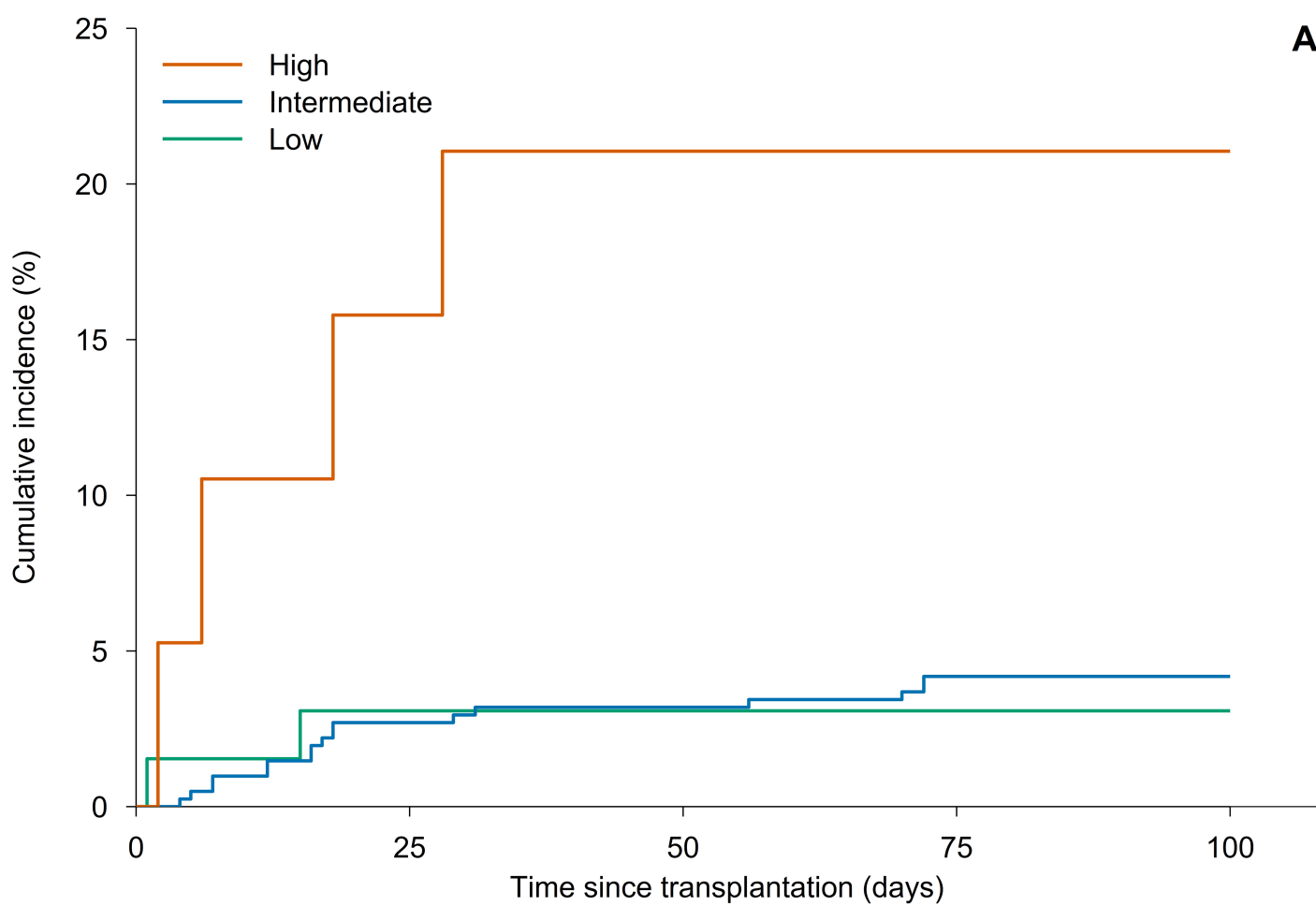


At risk 501
(All VTE)

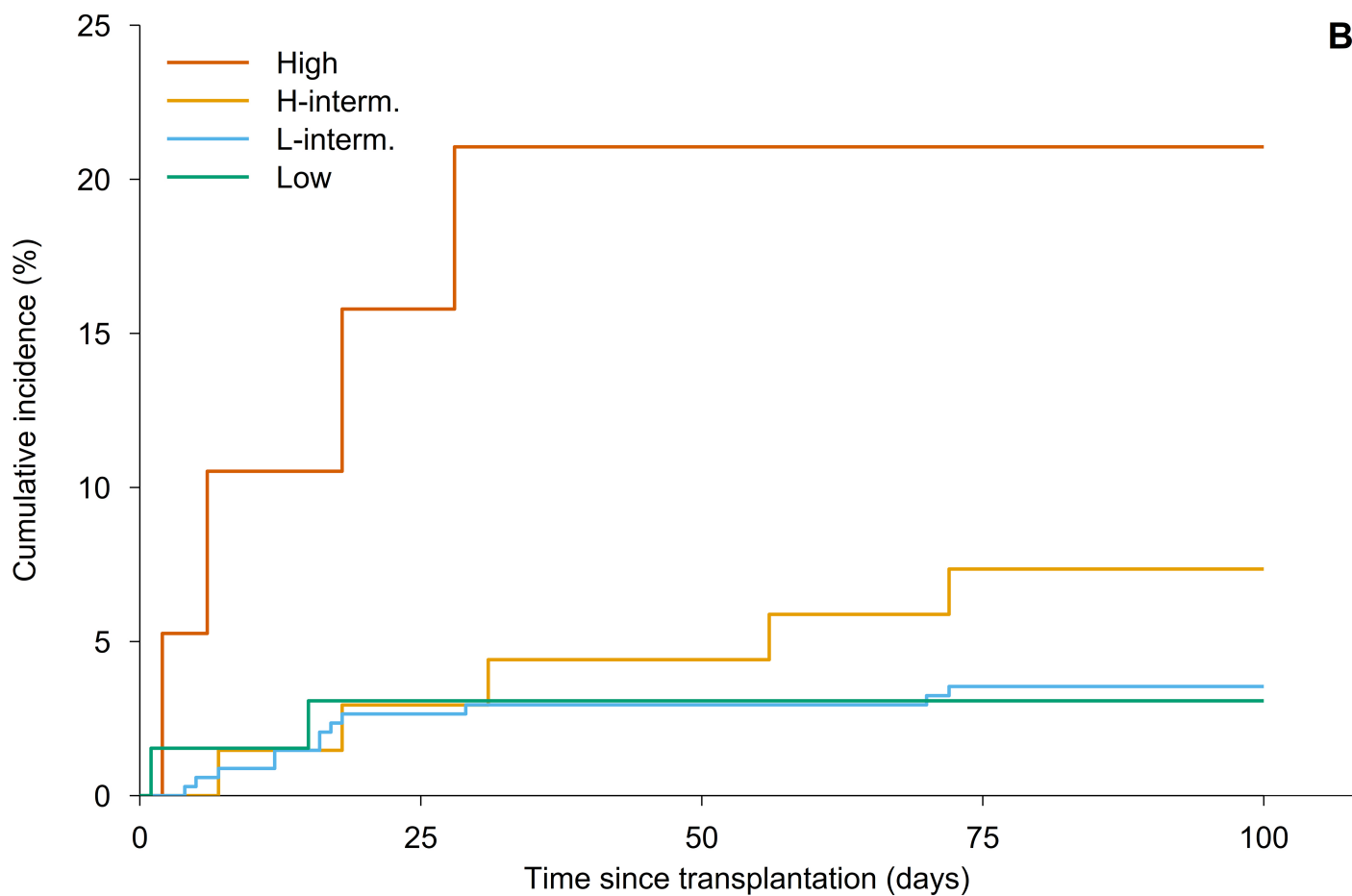
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A

At risk	19	16	15	15	15
High	19	16	15	15	15
Interm.	408	394	389	384	384
Low	65	62	62	62	62

B

At risk	19	16	15	15	15
High	19	16	15	15	15
H-interm.	68	65	64	62	62
L-interm.	340	329	325	322	322
Low	65	62	62	62	62

Supplementary material

Table S1. IMPEDE-VTE variables.

	<i>Number</i>	<i>(%)</i>
<i>IMPEDE-VTE (complete)</i>	492	98.2
<i>Low</i>	19	3.9
<i>Intermediate</i>	408	82.9
<i>High</i>	65	13.2
<i>Immunomodulatory drugs**</i>		
Yes	8	1.6
<i>Body mass index</i>		
$\geq 25 \text{ kg/m}^2$	285	57.9
<i>Pelvic, hip or femur fracture**</i>		
Yes	2	0.4
<i>Erythropoiesis-Stimulating Agent**</i>		
Yes	3	0.6
<i>Doxorubicin**</i>		
Yes	0	0
<i>Dexamethasone**</i>		
<i>High dose</i>	2	0.4
<i>Low dose</i>	490	99.6
<i>Asian/Pacific Islander</i>		
Yes*	0	0
<i>VTE-History</i>		
Yes	101	20.5
<i>Central venous catheter</i>		
Yes	492	100
<i>Anticoagulation**</i>		
<i>Therapeutic</i>	81	16.5
<i>Prophylactic</i>	76	15.4

Abbreviations: kg: kilogram; VTE: venous thromboembolism. *Because ethnicity is not routinely recorded in the medical dossier, we have assumed that no patients would be of Asian/Pacific Islander ethnicity due to the geographical location of the medical centre.

**Within 30 days before hospitalisation.

Table S2. Univariable Cox regression analysis of clinically relevant VTE risk factors during the first 100 days after transplantation.

	<i>N patients</i>	<i>HR (95% CI)</i>	<i>p value</i>
Age	501		
≤ 65 years	407	reference	
> 65 years	94	0.89 (0.30–2.63)	0.84
Sex	501		
Female	187	reference	
Male	314	1.39 (0.57–3.37)	0.47
VTE-history	501		
No	400	reference	
Yes	101	2.58 (1.12–5.97)	0.03
HCT-CI	501		
0-2	318	reference	
>2	183	0.75 (0.31–1.83)	0.53
WHO PS	417		
0	185	reference	
≥1	232	1.49 (0.59–3.73)	0.40
BMI¹	494		
< 25	209	reference	
≥ 25	285	0.46 (0.20–1.07)	0.07
BMI¹	494		
< 30	417	reference	
≥ 30	77	1.14 (0.39–3.36)	0.81
Depth of response	501		
Less than CR	160	reference	
CR or better	341	0.75 (0.30–1.91)	0.55
Anticoagulation²	501		
None	344	Reference	
Prophylactic	76	0.83 (0.24–2.86)	0.77
Therapeutic	81	1.08 (0.36–3.24)	0.89
Infection³	492 ⁴		
No	204	reference	
Yes	288	1.50 (0.58–3.90)	0.41

Abbreviations: BMI, body mass index; CI: confidence interval; CR: complete response; HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index adjusted for age; ISS: international staging system; N: number of patients; VTE: venous thromboembolism; WHO PS: World Health Organization Performance Status. ¹in the IMPEDE-VTE score the

BMI margin was set at 25, whereas in the Padua score the BMI margin was set at 30. ²at admission. ³treated as time-varying covariate. ⁴for 9 patients the date the infection was first diagnosed was not available.

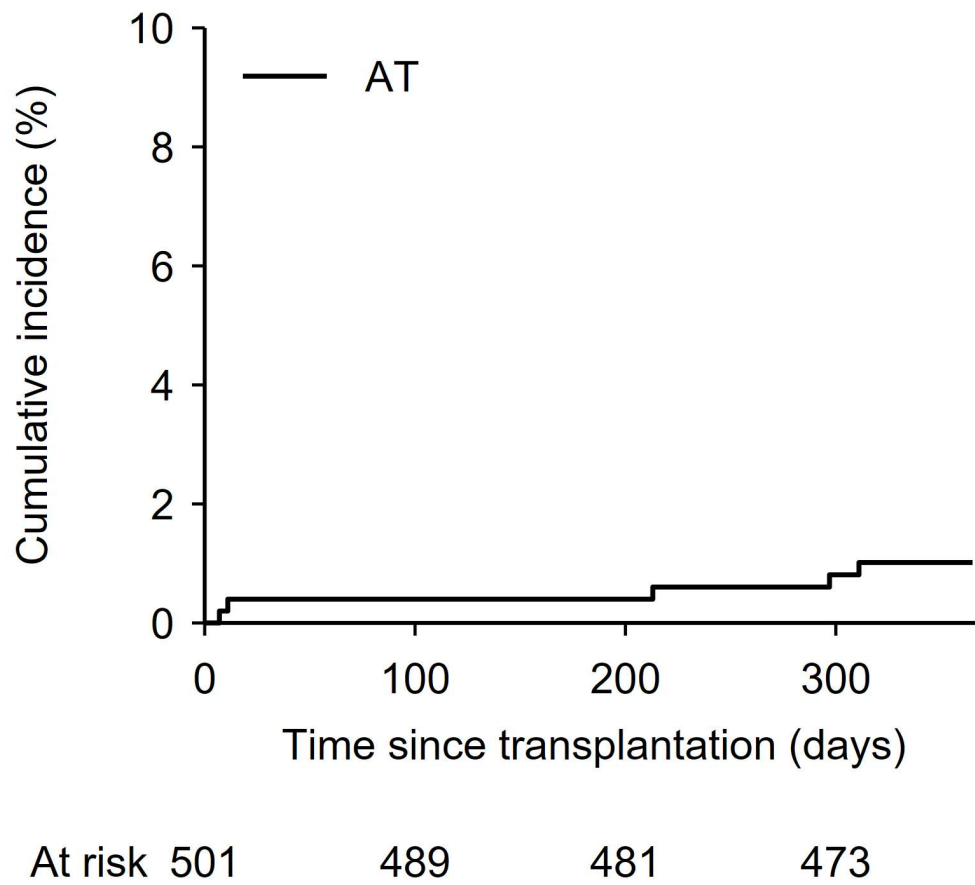


Figure S1. Cumulative incidence of arterial thrombosis with death as competing risk. Abbreviations: AT: arterial thrombosis.