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What is the impact of antithrombotic therapy and risk factors on the frequency of thrombovascular events in patients with metastatic breast cancer receiving epoetin beta?

Matti Aapro[a,*], *Agustí Barnadas*[b], *Robert C. Leonard*[c], *Maurizio Marangolo*[d], *Michael Untch*[e], *Lidia Ukarma*[f], *Hans-Ulrich Burger*[f], *Armin Scherhag*[f,g], *Bruno Osterwalder*[f]

[a]*Institut Multidisciplinaire d'Oncologie, Clinique de Genolier, CH-1272 Genolier, Switzerland*
[b]*Hospital de Sant Pau, Barcelona, Spain*
[c]*Cancer Services and Clinical Haematology, Imperial College, Charing Cross Hospital, London, UK*
[d]*Divisione Oncologia, Ospedale Provinciale Sta Maria delle Croci, Ravenna, Italy*
[e]*Helios Klinikum, Berlin Buch, Germany*
[f]*Hoffmann-La Roche Ltd., Basel, Switzerland*
[g]*I. Medical Clinic, University Hospital Mannheim, University of Heidelberg, Germany*

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ABSTRACT

Purpose, patients and methods: This retrospective analysis of the BRAVE study evaluated the impact of baseline risk factors and antithrombotic therapy on the risk of thrombovascular events (TVEs) in patients receiving epoetin compared to patients not receiving epoetin.
Results: Baseline risk factors have a significant impact on TVE risk under epoetin therapy. More than 2 risk factors increased the risk of TVEs in patients receiving epoetin (hazard ratio [HR] 2.89, confidence interval [CI] 1.04–8.02, *p* value [*p*] = 0.04). In patients on epoetin without antithrombotic therapy, the risk for TVEs was higher (HR 4.11, CI 1.37–12.4, *p* = 0.01) compared to those who received antithrombotics (HR 1.37, CI 0.59–3.18, *p* = 0.45).
Conclusions: Our analysis has identified several risk factors which may impact the risk of TVEs under epoetin therapy. These data suggest that antithrombotic therapy may have the potential to reduce the risk of TVEs under epoetin therapy. These findings are hypothesis-generating and need to be confirmed in a prospective, randomised study.

1. Introduction

The association between venous thromboembolism and cancer was first recognised in 1865.[1] Since that time, it has become clear that thrombovascular event (TVE) is a frequent complication in cancer patients and a significant cause of morbidity and mortality.[2–4] Compared with the general population, cancer alone carries an approximately 4-fold increased thromboembolic risk, which increases to 6.5-fold in those undergoing chemotherapy.[5] TVEs are likely to be underestimated as a potential cause of death in cancer patients. For instance, data from a number of large autopsy studies[6,7] indicated pulmonary emboli (PE) as the primary cause of death in up to 35% of cancer patients and as contributing fac-

* *Corresponding author:* Tel.: +41 (22) 366 91 06; fax: +41 (22) 366 91 31.
E-mail addresses: maapro@genolier.net (M. Aapro), lidia.ukarma@roche.com (L. Ukarma).
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tor in a further 43% of patients.[6–8] Most studies on the incidence of TVEs in malignancy have been performed in patients with breast cancer.[9] The annual rate of TVEs in patients with node-negative breast cancer has been estimated as 0.2% compared with 0.08% in healthy woman of similar age.[10,11] The incidence of TVE has been reported to be 6.8% in woman with Stage II breast cancer receiving chemo-hormonal therapy and up to 17.5% among women with advanced breast cancer receiving cytotoxic chemotherapy.[12,13] Erythropoietin therapy is associated with an increased frequency of TVEs in a variety of tumour types.[14–22] In the BEST study, 16% of patients in the epoetin alfa group versus 14% of patients in the placebo arm experienced a TVE.[18] A Cochrane meta-analysis in oncology patients receiving epoetins has confirmed a significantly increased risk of TVEs compared with control (relative risk 1.67, 95% confidence interval [CI], 1.35–2.06).[22] The most recent aggregated study data meta-analysis by Bennett et al. yielded a similar risk ratio.[20] The risk of TVEs may be influenced by the type and extent of malignancy, the type of cancer treatment given, the existence of comorbidities and advanced age.[21] A recent review by van Doormaal et al. discusses that the prophylactic use of antithrombotics may reduce the risk of TVEs in cancer patients.[23] Experimental data also suggest a potential anti-tumour effect of heparin.[24] However, no prospective clinical studies have been performed in cancer patients receiving chemotherapy and epoetins in order to evaluate the role of risk factors on the incidence of TVEs and to assess the impact of antithrombotic therapy.

Based on our prospective randomised study of epoetin beta in patients with metastatic breast cancer undergoing chemotherapy (BRAVE study) the objective of this retrospective analysis was to investigate the potential impact of antithrombotic therapy and risk factors on the incidence of TVEs in patients receiving epoetin beta versus control.[25]

2. Patients and methods

2.1. Study design

The design and primary results of this study have been recently published.[25] This was an open-label, randomised, multicentre, two-arm study in patients with metastatic breast cancer treated with chemotherapy. In brief, adult (aged $\geqslant$ 18 years) females were eligible for enrolment if they had histologically or cytologically diagnosed breast cancer with evaluable metastatic disease and were scheduled to receive anthracycline- and/or taxane-based chemotherapy. Patients had to have a haemoglobin (Hb) level < 12.9 g/dl at screening, a life expectancy > 6 months and a World Health Organisation (WHO) performance status of 0–2. All patients provided written informed consent prior to participating in the study. Eligible patients were randomised (1:1) centrally to receive epoetin beta (NeoRecormon®, F. Hoffmann-La Roche Ltd., Basel, Switzerland) subcutaneously (SC) 30.000 IU once weekly, or to the standard of care (control group) over a 24-week treatment period. The initial epoetin beta dose was doubled if during the first 4 weeks of therapy a blood transfusion was necessary or the Hb increase from baseline to week 4 was <0.5 g/dl. Administration of epoetin beta was interrupted in patients whose Hb level increased to >15 g/dl.

2.2. Methods

The following adverse events were prospectively defined as TVEs: thrombophlebitis, superficial thrombophlebitis, deep vein thrombosis, subclavian vein thrombosis, aortic thrombosis, extremity necrosis, superior vena cava occlusion, thrombosis, venous occlusion, pulmonary embolism, angina pectoris, age indeterminate myocardial infarction, cardiac arrest, cerebellar haemorrhage, cerebral infarction, disseminated intravascular coagulation and portal vein thrombosis. In addition, the current analysis also used an extended definition of TVEs which led to the inclusion of three cases originally coded as phlebitis (not prospectively defined as a TVE in the Statistical Analysis Plan). They were included after review of all cases, in order to give a more conservative estimate of the incidence of TVEs.

The following agents which have been administered to patients enrolled in the BRAVE study were considered as antithrombotic therapy for the purpose of our analysis: enoxaparin sodium, nadroparin calcium, acenocoumarol, fluindione, heparin sodium, certoparin sodium, dalteparin sodium, warfarin sodium, bemiparin sodium, heparin calcium, heparinoids, tinzaparin sodium, low molecular weight heparins, aspirin, salicylic acid, clopidogrel, dipyridamole, ticlopidine. One patient received a single dose of alteplase to re-open a blocked central venous catheter and one patient received defibrotide for treatment of haemorrhoids.

2.3. Statistical analysis

All analyses conducted for the purpose of this manuscript were retrospective and performed after all primary analyses had been completed. Nevertheless, a pre-defined statistical analysis plan was used. Time to event analyses for TVEs were performed utilising Kaplan–Meier methods. Multivariable Cox regression models were used to identify prognostic factors for TVEs in the overall population. In this analysis, all factors significant at an alpha level of 0.15 in the univariable model (with treatment as a factor) were also included in a multivariable model where factors which were not significant at an alpha level of 0.05 were removed in a stepwise fashion to diminish the correlation among prognostic factors. Multivariable analysis was used to investigate the potential role of the various established risk factors for TVEs. Risk factors were identified by the results from the multivariable procedure defined above.

The analysis for the evaluation of the role of antithrombotic therapy comprised all patients who received antithrombotic therapy before baseline, at baseline or after baseline but prior to the occurrence of a TVE. Subgroup analyses were performed on patients who received antithrombotic therapy versus those who did not receive such therapy. Separate analyses on patients experiencing serious TVEs were performed.

3. Results

3.1. Demographic and baseline characteristics

A total of 463 patients with metastatic breast cancer were enrolled in the study; 232 in the epoetin beta arm and 231 in the

control arm. One patient randomised to the control arm received no scheduled chemotherapy during the study, and was excluded from the safety analysis population. In total, 340 (73%) patients completed the study treatment period. One hundred and twenty three patients (27%) prematurely withdrew from the study (69 patients in the epoetin beta arm and 54 patients in the control arm). Patient demographic and clinical characteristics were generally well balanced, with no major differences among the two study arms (Table 1). Baseline risk factors for TVEs were balanced between the two study arms and importantly they did not impact on the time to TVE analyses[25] (Table 4).

3.2. *Frequency, distribution and severity of thrombovascular events*

Overall, 96% (222/231) of patients in the control arm and 95% (219/231) of patients receiving epoetin beta reported at least one adverse event during the treatment phase. A higher incidence of serious adverse events was observed in the epoetin beta arm, 42% (97/231) compared with the control arm, 31% (71/231).[25]

A total of 13 patients (6%) in the control arm experienced at least one TVE compared to 29 patients (13%) in the epoetin beta arm (Table 2). The higher rate of TVEs in the epoetin beta arm compared with the control arm was statistically significant (hazard ratio [HR] 2.36; CI 1.23–4.55, p value [p] = 0.01). The higher incidence of TVEs seen in the epoetin beta arm compared with that seen in the control arm was driven by more vascular events (9% versus 2%, respectively, e.g. thrombophlebitis 7 cases versus 1 case) and deep vein thrombosis (deep vein thrombosis [DVT]; 6 cases versus 1 case). The number of patients with PE was comparable in both groups (5 cases epoetin beta versus 6 cases control).[25] In the entire study population, there were less bleeding events reported in the epoetin arm (8 events) than in the control group (15 events), although there were more patients receiving anticoagulants at baseline in the epoetin arm (21 versus 18 patients).

However, despite the overall higher incidence of all TVEs in the epoetin beta arm compared with the control arm, serious TVEs (10/231 [4%] in epoetin beta versus 8/231 [3%] in control group, $p = 0.72$) or fatal TVEs (4 cases in each arm) occurred at a similar frequency in both arms (Table 2).

The Kaplan–Meier curve of time to TVE showed that the two curves started to separate early after study treatment start resulting in a significantly shorter time to TVE in the epoetin beta study arm compared with control ($p = 0.01$, log-rank test) (Fig. 1). The curves remained separated for the remainder of the study duration.

3.3. *Effect of baseline haemoglobin on risk of TVEs*

When stratified by baseline Hb level, an increased risk of TVEs associated with epoetin beta compared to patients in the

Table 1 – Baseline demographics and clinical characteristics (intent-to-treat population).

Characteristics	Control (n = 232)	Epoetin beta (n = 231)
Race, n (%)		
Caucasian	209 (90)	209 (90)
Black	2 (<1)	4 (2)
Oriental	16 (7)	14 (6)
Other	5 (2)	4 (2)
Median (range) age, years	57.5 (29–83)	56.0 (27–78)
Median (range) weight, kg	65.5 (30–112)	66 (42–118)
WHO performance status[a]*, n (%)*		
0	84 (36)	101 (44)
1	110 (47)	105 (45)
2	38 (16)	22 (10)
3	0	1 (<1)
Concomitant chemotherapy, n (%)		
Anthracycline based	90 (39)	94 (41)
Taxane based	119 (51)	117 (51)
Taxane-anthracycline based	23 (10)	20 (9)
Hormone receptor status, n (%)		
Negative	67 (29)	64 (28)
Positive	165 (71)	167 (72)
Neoadjuvant/adjuvant hormonal therapy, n (%)	98 (42)	113 (49)
Mean (SD) haemoglobin, g/dl	11.2 (1.2)	11.5 (1.1)
Antithrombotic therapy		
Anticoagulants	18(7)	21(10)
Salicylates	5(2)	8(4)
Platelet aggregation inhibitors	1(<1)	1(<1)

Abbreviations: WHO, World Health Organisation; SD, standard deviation.
a Data were missing for two patients in the epoetin beta treatment group.

Table 2 – Distribution of thrombovascular events.

	Control	Epoetin beta	Hazard ratio (95% CI)	*p* Value
Overall number of patients	231	232	–	–
Number of Patients with TVEs	13 (6%)	29 (13%)	2.36 (1.23–4.55)	0.01
Number of Patients with Serious TVEs	8 (3%)	10 (4%)	1.28 (0.50–0.23)	0.61
Number of Patients with fatal TVEs	4 (2%)	4 (2%)	1.02 (0.25–4.07)	0.98

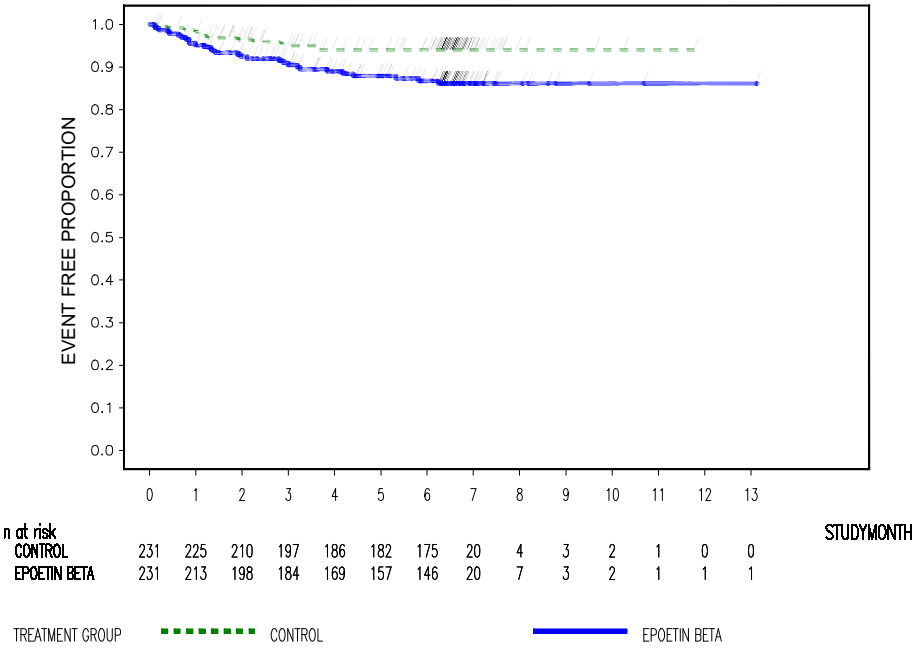

Fig. 1 – Thrombovascular events over time.

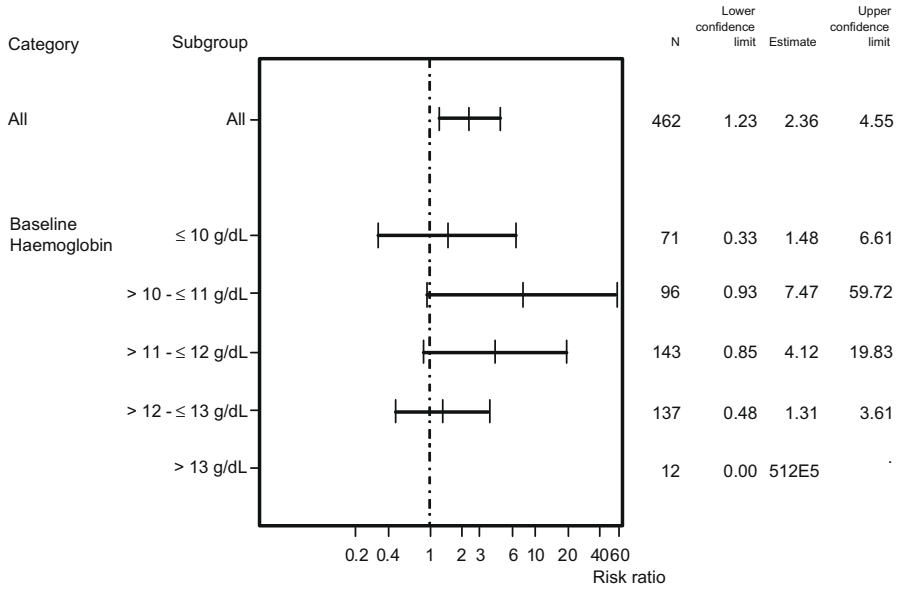

Fig. 2 – Impact of different baseline Hb levels on thrombovascular risk.

control arm was seen across all subgroups with HR estimates ranging from 1.31 (in the highest Hb category) to 7.47 in the category of 10–11 g/dl (Fig. 2) indicating no association of increased baseline Hb levels and risk of TVEs.

3.4. Prognostic value of baseline risk factors for TVEs

In the univariable analysis, age, number of metastatic sites, hormone receptor status and ductal histology were identified as independent negative prognostic factors for a TVE ($p < 0.15$) (Table 3). Treatment with epoetin beta significantly increased the risk of a TVE irrespective of the presence or absence of single baseline risk factors. The adjusted HRs for TVEs with epoetin beta compared with control in the various risk groups ranging from 2.29 to 2.63 are similar to that for the overall population (HR 2.36) (Table 4). The treatment effect estimates for TVEs in the multivariable Cox regression model were similar to those in the unadjusted model, indicating that the observed overall treatment effect was not influenced significantly by any single prognostic factor.

The majority of patients (133/231 [58%] epoetin beta versus 129/231 [56%] control) had more than 2 risk factors present at baseline. For the analysis of the presence of multiple risk factors, the significant factors in the multivariable model (i.e. age in 10 year steps, number of metastatic sites and hormone receptor status and in addition diabetes, baseline platelet counts and antithrombotic therapy) were assessed. In the subgroup of patients with more than 2 risk factors at baseline, the HR for a TVE was 2.89 (CI 1.04–8.02; $p = 0.04$) compared to the subgroup of patients with 0–2 baseline risk factors with a HR of 2.07 (CI 0.88–4.89, $p = 0.10$) (Table 5).

3.5. Prognostic impact of antithrombotic treatment on risk of TVEs

A significantly increased relative risk in TVE of epoetin beta versus control treatment group was observed in patients who did not receive any antithrombotic therapy (HR 4.11, CI 1.37–12.4, $p = 0.01$) compared to patients who received antithrombotic therapy. In the subgroup of patients who received antithrombotic therapy there was no difference between epoetin beta and control group (HR 1.37, CI 0.59–3.18, $p = 0.46$) Table 6.

4. Discussion

These data represent a first attempt to evaluate and identify the impact of risk factors on the incidence of TVEs and explore the potential impact and role of antithrombotic therapy in patients with metastatic breast cancer receiving epoetins and concurrent chemotherapy.

Multiple studies have established the increased risk for TVEs in cancer patients receiving epoetin therapy.[14–22] No prospective controlled studies have been conducted to define risk factors for TVEs in this setting and evaluate the potential role of antithrombotic therapy co-administered with epoetin therapy. This retrospective analysis, based on a prospective controlled trial with epoetin beta in patients with metastatic breast cancer was therefore performed to address these two questions.[17]

Our analyses have identified several baseline risk factors which may have an impact on the risk for TVEs under epoetin therapy (see Tables 3 and 4). Overall, the incidence of TVEs in the epoetin beta arm (13% = 29) of BRAVE is within the range reported in other studies conducted in a similar patient population. The significantly higher risk of TVEs amongst patients on epoetin (HR 2.36, CI 0.15–2.90, $p = 0.01$) is supported by data from two large meta-analyses although the estimated risk is in the range of 1.6–1.7 and therefore smaller than that in the breast cancer population of the BRAVE study.[17,22] Despite the increased incidence of TVEs in the epoetin beta arm compared with the control arm, the incidence of serious (4% = 10 versus 3% = 8, $p = 0.61$) and fatal TVEs (2% = 4 versus 2% = 4, $p = 0.98$) was comparable between the two study groups.[25] Although physicians are generally aware how to manage TVE complications, no guidelines for TVE treatment or prophylaxis in cancer patients undergoing epoetin treatment are available yet.

Activation of the antithrombotic pathways occurs in the majority of patients with malignancies.[9] Biological findings suggest that the mechanism of this hypercoagulative state involves activation of the clotting system as the result of proco-

Table 3 – Impact of risk factors on risk of thrombovascular events (explores the prognostic value of an individual covariate).

Effect/covariate	Covariate effect			
	Number of patients	Hazard ratio	95% CI for hazard ratio	p Value
Age (10-year-steps)	462	1.31	[0.99;1.73]	0.0609
Age ⩾ 60	462	1.22	[0.66;2.24]	0.5291
Risk factor: hypertension	462	1.21	[0.61;2.41]	0.5876
Risk factor: dyslipidaemia	462	0.94	[0.23;3.90]	0.9342
Risk factor: diabetes	462	1.86	[0.73;4.73]	0.1930
Risk factor: cardiovascular diseases excluding hypertension	462	1.00	[0.36;2.80]	1.0000
Platelets at Baseline [10**10/l]	459	1.02	[0.99;1.05]	0.1627
CRP ⩾ 1 mg/dl	386	0.99	[0.51;1.93]	0.9818
WHO – performance status	460	0.95	[0.61;1.49]	0.8169
Number of metastatic sites at baseline	457	1.28	[1.00;1.63]	0.0515
Visceral versus other metastases	460	1.26	[0.62;2.55]	0.5296
Non-chidbearing potential	462	>100	[0.00;.]	0.9857
Hormone receptor status (positive/negative)	462	0.56	[0.30;1.04]	0.0652
Histology: ductal concomitant anticoagulant/antiplatelet	462	0.44	[0.23;0.83]	0.0111
Therapy or thrombolytic agents at baseline	462	1.12	[0.44;2.84]	0.82

Table 4 – Impact of epoetin beta treatment on risk of thrombovascular events (adjusted for covariates defined in Table 3) – HR refers to the comparison of epoetin versus control.

Effect/covariate	Treatment effect adjusted for covariate			
	No. of Patients	Hazard Ratio	95% CI for hazard ratio	*p* Value
Only treatment	462	2.36	[1.23;4.55]	0.0099
Age (10-year-steps)	462	2.46	[1.28;4.73]	0.0072
Age ⩾ 60	462	2.42	[1.26;4.67]	0.0082
Risk factor: hypertension	462	2.36	[1.23;4.54]	0.0102
Risk factor: dyslipidaemia	462	2.37	[1.23;4.55]	0.0099
Risk factor: diabetes	462	2.34	[1.21;4.49]	0.0111
Risk factor: cardiovascular diseases excluding hypertension	462	2.37	[1.23;4.58]	0.0097
Platelets at Baseline [10**10/l]	459	2.34	[1.22;4.51]	0.0107
CRP ⩾ 1 mg/dl	386	2.63	[1.26;5.47]	0.0099
WHO – performance status	460	2.39	[1.24;4.61]	0.0093
Number of metastatic sites at baseline	457	2.35	[1.22;4.53]	0.0104
Visceral versus other metastases	460	2.34	[1.22;4.50]	0.0109
Non-chidbearing potential	462	2.29	[1.19;4.40]	0.0131
Hormone receptor status (positive/negative)	462	2.39	[1.24;4.61]	0.0089
Histology: ductal	462	2.40	[1.25;4.62]	0.0087

Table 5 – Impact of the number of risk factors by study group.

Subgroups	Control		Epoetin beta		Hazard ratio (95% CI)	*p* Value
	Number of patients	Number of events	Number of patients	Number of events		
All	231	13	231	29	2.36 (1.2–4.55)	0.01
With 0–2 risk factors	102 (44%)	8	98 (42%)	15	2.07 (0.88–4.89)	0.10[a]
With >2 risk factors	129 (56%)	5	133 (58%)	14	2.89 (1.04–8.02)	0.04[a]

a Summary of interaction testing between treatment and number of risk factors (>2 versus ⩽2). *p* Value = 0.63.

Table 6 – Summary of Cox regression analysis of thrombovascular events in patients who received and who did not receive antithrombotic therapy.

Factor	For	Hazard ratio	*p* Value
		95% confidence interval	
Treatment effect in patients who did not receive antithrombotic therapy	Epoetin beta versus control	4.11 1.37–12.4	0.01
Treatment effect in patients who received antithrombotic therapy	Epoetin beta versus control	1.37 0.59–3.18	0.45

agulant activity of tumour cells and procoagulant activity of monocytes, thrombocytes and endothelial cells in response to tumours. Of many substances with procoagulant activity isolated from animal and human tumours, the best characterised are tissue factors (47-kilodalton (kDa) transmembrane glycoprotein) and cancer procoagulant (68-kDa cysteine proteinase).[9]

Tumour necrosis factor – alfa (TNF-α), interleukin-1 (IL-1) or IL-like substances secreted by tumour cells may activate endothelial cells, suppress endothelial fibrinolytic activity and down-regulate thrombomodulin expression, diminishing the activation of protein C.[26] Furthermore, the endothelium may be damaged by cytotoxic chemotherapeutic agents and be penetrated by metastatic tumour cells.[27]

Epoetin treatment additionally increases the risk of TVE by potentially promoting thrombosis through a number of mechanisms. In the study of Tang et al. the 400 U/kg dose of epoetin attenuated the effect of aspirin on bleeding time and increased the platelet count in 96 healthy subjects.[28] In another study conducted in 30 healthy subjects, thrombin receptor-activating peptide induced expression of P-selectin and CD63 increased 2- to 3-fold during epoetin treatment.[29] The enhanced platelet activity was also reflected by a 50% increase in soluble P-selectin in plasma. Plasma E-selectin lev-

els increased in a dose-dependent fashion by more than 100% during epoetin treatment, indicating substantial activation of endothelial cells. A 10–20% increase in platelet counts was also observed. Heightened platelet reactivity and endothelial activation may increase the risk of thromboembolism.

In our study no correlation between baseline haemoglobin levels and risk of a TVE was found (Fig. 2). No similar analyses have been reported in the literature. However, an association between the target haemoglobin and the risk of TVEs has been reported based on a meta-analysis approach.[21] In contrast to these findings, in a recently published retrospective case-control study, no statistical difference in peak haemoglobin and haematocrit levels in patients with thrombosis and those without thrombosis was reported.[30] The size of the current study and the limited number of TVE events do not allow to confirm these findings.

However, it has to be noted that our study was not designed to evaluate an association between TVEs and target Hb levels. No signal was observed for the increased risk of TVEs in patients who achieved very high Hb levels (data not shown).

In the overall study population, only three patients had no risk factor for TVEs present at baseline whilst more than half (57% = 262) had more than 2 risk factors. In the overall study population, in patients receiving epoetin beta, the HR for TVEs was significantly increased versus the control group (HR 2.36, CI 1.2–4.55, $p = 0.01$). In the subset of patients with two or less risk factors, however, no significant difference to the control group could be observed (HR 2.07, CI 0.88–4.89, $p = 0.10$). Our data suggest that the significantly increased risk for TVEs in patients receiving epoetin beta versus the control group is driven by the significantly increased risk in patients with more than two risk factors (HR 2.89, CI 1.04–8.02, $p = 0.04$ (Table 5). Caution should, however, be exercised in the interpretation of these data considering the small number of events and the fact that the study was not designed for such a risk factor analysis. Moreover, some of the negative prognostic factors identified in the multivariable analysis were unexpected (e.g. ductal histology) whereas other expected risk factors (e.g. diabetes) were not significant in the model.

In our analysis, we observed a lower risk for TVEs in patients on epoetin who received antithrombotic therapy compared to those who did not receive antithrombotic treatment. These results may be confounded by the principle bias that treating physicians had most likely a good reason for prescribing antithrombotic therapy but this does not detract from the hypothesis-generating observation that the TVE risk in these patients versus the TVE risk in patients in the control group was considerably lower (HR 1.37, CI 0.59–3.18, $p = 0.46$ and HR 4.11, CI 1.37–12.4, $p = 0.01$). The results of this analysis suggest in our opinion a potential role for the prophylactic use of antithrombotic therapy in preventing TVEs. Even if these results must be interpreted with great caution given the post-hoc nature and potential confounders of this analysis.

However, the results of our study have several important limitations. Firstly, our findings are based on a retrospective analysis of data from a study for which the primary objective was to investigate the influence of epoetin beta in patients with metastatic breast cancer on overall survival. A second limitation of our analyses is the small number of TVEs in the various subgroups. Hence, the number of events in some subgroups was too small to allow clinically meaningful conclusions to be drawn. The third limitation with respect to the potential impact of antithrombotic on TVE risk is the fact that these analyses are likely to be confounded by possible differences in baseline risk.

In conclusion, in this retrospective analysis on TVE risk in the BRAVE study we have identified several baseline risk factors which impact the risk of TVEs during epoetin treatment. Patients with those risk factors may be at a particularly increased risk for future TVEs when receiving epoetin for anaemia correction. Our data suggest that prophylactic antithrombotic treatment might be an option to reduce this increased risk. However, given the post-hoc nature of our analyses, our findings have to be viewed as hypothesis-generating and ideally should be confirmed in an adequately powered, controlled, prospective, randomised study.

Conflict of interest statement

1. Matti S. Aapro has received grants for studies and honoraria from F. Hoffmann-La Roche, Amgen, Vifor, Sandoz, J&J and Amgen.
2. Agustí Barnadas received honoraria from Roche, Pfizer and Novartis. Received research funding from Lilly. Consultant for Roche and Pfizer.
3. Robert C. Leonard occasionally consultant for F. Hoffmann-La Roche on advisory boards and as a speaker at F. Hoffmann-La Roche sponsored meetings.
4. Maurizio Marangolo received research grants from Lilly Italia and honoraria from F. Hoffmann-La Roche.
5. Michael Untch holds an advisory arrangement with F. Hoffmann-La Roche.
6. Lidia Ukarma is employed by F. Hoffmann-La Roche.
7. Hans-Ulrich Burger is employed by F. Hoffmann-La Roche.
8. Armin Scherhag is employed by F. Hoffmann-La Roche and holds external Professorship for Internal Medicine at the University of Heidelberg, Germany
9. Bruno Osterwalder was employed by F. Hoffmann-La Roche at the time of writing this manuscript, stock ownership.

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