



## BRIEF REPORT

# Apixaban in low-weight patients with cancer-associated thrombosis: A cross sectional study of drug levels

Verónica Bravo Villa MD<sup>1</sup>  | Job Romero MD<sup>1</sup> | Eunice Rojas-Zaldivar MD<sup>1</sup> |  
Martha Cervantes BS<sup>2</sup> | María del Rosario Villa-Márquez BS<sup>3</sup> | Patricia Baz MD<sup>1</sup> |  
Gabriela Cesarman-Maus MD, PhD<sup>1</sup> 

<sup>1</sup>Hematology Department, Instituto Nacional de Cancerología, México City, CDMX, México

<sup>2</sup>Clinical Laboratory, Instituto Nacional de Cancerología, México City, CDMX, México

<sup>3</sup>Laboratorio Privado de Genética, México City, México

**Correspondence**

Gabriela Cesarman-Maus, Av. San Fernando # 22, Colonia Sección XVI, Tlalpan, Ciudad de México, México.  
Email: gcesarman@gmail.com

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**Abstract**

**Introduction:** Apixaban, a direct factor Xa inhibitor, has been shown to be at least as safe and probably more effective than dalteparin for the treatment of cancer-associated thrombosis (CAT) as reported in the ADAM-VTE and Caravaggio studies, which included a low percentage of underweight patients. Lower-weight-based dosing is supported by cancer-specific studies such as half-dose edoxaban in the Hokusai-VTE cancer trial in individuals weighing <60 kg.

**Objective:** To examine apixaban plasma trough levels in low-weight individuals with CAT, stably anticoagulated with full or half-dose apixaban.

**Methods:** This was a cross-sectional study of 61 routinely treated patients with active cancer and venous thromboembolism comparing three groups: patients weighing >60 kg treated with apixaban 5 mg twice daily, patients weighing ≤60 kg also receiving apixaban 5 mg twice daily, and patients weighing ≤60 kg given half-dose apixaban (2.5 mg twice daily). Apixaban plasma steady-state trough levels were determined on a single occasion.

**Results:** Mean apixaban plasma trough levels were similar for patients weighing >60 kg on full-dose apixaban to those weighing ≤60 kg taking 2.5 mg twice daily (mean, 109 ng/dL; 95% confidence interval [CI], 74-145; standard deviation [SD]: 77.6; and mean, 101 ng/dL, 95% CI, 67-135; SD: 80, respectively). Mean values for low-weight patients (≤60 kg) on the full 5 mg twice-daily dosing tended to be higher (mean, 136 ng/dL; 95%CI, 70-201; SD:114), without statistical significance ( $P = .22$ ).

**Conclusions:** This study supports the rationale for studying weight-based adjustments in apixaban dosing in prospective studies evaluating safety and efficacy of dose reduction in low-weight patients with cancer.

**KEYWORDS**

anticoagulants, apixaban, body weight, cancer, plasma levels, venous thromboembolism

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## Essentials

- This was a cross-sectional study of apixaban plasma trough levels in patients with cancer.
- Patients under 60 kg on half-dose apixaban attained levels similar to those over 60 kg on full dose.
- Creatinine clearances were all above 30 mL/min and did not correlate with apixaban trough levels.
- Findings support a rationale for research into weight-adjusted dosing for patients with cancer.

## 1 | INTRODUCTION

Apixaban has been shown to be an effective and relatively safe treatment for patients with cancer-associated thrombosis (CAT),<sup>1,2</sup> yet low-weight patients are underrepresented in cancer-specific prospective studies. Only close to 1 in 10 patients included in apixaban CAT trials weigh <60 kg.<sup>1</sup> Large studies using apixaban for the treatment of venous thrombosis conclude that additional information is needed regarding the efficacy and safety of apixaban in patients with cancer and low body weight.<sup>3,4</sup> In the AMPLIFY-EXT trial, a non-cancer-specific study examining the use of apixaban for extended treatment venous thromboembolic events (VTEs), the mean weight was 80 kg, with only 7% of patients weighing <60 kg. Notably, in these latter patients, there was no increased risk of bleeding with the use of 5 mg twice-daily dosing, nor was there a decreased benefit with 2.5 mg twice daily.<sup>3</sup> A concern in people with cancer is the higher rate of bleeding when using anticoagulants, as compared to people without cancer<sup>5</sup>; therefore in an attempt to decrease bleeding risk, dose adjustments according to weight have been used in clinical studies such as half-dose edoxaban for patients weighing <60 kg in the Hokusai-VTE cancer trial.<sup>6</sup> Weight-adjusted rivaroxaban in children and adolescents has been shown to result in similar exposures to those of adults receiving full-dose anticoagulation, supporting the concept that research into weight adjustment of apixaban dosing is reasonable.<sup>7</sup>

### 1.1 | Objectives

We sought to determine whether low-weight individuals ( $\leq 60$  kg) receiving full- or half-dose apixaban have similar plasma trough levels to patients >60 kg treated with standard-dose apixaban.

### 1.2 | Methods

We performed a cross-sectional study of 61 stably anticoagulated patients with active cancer and confirmed venous thromboembolism. Per standard procedure at our institution, patients with CAT weighing between 61 and 120 kg initially receive 10 mg twice daily of apixaban for 7 days, or, alternatively, patients complete at least 5 days of therapeutic enoxaparin if they have already been started on low-molecular-weight heparin in the emergency room; subsequently, patients receive apixaban 5 mg twice daily. Individuals

weighing  $\leq 60$  kg also receive 7 days of apixaban 10 mg twice daily or full-dose enoxaparin followed by apixaban 5 mg twice daily for the first month. Thereafter, the dose is dropped to 2.5 mg twice daily. Creatinine clearance results (estimated by the Cockcroft-Gault equation) reported in the electronic patient chart within 1 month from the development of a VTE were documented. Patient consent was obtained for an additional blood sample for measurement of apixaban plasma trough levels after a minimum of 7 days on steady-dose anticoagulation. Apixaban plasma levels in patients on 2.5 mg twice daily were also taken after a minimum of 7 days of anticoagulation at this dose. The sample was drawn before the morning dose during routine laboratory workup. Blood was drawn 10 to 12 hours after the prior dose of apixaban into sodium citrate (3.2%) tubes, and plasma was stored frozen at  $-70^{\circ}\text{C}$ . A validated STA-Liquid Anti-Xa assay kit with a STA-apixaban calibrator (STA Compact Max; Diagnostica Stago, Parsippany, NJ, USA) was used. Approval by the Institute's Research Committee in accordance with the Declaration of Helsinki was obtained (No. 2020/0083).

### 1.3 | Statistical analysis

Categorical variables are presented as frequencies and percentages. Student's *t* test was used to test whether weight or apixaban dose impact apixaban levels. Analysis of variance was used to determine mean values and confidence intervals for each group of patients. Data were analyzed using SPSS software for Windows, version 23 (IBM Corp., Armonk, NY, USA). A *P* value < .05 was considered statistically significant.

## 2 | RESULTS

Of all patients treated in the Thrombosis Unit at the Instituto Nacional de Cancerología throughout 2018-2019, 40% weighed <60 kg, and 25.4% weighed <55 kg. We included 61 patients with active cancer, as defined by the ISTH,<sup>8</sup> who were undergoing routine anticoagulant treatment for venous thrombosis. Twenty-one patients weighed >60 kg and were receiving full-dose anticoagulation (5 mg twice daily), 15 patients weighed  $\leq 60$  kg and were receiving the same full-dose treatment as part of their first month of routine anticoagulation. A third group of 25 patients who weighed  $\leq 60$  kg were receiving half-dose apixaban (2.5 mg twice daily). Patients' characteristics and laboratory measurements are summarized in

**TABLE 1** Clinical and laboratory characteristics

Characteristic	All patients (n = 61)	Group A >60 kg + 5 mg BID (n = 21)	Group B ≤ 60kg + 5mg BID (n = 15)	Group C ≤ 60kg + 2.5mg BID (n = 25)
Age (min-max)	59 (17-82)	53 (21-76)	56 (31 - 82)	63 (17-82)
Women N (%)	38 (62.3)	10 (47.6)	9 (60)	19 (76)
Body mass index (kg/m <sup>2</sup> )	24.1 ± 4.2	27.6 ± 3.7	22.7 ± 2.9	22.0 ± 3.4
Weight (kg)	58 (33- 90)	71 (62-90)	56 (41.5 - 60.0)	51.3 (33-60)
Tumor type				
Breast	14 (23)	4 (19)	3 (20)	7 (28)
Ovarian	8 (13)	1 (5)	3 (20)	4 (16)
Lung	5 (8)	2 (10)	1 (7)	2 (8)
Testicular	5 (8)	2 (10)	1 (7)	2 (8)
Other	29 (48)	12 (56)	7 (46)	10 (40)
Clinical Stage III/IV	52 (87)	18 (86)	13 (93)	21 (84)
Thrombosis site				
Lower Limbs	36 (62)	11 (52)	6 (50)	19 (76)
PE	5 (9)	1 (5)	2 (17)	2 (8)
Upper Limbs	7 (12)	4 (19)	3 (25)	
Other	13 (17)	5 (24)	4 (8)	4 (16)
Treatment N (%) <sup>a</sup>				
Chemotherapy	44 (72)	15 (71)	8 (53)	21 (84)
Radiotherapy	14 (23)	7 (33)	1 (7)	6 (24)
Creatinine clearance 30–60 ml/min <sup>b</sup>	11 (18)	0 (0)	5 (33)	6 (24)
Leukocyte count 10 <sup>9</sup> /L	6.1 (4.9–8.3)	5.7 (4.3–8.4)	5.9 (5.1–7.5)	6.5 (5.2–8.5)
Hemoglobin (g/dl)	12.3 ± 2.2	12.6 ± 2.1	12.1 ± 1.9	12.1 ± 2.5
Platelet count 10 <sup>9</sup> /L	298 ± 112	268 ± 79	312 ± 138	314 ± 118
VTE Bleed score ≤2 N (%)	41 (67)	17 (81)	10 (67)	14 (56)

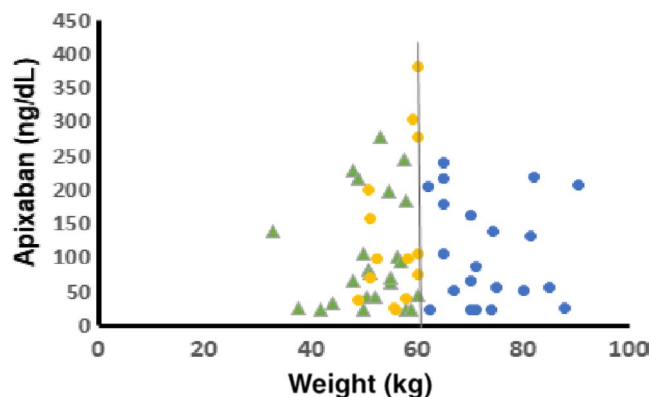
Note: Results are presented as median (minimum /max), and mean values +/- SD. Frequencies are presented as number of patients and percentages. Abbreviations: ECOG, Eastern Cooperative Oncology Group; PE: pulmonary embolism; SD, standard deviation; VTE, Venous thromboembolism.

<sup>a</sup>Treatment type at the time of plasma apixaban determination.

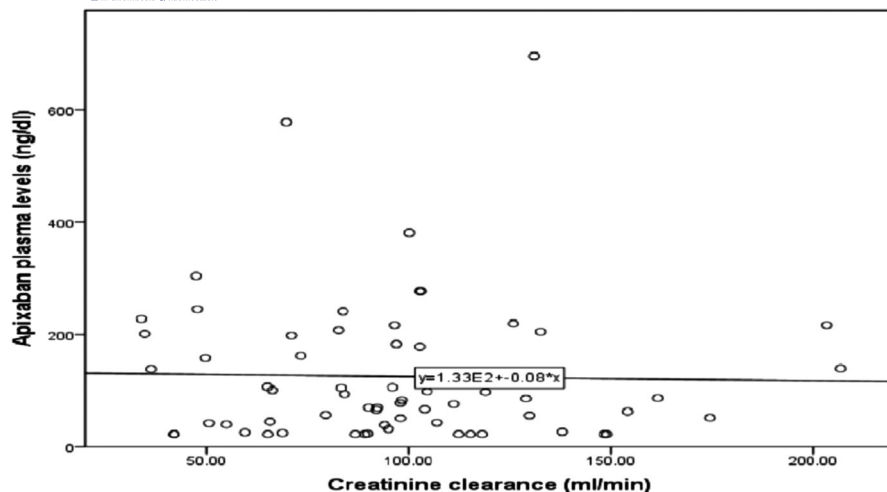
<sup>b</sup>All other patients had creatinine clearance above 60 ml/min.

Table 1. None of the baseline characteristics other than weight were significantly different between groups.

Apixaban plasma trough levels in patients weighing >60 kg on full 5 mg twice-daily dosing were used as reference (mean, 109 ng/dL; 95% confidence interval [CI], 74-145; standard deviation [SD], 77.6). These levels overlapped with those of patients weighing ≤60 kg and taking half-dose apixaban (mean, 101 ng/dL, 95% CI, 67-135; SD, 80), while patients weighing ≤60 kg taking 5 mg twice daily did show a tendency toward higher mean apixaban plasma levels (mean, 136 ng/dL; 95% CI, 70.-201; SD, 113.6), which was not statistically significant, as seen by cluster analysis (Figure 1). When we studied patients weighing <50 kg receiving half-dose apixaban, plasma trough levels were found to be similar to those of patients weighing >60 kg receiving full-dose apixaban ( $P = .32$ ) Creatinine clearance in all of our patients was >30 mL/min and did not correlate with apixaban plasma trough levels (linear  $R^2 = 5.332E-4$ ;  $P = .71$ ; Figure 2).



**FIGURE 1** Apixaban plasma trough levels. Cluster analysis of apixaban plasma trough levels in patients weighing ≤60 kg and taking twice-daily apixaban 2.5 mg (green triangles) or 5 mg (purple dots), and in those patients weighing >60 kg on twice-daily apixaban 5 mg (blue dots)



**FIGURE 2** Correlation between apixaban trough plasma levels and serum creatinine levels

**TABLE 2** Previously reported apixaban plasma levels under steady state exposure in patients without cancer

Patient characteristics and weight range	Trough levels 2.5 mg BID (ng/ml)	Trough levels 5 mg BID (ng/ml)	References
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE) >60 kg <sup>a</sup>	32 (11-90)	63 (22-77)	Package insert: Eliquis (apixaban): Bristol-Meyers Squibb Company, Princeton, NJ (11)
Atrial fibrillation Weight range 50-103 kg	48 (SD: 16-75) N = 10	77 (SD: 31-178) N = 60	Skepphoi M et al. (12)
Healthy volunteers Weight range 58.6-104.4 kg	21 (17% CV)	49.6 (20% CV)	Frost et al. (13)

Abbreviations: CV, coefficient of variation; DVT, Deep venous thrombosis; PE, Pulmonary embolism; SD, Standard deviation; VTE, venous thromboembolic event.

<sup>a</sup>No weight range is reported.

### 3 | DISCUSSION

We examined the association of lower weight with apixaban levels in cancer patients with venous thrombosis at our institution. Of all patients treated throughout 2018-2019, a high proportion weighed  $\leq 60$  kg (40%) and one-fourth weighed  $< 55$  kg. This represents a much higher proportion of patients with low weight when compared to published cancer-specific studies in which only close to 10% of patients weigh  $< 60$  kg.<sup>1-3,4</sup> When comparing apixaban plasma trough levels in individuals weighing  $> 60$  kg to those weighing  $\leq 60$  kg on full-dose anticoagulation, low-weight individuals had a tendency toward higher mean apixaban plasma levels, though this was not statistically significant. This could be due to the small number of patients. Individuals weighing  $\leq 60$  kg and receiving half-dose apixaban had similar apixaban plasma trough levels to patients weighing  $> 60$  kg on full anticoagulation. These findings suggest that underweight individuals may be adequately anticoagulated with lower-dose apixaban.

To our knowledge, studies of apixaban plasma levels in low-weight individuals with active cancer have not been published. Of note, mean apixaban trough levels in our study were higher than those previously reported by others for patients without cancer

(Table 2).<sup>9-11</sup> The underlying reason for this finding is probably multifactorial. Factors that may bear on apixaban levels include drug interactions, as well as poor oral intake or inadequate absorption.<sup>12</sup> Ethnic origin may also be relevant to apixaban plasma levels. Reports of Asian population pharmacokinetic analyses in individuals with nonvalvular atrial fibrillation or venous thromboembolism showed a 13.5% to 20.2% increase in apixaban area under the plasma concentration-time curve levels when compared to the White population.<sup>13-15</sup> There is little information on pharmacodynamics of apixaban in the Latin American population, which is known to have significant Asian ancestry.<sup>16</sup> In cancer-specific anticoagulation trials such as ADAM-VTE, only 0.4% were of Latin descent.<sup>1</sup> Renal function did not correlate with apixaban plasma trough levels (linear  $R^2 = 5.332E-4$ ;  $P = .71$ ), likely due to creatinine clearances above 30 mL/min in all of our patients (Figure 2).

The main limitations of our study are the small number of patients tested and the lack of information of confounding factors such as concomitant medication. In addition, patients who received apixaban 2.5 mg twice daily also survived their CAT, and lived long enough to receive this dose. This may have led to survival bias (ie, the best patients received 2.5 mg twice daily and may have different

apixaban levels than patients who were very ill and never received the 2.5-mg dosage), though not to a change in apixaban levels. Notably, the safety and efficacy of using half-dose apixaban requires prospective evaluation of these outcomes, which were not measured in this cross-sectional study.

## 4 | CONCLUSIONS

Weight-adjusted apixaban in patients weighing  $\leq 60$  kg results in drug concentrations similar to those attained with full-dose treatment in patients weighing  $>60$  kg. These findings support the rationale for studying weight-adjusted apixaban doses with prospective assessment of bleeding and rethrombosis.

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None.

### RELATIONSHIP DISCLOSURE


None.

### AUTHOR CONTRIBUTIONS

VB: data collection and article writing; JR: writing, laboratory work, and data collection; MC: laboratory work; ER: statistic work; MRVM: data collection and laboratory work; PB: data collection; and GC-M, research planning and article writing.

### ORCID

Verónica Bravo Villa  <https://orcid.org/0000-0002-7937-7403>

Gabriela Cesarman-Maus  <https://orcid.org/0000-0002-8397-0330>

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