



Anti-factor Xa Activity Is Not Associated With Venous Thromboembolism in Critically Ill Patients Receiving Enoxaparin for Thromboprophylaxis: A Retrospective Observational Study

Christoph Dibiasi^{1,2}, Johannes Gratz¹, Marion Wiegele¹, Andreas Baierl³ and Eva Schaden^{1,2*}

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*Correspondence:

Eva Schaden
eva.schaden@meduniwien.ac.at

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¹ Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, Vienna, Austria,

² Ludwig Boltzmann Institute for Digital Health and Patient Safety, Vienna, Austria, ³ Department of Statistic and Operations Research, University of Vienna, Vienna, Austria

Background: Anti-factor Xa activity has been suggested as a surrogate parameter for judging the effectiveness of pharmacological thromboprophylaxis with low molecular weight heparins in critically ill patients. However, this practice is not supported by evidence associating low anti-factor Xa activity with venous thromboembolism.

Methods: We performed a retrospective observational study including 1,352 critically ill patients admitted to 6 intensive care units of the Medical University of Vienna, Austria between 01/2015 and 12/2018. Included patients received prophylactically dosed enoxaparin (≤ 100 IU/kg body weight per day). We analyzed median peak, 12-h trough and 24-h trough anti-factor Xa activity per patient and compared anti-factor Xa activity between patients without vs. with venous thromboembolic events.

Results: 19 patients (1.4%) developed a total of 22 venous thromboembolic events. We did not observe a difference of median (IQR) anti-factor Xa activity between patients without venous thromboembolism [peak 0.22 IU/mL (0.14–0.32); 12-h trough 0.1 IU/mL (<0.1 –0.17), 24-h trough < 0.1 IU/mL (<0.1 – <0.1)] vs. patients with venous thromboembolism [peak 0.33 IU/mL (0.14–0.34); 12-h trough 0.12 IU/mL (<0.1 –0.26); 24-h trough < 0.1 IU/mL (<0.1 – <0.1)].

Conclusion: Patients who developed venous thromboembolism had anti-factor Xa activities comparable to those who did not suffer from venous thromboembolism.

Keywords: anti-factor Xa activity, low molecular weight heparin, thromboprophylaxis, venous thromboembolism, critical illness, anticoagulation

INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in hospitalized patients. Critically ill patients have a particularly high risk of VTE, and reported incidences vary between 1.4 and 15% (1–4). According to current European guidelines, pharmacological VTE prophylaxis in patients admitted to an intensive care unit (ICU) should preferentially be conducted using low molecular weight heparins (LMWH) at a fixed dose (2). LMWH can be monitored using the anti-factor Xa activity (antiXa) assay, but target ranges have thus far only been established for therapeutic anticoagulation (5). In patients receiving LMWH for thromboprophylaxis, antiXa should only be monitored to exclude LMWH accumulation when severe renal insufficiency is present (2). The utility of antiXa in judging the efficacy of LMWH thromboprophylaxis remains controversial, and it is uncertain whether (compared to patients on normal wards) decreased antiXa levels regularly encountered in critically ill patients are associated with an increased risk of VTE (6, 7). Nevertheless, recent studies have suggested lower VTE rates using dose-adjusted thromboprophylactic LMWH regimes targeting arbitrarily defined antiXa thresholds (8, 9). The results of these studies are limited by their small sample sizes, heterogeneous target antiXa thresholds and the uncertainty of whether peak or trough antiXa should be obtained. We thus performed a large retrospective observational study describing antiXa of critically ill patients who received prophylactically dosed enoxaparin. In addition, we assessed the relationship between antiXa and the development of VTE.

MATERIALS AND METHODS

Data Collection and Processing

This study was approved by the ethics committee of the Medical University of Vienna, Austria (reference number 1936/2019). The need to obtain informed consent was waived by the ethics committee due to the retrospective nature of this study. We screened the electronic health records of all patients admitted to six ICUs at the General Hospital of Vienna, a tertiary care center of the Medical University of Vienna, Austria, from 01/2015 to 12/2018 for eligibility. Patients were eligible if their age at the time of admission exceeded 18 years, the length of stay in the ICU exceeded 24 h and antiXa (calibrated for LMWH) was measured at least once during the ICU stay.

Data of eligible patients was exported from the IntelliSpace Critical Care and Anaesthesia patient data management system (Philips Austria GmbH, Vienna, Austria). Exported data included basic demographic data (age, weight, height, body mass index and primary diagnosis) at admission, all antiXa measured, and any antithrombotic medication administered during the ICU stay. In addition, we exported data on prothrombin time (Owren, reference range 24.6–32.7 s), activated partial thromboplastin time (reference range 27–41 s), fibrinogen concentration (Clauss, reference range 2–4 g L⁻¹) and antithrombin III activity (reference range 80–120%). We collected data from all eligible

patients with at least one valid antiXa. In the final analysis, we included patients who received prophylactic anticoagulation with enoxaparin either for the first 4 days after ICU admission or on 85% of overall ICU days. For this study, we defined prophylactic anticoagulation as a cumulative daily dose of ≤ 100 IU enoxaparin per kg actual body weight.

AntiXa was measured in the central clinical laboratory using the STA[®]-Liquid Anti-Xa assay (reference numbers 00311 and 00322, Diagnostica Stago, Asnières-sur-Seine, France) on a STA R Max 2 (Diagnostica Stago SAS, Asnières-sur-Seine, France). The detection range for this assay is 0.1–2.0 IU/mL. Measurement of antiXa was performed according to attending ICU clinicians. Clinical reasoning for obtaining antiXa was not documented. For each antiXa, we calculated the duration between the last documented enoxaparin administration and the time of measurement as documented by the lab report. Subsequently, we categorized each antiXa as either peak (interval 3–5 h), 12-h trough (interval 11–13 h) or 24-h trough (interval 23–25 h). We excluded all antiXa for which any of the following was true:

1. AntiXa was measured outside the ICU stay.
2. Oral or parenteral anticoagulants other than enoxaparin (rivaroxaban, dabigatran, apixaban, edoxaban, phenprocoumon, argatroban, and fondaparinux) were administered in the last 48 h before antiXa was determined.
3. Unfractionated heparin was administered on the same day as antiXa was measured.
4. Extracorporeal membrane oxygenation (ECMO) was instituted before the antiXa measurement.
5. AntiXa was measured after the patients had developed VTE.
6. No enoxaparin administration was documented before the antiXa measurement.
7. AntiXa could not be classified as peak, 12-h trough or 24-h trough, as described above.

Venous Thromboembolism

We defined VTE as either (a) lower or upper extremity DVT without intravenous catheters at the same anatomic site or (b) PE. DVT was diagnosed by duplex sonography and PE was diagnosed using computed tomography. As recommended by current guidelines, routine ultrasound screening for DVT is not conducted at our institution (2).

To assess the occurrence of VTE in our patient cohort, we screened admission and discharge documents alongside daily clinical progress notes and searched for keywords indicating the presence of lower or upper extremity DVT, respectively, PE. The list of keywords was compiled after manually reviewing the records of 198 eligible patients from 01/2018 to 05/2018. Search strategy, keywords and detailed results are provided as **Supplementary Material**. We regarded patients without any positive matches during the search as not having developed VTE during their ICU stays. Clinical notes identified by automated screening were subsequently assessed manually by one investigator (CD). If VTE was documented in the patient notes, its type (lower extremity DVT, upper extremity DVT, PE), anatomic location and date of diagnosis were recorded.

Patients with pre-existing VTE at ICU admission were excluded from the analysis.

Statistical Analysis

Categorical variables are given as absolute and relative frequencies. Continuous variables are given as medians with first and third quartiles. Wilcoxon rank sum tests were used for comparisons between two groups. Fisher's exact test and Pearson's Chi-squared test were used for comparison of categorical variables. To account for multiple antiXa measurements per patient, we summarized antiXa by calculating median, minimum and maximum antiXa per patient. All statistical tests were two-sided, and p -values < 0.05 were considered statistically significant.

Software

Available data was exported into comma-separated value files via the structured query language interface using Microsoft SQL Server Management Studio 17.9.1 (Microsoft, Redmond, Washington, United States of America). Data processing was conducted using R version 4.04 (R Foundation for Statistical Computing, Vienna, Austria).¹ Clinical notes were searched using Python version 3.7.7 (Python Software Foundation, Beaverton, Oregon, United States) using the *re* regular expression library.

RESULTS

We assessed electronic health records of 2,510 eligible patients and included 1,352 patients with a total of 8,231 antiXa in the final analysis (**Figure 1**). **Table 1** presents the baseline patient data.

Nineteen patients (1.4%) developed a total of 22 VTE (seven lower extremity DVT, five upper extremity DVT and ten PE). A detailed description of patients developing VTE is given as **Supplementary Material**. The median time to diagnosis of VTE after ICU admission was 36 days (4–48). All patients received pharmacological thromboprophylaxis with subcutaneous enoxaparin, which was started at a median of 8 h (6–16) after ICU admission, with a median daily cumulative dose of 4000 IU (4000–4900) on a median of 100% (94–100) of ICU days. We found no differences between patients without thrombosis and patients who developed VTE regarding the duration until the start of pharmacological thromboprophylaxis [8 (6–16) vs. 8 h (6–24), $p = 0.61$], cumulative daily enoxaparin dose [4000 IU (4000–4400) vs. 4200 IU (4000–5600), $p = 0.23$] and the proportion of days with pharmacological thromboprophylaxis [100 (94–100) vs. 96% (90–100), $p = 0.06$].

Overall, the included patients had a median of 2 (1–5) peak, 2 (1–6) 12-h trough and 2 (1–5) 24-h trough antiXa values. The median number of peak antiXa measurements in the respective subgroups (patients without thrombosis and patients with VTE) were 2 (1–5) vs. 1 (1–2; $p = 0.31$). The median number of 12-h trough values was 2 (1–6) vs. 5 (3–10; $p = 0.07$) and the median number of 24-h trough values was 2 (1–5) vs. 1 (1–4; $p = 0.31$). **Table 2** shows median, minimum and maximum antiXa at the

patient level in comparison between patients without thrombosis and patients with VTE.

In patients developing VTE, the most recent antiXa was obtained at a median of 2.5 days (1–25) prior to diagnosis of VTE. Median peak, 12 h and 24 trough antiXa prior to diagnosis of VTE were 0.27 IU/mL (0.1–0.3), 0.14 IU/mL (0–0.21) and 0 IU/mL (0–0).

Given that patients with VTE had a significantly higher severe acute physiology III (SAPS) score at admission, we performed a subgroup analysis and analyzed the relationship of antiXa with VTE in each of the four SAPS quarters. Median SAPS at admission in the first, second, third and fourth quarters was 35 (29–38), 46 (43–49), 58 (56–62), and 74 (69–81). The number of patients developing VTE in the respective groups was 3 of 317 (0.95%), 2 of 317 (0.63%), 6 of 317 (1.89%), and 8 of 316 (2.53%). For 85 patients, SAPS III at admission was missing and no patients developed VTE in this group. Median antiXa was not different between patients without VTE vs. patients who developed VTE in each of the four SAPS quarters. A detailed table is provided as **Supplementary Material**.

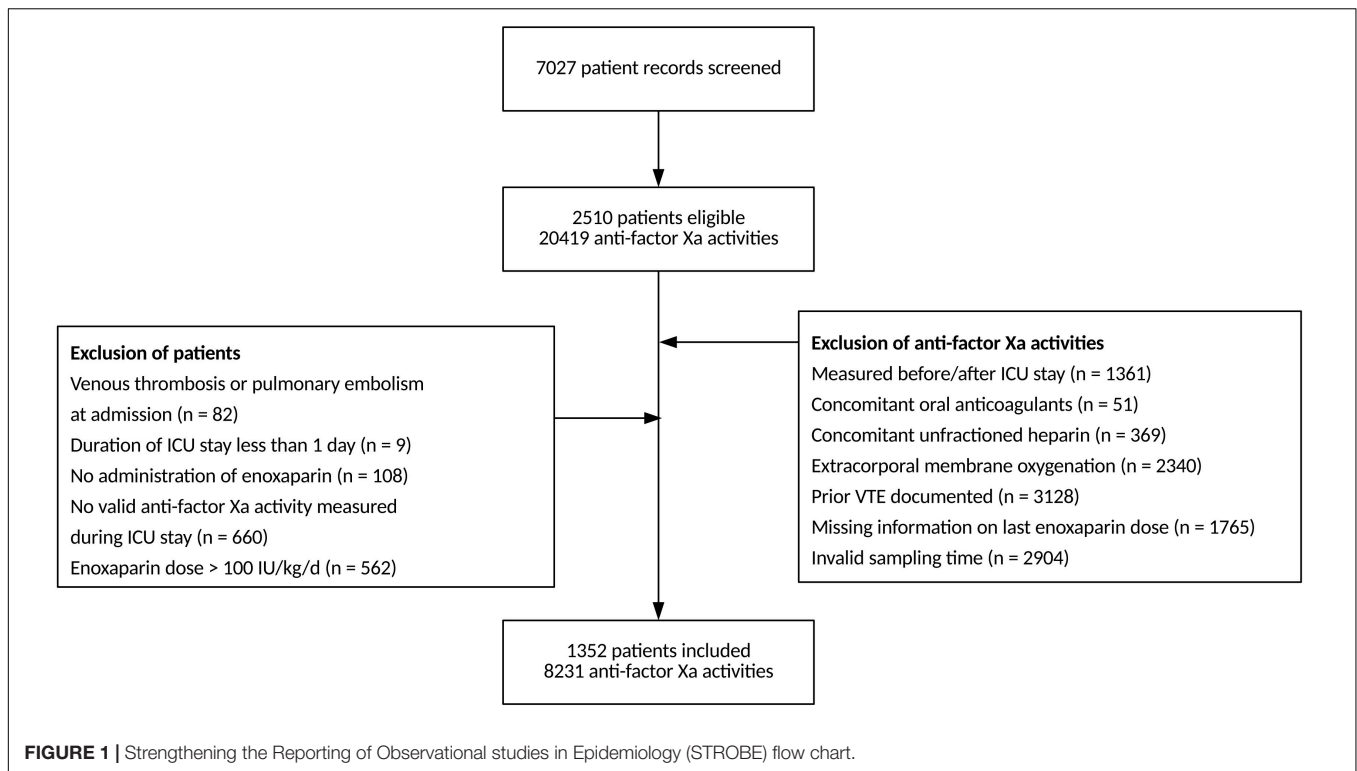
DISCUSSION

For this study, we analyzed a large cohort of critically ill patients and described antiXa obtained after prophylactic administration of enoxaparin. We also investigated the possible association between antiXa and the occurrence of VTE. Although 12 and 24-h trough antiXa were below thresholds that have been suggested to indicate effective thromboprophylaxis in previous studies, the incidence of VTE in our patient cohort was remarkably low. We did not identify a difference in peak, 12-h trough or 24-h trough antiXa between patients who did not develop venous thromboembolism and patients with VTE.

Throughout previous studies investigating weight-based or antiXa-guided LMWH dosing, considerable incongruity exists in which antiXa thresholds are regarded as indicating effective thromboprophylaxis. For instance, the combination of peak antiXa > 0.2 IU/mL and trough > 0.1 IU/mL was used in one study (10), whereas only trough levels between 0.1–0.2 IU/mL (9), peak levels > 0.2 IU/mL (8) or peak levels between 0.1–0.3 IU/mL (11), 0.2–0.5 IU/mL (12) or 0.3–0.5 IU/mL (13) were considered as targets by others. According to these studies, the patients included in the present study would have largely been classified as receiving inadequate pharmacological thromboprophylaxis. However, we observed a low VTE rate of 1.4%.

Compared to patients without thromboembolic complications, we found no differences in median, minimum or maximum antiXa in patients who developed VTE. This contrasts recent studies suggesting the measurement of antiXa to guide LMWH dosing for pharmacological thromboprophylaxis (14). The origins of antiXa-guided thromboprophylaxis are largely rooted in a study that found 12-h trough antiXa of at least 0.1 IU/mL to be associated with a significantly reduced VTE rate in non-critically ill patients (15). However, those findings lacked reproducibility in a similar study conducted 10 years later (16). Regarding critically ill patients, a recent systematic

¹<https://www.r-project.org>



review found no association between antiXa and the occurrence of VTE (17). It reported high heterogeneity in-between studies, which may reflect poor study quality. Of the 18 included studies, only Malinoski et al. found an association between antiXa and the occurrence of VTE. The authors investigated 54 critically ill trauma patients and showed that 11 of 27 patients with a 12-h trough antiXa ≤ 0.1 IU/mL developed VTE compared to 3 of 27 patients with a trough antiXa > 0.1 IU/mL (7). The generalizability of these results may, however, be questionable because of the small sample size and routine screening for VTE, which may have inflated the reported VTE incidence. Similarly, Ko et al. who reported a lower VTE rate in critically ill injured patients receiving antiXa-guided thromboprophylaxis, employed routine ultrasound screening for the detection of VTE (9). In addition, the statistical significance of their findings was largely based on the differences in isolated distal DVT. However, our data support the results of various previous studies demonstrating that low antiXa is highly prevalent in critically ill patients but cannot be linked to VTE (18–21).

The low VTE rate of 1.4% found in this study supports recent studies reporting similar incidences (1, 22) but contradicts earlier studies that reported substantially higher rates of VTE in critically ill patients (4, 23). This can be explained by the early initiation of pharmacological thromboprophylaxis after a median duration of 8 h following ICU admission in our patient cohort, which has been shown to reduce VTE incidence (24–26). However, previous studies investigating antiXa-guided dosing of LMWH for thromboprophylaxis have reported delays of up to 7 days after ICU admission until thromboprophylaxis was started (3, 9, 11). In addition, enoxaparin was administered on nearly

all days that patients were admitted to an ICU. Avoidance of missing LMWH doses is also known to reduce VTE incidence in critically ill patients (25). Another possible explanation for low VTE rates is that duplex ultrasound screening for DVT is not routinely performed at our institution. This follows current guidelines (2), given that the clinical impact of asymptomatic DVT is unclear (27). We also found that patients who developed VTE were significantly sicker at the time of ICU admission, as reflected by higher severe acute physiology scores and had a longer ICU stay alongside increased mortality. Thus, VTE might not necessarily represent failure of thromboprophylaxis but could rather be a manifestation of prolonged critical illness, as recently suggested (28).

Several limitations hinder the generalizability of our results and highlight the need for well conducted prospective trials. Most importantly, the retrospective nature of our study introduces a relevant risk of bias. Our assessment of the presence or absence of VTE relied on correct documentation by ICU physicians. It is thus possible that documented VTE were not captured by our search strategy or that VTE were not sufficiently documented by healthcare providers, both of which might cause an underestimation of true VTE incidence. Also, we did not assess VTE diagnosed after ICU discharge, which could possibly be dependent on thromboprophylaxis implemented during the ICU stay. As a result, our study is possibly underpowered due to the low VTE rate despite including a large cohort. We also did not conduct a power analysis for this study, but rather included all available patients confirming to inclusion, respectively exclusion criteria. Furthermore, we could not assess potential confounders, such as prior thromboembolic events or malignant disease in the

TABLE 1 | Baseline patient data.

Measures	No thromboembolic complications <i>n</i> = 1333	Venous thromboembolism <i>n</i> = 19	<i>p</i> -value
Age (years)	64 (52–73)	61 (40–72)	0.30
Male gender (%)	828 (62)	10 (53)	0.40
Weight (kg)	78 (65–90)	76 (58–94)	0.99
Height (cm)	172 (165–179)	170 (165–178)	0.79
Body mass index (kg m ⁻²)	26 (22–30)	22 (21–27)	0.14
Severe acute physiology score at admission (-)	52 (40–65)	58 (52–82)	0.009
ICU length of stay (days)	6 (2–13)	48 (18–84)	<0.001
ICU mortality (%)	98 (7.4)	6 (32)	0.002
Patient groups			0.648
Elective surgery (%)	619 (51)	10 (53)	
Emergency surgery/Trauma (%)	361 (30)	7 (37)	
Medical (%)	228 (19)	2 (11)	
Comorbidities			
Arterial hypertension (%)	594 (48)	8 (42)	0.59
Heart failure (%)	219 (18)	4 (21)	0.76
Diabetes mellitus (%)	226 (18)	5 (26)	0.37
Chronic obstructive pulmonary disease (%)	232 (19)	0 (0)	0.03
Malignant disease (%)	144 (12)	4 (21)	0.27
Chronic renal failure (%)	204 (17)	8 (42)	0.01
Liver cirrhosis (%)	94 (7.7)	2 (11)	0.65
Laboratory coagulation parameters at admission			
Activated partial thromboplastin time (s)	38 (34–44)	38 (36–48)	0.46
Prothrombin time (s)	33 (29–38)	37 (31–46)	0.039
Fibrinogen concentration (g l ⁻¹)	3.86 (2.89–5.17)	4.89 (2.86–5.77)	0.46
Antithrombin III activity (%)	78 (62–93)	72 (48–89)	0.25

271 patients did not have height data available; 85 patients had no information on severe acute physiology score; 125 patients did not have information on surgical status and 105 patients had no information on comorbidities available. *p*-values were obtained using Pearson's Chi-squared test (gender, comorbidities), Fisher's exact test (for patient groups, ICU mortality) and Wilcoxon rank sum test (for all remaining variables).

TABLE 2 | Aggregated anti-factor Xa activity stratified by development of VTE.

Anti-factor Xa Level	No thromboembolic complications <i>n</i> = 1,333	Venous thromboembolism <i>n</i> = 19	<i>p</i> -value
<i>Median anti-factor Xa values (IU/mL)</i>			
Peak	0.22 (0.14–0.32)	0.33 (0.14–0.34)	0.29
12-h trough	0.1 (<0.1–0.17)	0.12 (<0.1–0.26)	0.37
24-h trough	<0.1 (<0.1–<0.1)	<0.1 (<0.1–<0.1)	0.32
<i>Minimum anti-factor Xa values (IU/mL)</i>			
Peak	0.16 (<0.1–0.24)	0.30 (0.09–0.33)	0.13
12-h trough	<0.1 (<0.1–0.14)	<0.1 (<0.1–0.2)	0.26
24-h trough	<0.1 (<0.1–<0.1)	<0.1 (<0.1–<0.1)	0.45
<i>Maximum anti-factor Xa values (IU/mL)</i>			
Peak	0.29 (0.16–0.41)	0.33 (0.25–0.37)	0.67
12-h trough	0.14 (<0.1–0.21)	0.16 (<0.1–0.4)	0.32
24-h trough	<0.1 (<0.1–0.12)	<0.1 (<0.1–<0.1)	0.19

Median, minimum and maximum anti-factor Xa activities were calculated for each patient and summarized using median (interquartile range). *p*-values were obtained using Wilcoxon rank sum tests.

patients' past medical histories. However, we demonstrated that a low rate of clinical significant VTE can be achieved in the setting of highly effective prophylactic anticoagulation despite antiXa, that was lower than previously suggested "protective" levels.

In summary, we analyzed a cohort of 1,352 critically ill patients who received enoxaparin for pharmacological

thromboprophylaxis according to current guidelines and found antiXa trough levels below thresholds often cited as being protective of VTE. Yet, we found a low VTE incidence of 1.4%. Patients who acquired VTE had similar peak and trough antiXa levels compared to those who did not suffer from thromboembolic complications. AntiXa thresholds protective of

VTE still need to be determined for critically ill patients receiving prophylactically dosed LMWH.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Vienna. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CD and ES conceived and planned the study. CD collected the data, performed the initial data analysis, and drafted the first

version of the article. CD and AB performed the final statistical analysis. CD, JG, MW, ES, and AB critically discussed and interpreted the data. JG, MW, AB, and ES critically revised the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2022.888451/full#supplementary-material>

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