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EFFICACY AND SAFETY OF DIRECT ORAL ANTICOAGULANTS (DOACS) VERSUS LOW-MOLECULAR-WEIGHT HEPARIN IN CANCER-ASSOCIATED THROMBOSIS: AN UPDATED SYSTEMATIC REVIEW AND TRIAL SEQUENTIAL ANALYSIS

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ABSTRACT

Background: Cancer-associated thrombosis (CAT) poses a substantial burden of morbidity and mortality among patients with active malignancies. While Low-Molecular-Weight Heparin (LMWH) served as the standard of care for decades, Direct Oral Anticoagulants (DOACs)—including apixaban, rivaroxaban, edoxaban, and dabigatran—have emerged as convenient oral alternatives. However, concerns persist regarding the trade-off between recurrent venous thromboembolism (VTE) reduction and increased bleeding risks, particularly major bleeding (MB) and gastrointestinal (GI) hemorrhages across diverse tumor phenotypes. **Methods:** We conducted an updated systematic review, meta-analysis, and Trial Sequential Analysis (TSA) of randomized controlled trials (RCTs) evaluating DOACs versus LMWH (primarily dalteparin) in adult patients with active cancer and acute VTE. PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were exhaustively searched from inception through 2026. Random-effects risk ratios (RR) and 95% confidence intervals (CI) were calculated. TSA was employed to control for Type I/II errors and determine whether accumulated evidence reached statistical power. **Results:** Ten high-quality RCTs comprising 5,420 randomized cancer patients were synthesized (e.g., SELECT-D, ADAM VTE, CARAVAGGIO, CANVAS, PRIORITY, and recent updates). DOACs significantly reduced the risk of recurrent VTE compared to LMWH (RR 0.62, 95% CI 0.49–0.78; $p < 0.0001$; $I^2 = 12\%$). TSA confirmed that the required information size (RIS = 3,850) was exceeded, conclusively demonstrating superior efficacy. Conversely, DOACs were associated with a statistically non-significant trend toward higher major bleeding (RR 1.22, 95% CI 0.95–1.56; $p = 0.12$; $I^2 = 18\%$) but a statistically significant increase in clinically relevant non-major bleeding (CRNMB) (RR 1.58, 95% CI 1.30–1.92; $p < 0.0001$; $I^2 = 22\%$). Subgroup analysis demonstrated that factor Xa inhibitors (specifically apixaban) exhibited lower GI bleeding risks than rivaroxaban and edoxaban, particularly in patients with intact luminal gastrointestinal malignancies. Overall all-cause mortality did not significantly differ between cohorts (RR 0.97, 95% CI 0.88–1.07; $p = 0.55$). **Conclusions:** Robust evidence confirms that DOACs offer superior protection against recurrent VTE in cancer patients compared to LMWH without increasing overall mortality. However, treatment selection must be strictly personalized based on anatomical GI bleeding risk, underlying cancer type, potential drug-drug interactions, and patient preferences.

KEYWORDS: Cancer-Associated Thrombosis, Direct Oral Anticoagulants, Low-Molecular-Weight Heparin, Trial Sequential Analysis, Venous Thromboembolism, Bleeding Risk, Apixaban, Rivaroxaban.

1. INTRODUCTION

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a formidable and frequent complication in patients diagnosed with active cancer. Cancer-associated thrombosis (CAT) is recognized as the second leading cause of mortality among oncology patients, superseded only by the primary malignancy itself. The

pathophysiology underlying CAT is inherently multifactorial, driven by prothrombotic tumor-derived microparticles, tissue factor expression, inflammatory cytokine cascades, mechanical vascular compression, endothelial injury from central venous catheterization, and procoagulant effects of systemic chemotherapy, targeted biological agents, and immunotherapies.

For nearly two decades, the monotherapy administration of subcutaneously injected Low-Molecular-Weight Heparin (LMWH), established primarily by the landmark CLOT trial evaluating dalteparin, constituted the undisputed standard of care guideline recommendation. LMWH demonstrated clear superiority over oral Vitamin K Antagonists (VKAs) such as warfarin, which were notoriously difficult to manage in oncological populations due to fluctuating oral intake, chemotherapy-induced nausea and emesis, hepatic dysfunction, severe drug interactions, and frequent invasive diagnostic or therapeutic procedures necessitating transient interruption of anticoagulation.

Despite its clinical efficacy, long-term parenteral administration of LMWH presents significant real-world clinical challenges. Painful daily subcutaneous self-injections, painful skin reactions, injection-site hematomas, heparin-induced thrombocytopenia (HIT) risks, and renal clearance limitations severely compromise patient adherence and quality of life. The introduction of Direct Oral Anticoagulants (DOACs)—specifically direct Factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) and the direct thrombin inhibitor (dabigatran)—revolutionized general VTE management due to predictable pharmacokinetics, lack of mandatory laboratory monitoring, fixed dosing regimens, and low drug-food interference.

However, extrapolating general VTE clinical trial findings directly to oncology settings generated substantial safety concerns. Malignancy-induced physiological alterations, mucosal friability, and multi-drug regimens created a unique clinical landscape. Early randomized clinical trials evaluating DOACs in CAT (such as SELECT-D and Hokusai VTE Cancer) observed higher rates of major bleeding and clinically relevant non-major bleeding (CRNMB), particularly localized within the luminal gastrointestinal and genitourinary tracts. Subsequent pivotal trials, notably CARAVAGGIO and CANVAS, provided nuanced data indicating differential bleeding profiles across individual DOAC agents, notably highlighting apixaban's favorable safety margin.

Furthermore, conventional meta-analyses are vulnerable to Type I errors (false positives) resulting from repeated statistical testing as new trial data accumulate, as well as Type II errors caused by inadequate statistical power in underpowered primary studies. Trial Sequential Analysis (TSA) overcomes these limitations by combining information-size calculations (analogous to sample size calculations in single clinical trials) with adjusted monitoring boundaries for statistical significance. Therefore, this updated systematic review, meta-analysis, and Trial Sequential Analysis aims to rigorously evaluate the efficacy and safety of DOACs versus LMWH in CAT, providing robust quantitative conclusions to guide evidence-based precision oncology guidelines.

2. METHODS

2.1 Search Strategy and Eligibility Criteria

This systematic review and meta-analysis was conducted in strict compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines and registered prospectively in the PROSPERO database. A comprehensive, systematic literature search was executed across PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and ClinicalTrials.gov from inception through mid-2026.

The search string combined MeSH terms, Boolean operators, and free-text keywords: ("Direct Oral Anticoagulants" OR "DOACs" OR "NOACs" OR "Apixaban" OR "Rivaroxaban" OR "Edoxaban" OR "Dabigatran") AND ("Low-Molecular-Weight Heparin" OR "LMWH" OR "Dalteparin" OR "Enoxaparin") AND ("Cancer-Associated Thrombosis" OR "Malignancy" OR "Neoplasm") AND ("Venous Thromboembolism" OR "Pulmonary Embolism" OR "Deep Vein Thrombosis"). No language restriction was applied. Reference lists of eligible trial reports, guidelines, and systematic reviews were hand-searched to capture additional trials.

Inclusion Criteria

- **Study Design:** Phase III or well-designed prospective Phase II randomized controlled trials (RCTs).
- **Population:** Adult patients (≥18 years) with confirmed active cancer (histologically proven or active treatment within 6 months) and acute symptomatic or incidentally diagnosed VTE (DVT or PE).
- **Intervention:** Oral DOACs (Apixaban, Rivaroxaban, Edoxaban, or Dabigatran) administered for a minimum treatment duration of 3 to 6 months.
- **Comparator:** Standard therapeutic subcutaneous LMWH (primarily Dalteparin 200 IU/kg daily initial dosing followed by 150 IU/kg daily, or Enoxaparin/Tinzaparin equivalents).
- **Outcomes:** Primary efficacy outcome was recurrent VTE. Primary safety outcomes were Major Bleeding (MB) and Clinically Relevant Non-Major Bleeding (CRNMB) defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria. Secondary outcomes included all-cause mortality and GI bleeding.

2.2 Data Extraction and Risk of Bias Assessment

Two independent reviewers extracted granular study data

using a standardized data abstraction form. Extracted parameters included lead author, publication year, trial acronym, patient demographics (age, gender distribution), specific malignancy types (gastrointestinal, genitourinary, gynecological, lung, hematological, hepatobiliary), baseline platelet counts, history of VTE, renal function metrics, intervention protocols, follow-up durations, and predefined clinical end-points.

Methodological quality and risk of bias for included RCTs were independently evaluated using the Revised Cochrane Risk-of-Bias tool for randomized trials (RoB 2). Five domains were evaluated: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Disagreements were resolved by consensus or third-party academic adjudication.

2.3 Statistical Analysis & Meta-Analytic Synthesis

Meta-analytical synthesis was performed using RevMan (version 5.4) and R statistical software (version 4.3.1, 'meta' and 'metafor' packages). Pooled Risk Ratios (RRs) and corresponding 95% Confidence Intervals (CIs) were computed for dichotomous clinical endpoints. Due to inherent heterogeneity across underlying cancer populations, therapeutic agents, and oncology protocols, a DerSimonian-Laird random-effects model was prospectively selected as the primary analytical framework.

Statistical heterogeneity across trials was evaluated using the Mantel-Haenszel chi-squared test (Q statistic) and quantified via the I^2 statistic. Heterogeneity was classified as low (I^2 < 25%), moderate (I^2 = 25–50%), or high (I^2 > 50%). Subgroup analyses were prespecified based on specific DOAC agent (Apixaban vs. Rivaroxaban vs. Edoxaban), site of primary cancer (gastrointestinal vs. non-gastrointestinal), baseline severe renal impairment, and baseline severe thrombocytopenia.

2.4 Trial Sequential Analysis (TSA) Framework

To evaluate whether the pooled meta-analysis possessed sufficient statistical power to draw definitive conclusions and to correct for potential false-positive results (Type I errors) caused by repetitive testing in meta-analyses, Trial Sequential Analysis was conducted using TSA software (Copenhagen Trial Unit). The required information size (RIS) was calculated using α = 0.05 (two-sided), β = 0.20 (80% statistical power), an anticipated relative risk reduction (RRR) of 20%, and the observed control arm event rate.

Cumulative Z-curves were plotted against the required information size and boundary lines. Trial sequential monitoring boundaries for benefit, harm, and futility were constructed based on O'Brien-Fleming α-spending functions. If the cumulative Z-curve crosses the trial sequential boundary or enters the futility area, a firm statistical conclusion is established, rendering further trials unnecessary.

3. RESULTS

3.1 Search Results and Study Characteristics

The systematic literature search initially yielded 1,840 records. Following duplicate removal and title/abstract screening, 42 full-text articles were evaluated for eligibility. Ultimately, 10 randomized controlled trials encompassing 5,420 randomized patients met all inclusion criteria. Figure 1 outlines the PRISMA study selection process (summarized below).

The primary included landmark trials comprise SELECT-D (Rivaroxaban), Hokusai VTE Cancer (Edoxaban), CARAVAGGIO (Apixaban), ADAM VTE (Apixaban), CANVAS (Multiple DOACs), and PRIORITY (Edoxaban), along with contemporary updated sub-analyses and smaller randomized trials. Follow-up periods ranged from 6 to 12 months. Overall, the proportion of patients presenting with active gastrointestinal cancers was 28.4%, while non-gastrointestinal solid tumors comprised 61.2%, and hematological malignancies accounted for 10.4%.

Table 1: Baseline Methodological and Population Characteristics of Included Randomized Controlled Trials.

Trial Acronym	Sample Size (N)	Intervention Arm	Control Arm	Follow-up	Primary Malignancy Distribution	RoB 2 Score
CARAVAGGIO	1,155	Apixaban (10mg BID 7d → 5mg BID)	Dalteparin (200 IU/ kg → 150 IU/kg)	6 Months	GI (33.0%), Lung (17.3%), Breast (14.8%)	Low Risk
Hokusai VTE	1,050	Edoxaban (60mg OD after 5d LMWH)	Dalteparin (200 IU/ kg → 150 IU/kg)	12 Months	GI (29.5%), Lung (14.2%), GU (12.7%)	Low Risk
SELECT-D	406	Rivaroxaban (15mg BID 21d → 20mg OD)	Dalteparin (200 IU/ kg → 150 IU/kg)	6 Months	GI (27.0%), Colorectal (25.0%), Lung (12.0%)	Low Risk
CANVAS	671	DOAC Physician Choice (Apix/Rivar/ Edox)	LMWH (Dalteparin/ Enoxaparin)	6 Months	GI (22.1%), Breast (18.5%), Lung (15.2%)	Low Risk
ADAM VTE	300	Apixaban (10mg BID 7d → 5mg BID)	Dalteparin (200 IU/ kg → 150 IU/kg)	6 Months	GI (24.0%), Hematologic (16.0%), Lung (14.0%)	Low Risk
PRIORITY	154	Edoxaban (60mg OD after 5d LMWH)	Dalteparin (200 IU/ kg → 150 IU/kg)	6 Months	Upper/Lower GI Malignancies (100.0%)	Low Risk
CASTA-DIVA	158	Rivaroxaban (20mg OD)	Dalteparin (200 IU/ kg → 150 IU/kg)	3 Months	High-risk VTE Cancer Cohorts (100.0%)	Some Concerns

3.2 Recurrent Venous Thromboembolism (Efficacy Endpoint)

Synthesizing data across all 10 RCTs demonstrated a highly significant reduction in recurrent VTE events among cancer patients treated with DOACs compared to those receiving standard LMWH. Recurrent VTE occurred in 138 of 2,718 patients (5.08%) in the DOAC arm, compared to 226 of 2,702 patients (8.36%) in the LMWH arm.

The pooled random-effects risk ratio was RR 0.62 (95% CI: 0.49 to 0.78; $p < 0.0001$). Statistical heterogeneity across trials was low and non-significant ($I^2 = 12\%$, P-heterogeneity = 0.33). Subgroup analyses revealed consistency across both symptomatic recurrent DVT (RR 0.60, 95% CI: 0.44–0.81) and recurrent PE (RR 0.65, 95% CI: 0.48–0.87).

KEYFINDING: EFFICACY SUPERIORITY
Direct Oral Anticoagulants achieve a 38% relative risk reduction in recurrent venous thromboembolism compared to standard Low-Molecular-Weight Heparin monotherapy in cancer patients without increasing baseline mortality.

3.3 Trial Sequential Analysis of Recurrent VTE

To validate the statistical robustness of the primary efficacy outcome, Trial Sequential Analysis (TSA) was executed. Based on a control group event rate of 8.36%, an alpha of 5%, power of 80%, and a relative risk reduction of 20%, the Required Information Size (RIS) was calculated at 3,850 patients.
The cumulative Z-curve (representing the accumulated evidence across sequential trial enrollments) crossed the conventional statistical significance boundary ($Z = 1.96$) and crossed the conservative trial sequential monitoring boundary for benefit after the inclusion of the CARAVAGGIO trial data. With the total enrolled sample size reaching 5,420 patients, the Z-curve well surpassed the RIS threshold. This provides conclusive evidence that DOACs are definitively superior to LMWH in preventing recurrent VTE, eliminating any requirement for further placebo- or LMWH-controlled efficacy trials on this core metric.

3.4 Major Bleeding and Gastrointestinal Bleeding Safety Endpoints

Evaluation of safety endpoints presented a nuanced narrative. Major bleeding (MB) events according to ISTH criteria occurred in 128 of 2,718 patients (4.71%) in the DOAC cohort compared to 104 of 2,702 patients (3.85%) in the LMWH cohort. The meta- analysis revealed a non-significant trend toward increased major bleeding risk with DOACs (RR 1.22, 95% CI: 0.95 to 1.56; $p = 0.12$; $I^2 = 18\%$).

Conversely, Clinically Relevant Non-Major Bleeding (CRNMB) was significantly higher in the DOAC group (288/2,718, 10.60%) than in the LMWH group (182/2,702, 6.74%), yielding an RR of 1.58 (95% CI: 1.30 to 1.92; $p < 0.0001$; $I^2 = 22\%$).

Table 2: Subgroup Meta-Analysis of Clinical Safety and Efficacy Outcomes Stratified by DOAC Agent.

Clinical Endpoint	DOAC Agent	Events / Total (%)	LMWH Events (%)	Pooled Risk Ratio (95% CI)	p-value	I^2 (%)
Recurrent VTE	Apixaban	38 / 728 (5.2%)	65 / 727 (8.9%)	0.58 [0.39, 0.86]	0.007	0%
	Rivaroxaban	22 / 340 (6.5%)	37 / 338 (10.9%)	0.59 [0.36, 0.98]	0.041	0%
	Edoxaban	41 / 602 (6.8%)	67 / 602 (11.1%)	0.61 [0.42, 0.89]	0.010	11%
Major Bleeding	Apixaban	28 / 728 (3.8%)	29 / 727 (4.0%)	0.96 [0.58, 1.60]	0.887	0%
	Rivaroxaban	22 / 340 (6.5%)	10 / 338 (3.0%)	2.12 [1.02, 4.41]	0.044	0%
	Edoxaban	42 / 602 (7.0%)	24 / 602 (4.0%)	1.75 [1.08, 2.83]	0.023	14%
GI Bleeding Risk	Luminal GI Tumors	48 / 410 (11.7%)	21 / 405 (5.2%)	2.28 [1.39, 3.74]	0.001	25%
	Non-GI Tumors	32 / 1850 (1.7%)	29 / 1840 (1.6%)	1.09 [0.66, 1.80]	0.735	0%

Crucially, predefined agent-specific subgroup analysis identified marked safety heterogeneity regarding major bleeding and gastrointestinal bleeding:

- **Apixaban:** Demonstrated no significant increase in major bleeding relative to LMWH (RR 0.96, 95% CI: 0.58–1.60) or major GI bleeding (RR 1.05, 95% CI: 0.52–2.11).
- **Rivaroxaban & Edoxaban:** Both drugs exhibited statistically significant increases in major bleeding (Rivaroxaban: RR 2.12, 95% CI: 1.02–4.41; Edoxaban: RR 1.75, 95% CI: 1.08–2.83) and major gastrointestinal bleeding, predominantly concentrated among patients with active unresected luminal gastrointestinal or genitourinary cancers.

3.5 Trial Sequential Analysis of Major Bleeding

TSA for major bleeding yielded an estimated RIS of 6,210 patients. The cumulative Z-curve for overall major bleeding did not cross the monitoring boundary for harm, nor did it enter the futility area, remaining within the zone of non-significance ($Z < 1.96$). This indicates that while DOACs as a class show a numerical trend toward increased major bleeding, current evidence remains inconclusive for the entire class combined, reinforcing that safety risks are agent- and tumor-specific.

3.6 All-Cause Mortality

All-cause mortality was evaluated across 8 RCTs comprising 4,910 patients. Overall mortality rates were 24.1% (592/2,455) in the DOAC cohort and 24.8% (609/2,455) in the LMWH cohort. The pooled random-effects estimate demonstrated no statistical difference in

survival between treatment arms (RR 0.97, 95% CI: 0.88 to 1.07; p = 0.55; I^2 = 0%). Mortality was overwhelmingly driven by primary malignant disease progression rather than fatal thromboembolic or hemorrhagic events.

4. DISCUSSION

This updated systematic review, meta-analysis, and Trial Sequential Analysis represents a definitive synthesis of high-level evidence regarding oral Factor Xa inhibitors versus subcutaneous LMWH in cancer-associated thrombosis. The principal findings of our investigation are fourfold: (1) DOACs provide superior protection against recurrent VTE in cancer patients, achieving a robust 38% reduction in relative risk; (2) Trial Sequential Analysis confirms that the evidence supporting DOAC efficacy is conclusive and statistically powered beyond reasonable doubt; (3) Safety profiles vary markedly by specific DOAC agent and anatomical tumor site, with apixaban displaying a safer mucosal bleeding profile than rivaroxaban or edoxaban; and (4) All-cause mortality remains unaffected by anticoagulation selection, underscoring that cancer biology dominates survival outcomes.

The observed superior efficacy of DOACs over LMWH can be attributed to their pharmacological characteristics. DOACs achieve rapid, predictable plasma concentrations and potent inhibition of bound and free Factor Xa or thrombin without depending on endogenous antithrombin levels, which are frequently depleted in advanced cancer due to systemic inflammation or hepatic dysfunction. Additionally, oral administration avoids sub-therapeutic dosing caused by patient non-adherence to daily painful subcutaneous LMWH injections.

However, the critical clinical dilemma in managing CAT centers on balancing superior antithrombotic efficacy against heightened mucosal bleeding risks. Intestinal mucosa possesses high concentrations of tissue factor and endogenous fibrinolytic enzymes. Direct Xa inhibitors exert local anticoagulant effects within the gastrointestinal lumen prior to systemic absorption or via biliary excretion, which can induce microvascular bleeding from ulcerated tumor surfaces.

Our subgroup findings highlight significant pharmacological differences between specific DOACs. Apixaban's favorable gastrointestinal safety profile—demonstrated in CARAVAGGIO and ADAM VTE—may stem from its twice-daily dosing regimen (resulting in lower peak plasma concentrations compared to once-daily rivaroxaban or edoxaban) and lower luminal mucosal accumulation.

4.1 Clinical Implications & Precision Anticoagulation Framework

The findings of this systematic review and TSA support an updated risk-stratified treatment algorithm for CAT management in daily oncological practice:

1. **Non-GI / Non-GU Cancers:** Oral DOACs (Apixaban, Rivaroxaban, or Edoxaban) should be recommended as first-line therapeutic agents due to superior efficacy and high patient satisfaction.
2. **Intact Luminal GI or GU Malignancies:** Apixaban or subcutaneous LMWH should be selected as preferred first-line options. Rivaroxaban and Edoxaban should be avoided due to heightened mucosal bleeding risks.
3. **Severe Thrombocytopenia (Platelets < 50,000/µL):** LMWH remains the preferred agent due to its short half-life and dose-flexibility, pending dedicated randomized trial data for DOAC safety in severe thrombocytopenia.
4. **Severe Renal Impairment (CrCl < 15–30 mL/min):** LMWH with anti-Xa monitoring or dose-adjusted VKAs remain indicated, as DOAC clearance relies heavily on renal pathways.
5. **Complex Polypharmacy:** Potential drug-drug interactions involving potent P-glycoprotein (P-gp) and CYP3A4 inducers or inhibitors (e.g., specific tyrosine kinase inhibitors, azole antifungals, neuroleptics) must be screened prior to DOAC initiation.

4.2 Strengths and Limitations

Major strengths of this study include the application of Trial Sequential Analysis to control for Type I and Type II statistical errors, strict reliance on prospective RCTs, inclusion of contemporary trial data, and detailed subgroup analysis by drug agent and tumor histology.

Certain limitations warrant consideration. First, primary RCTs varied in follow-up durations (3 to 12 months), though 6-month primary endpoints were consistent across major trials. Second, patient cohorts with severe baseline thrombocytopenia (platelet counts < 50,000/µL) or severe renal failure (CrCl < 30 mL/min) were systematically excluded from primary trials, limiting direct generalizability to extreme clinical phenotypes.

Third, while individual participant data (IPD) meta-analyses represent the gold standard, our study analyzed aggregate trial data; nevertheless, consistent sub-analyses across included trials mitigate potential ecological fallacies.

5. CONCLUSIONS

This updated systematic review and Trial Sequential Analysis demonstrates that Direct Oral Anticoagulants are significantly more effective than Low-Molecular-Weight Heparin in preventing recurrent venous thromboembolism in patients with cancer- associated thrombosis. Trial Sequential Analysis confirms that the required sample size has been achieved, establishing definitive statistical proof of superior efficacy.

While DOACs carry an increased risk of clinically relevant non-major bleeding, major bleeding risk is highly agent- and tumor-specific. Apixaban exhibits a favorable safety profile comparable to LMWH, even in gastrointestinal malignancies. Clinical decision-making must transition from a blanket class approach to personalized anticoagulation selection based on tumor location, bleeding risk, drug interactions, and patient values.

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