

Thrombosis

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Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major global public health issue that contributes significantly to preventable morbidity and mortality, accounting for one in four deaths globally [1]. Although most commonly associated with older populations, VTE also affects younger women, particularly due to iatrogenic factors such as the use of combined hormonal contraceptives (CHCs) [2]. Large observational studies estimate the VTE risk with COC use at roughly 5–12 events per 10,000 woman-years [3]. This risk can be influenced by the estrogen dose and type [2]. Although the progestin component is commonly thought to impact risk as well [2], this effect is actually a modulation of the estrogen effect [4–6]. The individual absolute risk is modest; however, the vast global uptake of CHCs translates into a substantial population burden: worldwide, more than 100,000 women are thought to experience a CHC-related VTE each year [7].

Importantly, following an initial VTE, the risk of recurrence remains substantial. Reports showed that women who discontinue both anticoagulation and their combined oral contraceptive (COC) experience a recurrence rate of approximately 1.3 events per 100 woman-years compared to 4.8 events per 100 woman-years in those who resume COC use [8,9]. Patients are also at risk for long-term complications, most notably post-thrombotic syndrome (PTS), which affects 20–50% of DVT patients, leading to pain, swelling, and a reduced quality of life [10,11]. Even in the absence of traditional cardiovascular risk factors, young women may experience thrombotic events due to inherited thrombophilias, including factor V Leiden or prothrombin gene mutations, or due to particular metabolism of ethinylestradiol (EE), the most commonly used estrogenic component in CHC [7,12].

VTE risk with combined oral contraceptives

CHCs, including COCs, influence haemostasis by shifting the coagulation balance toward a prothrombotic state [13]. These changes include increases in procoagulant factors (e.g., FII, FVII, FVIII, FX) and decreases in endogenous anticoagulants such as protein S, antithrombin, and tissue factor pathway inhibitor (TFPI). As a result, increases in activated protein C (APC) resistance and thrombin generation occur [14,15], both of which are recognised as reliable surrogate markers for thrombosis risk [16,17].

Importantly, the elevated risk is primarily attributable to the estrogen component rather than the progestin [4–6]. Biological studies have shown that EE drives the prothrombotic response, whereas progestins modulate this effect to varying degrees [13]. For example, EE combined with levonorgestrel (LNG) consistently results in the lowest VTE risk among EE-based formulations because LNG blunts the effect of EE on the hepatic system and consequently on coagulation parameters [6,13,18]. This suggests that while the choice of progestin influences overall risk, it does not override the dominant impact of EE, even with reduced doses (e.g., 20 mcg) [14,19,20].

A consistent body of epidemiological evidence now shows that the thrombotic safety of COCs hinges on the following drug attributes: the synthetic nature or not of the estrogen component, its dose, and the estrogenic blunting capacity of the associated progestin on the liver. Large retrospective database studies have demonstrated that, when EE is paired with progestins that have less impact on the liver (and, notably, are also less androgenic or anti-androgenic) such as drospirenone (DRSP), desogestrel (DSG) or gestodene (GSD), the risk of venous thromboembolism (VTE) increases two- to three-fold compared with the benchmark EE/levonorgestrel (LNG) combination [21,22].

Interestingly, recent randomised proteomic evidence also demonstrates that EE can significantly influence haemostasis compared to natural estrogens. In a trial

by Kangasniemi et al., EE combined with dienogest affected over 120 serum proteins involved in complement, coagulation, and acute-phase pathways, whereas E2V/DNG altered only five, and DNG alone had no effect [23]. These changes included notable increases in hepatic proteins such as SHBG, CBG, angiotensinogen, and fetuin-B, emphasising that EE triggers a widespread hepatic and inflammatory response [23]. This mechanistic profile aligns with the epidemiological findings and highlights why EE remains the main factor in thrombotic risk, while natural, body-identical estrogens like E2 tend to have a considerably milder impact on haemostasis.

Because of accumulating signals linking EE-containing COCs, particularly those with less-androgenic progestins, to higher thrombotic risk, the French medicines agency in 2013 requested a European-wide referral that ultimately led the Pharmacovigilance Risk Assessment Committee (PRAC) to re-examine combinations containing chlormadinone acetate (CMA), desogestrel (DSG), dienogest (DNG), drospirenone (DRSP), etonogestrel (ENG), gestodene (GSD), norgestimate (NGM), and nomegestrol acetate (NOMAC) [3].

More than two decades of observational studies examining VTE risk associated with COC use laid the foundation for quantitative syntheses, most notably the 2014 Cochrane review, which provided comprehensive estimates of excess VTE risk, stratified by progestin type and EE dose [18]. These analyses, though, were conducted before any meaningful data were available on COCs containing body-identical estrogens such as estradiol (E2) or estetrol (E4), as these formulations had only recently entered the market. In the absence of evidence, VTE risks with these newer natural estrogen products were initially categorised alongside EE-based COCs. Regulatory post-authorisation safety studies (PASS) such as PRO-E2 and INAS-SCORE, which aimed to fill this gap, did not report results until the 2020s [24,25].

The market introduction of E2 valerate/DNG (E2V/DNG) in 2009 and E2/NOMAC in 2011 allowed head-to-head evaluation of body-identical estrogens with EE-based pills [24,25]. Early biological data demonstrated that E2-based COCs had less impact than EE-based COCs on the haemostatic system. E2/NOMAC showed minimal changes in key coagulation markers, such as prothrombin fragment 1+2, D-dimer, and APC resistance, whereas EE/LNG induced significant prothrombotic shifts [26]. Similarly, E2V/DNG was associated with no significant increase in prothrombin fragment 1+2 or D-dimer levels, whereas EE/LNG users presented marked elevations [27,28]. A comparative trial with E2V/DNG and EE/DNG reported that E2V/DNG had a neutral effect on thrombin generation, whereas EE/DNG significantly increased both peak thrombin and endogenous thrombin potential, a pattern consistent with increased VTE risk [29]. Thus, switching from synthetic to body-identical estrogens shifted the impact on the haemostatic system, even when the

progestin was the same. Although not recognised as clinically relevant by the regulatory bodies at that time, these biological data already provided a reassuring message.

Since then, every large observational study of thrombotic outcomes comparing COC formulations with E2 to an EE-based reference has found E2-based pills to be at least non-inferior, and in some cases safer [24,25,30–32]. In the INAS-SCORE study, the adjusted hazard ratio (HR) for VTE with E2V/DNG was 0.46 (95 % CI 0.22–0.98) versus EE/LNG [24], while the PRO-E2 study reported an adjusted HR of 0.59 (95 % CI 0.25–1.35) for E2/NOMAC [25]. A nationwide Finnish registry analysis of more than half a million women corroborated these data; after exclusion of cyproterone-containing preparations, the adjusted odds ratio for VTE with E2-based COCs was 1.05 (95 % CI 0.66–1.66), i.e. indistinguishable from non-use and clearly lower than the 2.15 (95 % CI 1.78–2.59) observed with EE combinations [31]. Taken together, these convergent observational findings consistently demonstrate that E2-containing COCs are highly likely to result in lower VTE risk than EE-containing COCs.

A recent meta-analysis incorporating these latest datasets on E2 confirms these findings [5]. This comprehensive study, collectively representing more than 560,000 woman-years of COC use, demonstrated a 33% reduction in VTE odds for E2-based compared with EE-based COC users (pooled OR 0.67, 95% CI 0.51–0.87) [5]. Subgroup analyses revealed an even greater relative risk reduction when E2 pills were contrasted with EE products formulated with progestins other than levonorgestrel (pooled OR 0.60, 95 % CI 0.45–0.81). More importantly, pooled adjusted hazard ratios derived from the two regulatory-imposed studies [24,25] reinforced this pattern, indicating a 49% lower thrombotic risk for E2-based COC versus EE/LNG users (pooled HR 0.51, 95 % CI 0.29–0.90) [5]. Collectively, these data provide further evidence that E2-based COCs confer less thrombotic risk than EE-based COCs.

In 2021, a second body-identical estrogen, estetrol (E4), was introduced to the market. Owing to its unique pharmacology, E4 causes little hepatic activation and consequently has only a modest impact on haemostasis [33]. In a laboratory marker study, E4/DRSP pill users showed a markedly smaller rise in APC resistance, quantified with the EMA- and ISTH-endorsed endogenous thrombin-potential (ETP) method [17,34], than users of either EE/levonorgestrel (LNG) or EE/DRSP (30 % vs 165 % and 219 %, respectively) [14]. A follow-up study confirmed this profile over six treatment cycles, after which thrombin-generation parameters remained unchanged with E4/DRSP but rose significantly with EE/LNG and EE/DRSP, placing users of the EE combinations in a hypercoagulable range [15]. These findings suggest that, like E2, which also exerts less effect on the liver than EE [26,27,29] E4 helps maintain a more physiological haemostatic balance than EE. To clarify the clinical relevance of these laboratory

signals, two regulator-mandated post-authorisation safety studies, i.e. INAS-NEES and INAS-SEES, are following real-world users of E4/DRSP and EE/LNG in nationally representative cohorts [34,35]. Results are not expected before 2029.

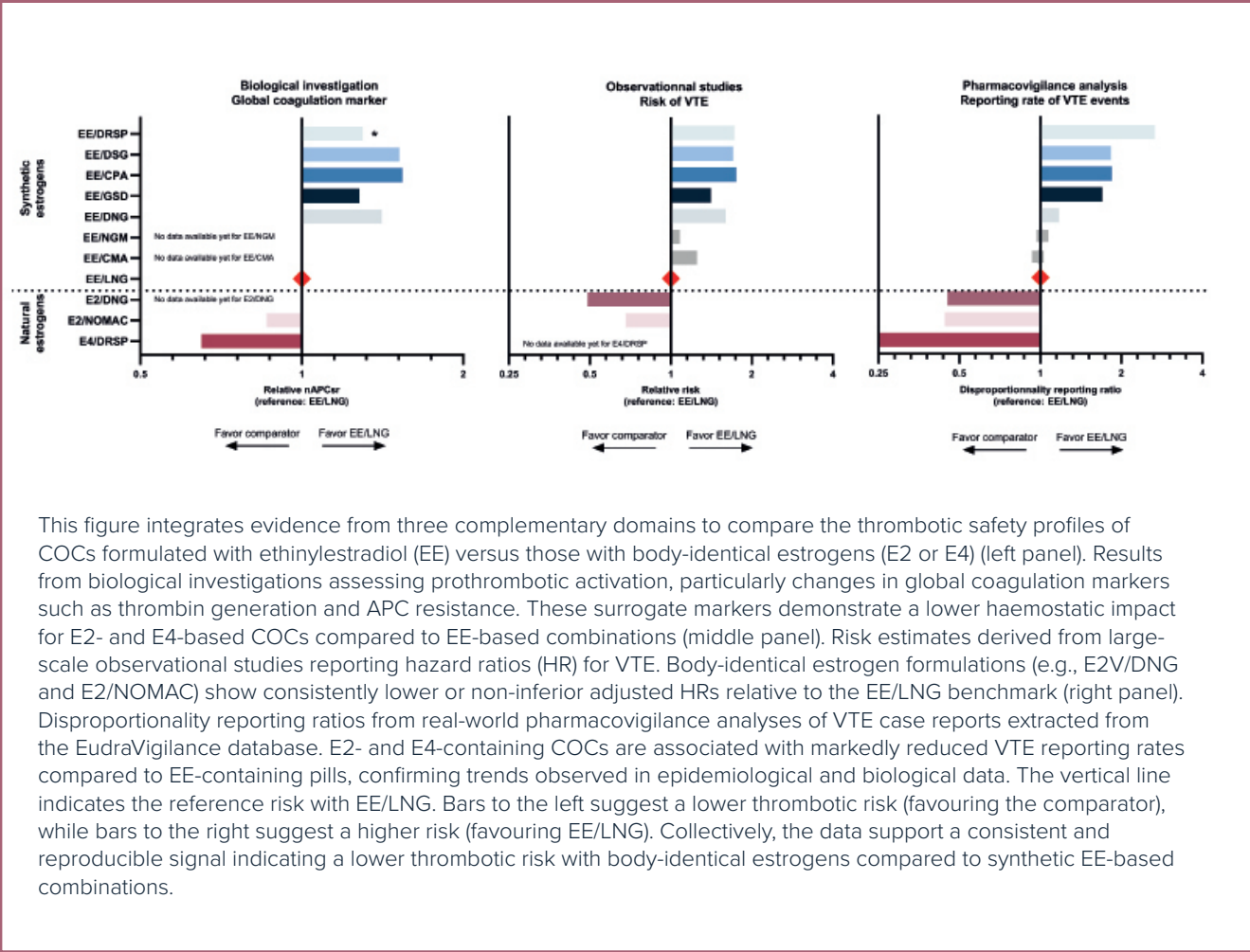
In the meantime, real-world pharmacovigilance data have been used to further evaluate VTE risk with E2- and E4-based pills [4]. In a 2024 analysis of the EudraVigilance database, the proportionality reporting ratio (PRR) of VTE events for E4/DRSP, E2/NOMAC and E2V/DNG was markedly lower compared to EE/LNG (PRRs of 0.24, 0.44 and 0.45, respectively, $p<0.001$) [4]. This real-world signal confirms the lower VTE risk observed in observational studies with body-identical estrogens [4].

Given this accumulating body of evidence, natural, body-identical estrogens should be considered a cornerstone of risk mitigation strategies for COC-related thrombosis. Furthermore, the selection of safer estrogens could have a meaningful public health impact.

It has been estimated that replacing EE with E2 or E4 in CHCs could prevent between 7,000 and 10,000 VTE cases annually in the European Union, resulting in a saving of 400 to 600 lives per year [20,36]. This reduction is not only beneficial to the patient directly, but also to the entire society, as this reduction of the risk can be cost-effective considering the cost of a VTE event in this young population [37].

In conclusion, the use of natural, body-identical estrogens such as E2 and E4 in CHCs represents a safer alternative to EE. Robust evidence from biological assays, prospective cohort studies, meta-analyses, and real-world reports supports the conclusion that body-identical estrogen-containing CHCs, especially E4/DRSP, E2V/DNG, and E2/NOMAC, are associated with a significantly lower risk of VTE (Figure 1). This should prompt a re-evaluation of current prescribing practices and inform future regulatory recommendations aimed at reducing preventable thrombotic events among women using CHCs.

Figure 1: Comparative thrombotic risk of combined oral contraceptives containing body-identical versus synthetic estrogens across biological, epidemiological, and pharmacovigilance datasets



Strategies for COC-related VTE risk minimisation

Individual risk assessment

Recent developments in phenotypic coagulation assays, such as the endogenous-thrombin-potential-based normalised activated protein C sensitivity ratio (nAPCsr, QUALIblood sa, Liège, Belgium), now provide a pragmatic, evidence-driven means of stratifying women according to their intrinsic thrombogenicity [7]. By quantifying the degree of resistance to APC, the test captures both inherited pro-coagulant traits (e.g., Factor V Leiden or prothrombin G20210A) and the acquired APC resistance that frequently develops after exposure to estrogenic contraceptives, an early surrogate for the global pro-thrombotic shift induced by EE [16] (Heinemann et al., 2002). Robust epidemiological data show that higher APC resistance scores are tightly linked to VTE, with relative risk estimates that rise in parallel with the nAPCsr value [6,38].

When incorporated into multivariate clinical algorithms that already account for conventional risk factors, such as personal or family history of VTE, body mass index, smoking, age, and concomitant thrombogenic comorbidities, the nAPCsr testing materially improves the identification of women whose baseline haemostatic milieu renders them poor candidates for standard EE-based COCs. A woman displaying even mild APC resistance in the absence of other risk factors would, for example, be advised to avoid EE preparations, whereas one with a normal nAPCsr could safely start any pill. Moreover, because the assay defines contraceptive-specific therapeutic intervals, it can be repeated one to two cycles after initiation to determine whether an individual is an “over-responder” to the estrogenic component; women whose post-treatment nAPCsr exceeds the acceptable range can then be redirected toward progestin-only methods or COCs formulated with body-identical estrogens such as E2 or E4 [7].

The utility of this strategy is no longer hypothetical. A 2025 health-economic analysis projected that targeted nAPCsr screening at €70–100 per test, combined with selective contraceptive counselling, could avert approximately 13,500 COC-related VTE events each year in the European Economic Area, generating net annual savings of €1.0–1.2 billion once direct and indirect costs are considered [7]. Importantly, the assay has already been fully automated on the ST-Genesisia platform (Diagnostics Stago, Asnières-sur-Seine, France), yielding excellent inter-laboratory reproducibility and a sensitivity of ~97 % for the two most prevalent thrombophilias. These attributes make routine implementation feasible even in medium-throughput clinical laboratories, addressing the cost-effectiveness, practicality and equity concerns that have historically led international guidelines [39–43] to discourage

universal thrombophilia screening. Taken together, emerging data advocate for the integration of nAPCsr testing into modern contraceptive algorithms to deliver genuinely personalised, safer estrogen therapy.

Selection of lower-risk estrogen formulations

Risk minimisation also involves careful selection of CHC formulations, prioritising those with a lower thrombogenic profile as first-line therapy. As discussed above, multiple lines of evidence indicate that CHCs containing body-identical estrogens, such as E2 and E4, have a significantly reduced impact on thrombin generation, APC resistance, and fibrinolysis compared with those containing EE [13]. Epidemiological studies and biological markers consistently show that replacing EE with E2 or E4 reduces VTE risk by approximately 33–50% [5].

As such, E4/DRSP and E2-based combinations should be considered first-line options in women desiring a safer oral contraception without contraindications for CHC. Clinicians should compare available data on tolerability, especially cycle control, between body-identical estrogen preparations when discussing these options with patients.

Patient education and shared decision-making

Risk minimisation is also enhanced through comprehensive patient education and shared decision-making. Women should be informed not only about the general risks associated with CHCs but also about the role of estrogen type in determining those risks. Decision aids that incorporate personalised risk stratification with objective data, such as the nAPCsr, visual risk communication tools, and real-world safety data, can help facilitate meaningful discussions between patients and healthcare providers. Educating women on early signs of thrombotic complications, such as unexplained leg swelling or sudden shortness of breath, can also lead to earlier detection and improved outcomes. Importantly, this individualised approach respects patient autonomy while aligning treatment choices with evolving safety evidence.

Public health implications

Replacing EE with body-identical estrogens in CHCs represents a pragmatic public health approach and cost-effective strategy to reduce preventable thrombotic events in reproductive-aged women. Modelling studies suggest that such a substitution across the EU could prevent between 7,000 and 10,000 VTE events annually [20]. Notably, CHCs based on body-identical estrogens (E2 or E4) are associated with a 33% to 49% reduction in VTE risk compared to EE-based pills [4], resulting in substantial economic benefits. According to recent estimates, the cumulative direct and indirect

cost of a single VTE episode over three years exceeds €100,000 [7]. Importantly, the burden of VTE extends beyond the acute phase, with a significant proportion of patients developing long-term sequelae such as PTS, chronic pain, functional impairment, and chronic thromboembolic pulmonary hypertension (CTEPH) [39]. Integrating safer estrogenic compounds into clinical guidelines and prescribing practices thus aligns with both evidence-based pharmacotherapy and long-term healthcare cost containment, reinforcing the urgency of regulatory and public health action.

Conclusion

In conclusion, the use of natural estrogens such as E2 and E4 in combined hormonal contraceptives represents a safer alternative to EE. Robust evidence from prospective cohort studies, biological investigations, meta-analyses, and real-world reporting supports the conclusion that body-identical estrogen-containing CHCs are associated with a significantly lower risk of VTE. This risk can also be lowered by integrating laboratory-based strategies like the nAPCsr to guide the prescription of the appropriate contraceptive method. This should prompt a re-evaluation of current prescribing practices and inform future regulatory recommendations aimed at reducing preventable thrombotic events among women using CHCs.

Current knowledge gaps

Despite recent advances in the understanding of estrogen-related thrombogenicity and the development of safer hormonal contraceptives, significant gaps persist in both clinical practice and health policy, particularly regarding the long-term impact and economic implications of VTE in reproductive-aged women.

One of the most striking omissions in current research is the underestimation of the long-term consequences of VTE following CHC use. While much of the existing literature, including recent pharmacovigilance and PASS studies, focuses on acute events such as DVT and PE, there is a paucity of data describing PTS and CTEPH in women who experience CHC-related VTE. These sequelae are associated with chronic pain, reduced physical function, impaired quality of life, and, importantly, substantial health care utilisation. Yet, most pharmacoeconomic models evaluating contraceptive safety omit these chronic outcomes, thereby underestimating the true cost of burden. Available estimates suggest that the three-year cumulative cost of a single VTE episode, including direct medical care, productivity losses, and long-term disability, can exceed €100,000 per patient, but this figure likely underrepresents the burden when considering the lifelong implications for young women.

Despite robust evidence supporting the lower thrombogenic profile of body-identical estrogens,

such as E2 and E4, health technology assessments (HTA) frameworks and reimbursement models have not been updated to reflect these benefits. Current HTA analyses continue to rely on legacy data derived from EE-based formulations, failing to incorporate more recent findings from biological, epidemiological, and pharmacoeconomic estimates that demonstrate clinical and potential economic superiority of body-identical estrogen-containing COCs. The absence of modern HTA evaluations that integrate both short- and long-term thrombotic outcomes and potential cost savings from reduced chronic morbidity represents a critical barrier to the broader adoption and reimbursement of safer estrogenic options.

In parallel, clinical guidelines have not kept pace with the growing body of evidence. National and international recommendations, including those from the WHO, FSRH, and CDC, still classify E2- and E4-based CHCs within the same risk category as EE-based formulations, despite large-scale observational data and meta-analyses showing a 33–49% lower VTE risk for body-identical estrogens. Thus, there is a need to different classification based on the estrogenic component of the CHC. This regulatory inaction contributes to inertia in clinical prescribing patterns and may limit access to safer contraceptive options, especially in health systems where reimbursement and prescriber behaviour are tightly coupled to guideline recommendations.

Another overlooked dimension is the lack of integration of phenotypic risk assessment tools into contraceptive counselling algorithms. While the nAPCsr has demonstrated high sensitivity in identifying both inherited and acquired thrombophilic states, it remains largely absent from routine practice. The absence of prospective implementation studies and real-world evaluations of cost-effectiveness hampers its adoption, despite modelling data indicating that nAPCsr-guided counselling could avert over 13,000 COC-related VTE cases annually in the European Economic Area, yielding €1–1.2 billion in net savings.

Moreover, current evidence is disproportionately based on data from high-income, predominantly Caucasian populations. There is a critical need to generate evidence across diverse ethnic and socioeconomic groups, particularly in low- and middle-income countries, where genetic risk factors and health system infrastructure may alter both baseline thrombotic risk and the feasibility of implementing personalised prevention strategies. Without such data, equitable contraceptive safety remains an unfulfilled objective.

Finally, there remains no standardised, predictive framework that incorporates both biological and behavioural factors to guide personalised contraceptive choices. While advances such as the nAPCsr assay offer biologically precise risk stratification, real-world contraceptive behaviour is also shaped by accessibility, health literacy, perceived risk, and adherence patterns.

Integrated models combining clinical, biological, and psychosocial variables are needed to bridge this translational gap.

In summary, addressing the current gaps in VTE risk management in CHC users, particularly those related to long-term outcomes, health economic valuation, and regulatory updates on body-identical estrogens, requires a concerted effort across clinical research, HTA bodies, and regulatory agencies. Modernising contraceptive care to incorporate emerging biological tools, safer estrogen formulations, and updated economic evidence has the potential to not only improve individual outcomes but also to generate significant societal value across all global regions.

Key messages

Compared with synthetic estrogens such as EE, body-identical estrogens, such as E2 and E4, have a lower impact on the coagulation cascade.

Combined oral contraceptives containing body-identical oestrogens are associated with a 33% reduction in VTE risk compared with synthetic alternatives.

Body-identical estrogens induce less pronounced changes in liver-synthesised coagulation markers, resulting in lower activated protein C resistance.

Risk stratification for patients considering combined hormonal contraception could be rationalised using appropriate laboratory-based methods aiming at identifying pre-existing thrombophilia and over-response to estrogens.



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