

# Venous Thromboembolism Prophylaxis in Critically Ill Patients

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## Abstract

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is recognized as a common complication in critically ill patients. Risk factors including critical illness, mechanical ventilation, sedative medications, and central venous catheter insertion are major contributing factors to the high risk of VTE. Because of their impaired cardiopulmonary reserve, PE arising from thrombosis in the deep veins of the calf that propagates proximally is poorly tolerated by critically ill patients. Pharmacologic prophylaxis with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) has been shown to decrease the incidence of VTE in medical, surgical, and critically ill patients. As a result, over the past decades, VTE prophylaxis had become a standard of preventive measure in the intensive care unit (ICU). In clinical practice, the rate of VTE prophylaxis varies and may be inadequate in some centers. A perception of a high bleeding risk in critically ill patients is a major concern for most physicians that may lead to inadequate prophylaxis.

## Keywords

- venous thromboembolism
- prevention
- critical illness

## High Risk for VTE in ICU Patients: Role for VTE Prophylaxis

Critically ill patients are at high risk for the development of VTE. Without VTE prophylaxis the incidence of DVT ranges from 13 to 30%.<sup>1,2</sup> There is geographic variation in the frequency with which VTE occurs; studies from Asia report a prevalence of VTE in medical-surgical critically ill patients ranging from 6.6 to 10.5%,<sup>3,4</sup> slightly less than that reported in Western European and North America.

UFH effectively prevents DVT.<sup>5</sup> However, a failure rate as high as 5.1 to 15.5% has been reported.<sup>6,7</sup> This rate underlines the high risk of VTE in critically ill patients despite anticoagulation. In a prospective cohort study of 261 medical-surgical ICU patients given UFH 5,000 units subcutaneously bid, DVT developed in 9.6% of patients during hospitalization. Patients with DVT had a significantly longer duration of mechanical ventilation, ICU stay, and hospitalization than

those without DVT.<sup>8</sup> In a study conducted in Australia and New Zealand including 175,665 critically ill adult patients, omission of thromboprophylaxis within 24 hours of ICU admission was reported to be associated with an increased risk of mortality in critically ill adult patients.<sup>9</sup> A recent observational study, conducted in adult ICU patients in the United States, included 294,896 episodes of critical illness and reported that the group of patients who received prophylactic anticoagulation had a significantly lower risk of death than those not provided VTE prophylaxis.<sup>10</sup>

In summary, critically ill patients have high risk of developing VTE, which may occur despite prophylaxis that is effective in other, lower-risk, settings. VTE in critically ill patients is associated with poorer outcome. These results suggest that VTE pharmacological prophylaxis should be applied to all patients who do not have a contraindication to anticoagulants, and that intensification of anticoagulation may be warranted to further reduce the risk of VTE.

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## Pharmacologic Prophylaxis: Evidence-Based Efficacy

### UFH, LMWH versus Placebo

Evidence of efficacy of UFH or LMWH prophylaxis has been demonstrated in four randomized controlled trials (► **Table 1**). The first trial of 119 medical-surgical critically ill patients compared UFH 5,000 units subcutaneously twice daily with placebo and showed the risk of screening detected VTE was reduced from 29 to 13%, a risk reduction of approximately 50%.<sup>5</sup> The second trial, published only in abstract form, randomized medical ICU patients to UFH 5,000 units subcutaneously twice daily versus placebo. The UFH group had a significant reduction in the rate of DVT compared with the placebo group (11 vs. 31%,  $p = 0.001$ ).<sup>11</sup> The third trial randomized mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) to LMWH (nadroparin 65 U/kg) versus placebo. Patients allocated to LMWH had a 45% reduction in incidence of DVT (15.5 vs. 28.2%,  $p = 0.045$ ).<sup>12</sup> Finally, a subgroup analysis of sepsis patients receiving drotrecogin alfa compared UFH 5,000 units subcutaneously twice daily versus LMWH (enoxaparin) 40 mg subcutaneously daily versus placebo. The rate of symptomatic and asymptomatic lower extremity DVT during days 0 to 6 were not significantly different between three groups (5.6 vs. 4.9 vs. 5.5%, 5.1 vs. 4.0 vs. 4.4%, respectively).<sup>13</sup>

A pooled analysis of outcomes from a recent systematic review and meta-analysis that included the four trials above

and found the use of UFH or LMWH compared with placebo was associated with a significantly lower risk of DVT (relative risk [RR] = 0.51; 95% confidence interval [CI]: 0.41, 0.63], PE (RR = 0.52; 95% CI: 0.28, 0.97). No difference in the risk of major bleeding or ICU mortality was identified; however, the analysis was underpowered to detect even large differences in rates for these less common outcomes.<sup>14</sup> These results (which are consistent with those found in other high-risk groups) underscore the significant reduction in VTE in the prophylaxis group and have led, for example, to the 9th American College of Chest Physicians (ACCP) evidence-based clinical practice guideline recommending prophylaxis of critically ill patients with LMWH or low-dose UFH over no prophylaxis.<sup>15</sup>

### UFH versus LMWH

UFH clearance is not dependent on renal function, which is a major advantage over LMWH. A high proportion of critically ill patients have impaired renal function that might limit the use of LMWH. However, LMWH might be preferred in critically ill patients if it demonstrates superior efficacy, and because it has a reduced likelihood of heparin-induced thrombocytopenia, it requires only once-daily administration and is commercially available in a unit dose, reducing the likelihood of medication error.<sup>16,17</sup>

Three randomized controlled trials have compared UFH with LMWH for VTE prophylaxis in critically ill patients (► **Table 1**). The first, a prospective study in 156 surgical

**Table 1** Summary of randomized trials demonstrated efficacy of pharmacologic prophylaxis

UFH, LMWH vs. placebo				
Author	Patient	Intervention	Incidence of DVT (%)	Sig.
Cade <sup>5</sup>	119 medical-surgical ICU	UFH 5,000 units sc bid vs. placebo	13 vs. 29	<0.001
Kapoor et al <sup>11</sup>	791 medical ICU	UFH 5,000 units sc bid vs. placebo	11 vs. 31	0.001
Fraisse et al <sup>12</sup>	223 mechanically ventilated COPD	LMWH (nadroparin) 65 IU/kg sc od vs. placebo	15.5 vs. 28.2	0.045
Shorr and Williams <sup>13</sup>	1,935 sepsis receiving drotrecogin alfa	UFH 5,000 units sc bid vs LMWH (enoxaparin) 40 mg sc od vs. placebo	5.0 vs. 4.2 vs. 5.1 <sup>a</sup> 5.6 vs. 4.9 vs. 5.5 <sup>b</sup> 5.1 vs. 4.0 vs. 4.4 <sup>c</sup> 0.2 vs. 0 vs. 0.2 <sup>d</sup>	NS
LMWH vs. UFH				
De et al <sup>18</sup>	156 surgical ICU	LMWH (enoxaparin) 40 mg sc od vs. UFH 5,000 units sc bid	1.2 vs. 2.7	NS
PROTECT <sup>19</sup>	3,764 medical-surgical ICU	LMWH (dalteparin) 5,000 units sc od vs. UFH 5,000 units sc bid	5.1 vs. 5.8 1.3 vs. 2.3 <sup>d</sup>	NS 0.01
Goldhaber et al <sup>20</sup>	310 medical ICU	LMWH (enoxaparin) 30 mg sc bid vs. UFH 5,000 units sc bid	25 vs 20	NS

Abbreviations: bid, twice a day; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ICU, intensive care unit; LMWH, low-molecular-weight heparin; NS, not statistically significant; od, once daily; sc, subcutaneous; UFH, unfractionated heparin.

<sup>a</sup>Incidence of any VTE.

<sup>b</sup>Incidence of symptomatic lower extremity DVT.

<sup>c</sup>Incidence of DVT by screening ultrasound.

<sup>d</sup>Incidence of PE.

ICU patients, compared the efficacy of UFH 5,000 units subcutaneously twice daily and LMWH (enoxaparin) 40 mg subcutaneously once daily. There was no significant difference in incidence of DVT (2.66 vs. 1.23%).<sup>18</sup> Owing to small sample size, this study might be underpowered to detect a significant difference. The second trial studied critically ill patients and compared the efficacy of UFH 5,000 units subcutaneously twice daily with LMWH (dalteparin) 5,000 units subcutaneously once daily. There was no significant difference in incidence of DVT; however, in the dalteparin group there was significant lower of incidence of PE (2.3 vs. 1.3%,  $p = 0.01$ ).<sup>19</sup> This study systematically screened for leg DVT, but all episodes of PE were clinically suspected and confirmed as a component of routine clinical care. The third trial studied medical ICU patients and compared enoxaparin 30 mg subcutaneously twice daily with UFH 5,000 units subcutaneously twice daily. There was no significant difference in DVT rate (25 vs. 20%).<sup>20</sup>

Pooled outcomes from a meta-analysis reported that LMWH was not associated with a lower risk of DVT when compared with UFH (RR = 0.90; 95% CI: 0.74, 1.08), and there was no significant difference seen in the incidence of symptomatic DVT, major bleeding, or ICU mortality in this analysis.<sup>14</sup> LMWH use was associated with a reduction in asymptomatic PE and symptomatic PE when compared with UFH. There are no direct comparisons between different types of LMWH in critically ill patients.

In summary, current evidence suggests that LMWH might be superior to UFH as it decreases the incidence of symptomatic and asymptomatic PE. These data should be interpreted with caution because they are driven by one large study. Further trials are needed to confirm this benefit of LMWH.

## New Anticoagulants

Recently a series of oral, highly effective antithrombotic medications have become available. These agents have been shown effective for primary and secondary prevention of venous thrombosis and stroke and systemic embolization in patients with atrial fibrillation.<sup>21–24</sup> However, two large studies in seriously ill medical patients failed to demonstrate net benefit of these medications over LMWH.<sup>25,26</sup> This evidence, coupled with the need for oral administration, renal dependency with some of the agents, and the lack of effective reversal agents, suggests that these new agents will have little or no role in VTE prophylaxis in critically ill patients.

## What Is the Role of Pharmacological Prophylaxis in Critically Ill Patients with a High Bleeding Risk?

Despite their high risk for VTE, critically ill patients are also at high risk of bleeding due to their comorbidities, admitting illness (es), and the use of multiple medications and interventions that may cause hemorrhage. Despite this, in one meta-analysis there was no evidence that pharmacologic prophylaxis increased the risk of major bleeding when heparin prophylaxis was compared with placebo.<sup>14</sup> A large observational study using data from

International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) assessed in-hospital bleeding risk in acutely ill medical patients. Three factors were associated with a high bleeding risk: active duodenal ulcer, bleeding within the 3 months before admission, and platelet count less than  $50 \times 10^9$  cells/L. Admission to the ICU/coronary care unit (CCU) also contributed to bleeding risk.<sup>27</sup>

In day-to-day clinical practice the risk of bleeding and thrombosis will have to be weighed in an individual patient when selecting the type of anticoagulant prophylaxis. In patients with a sufficiently high bleeding risk, mechanical prophylaxis should be considered, and when the bleeding risk decreases, we suggest resuming pharmacologic thromboprophylaxis.

## Is Mechanical VTE Prophylaxis Effective?

Mechanical prophylaxis including graduated compression stocking (GCS) and intermittent pneumatic compression devices (IPC) is indicated in patients who have a contraindication to pharmacologic prophylaxis. GCS generally seems to be less effective than pharmacologic prophylaxis<sup>28</sup> and whether they provide significant benefit as VTE prophylaxis, particularly in high-risk patients, remains unclear.<sup>29</sup> IPC has more evidence to support its efficacy. Three recent randomized controlled trials have been published. The first trial was conducted in medically critically ill patients in which one group received IPC prophylaxis and another received none, with both groups having received no anticoagulation. The IPC group had significantly reduced DVT (3.8 vs. 19.28%,  $p < 0.01$ ), PE (0 vs. 9.64%,  $p < 0.01$ ), and non-sudden cardiac death (1.26 vs. 7.23%,  $p < 0.01$ ).<sup>30</sup> The second trial was conducted in 798 ICU patients and compared the efficacy of GCS, and IPC combined with either UFH or LMWH. IPC use was associated with a significant reduction in VTE (4.8%) compared with no mechanical prophylaxis (7.2%) or with GCS (10%).<sup>31</sup> The third study randomized ICU patients to IPC plus GCS or GCS alone. There was no significant difference (5.6 vs. 9.2%) in DVT rate between the two groups; however, the large numerical difference suggests that the comparison was underpowered to detect large differences in event rates.<sup>32</sup>

In summary, IPC decreased the rate of VTE in the setting of ICU patients compared with no mechanical prophylaxis, but less is known about the effectiveness of GCS compared with other prophylaxis strategies.

## Inferior Vena Cava Filters

Inferior vena cava (IVC) filters are indicated in patients who have an absolute contraindication to anticoagulants and who have an active DVT, or PE with evidence of thrombosis below the level of the IVC at which the filter will be inserted. Data from a randomized controlled trial that allocated patients to anticoagulation alone, or anticoagulation plus filter placement, found reduced PE, but no difference in mortality.<sup>33</sup> In long-term follow-up, patients with IVC filters (with varying exposure to anticoagulants) had an increased risk of recurrent DVT.<sup>34</sup> Although widely used for VTE prophylaxis, there is no evidence that filters are effective in this setting, and they are

known to have complications including DVT and IVC thrombosis with potential extension into the renal veins, fracture, strut perforation, and embolization, they are expensive, and they are rarely removed (<10% of the time in one recent survey).<sup>35</sup> IVC filters should not be used for DVT prophylaxis in any critically ill patient. If patients cannot receive pharmacologic prophylaxis due to bleeding or other reasons and IPC cannot be used for prophylaxis, the patient should be monitored with serial ultrasonography and treatment with an IVC filter if DVT is seen.

## Thromboprophylaxis Compliance and “Real-World Use” of VTE Prophylaxis

Compliance with VTE prophylaxis in medical ICU patients is variable, and highly center dependent. Recent studies suggested prophylaxis administration rates of 33% in medical ICUs,<sup>36</sup> 63 to 86% in medical-surgical ICUs,<sup>37,38</sup> and 86.7% in surgical ICU.<sup>39</sup> In one prospective, multicenter, point prevalence survey in Australia and New Zealand in hospitalized ICU patients 431/502 (86%), patients were given VTE prophylaxis. Of those given prophylaxis, 20% were given only pharmacologic prophylaxis (UFH 74%, enoxaparin 23%), 36% only mechanical prophylaxis, and 44% both.<sup>40</sup>

In a multicenter, observational study in medical ICU/CCU patients in China including 1,247 patients who had one or more VTE risk factors and excluding patients with the presence of predefined potential risk factors for bleeding, 49% of patients received at least one type of pharmacologic prophylaxis. Interestingly, antiplatelet drugs were the most commonly used form of pharmacologic prophylaxis. Only 20.2% of patients received an ACCP recommended VTE prophylaxis strategy.<sup>41</sup>

A small prospective study in Saudi Arabia demonstrated the effect of implementation of a clinical practice guideline on prophylaxis use in medical ICU patients. Use of the guideline in 104 patients resulted in compliance of 98% with UFH prophylaxis and an incidence of screening detected DVT of 9.6%.<sup>42</sup>

In a multinational observational study in Asia including 2,969 medical ICU patients, 98% received some form of VTE prophylaxis. Prophylaxis consisted of mechanical prophylaxis in 22.9%, pharmacologic prophylaxis in 31.2%, and both mechanical and pharmacological in 44.2%. The major reasons cited for nonuse of prophylaxis was perceived bleeding risk (52.1%), low-risk of VTE (27.6%), and early immobilization (10.3%). Overall 80.6% of patients receive VTE prophylaxis according to the ACCP guideline, and 4.7% per Japanese guidelines.<sup>43</sup>

In a single-point prevalence survey conducted in Japan, 470 patients were admitted to a medical-surgical ICU and a VTE prophylaxis compliance rate of 85.3% was observed. Of these patients, 69.8% were given only mechanical, 12.5% only pharmacologic, and 17.7% both mechanical and pharmacologic VTE prophylaxis. From this study, hospitals using standardized prevention protocols have significantly better compliance rates than those not having such protocols (88.8 vs. 80%,  $p < 0.01$ ).<sup>44</sup>

Another point prevalence survey conducted in Spain, using an electronic questionnaire in medical, surgical, and major trauma critical care units enrolled 777 patients, 81% of whom

were given VTE prophylaxis (63% pharmacologic prophylaxis only, 12% mechanical only, and 6% both). No VTE prophylaxis was given to 19% of the patients.<sup>45</sup>

In a large observational study of 294,896 hospital discharges from adult ICUs in the United States, 93% of patients admitted to medical-surgical ICUs received VTE prophylaxis (27% anticoagulant only, 34% mechanical only, and 32% both).<sup>10</sup>

In summary, almost all recent studies have demonstrated that more than 80% of critically ill patients receive appropriate VTE prophylaxis (—Table 2). Low prophylaxis rates are attributable to fear of bleeding and low (and probably underestimated) perceived risk of VTE.

Strategies to improve compliance include continual education strategies for physicians. A two-phase 1-year study examined the effect of an educational program on implementation of DVT prophylaxis in surgical-trauma ICU patients. Phase 1 was retrospectively examined the “historical” rate of VTE prophylaxis. Phase 2 was a prospective study after completion of a 1-year of educational program. Compared with the retrospective data, the incidence of DVT after the education program had declined significantly (11.9 to 4.5%,  $p < 0.01$ ).<sup>46</sup>

Another three-phase prospective longitudinal observational study has been reported in medical-surgical ICU. The primary outcome of study was to assess the number of patients on heparin prophylaxis after using a multiple method approach. Phase 1 was a 3-month documented baseline of VTE prophylaxis and phase 2 was a 1-year period using a multiple-method approach to implement thromboprophylaxis. The method included interactive multidisciplinary educational in-services, verbal reminders to ICU team, computerized daily nurse recording of thromboprophylaxis, weekly graphic feedback, and publicly displayed graphic feedback on group performance. Phase 3 was a 3-month follow-up period 10 months later that examined computerized recording of thromboprophylaxis. The proportion of ICU days during which heparin prophylaxis was administered was significantly increased from 60.0% (0, 100) in phase 1 to 90.9% (50, 100) in phase 2 and 100% in phase 3 ( $p < 0.01$ ).<sup>47</sup>

A study reported measurable outcomes and 2-year-sustainability of a quality improvement program in a surgical ICU, using a daily quality round checklist (QRC).<sup>48</sup> For this study, a cost-effective QRC was established as a tool to improve the compliance rates with prophylactic measures and to improve outcomes.<sup>49,50</sup> The checklist is composed of 22 data points and 16 preventive measures including DVT prophylaxis. During a 2-year program with routine implementation of the QRC, overall DVT prophylaxis compliance was 98%.

Electronic reminders are another strategy to improve adherence with VTE prophylaxis. A study randomized 2,506 hospitalized patients to an intervention group that used a computer program linked to a patient database that identified and alerted the physician if the patient was at risk of developing DVT, and compared these patients with a control group. In the intervention group, more patients received mechanical prophylaxis (10 vs. 1.5%,  $p < 0.001$ ) and pharmacologic prophylaxis (23.6 vs. 13%,  $p < 0.001$ ).

**Table 2** Summary of recently trials demonstrated VTE thromboprophylaxis compliance

Author	Study design	Patient	Rate of VTE prophylaxis (%)			
			Pharmacologic	Mechanical	Both	Overall
Roberson et al <sup>40</sup>	Point prevalence survey	502 ICU patients in Australia and New Zealand	20	36	44	86
Ge et al <sup>41</sup>	Cross-sectional	1,247 ICU/CCU patients in China	49 <sup>a</sup>	13.3	NM	20.2 <sup>b</sup>
Al-Otaib <sup>42</sup>	Prospective study	104 medical ICU patients in Saudi Arabia	NM	NM	NM	98
Parikh et al <sup>43</sup>	Cross-sectional	2,969 medical ICU patients in Asia	31.2	22.9	44.2	80.6 <sup>b</sup> 4.7 <sup>c</sup>
Yamamoto et al <sup>44</sup>	Point prevalence survey	470 medical-surgical ICU patients in Japan	12.5	69.8	17.7	85.3
Garcia-Olivares et al <sup>45</sup>	Point prevalence survey	777 medical-surgical-trauma- ICU patients in Spain	63	12	6	81
Lilly et al <sup>10</sup>	Observational cohort	294,896 hospital discharge from ICU in United States	27	34	32	93

Abbreviations: ICU/CCU, intensive care unit/coronary care unit; NM, not mention; VTE, venous thromboembolism.

<sup>a</sup>Receiving one or more types of VTE prophylaxis including antiplatelet, traditional Chinese medicine.

<sup>b</sup>According to ACCP guideline.

<sup>c</sup>According to Japanese guideline.

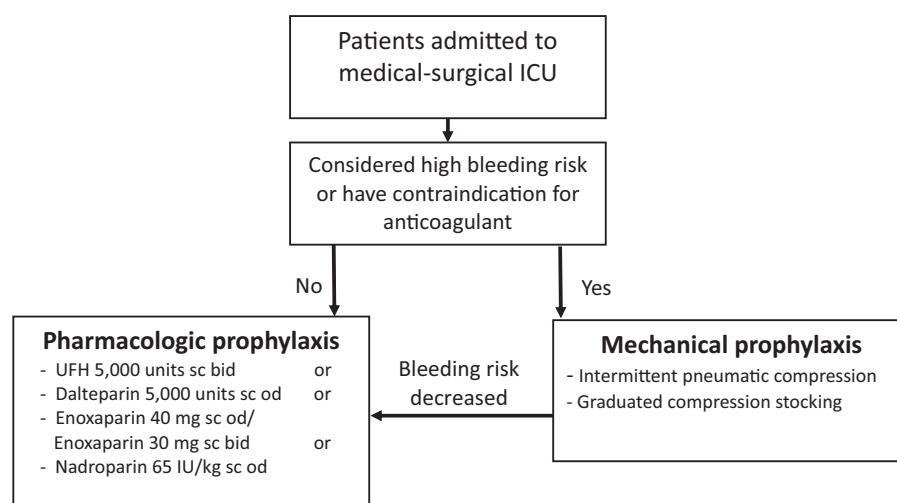
The computer alert also reduced the risk of symptomatic DVT or PE at 90 days by 41%.<sup>51</sup>

Another study used electronic reminders added to the electronic medical record in medical, surgical, and ICU patients. The control group enrolled 2,888 patients and recorded baseline VTE prophylaxis in the 6 months prior to implementation of the intervention. In the intervention group of 2,350 patients, the rate of appropriate prophylaxis was significantly increased (42.8 vs. 60.0%,  $p < 0.001$ ). Fewer patients were diagnosed with VTE after reminder was added (1.1 vs. 0.3%,  $p = 0.001$ ). However, in the subset of critical medical care service, including 53 patients, the rate of pro-

phylaxis was not significantly increased (63 vs. 79%,  $p = 0.17$ ).<sup>52</sup>

These studies suggest electronic reminders to be an effective way of increasing the rate of adherence to VTE prophylaxis in medical-surgical patients; however, they provide limited data on the efficacy in critically ill patients.

In summary, compliance with thromboprophylaxis is crucial for critically ill patients. The ideal strategies to improve the compliance should be effective, practical, and sustainable. Routine measures, such as VTE prophylaxis, are easily forgotten in the dynamic and evolving clinical situation found in the ICU. Physician education, use of care pathways, and electronic



**Fig. 1** Summary of venous thromboembolism (VTE) prophylaxis in intensive care unit (ICU). bid, twice a day; od, once daily; sc, subcutaneous; UFH, unfractionated heparin, IU, international units.



reminders and tools such as a QRC are effective strategies to improve the VTE compliance.

## Conclusion

VTE prophylaxis is a standard of care in critically ill patients. Omission of prophylaxis is associated with poorer outcomes. UFH and LMWH significantly decrease VTE rates compared with placebo. LMWH might be superior to UFH in terms of reductions in PE. Assessment of the bleeding risk for an individual patient is crucial. If the risk of bleeding is excessive, mechanical prophylaxis should be considered (—Fig. 1). IPC has better evidence than GCS alone. Strategies to improve thromboprophylaxis compliance include physician education, electronic order sets and reminders, and a QRC.

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