

EDUCATIONAL ARTICLE

Update on In Hospital Venous Thromboembolism Prophylaxis

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The surgical and hereditary risk factors for post-operative venous thromboembolism (VTE) are discussed and the heightened risk associated with particular risk factors quantified. Mechanical and pharmacological methods of prophylaxis are described, together with the different recommendations for use with general and regional anaesthesia. Prophylaxis may be started post-operatively and the duration of prophylaxis is discussed. The use of prophylaxis in vascular surgery is illustrated with case examples.

Keywords: Deep venous thrombosis; Venous thrombosis; Fatal pulmonary embolism; Prophylaxis.

Venous thromboembolism (VTE) is one disease entity, where deep vein thrombosis (DVT) in the acute phase can embolize, a condition which is potentially fatal. Long-term consequences are the development of a post-thrombotic venous insufficiency, perhaps leading to venous ulceration, and chronic pulmonary embolism with pulmonary hypertension. VTE is a life threatening condition, as well as a disease with chronic problems, causing suffering for the patients and great cost for society. In Sweden with a population of around 9 million inhabitants each year some 11,000 patients are treated for VTE, 1000 patients die from pulmonary embolism (PE), 250,000 operations are performed requiring prophylaxis, and 50,000 have a post-thrombotic venous ulcer, all this costing around 100 million €. Nevertheless many doctors do not encounter the problem very often, particularly since fatal PE is rare, although without prophylaxis PE would be one of the leading causes of death.

The aim of this review is to consider the contemporary problems and strategies concerning the prophylaxis of VTE.

Risk Factor Classification

Several attempts have been made to classify patients into different risk categories for VTE to enable the

delivery of prophylaxis to those who really need it. By giving a statistical risk estimate such classifications can be made, although in the individual patient we do not necessarily know if he or she would really develop VTE. However, the prophylactic methods available today are very safe and often inexpensive, so treating the many to benefit a few (for instance to prevent fatal PE) is not a major problem.

Table 1 shows one way to classify patients into various categories of risk to help in decision making about whether or not to use prophylaxis.

Surgical risk factors

Surgery, and above all the type of surgery, is one of the most important risk factors for VTE. The duration of the operation as a risk factor is difficult to evaluate, as a long duration is associated with other risk factors related to thrombosis, such as longer time for venous outflow obstruction, more complicated and traumatic surgery, major blood loss and transfusion, vein trauma etc. Some standardized orthopaedic operations, e.g. hip arthroplasty, have been used as a model for studies of postoperative thrombo-embolic problems and prophylaxis efficacy.

The frequency of postoperative thrombosis after neurosurgery is high. Although the surgical trauma in itself is rather small the operation time is often long. Neurosurgical operations have special

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Table 1. Risk classification for postoperative venous thromboembolism

• Low risk
- <40 years, no further risk factors
- >40 years, minor surgery
• Moderate risk
- major abdominal/pelvic surgery plus at least one further risk factor
• High risk
- >40 years; major orthopaedic surgery or abdominal/pelvic surgery for malignancy

considerations for prophylaxis, since the risk of bleeding has to be minimal.

When performing peripheral vascular surgery pharmacological substances are generally added to prevent arterial occlusion and those substances can contribute to a venous thromboprophylactic effect. Consequently information on the frequency of venous thrombo-embolism in untreated patients is lacking. Heparin, low molecular weight heparins, dextran and different platelet inhibitors are often used in combination. During long operations the thrombotic risk increases because of major trauma, vascular clamping with stasis, venous injury, frequent re-operations etc. The frequency of thrombosis in aorto-ilio-femoral surgery seems to be of the same magnitude as in other types of major abdominal and pelvic surgery (20–30%). The incidence of symptomatic VTE within 3 months after major vascular surgery was 1.7 to 2.8% in a population study of 1.6 million surgical patients.¹ In addition, there is increasing evidence that atherosclerosis is an independent risk factor of VTE.²

A speciality with rapidly increasing volumes is laparoscopic surgery. The frequency of clinical VTE is less than 0.5% after laparoscopic cholecystectomy. Out-patients undergoing ambulatory surgery also have a low risk for thrombosis with few clinically relevant consequences.

Distal thrombosis dominates post-operatively. Proximal thrombosis at hip arthroplasty often is localized to the operated side, in the area of surgical trauma. With phlebographic assessment, or post mortem studies, it has been shown that the femoral vein is kinked and compressed during hip surgery. It is easy to imagine a local endothelial injury as a starting point for these proximal thromboses. Furthermore, the venous flow diminishes during certain stages of the operation. The highest risk for thrombosis is in the immediate postoperative period, this risk decreasing during the first postoperative week. If VTE prophylaxis is limited to one week post-operatively, after major abdominal surgery as well as after hip surgery, thrombosis can develop in up to 25% after discharge from hospital. The most common diagnosis for

re-admission after hip arthroplasty is VTE. It is important to identify patients with risk of developing late clinically relevant thrombosis and assess duration of the prophylaxis. Local injury of the femoral vein, reduced venous emptying for several weeks and the thrombogenic haemostatic activation lasting for at least one month are three important factors for late VTE after hip surgery. In case of malignant disorders the disease itself is often thrombogenic.

Patients with lower leg fracture, hip fracture and traumatic spinal injury with paraparesis have a high risk of developing VTE. In the latter case the lack of muscle pump function with slow venous emptying is of pathogenic importance.

Some non-surgical and non-traumatic diagnoses and conditions also are associated with an increased risk of VTE such as stroke, medical intensive care, cancer, radiation therapy. The high frequency of thrombosis in the paralysed leg in stroke patients illustrates, as for paraplegia, the important function of a normal muscle pump for venous flow. Thrombo-embolic risk and consequently the risk of PE after stroke last a long time. In medical in-patients history of recent trauma, leg oedema, pneumonia and elevated platelet count are significantly associated with VTE.³

The problem of determining the frequency of fatal PE depends both on diagnostic difficulty and generally low autopsy rate (see Table 2). The frequency is low in most patient groups, but PE is one of the leading causes of postoperative death. At least half of the post-operative PE deaths occur in patients with otherwise good prognosis. PE also is an important cause of death in some non-surgical conditions such as stroke, spinal injury and infection in the respiratory organs.

Risk factors for development of venous thrombosis

The pathogenesis of DVT is multifactorial with interaction between hereditary and acquired risk factors. A statistically significant relationship with a single risk factor does not necessarily indicate a causal connection. Several risk factors in combination often are needed for thrombosis to develop. Many patients

Table 2. The frequency of fatal pulmonary embolism without prophylaxis

Surgery	Frequency in %
General surgery	0.5–1.0
Hip arthroplasty	0.1–0.4
Hip fracture surgery	3.6–12.9
Laparoscopic cholecystectomy	0.02
Knee arthroplasty	0.1–0.2
Pelvic fracture	0.2

have several risk factors and the risk is cumulative. The evidence for various risk factors for post-operative DVT has been analyzed recently and is summarised in Table 3.⁴ It can be difficult to differentiate between risk factors to decide which factors will be important in individual patients.

Hereditary risk factors

Hereditary defects in the haemostatic system have been identified as a cause of VTE (Table 4). Consideration needs to be given to the prevalence as well as to the relative risk of mutations in causing thrombosis. For instance, lack of protein C is a strong factor predisposing to thrombosis, but this is rare. In contrast, a high level of factor VIII is common but only increases risk slightly. Some defects such as activated protein C-resistance show great geographical and ethnic variations. As each genetic defect is an independent risk factor for thrombosis a person with multiple defects has a considerably increased risk. Usually, the more common a hereditary risk factor is, the weaker it is, and only a few persons with this risk factor will develop thrombosis. Half of the diagnosed VTE events in patients with hereditary thrombophilia are caused by occasional provocation and these events could be avoided with short term, targeted prophylaxis.

Thromboprophylactic Methods

General methods

Few general methods have been properly evaluated in randomized studies. These general methods include good quality medical care and nursing for the patient e.g. atraumatic surgery, optimal fluid replacement and early mobilization.

Specific methods

The specific methods can be divided into mechanical and pharmacological ones. Different combinations

Table 3. Risk factors for postoperative thromboembolism

Type of surgery	Hormone replacement therapy
Age	Contraceptive pills
Obesity (BMI >30)	Malignancy
Varicose veins	Thrombophilia*
Immobilization	
Previous venous thromboembolism	

*Factor V Leiden mutation.

are possible, but studies on combined prophylaxis are few.⁵

Mechanical methods

The aim of mechanical methods is to stimulate emptying from calf veins, which is considerably slower when the patient is under anaesthesia and the calf muscle pump non-functioning. The mechanical methods are of different types. Both active and passive foot pedals make the calf muscles to contract. Different pump systems with external compression have similar effects. Compression systems can be applied to the sole of the foot to empty venous plexa or muscles can be stimulated to contract by electric stimulation.

Graded compression stockings with correct size and application will increase the blood flow velocity in the veins. Knee- and full leg stockings seem to have equivalent effect in reducing venous stasis. Knee stockings are easier to use and more comfortable. There is level 1 evidence for the effectiveness of graded compression in thromboprophylaxis, but the protection against fatal PE has not been studied in large enough studies. This also is true for intermittent pneumatic compression. However, in patients with arterial insufficiency graded compression stockings may provoke ischaemic wounds and gangrene and if arterial insufficiency is suspected ankle pressures should be measured before deciding on the best mechanical method of thromboprophylaxis.

In operations where even a minor bleeding risk must be avoided, i.e. in neurosurgical operations and in head and spinal trauma, mechanical methods may be useful.⁶

Pharmacological methods

Vitamin K-antagonists. The anti-coagulant effect of vitamin K-antagonists is ascribed to the blocking of hepatic synthesis of the normal coagulation factors II, VII, IX and X. There are several oral vitamin K-inhibitors. The effect of warfarin is predictable and bioavailability good. It is available for parenteral administration but the oral form dominates treatment protocols. Warfarin is metabolised by the P450-system in the liver, and hence it is susceptible to numerous drug interactions, both beneficial and adverse. Even food containing phylokinons influences the anticoagulant effect. Elderly patients appear more sensitive to warfarin or at least have a higher risk for bleeding.

Prophylaxis against postoperative VTE with vitamin K-antagonists is possible but three factors speak against

Table 4. Risk factors for venous thromboembolism – prevalence and relative risk

	Prevalence in the population (%)	Prevalence in patients with DVT (%)	Prevalence at recurrent DVT (%)	Risk increase for venous thromboembolism
Insufficiency of antithrombin	0.02–0.2	1	0.5–0.7	>15 fold
Insufficiency of protein C	0.2–0.4	3	1–9	~10 fold
Insufficiency of protein S	0.2	1–2	1–13	~10 fold
APC-resistance	5 ¹	20	50	~8 fold
Protrombin G20210A	2 ¹	6		2–3 fold
High concentration of factor VIII	11	25		~6 fold
Hyperhomocysteinaemia (age dependent)	5	10–15		3–4 fold
Contraceptive pills	6	20		4 fold
Previous DVT	2	14		8 fold

¹ Great variations between populations.

its general use: need for monitoring, risk of bleeding and potential interactions.

Glycosaminoglycans. Heparin and heparin derivatives such as low molecular weights heparins (LMWH) and heparan sulphates are a mixture of sulphated anionic polysaccharides and with alternate D-glucosamines and uronic acid. The derivation of these substances may cause problems in some ethnic and religious groups. For instance, in Europe pig mucosa has been used for heparin production and bovine lung tissue in the USA.

The principal anticoagulant effect of heparin arises from a unique pentasaccharide sequence which binds anti-thrombin and can be found in one third of unfractionated heparin. When heparin binds to anti-thrombin a configuration change is induced which accelerates the capacity of anti-thrombin to inactivate different coagulation enzymes: thrombin, factor Xa and factor IXa. After the complex binding between anti-thrombin and these enzymes, heparin is released and can function again. Heparin with less than 18 saccharide units cannot bind thrombin and anti-thrombin at the same time and consequently does not function as an accelerant in this reaction, although the inhibitor effect on factor Xa remains.

Unfractionated heparin is heterogenous with respect to molecular weight, anticoagulant activity and pharmacodynamic effects. The mean molecular weight is around 12,000–15,000 daltons. Heparin has to be given as an injection, intravenously or subcutaneously. Bioavailability has considerable individual variations and varies with dose. Unfractionated heparin binds to several plasma proteins which reduces the bioavailability, and contributes to the inter-individual anticoagulant effect and heparin resistance. Heparin also binds to macrophages and endothelial cells. The biological half life is around 30–150 minutes, depending on the dose. With unfractionated heparin post-operative thrombosis can be prevented effectively with reduction in the risk of

PE, fatal PE and total peri-operative mortality. In a meta-analysis Collins and co-workers⁷ collected 62 studies in general surgery, urology and orthopaedic surgery where subcutaneous unfractionated heparin (5000 IE 2 or 3 times daily) was compared with untreated control groups. Prophylaxis reduced the incidence of fatal PE (0.8–0.3%), symptomatic PE (2.0–1.3%), asymptomatic DVT (22–9%) and total mortality (4.2–3.3%).

Heparin has pharmacokinetic, biophysical as well as biological limitations. The first limitation is plasma protein binding. The biophysical limitation is due to the fact that the heparin-anti-thrombin complex cannot inactivate thrombin bound to fibrin and factor X bound to phospholipids within the prothrombinase complex. The biological limits are due to bleeding complications, thrombocytopenia and osteoporosis.

LMWHs are also heterogeneous with respect to molecular weight and anticoagulant effect. The mean molecular weight varies from 4000 to 5000 daltons. There are several ways to produce LMWH. Fragmentation can be induced by chemical reaction or by bacterial heparinase. Different LMWHs show variations in biochemical and pharmacological qualities, and each one is considered as a unique substance by regulatory authorities.

LMWHs, in comparison to unfractionated heparin, have reduced binding to:

- plasma proteins giving more consistent dose-response effects and better bioavailability.
- macrophages and endothelial cells which prolongs plasma half life
- platelets
- osteoblasts

LMWH excretion is mainly renal, with prolonged half life in patients with renal insufficiency. LMWHs have been evaluated in many studies regarding the prophylactic effect in patients with increased risk for VTE.⁸ In most studies unfractionated heparin has

been used for comparison, LMWH being at least as effective as unfractionated heparin for thromboprophylaxis. Both treatments reduce the risk of VTE in general surgery by at least 60%. The prophylactic effect on PE seems even better with LMWH. LMWH can be administered subcutaneously once daily, compared with the need to administer heparin twice or three times daily. Most studies have investigated the prophylactic effect of LMWH given for a period of one week. There is some evidence that shorter prophylaxis, for instance 1–2 days, is not as effective.

The main side effects of heparin (bleeding, heparin induced thrombocytopenia and osteoporosis) are less frequent with LMWH. The bleeding risk is dose related. In a recent systematic review with 33,813 patients concluded that most patients undergoing general surgery could receive prophylaxis safely.⁹

Specific thrombin inhibitors and inhibitors of activated factor X. Today, factor Xa and IIa inhibitors are major targets for antithrombotic drug design. The role of thrombin in the haemostatic system is complex. Thrombin controls several important functions and is part of the final step in coagulation when fibrinogen is converted into fibrin. Thrombin activates factor XIII, which stabilises the fibrin clot and makes it resistant to thrombolysis. Thrombin is very potent at inducing platelet aggregation. It also prevents coagulation through a negative feedback mechanism (via thrombomodulin and protein C) as well as contributing to release of t-PA from endothelial cells.

Given the key role of thrombin it is understandable that research has focused on specific and direct thrombin inhibition. The best known natural and direct thrombin inhibitor, hirudin, is produced in the leech salivary glands. Natural hirudin is a polypeptide with a molecular weight of about 7000 dalton. Its inhibition of thrombin is not dependent on other cofactors. Several synthetic low molecular direct thrombin inhibitors are being studied at different stages in trials. Of great clinical interest are the synthetic thrombin inhibitors which can be administered orally.

The specific pentasaccharide sequence of heparin which binds to antithrombin has been synthesized (Fondaparinux) and acts as a selective, potent, indirect antithrombin-dependent inhibitor of factor Xa. The clinical thromboprophylactic effect has been studied in orthopaedic surgery (hip fracture, elective hip arthroplasty, elective knee surgery) and once in major abdominal surgery.¹⁰ Apart from its thromboprophylactic effect the studies are of theoretical interest because they show that isolated inhibition of factor X

is sufficient to prevent thrombosis. A large number of direct factor Xa inhibitors are under development.

Thromboprophylaxis to Different Patient Categories

General surgery

In most studies unfractionated heparin, or in recent years LMWH, has been proven to be effective for DVT as well as for PE. LMWH seems the better of the two for prevention of embolism. Both methods have a dose-related bleeding risk. At surgery for malignant diseases (abdomen, pelvis) a higher dose is more effective than a low dose, without increasing the bleeding risk. Body weight adjusted dose does not give any advantages.

During the past years the frequency of laparoscopic surgery has increased dramatically. Prophylaxis has been introduced without studying the scientific need. The risk of clinically relevant VTE is small and prophylaxis should probably be given only in the presence of other risk factors.¹¹

Orthopaedic surgery

In major orthopaedic surgery (hip and knee arthroplasty, hip fracture surgery and spinal surgery) LMWH remains effective although the frequency of thrombosis is high even with adequate prophylaxis. Higher doses are used than in general surgery (apart from cancer surgery). An increased bleeding risk has not been shown. Fondaparinux seems to have a better effect than LMWH, at least as far as phlegographically detected DVT is concerned.

Neurosurgery

In neurosurgery mechanical prophylactic methods dominate in many countries due to fear for bleeding complications with pharmacological methods. However, LMWH has a good effect with little risk of bleeding intra- or postoperatively.

Vascular surgery

There have been four small randomized clinical trials of prophylaxis against VTE after arterial surgery.^{12–15} All patients received intravenous heparin during the procedure. The results are not consistent but the effects are small, probably because the patients are given several other antithrombotic substances

perioperatively. Therefore, vascular surgeons are encouraged to make VTE prophylaxis decisions based on individual patient risk factors or on local hospital policy. Some clinical situations are given to exemplify and help in this decision, although strict scientific evidence is lacking and many of the recommendations are based on extrapolations from other types of surgery together and informed opinion. Patients undergoing aortic repair should receive heparin, not to increase patency but to diminish the risk of postoperative myocardial infarction.¹⁶ At the same time it is reasonable to assume a prophylactic effect against VTE. Patients with thrombophilia (see Table 4) should be given prophylactic LMWH, irrespective of type of vascular reconstruction. Patients with peri-operative development of stroke and expected long-term immobilization should be considered for prolonged prophylaxis below knee stockings and LMWH if there is but trivial risk of bleeding.

Acutely ill general medical patients

In three recent placebo-controlled studies with several thousand of patients^{17–19} it has been shown that either LMWH or Fondaparinux are well tolerated and provide effective thromboprophylaxis. In the MEDENOX study¹⁷ the reduction of venographic DVT was 63%, in the PREVENT study¹⁸ the reduction of the composite of clinical VTE, sudden death and proximal DVT by ultrasonography was 44% and in the ARTEMIS study¹⁸ venographic DVT and symptomatic VTE was reduced with 47%. More studies are urgently needed to further analyze clinical relevance of thromboprophylaxis in acutely ill medical patients.

Acute myocardial infarction

Several old and small studies showed that unfractionated heparin reduces the risk and mortality of PE and asymptomatic DVT after myocardial infarction. With modern heart infarction care there have been many changes which could favour thromboprophylaxis (rapid mobilisation, thrombolysis, platelet inhibitors, LMWH etc.) and an evaluation of the thromboprophylactic effect of LMWH is lacking.

Acute ischemic stroke

LMWH in high prophylactic doses diminishes the risk of PE and DVT but simultaneously increases the risk for serious bleeding.

Start of Prophylaxis

When low dose unfractionated heparin was introduced some 40 years ago prophylaxis started at pre-medication around 2 hours before surgery. This was practical since the risk period for DVT was known to be during the surgical procedure, with immobilization, defective calf muscle pump and activated coagulation. This approach has a somewhat increased risk of peri-operative bleeding, which made American surgeons reluctant to start preoperative prophylaxis. In several American studies it was shown that starting prophylaxis post-operatively was possible, with reasonably good effect. However, a randomized trial then showed that pre- and postoperative start of the LMWH dalteparin had the same effect.²⁰ A systematic review supported this finding, showing that the optimal start time for prophylaxis was between 2 hours preoperatively and 10 hours post-operatively.²¹ When Fondaparinux was introduced, it was started 6–8 hours postoperatively with excellent effect and low bleeding risk.

Duration of Prophylaxis

In most studies the prophylactic duration has been around one week. Today there are data indicating that prolonged prophylaxis (around 1 month) gives better effect after certain types of surgery. In elective hip surgery there is now evidence from a meta-analysis that prolonged prophylaxis with LMWH significantly reduces the incidence of both phlebographic asymptomatic DVT and clinically symptomatic VTE.²¹ The correlation between reduction of asymptomatic thrombosis and clinical thromboembolism is good. Prolonging prophylaxis in elective hip surgery does not increase the bleeding risk. One recent study has shown prolonged Fondaparinux prophylaxis to be beneficial in hip fracture surgery.²² Another group where prolonged prophylaxis could be of value is patients operated on for abdominal or pelvic malignancy. In a double-blind study of cancer surgery patients the frequency of phlebographic thrombosis was reduced from 12 to 5% when prophylaxis with the LMWH enoxaparin was prolonged from 1 week to 1 month.²³ In another recent open study a similar effect was obtained with the LMWH dalteparin in major abdominal surgery, reducing the frequency of phlebographic thrombosis from 16 to 7%.²⁴ Many questions remain to be answered regarding prolonged prophylaxis, i.e. the definition of risk groups (including patients not undergoing surgery), optimal duration, the value of oral thrombin inhibition and health economic

consequences. The EXCLAIM study is analyzing the potential benefit of prolonged prophylaxis in acutely ill high risk non-surgical patients.²⁵

Thromboprophylaxis and Regional Anaesthesia

A special situation arises when the combination of LMWH and spinal/epidural anaesthesia may cause a spinal/epidural haematoma with residual neurological sequelae. Low dose unfractionated heparin has been used without restrictions in patients who have been operated on under spinal anaesthesia. One case from 1989 of a possible connection between LMWH and epidural/spinal bleeding commenced a debate on the suitability of this combination. The incidence is probably low and must be put in the context of the incidence of haematomas in patients without any pharmacological haemostatic influence undergoing spinal anaesthesia. The figures vary between 0.5 and 4.5 of 100,000 spinal anaesthetics and 0.7 and 5.2 of 100,000 epidural anaesthetics.

The dominating risk factors for spinal/epidural bleeding are:

- Anatomic risk, i.e. spinal deformation, presence of vascular tumour, vascular anomaly etc.
- Presence of haemostatic defects (hereditary or acquired disease, haemostasis influencing pharmaceuticals)
- Complicated puncture or catheterisation (technically difficult puncture, several puncture trials, bloody tap).

One problem with a complication of such low incidence (also likely to occur in the absence of LMWHs) is that a randomized trial will never be performed, since it would require a very large sample size. Nevertheless it is important to obtain an understanding of the problem from available data and ensure that all cases are reported to facilitate this.

According to the seventh ACCP Consensus Conference on Antithrombotic Therapy²⁶ LMWH in combination with spinal anaesthesia can be used if some precautions are taken:

- Spinal anaesthesia should be avoided in patients with clinical bleeding disease.
- In patients given substances which affect haemostasis (i.e. acetylsalicylic acid or other platelet inhibitors) puncture should be performed when

the anticoagulant effect is minimal (usually 8–12h after injection of prophylactic LMWH).

- In cases of puncture bleeding prophylactic LMWH should be avoided.
- Removing an epidural catheter should be performed at lowest LMWH levels, i.e. immediately before the next injection.
- Prophylaxis with LMWH should not be given less than 2 h after puncture or removal of the catheter.

Summary

Today it is possible to define certain risk groups for the development of venous thromboembolism (VTE), most studies having been made on post-operative VTE. Nonetheless, the risk classification is inexact and many patients are given prophylaxis when they never would have developed VTE. However, the current prophylactic methods are safe and therefore can be used in the post-operative situation. The dominating pharmaceutical agents are unfractionated heparin, low molecular weight heparins and the pentasaccharide Fondaparinux and are usually given for 1 week after surgery. In some situations (elective hip surgery, probably hip fracture surgery and in many cases operation for malignant diseases within the abdomen/pelvis) extended prophylaxis to 1 month should be considered. Today, there are several guidelines, which should be used when deciding on prophylaxis.^{26,27} Moreover, a computer-alert program may help with compliance and thereby reduce the risk for VTE.²⁸

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