REGULAR ARTICLE

Venous thromboembolism after orthopedic surgery: Implications of the choice for prophylaxis ☆

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Abstract

Introduction: Venous thromboembolism (VTE) is an important cause of morbidity and mortality following major orthopedic surgeries. In clinical trials, fondaparinux and low molecular weight heparins have been shown to be more effective than unfractionated heparin (UFH) in preventing VTE. We retrospectively analyzed a large hospital discharge database to assess the occurrence of clinically detected VTE as a function of the injectable antithrombotic agent used for VTE prophylaxis in orthopedic surgery.
Methods: The Premier's Perspective database, representing over 500 hospitals across the US, was utilized to identify patients receiving dalteparin, enoxaparin, fondaparinux, or UFH following hip or knee replacement or hip fracture surgery between January 2003 and March 2005. The primary outcome was the proportion of patients in each cohort with a VTE, while secondary outcomes included VTE occurrence during index hospitalization, and proportion of patients with a VTE-associated hospital readmission.

Results: A total of 144,806 patients were included in the study. Significantly fewer fondaparinux patients experienced a VTE event (1.5%) compared to enoxaparin (2.3%), dalteparin (2.1%), and UFH (4.2%). After controlling for baseline covariates, the odds of experiencing a VTE was significantly higher for other treatments when compared to fondaparinux (odds ratios: dalteparin=1.22 [95% CI: 1.01 to 1.46] $p=0.0370$; enoxaparin=1.39 [1.19 to 1.62], $p<0.0001$; UFH=1.98 [1.67 to 2.34], $p<0.0001$). Significantly fewer fondaparinux-treated patients experienced an event during the index hospitalization or were readmitted for a VTE compared to other treatments.

Conclusions: Similar to clinical trial findings, patients receiving fondaparinux in this study experienced fewer VTE events following orthopedic surgeries.

Venous thromboembolism (VTE) remains an important cause of morbidity and mortality [1], resulting in over 600,000 symptomatic events and 296,000 deaths annually in the United States (US) [2]. The risk of VTE is highest in patients undergoing major surgery, particularly hip and knee replacement surgeries [3,4]. Without prophylaxis, between 40% and 60% of patients have venographically-detected postoperative deep vein thrombosis (DVT) [3,5,6] and between 0.1% and 7.5% will suffer a fatal pulmonary embolism (PE) [3,7] Therefore, the 2004 American College of Chest Physicians (ACCP) guidelines strongly recommend routine pharmacologic prophylaxis for VTE following orthopedic surgeries [3]. More specifically, for patients undergoing hip or knee arthroplasty, the ACCP recommends prophylaxis with low molecular weight heparins (LMWHs), fondaparinux, or vitamin K antagonists; while recommendations for prophylaxis in hip fracture surgery patients include fondaparinux, LMWHs, and low dose unfractionated heparin (UFH).

Each of these therapies has been studied extensively. Several clinical trials demonstrate that LMWHs have similar or greater efficacy and possibly improved safety over UFH [8–10]. More recent studies indicate that the selective factor Xa inhibitor fondaparinux is superior to the LMWH enoxaparin in VTE prophylaxis following orthopedic surgery, while a meta-analysis of four Phase III clinical trials in hip and knee surgeries revealed that fondaparinux is associated with a 55% relative risk reduction for VTE compared to enoxaparin [11,12].

However, results from these studies and their applicability to clinical practice may be limited due to strict inclusion and exclusion criteria, stringent dosing and administration protocols, and reliance on venographically-detected (rather than clinically diagnosed) VTE as a primary outcome measure. These factors limit the generalizablility of the findings. In essence, clinical trials can demonstrate the efficacy of a compound in a controlled setting, yet not its effectiveness in the setting of usual care without the artificial constraints of controlled clinical trials (*i.e.*, outcomes outside the rubric of a controlled study).

Therefore, we conducted a retrospective analysis of a large hospital discharge database to assess the occurrence of clinically detected VTE as a function of the injectable antithrombotic agent used for prophylaxis in orthopedic surgery patients. We hypothesized that the effectiveness of fondaparinux for VTE prevention in orthopedic surgery would mirror the efficacy reported in clinical trials.

Methods

Data source

This retrospective cohort analysis was conducted using data from 509 hospitals that participated in Premier's Perspective™, a HIPPA-compliant database developed for measuring quality and use of health care. Participating hospitals represent all regions of the US, are predominantly small-to mid-size non-teaching facilities, and serve a largely urban population [13–16]. The data set links deidentified, patient-level medical and pharmacy files through unique identifiers and contains all billed items, including medications, laboratory and diagnostic procedures, therapeutic services, and primary and secondary diagnoses. Demographic and payer information were obtained from identifier-linked enrollment files.

Sample selection

Patients ≥18 years of age who received dalteparin (Fragmin®; Pfizer; New York, NY), enoxaparin (Lovenox®; sanofi aventis; Bridgewater, NJ), fondaparinux (Arixtra®; GlaxoSmithKline; Research Triangle Park, NC), or UFH within one day prior or two days after hip or knee replacement or hip fracture surgery between January 2003 and March 2005 were included in the

analysis. These four study comparators were chosen since they represent the most commonly used parenteral anticoagulants indicated for VTE prophylaxis following orthopedic procedures. Patients were required to have a primary or secondary diagnosis for hip replacement (ICD-9 codes: 81.40, 81.51, 81.52, 81.53), knee replacement (81.42, 81.43, 81.44, 81.45, 81.46, 81.47, 81.54, 81.55) or hip fracture surgery (79.15, 79.35, 820) during their initial (*e.g.* index) hospitalization.

Patients were excluded from the study if they received more than one anticoagulant of interest on their first day of injectable anticoagulant therapy, received UFH only at subtherapeutic prophylactic doses (heparin flush or <5000 units), had an admitting diagnosis of VTE, or had an outpatient emergency room or hospital outpatient clinic visit including a VTE diagnosis during the three months prior to initial hospital stay. Patients meeting all selection criteria were then placed into treatment cohorts based on the first anticoagulant used during their hospitalization. If a patient's anticoagulant therapy was switched after treatment day one, all outcomes were attributed to the first agent.

Because a high proportion of VTEs occur two to five weeks following hospitalization [17], the study time period encompassed the index hospitalization plus two months postdischarge, or until in-hospital death. In addition, baseline data were collected on patients up to six months prior to their index hospitalization.

Outcomes of interest

The primary outcome measure was the proportion of patients in each cohort with a coded VTE during the study time period (index hospitalization plus the two months after discharge). Postoperative thrombotic events were identified using relevant codes from the *InternationalClassification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) and *Current Procedural Terminology* (CPT®) codes (DVT: 451.11, 451.19, 451.2, 451.81, 451.9 453.8, or 453.9; PE: 415.1, 415.11, 415.19, 459.1*x*) as reported in the hospital database. Only events that were recorded by a hospital reporting to the data source were available in the data. Secondary endpoints included the proportion of patients with a coded VTE during the index hospitalization stay and the proportion of patients who were readmitted to the hospital with a coded VTE. Additionally, VTE events were stratified into the occurrence of DVT and PE. Because safety is a concern with injectable anticoagulants, we also assessed occurrence of bleeding events and all-cause inpatient mortality. Bleeding was defined by ICD-9 codes for hemoperitoneum bleed (568.81), intracranial hemorrhage/

hemorrhagic stroke (430–432), hemorrhage complicating a procedure (998.11), or other bleeding accompanied by >2 units of blood transfused as recorded in the billing file. All-cause inpatient mortality was assessed by patient discharge status.

Comorbidity assessment

To assess comorbidities, the Charlson Comorbidity score with Deyo modification was utilized [18,19]. The Charlson–Deyo score has been shown to be valid and reliable in numerous administrative database analyses of hospitalized and nonhospitalized patients [19–23]. The calculated Charlson–Deyo summary score assigns weights for a number of major conditions (range 1 to 6). The index severity score is calculated in each patient by totaling the assigned weight for each comorbidity ranging from 0 to 33, with higher scores representing a higher burden of comorbidity.

Statistical analyses

Univariate analyses of frequencies, medians, and means with standard deviations (SD) were performed to describe the study population. Statistical differences were assessed using Chi-square tests of proportionality for categorical variables and analysis of variance (ANOVA) for continuous variables.

A step-wise parsimonious binary logistic–regression model was derived to assess differences in the proportion of patients experiencing an event between the four anticoagulants, controlling for baseline covariates which may have impacted occurrence of VTE. Baseline covariates considered include age, gender, orthopedic surgery type, comorbidities (Charlson–Deyo score), length of stay, cancer diagnosis, hypercoagulable states (*e.g.*, platelet disorder), payer type, number of hospitalizations prior to index hospitalization, mechanical ventilation, aspirin use, use of pneumatic compression stockings, warfarin use, hospital geographic location (*e.g.*, Northeast, West, Midwest, and South), hospital type (*e.g.*, teaching, nonteaching), urban *vs.* rural hospital location, and hospital bed size. The alpha level of significance was set *a priori* at ≤0.05. All analyses were carried out with the use of SAS® software (version 9.1).

Results

Patients

A total of 170,683 patients received one or more of the anticoagulants of interest and had an ICD-9 diagnostic code for major orthopedic surgery. Among

Table 1 Demographic and baseline characteristics of patients by total sample and anticoagulant cohort, $N = 144{,}806$

Patient characteristics	Total [a]	Fondaparinux	Enoxaparin	Dalteparin	Unfractionated heparin
Number of Patients (%)	144,806 (100.0)	12,532 (8.7%)	97,827 (67.6%)	16,109 (11.1%)	18,338 (12.7%)
Median age	69	68	70 $p<.0001$	69 $p<.0001$	69 $p<.0001$
% Female (n)	64.7% (93,643)	63.4% (7949)	65.2% (63,803) $p<.0001$	63.5% (10,222) $p=.9644$	63.6% (11.669) $p=.7156$
Surgery type (n)					
Hip fracture	34.2% (49,460)	20.4% (2551)	37.0% (36,237)	27.9% (4,501)	33.7% (6,171) $p<.0001$
Hip replacement	23.8% (34,397)	27.4% (3432)	$p<.0001$ 20.6% (20,186)	$p<.0001$ 32.2% (5194)	30.5% (5,585) $p<.0001$
Knee replacement	42.1% (60,949)	52.3% (6549)	$p<.0001$ 42.32% (41,404) $p<.0001$	$p<.0001$ 39.8% (6414) $p<.0001$	35.9% (6582) $p<.0001$
Payer type (n)					
Medicare	64.6% (93,502)	61% (7641)	65.4% (64,007)	61.6% (9922)	65.1% (11,932)
Commercial	28.4% (41,168)	32.6% (4083)	27.4% (26,791)	31.2% (5030)	28.7% (5264)
Medicaid	2.6% (3767	2.2% (276)	2.6% (2567)	2.8% (446)	2.6% (478)
Direct employee or Government	2.4% (3452)	2.5% (316)	2.6% (2512)	1.7% (278)	1.9% (346)
Self pay	1.0% (1439)	1.0% (123)	1.1% (1027)	1.1% (181)	0.6% (108)
Other	1.0% (1478)	0.7% (93)	0.9% (923)	1.6% (252)	1.2% (210)
Mean Charlson-Deyo Comorbidity score [b] (±SD)	0.91 (1.3)	0.77 (1.2)	0.93 (1.4) $p<.0001$	0.85 (1.3) $p<.0001$	0.98 (1.4) $p<.0001$
Most common daily dose	–	2.5 mg	40 mg	5000 units	10,000–15,000 units
Average duration of therapy	–	3.5±1.9	3.9±2.9	3.7±2.5	3.4±4.0
Rate of switching parenteral anticoagulant therapies	–	2.8%	1.8%	2.7%	26.6%
Mean length of hospital stay in days (±SD)	5.1 (4.3)	4.4 (2.6)	5.1 (4.1) $p<.0001$	4.6 (3.3) $p<.0001$	5.6 (6.2) $p<.0001$
Mean number of inpatient hospitalizations 6 months prior to index visit (±SD)	.07 (0.3)	0.05 (0.3)	.07 (0.3) $p<.0001$	0.06 (0.3) $p=.3085$	.07 (0.3) $p=.0002$
% that received warfarin (n)	19.1% (27,618)	13.3% (1672)	14.9% (14,583) $p<.0001$	21.1% (3392) $p<.0001$	43.5% (7971) $p<.0001$
% that received aspirin (n)	10.1% (14,663)	6.8% (852)	10.0% (9740) $p<.0001$	7.8% (1251) $p=.0019$	15.4% (2820) $p<.0001$
% that required mechanical ventilation (n)	0.09% (126)	0.13% (16)	0.06% (59) $p=.0078$	0.23% (37) $p=.0494$	0.08% (14) $p=.1598$
% using compression stockings (n)	60.0% (86,931)	63.0% (7897)	58.7% (57,442) $p<.0001$	68.7% (11,071) $p<.0001$	57.4% (10,521) $p<.0001$

p values represent differences between comparisons of agents *vs.* fondaparinux.
[a] Numbers may exceed 100% due to rounding.
[b] Ranges 0–29, higher scores indicate higher comorbidity.

Table 2 Proportion of patients experiencing a coded VTE by injectable anticoagulant for orthopedic surgeries

Outcome time horizon	Fondaparinux (N = 12,532)	Enoxaparin (N = 97,827)	Dalteparin (N = 16,109)	Unfractionated heparin (N = 18,338)
Total study period, % (n)	1.5% (n = 184)	2.3% (n = 2292) p < 0.0001	2.1% (n = 344) p < 0.0001	4.2% (n = 766) p < 0.0001
During hospitalization for orthopedic surgeries	0.7% (n = 85)	1.2% (n = 1212) p < 0.0001	0.9% (n = 152) p = 0.0144	3.2% (n = 594) p < 0.0001
Within two months after orthopedic surgeries	0.9% (n = 115)	1.3% (n = 1249) p = 0.0006	1.4% (n = 227) p = 0.0002	1.3% (n = 233) p = 0.0041

p values represent differences between comparisons of agents *vs.* fondaparinux.

this group, 15.2% (n = 25,877) met one or more documented exclusion criteria. The most common reasons for exclusion were the absence of a documented anticoagulant within two days of surgery (n = 13,694), subtherapeutic prophylactic UFH doses (n = 5449), and no recorded surgery day (n = 3920). Therefore, 144,806 patients were included in the final study sample.

Table 1 presents the baseline characteristics of the study population. Enoxaparin was overwhelmingly the most frequently prescribed anticoagulant, with 67.6% (n = 97,827) of the study population receiving this agent. The median age of the total sample was 69 years and 64.7% were women. The most common payer source was Medicare (64.6%). A total of 42.1% were undergoing knee replacement surgery, 34.2% had hip fracture surgery, and the remaining 23.8% had a hip replacement procedure. The mean length of hospital stay was 5.1 days.

Those given fondaparinux spent less time in the hospital compared to patients treated with the other agents (Table 1). Patients receiving UFH were more likely to be concurrently treated with aspirin or warfarin and to have a higher comorbidity index compared to the other drug cohorts. Use of pneumatic compression stockings was generally similar across the cohorts, while a higher proportion of dalteparin-treated patients required mechanical ventilation.

Anticoagulant dosing and duration

During their inpatient stay, 91% of patients treated with fondaparinux received 2.5 mg per day (Table 1). The most common daily doses in the enoxaparin group were 40 mg (40%) or 60 mg (26%); while 26% of patients received 2500 units and 58% of patients received 5000 units in the dalteparin group. The low dose prophylaxis regimen was given most commonly in the UFH group, with 54% of patients receiving 10,000 to 15,000 units per day. The average duration of anticoagulant therapy was

longest in the enoxaparin group (3.9 days) and switching parenteral anticoagulant therapies was most common in the heparin cohort (26.6%).

Primary outcome

Of the total eligible patients, 2.5% (n = 3586) experienced a VTE during the study period. As shown in Table 2, significantly fewer fondaparinux patients suffered a VTE (1.5%) compared to each other agent studied. Fondaparinux was associated with a relative risk reduction ranging from 27.9% when compared to dalteparin (95% CI: 6.1% to 44.6%) to 78.1% when compared to UFH (95% CI: 73.7% to 83.3%).

After controlling for baseline covariates (as enumerated in the Methods section), patients on fondaparinux were least likely to experience a VTE. As shown in Fig. 1, the odds of experiencing a VTE event for each anticoagulant when compared to fondaparinux were: dalteparin OR = 1.22 (95% CI:
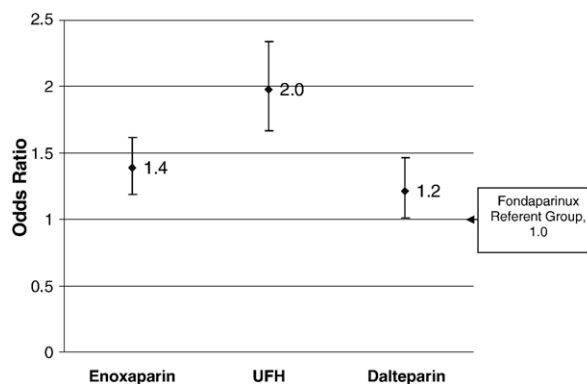
Figure 1 Odds ratio of experiencing a VTE event for enoxaparin, unfractionated heparin, and dalteparin compared to fondaparinux (adjusted). Pearson's Chi-square: fondaparinux *vs.* enoxaparin (p < 0.0001), unfractionated heparin (p < 0.0001), dalteparin (p = 0.0370). Error bars represent the 95% confidence intervals surrounding the adjusted odds ratio.

1.01 to 1.46, $p=0.0370$); enoxaparin OR = 1.39 (95% CI: 1.19 to 1.62, $p<0.0001$); UFH OR = 1.98 (95% CI: 1.67 to 2.34, $p<0.0001$). Other variables in the model that significantly increased the risk of VTE by at least 20% included cancer diagnosis (OR = 1.3, 95% CI: 1.14 to 1.49), warfarin use (OR = 1.5, 95% CI: 1.37 to 1.61), mechanical ventilation (OR = 2.3, 95% CI: 1.16 to 4.70), and hospital geography (Northeast OR = 1.7, 95% CI: 1.51 to 1.83). Hip replacement surgery (relative to other surgical procedures was the only variable that was significantly correlated with a decreased incidence of VTE (OR = 0.6, 95% CI: 0.57 to 0.71).

Secondary endpoints

The overall proportion of patients experiencing a coded VTE during the index hospitalization was 1.4%, while the proportion of patients experiencing an event after discharge was 1.3% (Table 2). Significantly fewer fondaparinux-treated patients experienced an event during their initial hospitalization and postdischarge (requiring readmission) when compared to each other therapy studied.

The distribution of DVT *vs*. PE did not differ clinically as a function of the anticoagulant utilized. Specifically, DVT accounted for 71% of VTEs diagnosed among those receiving fondaparinux, *vs*. 81% for dalteparin, 73% for enoxaparin, and 71% for UFH.

With respect to safety and complications, bleeding events and all-cause inpatient mortality were infrequent in the entire population. Bleeding occurred in 1.5% of persons given fondaparinux and in 1.5% of those treated with any form of LMWH ($p=$NS). Subjects receiving UFH for VTE prophylaxis suffered 25% more bleeding events than those on fondaparinux (OR 1.27, 95% CI: 1.06−1.52, $p=0.021$). All-cause inpatient mortality was significantly lower in patients receiving fondaparinux (0.6%) compared to those who received LMWH (1.1%, $p<0.001$) or UFH (2.2%, $p<0.001$).

Discussion

This large, retrospective analysis confirms the differences noted in the controlled settings of clinical trials of fondaparinux for VTE prophylaxis in orthopedic surgery. Compared to UFH and two LMWHs, we observed that fondaparinux is associated with a significant reduction for VTE complicating orthopedic procedures. More importantly, the magnitude of risk reduction with fondaparinux is similar to that reported in the clinical trials [24–26]. In other words, we were able to verify the results of these earlier studies from an effectiveness, rather than an efficacy, perspective. The differences

documented arose independent of multiple potential confounders, including underlying VTE risk factors, disease severity, type of surgery, and process of care.

Several distinctions between the earlier trials and our analysis merit comment. Most importantly, the endpoints varied between the two approaches. In the majority of the clinical trials, assessment for VTE ended on day eleven, while this study assessed a longer period. This is particularly important as the risk for VTE often peaks late after hip surgery. As a result, clinicians require confirmatory information that documents the sustained efficacy of any prophylactic strategy.

Additionally, the randomized studies mandated a screening assessment (either venographic or ultrasound) at the end of the study if the patient had not suffered a clinical VTE event. The importance of clinically silent VTE in this setting, which accounted for the vast majority of all the VTEs detected in the trials, is unknown. We, however, only identified clinically documented events since subjects in the US are not routinely screened for VTE following orthopedic surgery. This fact explains why the VTE rate we report is substantially less than the rates observed in the clinical trials. Nonetheless, we still were able to identify an independent risk reduction with fondaparinux *vs*. both LMWHs and UFH.

Our analysis has several important strengths. First, our study population is perhaps the largest ever studied in this area. Examining outcomes in over 144,000 subjects provided important statistical power and allowed us to detect significant differences which otherwise might have been missed. Second, because of the size of the database we could control for multiple, important confounders. Confounders included not only underlying risk factors for VTE, but also measures of severity of illness, and process of care. This aspect of our investigation along with our sample size underscores the robustness of our findings. Third, that we were able to study multiple hospitals in the US illustrates the generalizability of our conclusions. Our population, as shown by its demographics, was representative of the patients undergoing orthopedic surgeries in the US. Similarly, the geographic distribution of the institutions was diverse and incorporated information from both teaching and nonteaching facilities.

Economically, given the burden of VTE, even small differences in the occurrence of VTE as a function of prophylaxis may affect financial outcomes for third party payers and healthcare institutions. From the third party payer perspective, treatment of a VTE following orthopedic surgery results in nearly $12,200 in additional costs, and the major driver of cost in

postorthopedic surgery VTE is the need for readmission [27]. Hence, any intervention that minimizes the risk for VTE can be financially attractive. Indicating the potential for cost savings with fondaparinux, along with a reduction in VTEs overall, we documented lower rates of hospital readmission with fondaparinux use. For institutions, VTEs diagnosed during the initial hospitalization prolong length of stay without necessarily leading to higher reimbursements. For administrators, therefore, enhancing VTE prevention can represent a mechanism for limiting the impact of un-reimbursed care.

Our study has several significant limitations. First, by design, the analysis was retrospective. Hence, it was prone to multiple forms of potential bias and confounding. However, our objective was to attempt to confirm if the findings from clinical trials translated into measurable differences in a less controlled clinical setting. As such, the only mechanism to explore this was through use of a registry. Second, because of reliance on administrative data, we were limited as to the data we could collect and analyze. Specifically, we lacked precise information on the timing of administration of prophylactic agents. Similarly we could not control for all potential confounders such as obesity or renal dysfunction, as these covariates are not well captured in administrative data. Moreover, any effort at modeling to capture confounders is essentially only as robust as the effort one makes to enter potential variables into a model when adjusting for risk. In that same vein, errors in coding may have systematically influenced our observations. It seems, though, that there is no reason to assume that complications or events would be either more or less precisely captured as a function of the anticoagulant utilized for VTE prevention. In other words, either over- or under-coding of events of interests should have occurred across the dataset rather than be skewed in favor of (or against) one agent. Third, because our period of observation extended beyond the initial hospitalization, we may have missed outcomes that were not treated at the initial hospital where the surgery took place. Patients may have had their surgery at one institution but sought care for a VTE or bleed after discharge at another facility. To adjust for this concern, we performed a subanalysis which was limited to events only occurring during the index hospitalization. The results from this effort were consistent with our overall findings and should somewhat allay the concern about missing events. Furthermore, anecdotally, when patients do suffer complications they do tend to follow up with their primary surgeon who in turn refers the subject back to the hospital where the surgery transpired. Some complications may also have been treated purely on an outpatient basis. We doubt this happened frequently since most postoperative subjects needing full anticoagulation are admitted to the hospital initially to facilitate this. Nonetheless, because of the nature of our study we cannot exclude any of these possibilities. Fourth, we did not have information regarding the use of extended out of hospital prophylaxis. Despite each of these important limitations, we believe our findings enhance our understanding of how choices for VTE prophylaxis affect clinical outcomes. Nevertheless, from a health services research perspective, our results can only be seen as confirming the observations of randomized trials and as generating future hypotheses that warrant formal investigation.

In this large hospital dataset, patients receiving fondaparinux experienced lower rates of clinically diagnosed VTE relative to dalteparin, enoxaparin, and UFH. This finding is consistent with the results of multiple randomized controlled trials and is independent of multiple potential cofactors that alter the risk for VTE.

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