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Full Length Article

Worldwide adherence to ACCP guidelines for thromboprophylaxis after major orthopedic surgery: A systematic review of the literature and meta-analysis



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ABSTRACT

Introduction: Increased risk of venous thromboembolism following major orthopedic surgery (MOS) is well described. The American Academy of Chest Physician (ACCP) has generated evidence-based recommendations for thromboprophylaxis; however, there is a gap between guidelines recommendations and clinical practice. The aim of this study is to compare worldwide adherence rates to the last 4 editions of ACCP guidelines for thromboprophylaxis after MOS.

Materials and methods: A systematic review of literature and meta-analysis was performed. Studies reporting adherence to ACCP guidelines between January 2004 and October 2014 were included. Adherence rates after MOS for in-hospital (IH), extended (EXT), and global thromboprophylaxis (in-hospital plus extended) were assessed. *Results*: Of 3993 titles, 13 studies reporting data of 35,303 patients were selected. Studies assessing the 6th, 7th or 8th editions of ACCP guidelines were found. No studies evaluating the 9th edition were available. For MOS, global adherence rates for the 6th, 7th and 8th editions were 62% (95% CI: 61%–63%), 70% (95% CI: 69%–71%), and 42% (95% CI: 41%–43%), respectively. Likewise, in-hospital adherence was 52% (95% CI: 50%–54%), 51% (95% CI: 50%–52%) and 85% (95% CI: 84%–86%). For extended prophylaxis, adherence rates were reported only for the 8th edition (59%; 95% CI: 58%–60%).

Conclusions: Adherence to ACCP recommendations for thromboprophylaxis during hospitalization has increased over time. Nevertheless, adherence rates to global thromboprophylaxis decrease due to an insufficient implementation of recommendations after discharge.

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1. Introduction

One of the most common complications after joint replacement surgery is venous thromboembolism [1–3]. The risk of developing this complication increases with age, weight and previous history of thromboembolic disease [4]. Incidence of symptomatic venous thromboembolism has been reported in the literature in approximately 2.8% of patients undergoing hip arthroplasty and 2.1% of knee arthroplasty patients [5]. Furthermore, in absence of adequate prophylaxis, this complication can occur between 41 and 85% when non-symptomatic events are included [6,7].

Due to the preventable nature of this disease, pharmacological prophylaxis has become a standard of care for patients undergoing major orthopedic surgery [8]. Different organizations such as the American College of Chest Physicians [9], the American Academy of Orthopedic Surgeons [10], and the National Institute for Health and Care Excellence [11] have developed evidence-based clinical practice guidelines for appropriate use of thromboprophylaxis [12,13].

During the past 28 years, the American College of Chest Physicians has published nine editions of their guidelines for Prevention of Venous Thromboembolism [14], including recommendations for elective hip and knee surgery and patients with hip fractures, from the third edition onwards [15]. These guidelines comprise data obtained from systematic reviews of the literature and generate recommendations from the best evidence available [16]. However, there is a gap between real-life clinical practice and the implementation of these recommendations, thus increasing the incidence of postoperative thromboembolic events [5,16].

Several multi-center studies evaluating adherence to ACCP guidelines for VTE prevention after major orthopedic surgery have been carried out [17–20]. Nevertheless, to our knowledge, there are no reports in the literature that provide evidence of the evolution of adherence rates through time. The aim of this study is to compare the worldwide



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adherence to ACCP guidelines for thromboprophylaxis after MOS during the last 10 years.

2. Materials and methods

2.1. Search strategy and study selection

A systematic review of the literature was performed in Medline, Embase, and Cochrane databases using a combination of MeSH and free text terms related to venous thromboprophylaxis for major orthopedic surgery and guidelines adherence (see appendix 1). Search strategy was adapted according to each database. No language limits were used. References of selected articles were also reviewed. Contact with authors was established when full text articles were not available or in cases in which additional information regarding reported outcomes was required. Last search was performed in October 2014.

Studies reporting adherence rates to the last four editions (6th, 7th, 8th, and 9th) of ACCP guidelines for VTE prevention after hip or knee replacement and hip fracture surgery, for global (combining in-hospital and extended), in-hospital (IH), or extended regimes (EXT), were considered for inclusion. Surveys and studies in patients with full anticoagulation therapy were excluded.

Titles and abstracts related to the subject of study were selected; from these, articles that fully met inclusion criteria were screened and assessed for methodological quality with The Methodological Index for Non-Randomized Studies (MINORS) [22].

2.2. Data extraction

From each study data of adherence rates (absolute values and percentages) by type of surgery, type of prophylaxis (inpatient/extended/ global), ACCP edition evaluated, author, year of publication, country of origin, countries assessed, and number of patients included in the study were obtained. From multi-center studies, rates of adherence reported for each country included were extracted independently. Data was registered in a Google Sheets® database by two authors and audited by a senior author.

2.3. Statistical analysis

Adherence rates were calculated as the proportion of patients who were classified according to each study as "adherent" over the total number of patients included in the analysis. Rates of adherence by type of surgery, prophylaxis regime, country of origin and edition were calculated from extracted data. Data was also grouped in the following regions: North America, Latin America and the Caribbean, Europe, Africa, Asia and Oceania. A chi-square (χ^2) test was used to assess statistical significance of differences between countries and a pvalue < 0.05 was considered significant. Ninety-five percent confidence intervals (95% CI) were calculated for differences.

To assess in-hospital, extended and global (in-hospital plus extended) adherence for each guideline and to compare rates of adherence between editions, a meta-analysis of the studies available was performed through a fixed effect model. Studies included in the meta-analysis were selected according to the data reported by each author (Table 1). Analysis for all orthopedic surgery patients and subgroup analysis by type of surgery (hip replacement, knee replacement, hip fracture surgery) was completed. Considering that the effect measure (rate of adherence) is a proportion, statistical methods to model binomial data were used.

Ninety-five percent confidence intervals (95% CI) for each study were calculated by the confidence limits of an exact binomial proportion (Clopper-Pearson). For the estimation of the pooled proportions and their 95% CI, an approximate likelihood approach was used, transforming a binomial distribution to the normal by the Freeman-Tukey arcsine double transformation model. p-Values and Z statistics

Chudu/Vaar	Country	MINORG	MINORS ^a Edition Total	Total	nemezcluer niH	ramarc	,			Knee	Knee rentscement	mant			Ë	o fractura	111001110			41	All orthonodic nation ts	io natio	ote		
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GLORY [20] 2008	Global	16	6th	7832	2189 3	3775				2645	5 4057									48	4834 7832				
Yu [23] 2007	NSA	14		2324																11	1217 2324				
ENDORSE [18] 2010	Global	16	7th	2300																16	1979 2300				
ETHOS [19] 2012	Europe	16		4388	1411 2217	2217				955	5 1059				701	1 1112				30	3067 4388				
Robinson-Cohen	Canada	22		227																		213	227		
[24] 2011																									
Amin [25] 2010	USA	14		6666		~	789 21	2106				1506	3746				139	814				2434	6666		
Eikelboom [26] 2004	Australia	14		396																		204	396		
DEIMOS [17] 2013	Global	16	8th	2162	254	646 5		646 372	2 646	6 437	7 740	621	740 4	455 7	740 292	2 776	702	776	542 7	776 9	983 2162	1853	2162	1371	2162
Tiryaki [27] 2011	NSA	14		98			20	28				16	53				13	17				49	98		
Selby [5] 2012	Canada/USA 14	A 14		3497																1	1395 3497				
Amin [28] 2011	NSA	14		5315																		4517	5315	3104	5315
MacElwee [29] 2010	Canada	16		170				51	4 51	1		2	56	ŝ	56		25	63	12	63		33	170	19	170
Zoubida [30] 2014	Morocco	15		22			7	6				4	9				7	7				18	22		
^a 14 to 15 points: acceptable methodological quality; 16 to 22 points: ideal methodological quality	eptable meth	odological qu	ality; 16 to	o 22 points:	ideal me	thodolc	spical qui	ality.																	
^b Number of patients adherent to ACCP recommendations.	adherent to	ACCP recomm	nendations																						
 Number of patients analyzed. 	analyzed.																								

were used to determine statistical significance of the differences between pooled adherences. Results are reported in forest plots.

All analyses were performed with statistical software STATA/IC version 12.0.

2.4. Risk of bias

Publication bias was not assessed in this systematic review. All studies included were observational and descriptive. As adherence was defined and assessed according to different parameters in each study, misclassification and information bias, as well as high heterogeneity, can be expected. Similarly, assessment of adherence within different regions could represent an additional risk of bias, due to natural variation in populations and clinical practices. On the other hand, among selected studies, multi-center registries with large, representative and homogeneous samples were included, reducing the risk of selection bias. Reports of bias within each study were also assessed using the MINORS scale [21]. Data extraction and calculation was carried out manually in order to avoid false estimates and duplication of information.

3. Results

A total of 3993 titles were identified. From these, 3725 titles unrelated to the subject of study were excluded. The abstracts of the remaining 268 titles were examined, but 212 additional titles were also excluded because they did not contain information regarding adherence to ACCP guidelines. In the outstanding 56 articles, we eliminated 7 duplicates. Lastly, 49 potentially eligible studies were assessed with the MINORS scale. Thirty-six articles were further eliminated and a total of 13 studies including data from 35,303 patients were selected for final analysis (Fig. 1). All selected articles were cohort studies [5,17–19, 23–31].

Six studies obtained a score of 14 in the MINORS scale [5,24,26–29], one study obtain a score of 15 [31], five studies obtained a score of 16 [17–20,30] and one study a score of 22 [25]. This indicates that all

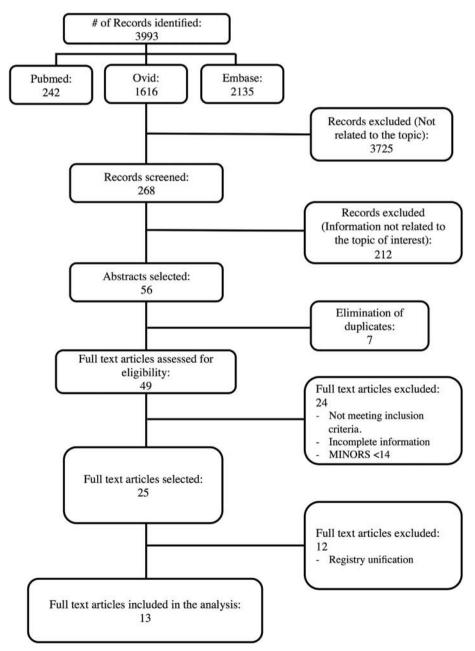


Fig. 1. Flowchart of selection of studies.

studies are at least of acceptable methodological quality [22]. Study characteristics are summarized in Table 1.

Studies assessing the 6th, 7th and 8th editions were included. No studies evaluating the 9th edition were found. Two articles evaluated ACCP guidelines published in 2001 (6th Ed.) [20,24], five articles evaluated those published in 2004 (7th Ed.) [18,19,25–27] and six articles evaluated the 2008 guidelines (8th Ed.) [5,17,28–31]. In all studies, the proportion of adherence to recommendations from ACCP guidelines for VTE prophylaxis after mayor orthopedic surgery was evaluated.

For total hip replacement, three studies reported global adherence (in-hospital and extended regime) [17,19,20], six reported in-patient adherence [17,19,26,28,30,31] and two reported adherence to extended regime [17,30]. For knee replacement three studies [17,19,20], six studies [17,19,26,28,30,31] and two studies [17,30] reported global, in-patient and extended adherence respectively. Global adherence to recommendations for hip fracture surgery, was reported in two studies [17,19], in-patient adherence in six studies [17,19,26,28,30,31] and extended adherences in two studies [17,30]. From all 13 studies included, 38.5% reported adherence to in-patient regime [17,19,28,29,31], 30.8% reported adherence to extended regime [17,19,29,30] and 69.2% to global adherence [5,17–20,24–27] (Table 1).

3.1. Worldwide adherence

From the systematic review of the literature, it was observed that North America was the only region that reported adherence rates to the 6th edition, but all 6 regions reported rates of adherence to the 7th edition. North America, Latin America and the Caribbean, Asia and Africa reported adherence to the 8th edition. Europe and Oceania reported only adherence to the seventh edition (Table 2).

Only eight countries had at least two different measurements within the last 10 years that could be compared. The percentage of adherence in five countries decreased. A comparison between the 6th and the 7th edition was performed for United States and a decrease of 15.9% (p < 0.005) in the rate of adherence was found. Similarly, as shown in Table 2, rates of adherence for Brazil, Mexico, Egypt and Venezuela decreased between the seventh and the eighth editions. Colombia, Saudi Arabia and United Arab Emirates evidenced an increase in adherence rates.

3.2. Adherence rates for all orthopedic patients

A meta-analysis was performed in order to identify the progression through time of the adherence rates to ACCP guidelines for thromboprophylaxis after MOS. For all orthopedic patients global adherence (in-hospital plus extended) to the sixth edition was 62% (95% CI: 61%–63%), to the seventh edition was 70% (95% CI: 69%–71%) and 42% (95% CI: 41%–43%) to the eighth edition (Fig. 2). In-hospital adherence was nearly unchanged between the sixth (52%; 95% CI: 50%–54%) and the seventh edition (51%; 95% CI: 50%–52%) (p = 0.084), but a significant increase was observed in the eighth edition (85%; 95% CI: 84%–84%) (p < 0.05) (Fig. 3). Adherence rates to extended regime were

Table 2

Reported rates of adherence to ACCP guidelines from different countries by year of edition.

Region/Country	Ν	6th Ed. (2001)	Ν	7th Ed. (2004)	p-Value	Ν	8th Ed. (2008)	p-Value ^a	p-Value ^b
Africa				93.5%					
Algeria			23	100%					
Egypt			8	75%		360	26.10%		< 0.005
Tunisia			0			277	51.80%		
Morocco			0			301	59.90%		
Asia									
Kuwait									
India			30	26.70%		100	61.70%		
Pakistan			3	33.30%					
Russia			61	63.90%					
Saudi Arabia			13	38.5%		121	62.0%		< 0.005
United Arab Emirates			13	61.50%		22	63.6%		0.901
Europe			4388	72.7%					
Bulgaria			113	96.50%					
Czech Republic			110	92%					
France			85	85.90%					
Germany			206	96.10%					
Greece			78	98.70%					
Hungary			28	100%					
Ireland			22	81.80%					
Poland			74	97.30%					
Portugal			57	84.20%					
Rumania			124	94.40%					
Slovakia			81	96.30%					
Spain			137	99.30%					
Switzerland			94	89.40%					
United Kingdom			281	77.60%					
Latin America and the Caribbean									
Brazil			19	68.40%		250	31.20%		< 0.005
Colombia			12	50%		244	74.20%		< 0.005
Mexico			11	81.80%		253	15.4%		< 0.005
Venezuela			2	100%		243	49.8%		< 0.005
North America									
United States of America	3031	55.72%	471	38.3%	< 0.005				
United States of America	2324	52.40%							
Canada			237	93.80%					
USA/Canada						3497	39.89%		
Oceania									
Australia			73	94.5%					
Australia			396	51.5%					

^a p-Value comparing rates of adherence between 6th and 8th editions.

^b p-Value comparing rates of adherence between 7th and 8th editions.

Study	Adherent	Total				ES (95% CI)	% Weight
6th ACCP				1			
GLORY, 2008	4834	7832		=		0.62 (0.61, 0.63)	100.00
7th ACCP							
ETHOS, 2012	3067	4388			•	0.70 (0.69, 0.71)	100.00
Bth ACCP							
Selby, 2012	1395	3497		1		0.40 (0.38, 0.42)	61.79
DEIMOS, 2013	983	2162	-			0.45 (0.43, 0.48)	38.21
Subtotal			\diamond			0.42 (0.41, 0.43)	100.00
Overall				¢		0.58 (0.57, 0.58)	
		.3	.4 .5	.6	.7	1	

All Orthopaedic Patients ACCP Guidelines Global (IH+EX) Adherence

Fig. 2. Forest plot of global adherence to ACCP guidelines for all orthopedic patients.

reported only for the eighth edition and the overall rate was 59% (95% CI: 58%–60%) (Fig. 4).

3.3. Analysis by type of surgery

For hip replacement surgery, global adherence rate to the 6th edition was 58% (95% CI: 56%–60%), 64% (95% CI: 62%–66%) to the 7th edition

and 39% (95% CI: 36%–43%) to the 8th edition. A difference of -18.7% (95% CI: -14.6% to -22.8%) was observed between 6th and 8th edition. Adherence rates for knee replacement were 65% (95% CI: 64%–67%), 90% (95% CI: 88%–92%) and 59% (95% CI: 55%–63%), respectively (difference of rates: -6.1% (95% CI: -2.3 to -10) between the 6th and 8th edition). For hip fracture surgery, only the seventh and the eighth editions were compared and a variation of -25.4% (95% CI:

All Orthopaedic Patients ACCP Guidelines Intrahospital Adherence

Study	Adherent	Total				ES (95% CI)	% Weight
6th ACCP				1			
Yu, 2007	1217	2324		•		0.52 (0.50, 0.54)	100.00
7th ACCP							
Eikelboom, 2004	204	396		-		0.52 (0.47, 0.56)	4.13
ENDORSE, 2010	1979	2300				0.86 (0.85, 0.87)	23.99
Amin, 2010	2434	6666				0.37 (0.35, 0.38)	69.51
Robinson-Cohen, 2011	213	227		i i	-	0.94 (0.90, 0.96)	2.37
Subtotal				٥		0.51 (0.50, 0.52)	100.00
8th ACCP							
Tiryaki, 2011	49	98	-			0.50 (0.40, 0.60)	1.30
Amin, 2011	4517	5315			-	0.85 (0.84, 0.86)	70.16
DEIMOS, 2013	1853	2162		1		0.86 (0.84, 0.87)	28.54
Subtotal					٥	0.85 (0.84, 0.86)	100.00
Overall				0		0.66 (0.65, 0.66)	·
			3.4	.5 .6 .	7.8.9		

Fig. 3. Forest plot of in-hospital adherence to ACCP guidelines for all orthopedic patients.

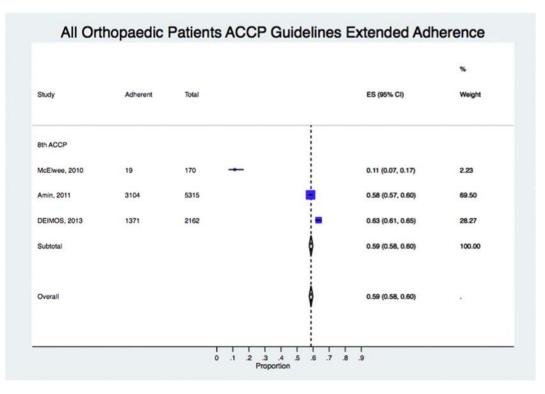


Fig. 4. Forest plot of extended adherence to ACCP guidelines for all orthopedic patients.

-21% to -29.8%) was found. Detailed rates of adherence to global, inhospital and extended thromboprophylaxis by type of surgery are shown in Table 3.

4. Discussion

The American College of Chest Physicians guidelines for venous thromboembolism prophylaxis summarizes evidence-based data in a well-organized manner and provides recommendations that can be implemented in order to standardize clinical care. These guidelines are perceived as one of the most important tools for prevention of thromboembolic disease after major orthopedic surgery [13,31]. Since pharma-cologic prophylaxis has demonstrated to reduce the incidence of this complication from 30% to around 2% for both hip and knee replacement surgery [8,16], encouraging physicians to prescribe adequate thromboprophylaxis is determinant to prevent increased morbidity and costs associated with this complication.

Over the 3 editions compared in this review, few modifications to the ACCP recommendations have been made. The sixth edition [32] established the use of Low Molecular Weight Heparin (LMWH) and Warfarin as VTE prophylaxis after major orthopedic surgery, recommended the use of intermittent pneumatic compression as an alternative to pharmacologic prophylaxis for knee surgery, and the extended regime length was 7 to 10 days after surgery. The seventh edition [33] included Fondaparinux and increased the length of extended prophylaxis for hip replacement and hip fracture surgery to a minimum of 10 days and an ideal period of 28 to 35 days. The eighth edition [7], in 2008, included new oral anticoagulants, recommended the solely use of intermittent pneumatic compression as VTE prophylaxis for hip replacement or hip fracture surgery in patients with increased risk of bleeding and the extended prophylaxis regime for knee surgery changed from 10 days to a period of 28 to 35 days.

Several multicenter studies have measured adherence to ACCP guidelines for VTE prophylaxis and have shown variable results [17–20]. However, to our knowledge there are no reports in the literature that describe variations in the rates of adherence through time or the effect of the changes in the recommendations depending on new evidence available.

Despite major efforts to ensure systematic implementation into clinical practice [31,34], our results also demonstrated that adherence to ACCP guidelines has decreased significantly over the last 10 years and the gap between the guidelines recommendations and their implementation in clinical practice is still present [5,34–37].

After comparing the 6th and the 8th edition, global adherence rates (combining in-hospital and extended) for all orthopedic patients decreased over time (Fig. 2). This reduction was also observed when pooled global adherence rates were calculated by type of surgery (Table 3). Conversely, in-hospital adherence rates increase as new guidelines are published. Even though adherences rates for the extended regime were available only for the 8th edition, a pooled rate of 59% for all orthopedic patients is lower compared to what had been previously described in the literature [38–40]. This insufficient rate of

Table 3

Rates of adherence to different editions of	ACCP guidelines by type of surgery.
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	Hip replaceme	ent		Knee replacem	ient		Hip fracture su	rgery	
Edition	Global	IH	EXT	Global	IH	EXT	Global	IH	EXT
	% (95% CI)								
6th	58 (56-60)			65 (64-67)					
7th	64 (62-66)	37 (35-40)		90 (88-92)	40 (39-42)		63 (60-66)	17 (15-20)	
8th	39 (36-43)	78 (75–81)	53 (50-57)	59 (55-63)	77 (74–80)	57 (54-60)	38 (34–41)	69 (66–72)	66 (63-69)

adherence to discharge recommendations of thromboprophylaxis after MOS might explain why pooled global adherence for hip and knee replacement and hip fracture surgery are decreasing. This difference was also observed in the rates of adherence reported by country. Countries in North America, Latin America and the Caribbean and Africa evidenced a significant decrease in the rates of adherence while countries in Asia were the only ones in which the rates of adherence increased (Table 2).

In a systematic review carried out in 1999 by Cabana and colleagues, lack of awareness, lack of agreement with the recommendations, outcome expectancy, and ability to change current practices, were identified as the most common barriers to physician's adherence to clinical practice guidelines [41]. In addition, other factors that could be associated with our findings are the introduction of new oral anticoagulants [42], the presentation of aspirin as an effective strategy for VTE prophylaxis before they were officially included in the ACCP guidelines [16,43], and the implementation of the recently developed NICE and AAOS guidelines. Given that the latest editions of both ACCP and AAOS guidelines include the use of Aspirin for VTE prophylaxis and are now in close agreement, an increase in the rate of adherence could be expected. This increase, if any, would not be due to improved physician's compliance but to more flexible guidelines. Whether these new recommendations could increase rates of VTE after major orthopedic surgery remains to be determined

The main limitation of this study is the heterogeneity within studies due to the diverse assessment of adherence in different populations of patients undergoing major orthopedic surgery. However, the results from the worldwide analysis and independent analysis by type of surgery and the reported rates of adherence by countries, showed a similar statistically significant decrease in the rate of adherence with the eighth edition of ACCP guidelines compared to previous editions. Another limitation of this study was that it was not possible to extract data for each outcome assessed in this review from every study selected, as shown in Table 1.

On the other hand, there are four major strengths of this study: 1) the amount of patients included in the final analysis, 2) assessment of adherence was performed objectively by comparing actual clinical practice against ACCP recommendations in all studies, 3) this assessment strategy has not varied during the last 10 years and 4) consistency of results regardless the analysis by country or type of surgery, becomes itself a strength of this study.

We can conclude that adherence to ACCP guidelines has not improved over time and the decrease in the rate of patients that receive VTE prophylaxis according to their recommendations is significant. However, adherence to in-hospital recommendations seems to be increasing, therefore global reduction in adherence rates are more likely to be a result of an insufficient implementation of outpatient recommendations. According to these results, guideline developers and institutions should encourage physicians and patients to adhere to the extended regime of VTE prophylaxis after major orthopedic surgery.

Supplementary data to this article can be found online at http://dx. doi.org/10.1016/j.thromres.2016.03.029.

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