Recommendations from the ICM-VTE: Hip & Knee

The ICM-VTE Hip & Knee Delegates*

1 - Is VTE after elective total joint arthroplasty a "never event"?

Response/Recommendation: Venous thromboembolism (VTE) after elective total joint arthroplasty (TJA) continues to occur despite various strategies in prophylaxis and should not be considered a "never event."

Strength of Recommendation: Moderate.

Delegates vote: Agree 94.87% Disagree 5.13% Abstain 0.00% (Strong Consensus).

Rationale: As part of an initiative to address quality of care and control healthcare costs, in 2002, the United States Centers for Medicare and Medicaid Services (CMS) defined "never events" as hospital-acquired conditions that were considered reasonably preventable[1]. In 2008, CMS added deep venous thrombosis (DVT) and pulmonary embolism (PE) following total knee arthroplasty (TKA) and total hip arthroplasty (THA)[2].

Historically, DVT and PE were important risks for patients undergoing TJA. In a study of 7,959 patients between 1962 and 1973, Charnley et al., reported a non-fatal PE rate of 7.89% and a 1.04% rate of fatal PE which constituted the highest single cause of death after a THA[3]. Coventry et al., identified a cohort of 2012 THA from 1969 to 1971 of which 58 did not receive chemoprophylaxis past post-operative day five and observed a DVT rate of 3.4%, a non-fatal PE rate of 5.2%, and a fatal PE rate of 3.4%[4,5]. In a series performed between 1990 and 1991, Warwick et al., identified 1,162 patients undergoing THA without routine chemoprophylaxis, with DVT confirmed by venography in 1.89% of patients and a PE rate of 1.20% with a subsequent mortality rate of 0.34%[6].

Early studies demonstrated a much higher incidence of VTE for TKA[7,8]. However, DVT in TKA patients occur distally in the calf which are less likely to progress into a PE which was observed at a rate of 1.3%[9] with fatalities of 0.19 to 0.4%[9,10]. Stulburg et al., examined a series of 638 patients from 1974 to 1979 among which 49 patients inadvertently did not receive prophylaxis; an impressive 83% of these patients developed a DVT[11].

In a prospective study with 34,397 consecutive and unselected THA or TKA procedures, 32 (0.09%) had a VTE after median two days despite ongoing thromboprophylaxis[12]. All surgery was done in a fast-track setup with accelerated mobilization and discharge. Another study has shown a 90-day incidence of 0.41% of VTE after unicompartmental knee arthroplasty[13]. All patients received thromboprophylaxis until discharge and were operated in a fast-track setup with a median length of stay of one day.

With VTE as a common and potentially dangerous complication after TKA and THA, safe and effective strategies for prophylaxis were developed and studied. When warfarin dosage is titrated to an international normalized ratio (INR) of 1.5 to 2.0 and administered for approximately six weeks, DVT occurred at a rate of 0.2 to 1% with a non-fatal PE rate of 0.1 to 0.3%[14-16]. Warfarin was found to consistently decreased rates of VTE when utilized after THA or TKA, but may lead to a significant risk of bleeding complications[17-19].

Low-molecular-weight heparin (LMWH) has been used for post-operative VTE prophylaxis. With LMWH, DVT rates for THA have been reported from 8 to 20.8% LMWH vs. 14 to 23.2% warfarin with a non-fatal PE rate of 0 to 0.2% observed with LMWH; DVT rates for TKA ranged from 23 to 45% LMWH vs. 23.2 to 51.7% warfarin and a non-fatal PE rate of 0 to .2% LMWH vs. 0 to 0.3% warfarin[20-23].

Recently, direct-acting oral anticoagulants (DOAC) have gained popularity for VTE prophylaxis due to ease of administration and lack of monitoring[9]. Rivaroxaban used after THA had an incidence of DVT of 0.8 to 1.6% compared to 3.4 to 6.5% for LMWH and a non-fatal PE rate of 0.1 to 0.3% vs. 0.1 to 0.5% for LMWH[24,25]. When rivaroxaban VTE prophylaxis was used after TKA, the DVT rate was 6.3 to 6.9% compared to 9.0 to 18.2% for LMWH and the non-fatal PE rate was 0 to 0.3% compared to 0.5% for LMWH[26,27]. When apixaban was used for VTE prophylaxis after THA, the DVT incidence was 1.1 versus 3.6% for LMWH and a non-fatal PE rate was 0.1 versus 0.2% for LMWH[28]. For VTE prophylaxis after TKA, the

*A list of the ICM-VTE Hip & Knee Delegates is included in a note at the end of the article.

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/G877).

incidence of DVT for apixaban was 7.8 to 14.6% compared to 8.2 to 24.4% for LMWH, the non-fatal PE rate was 0.26 to 1.0% apixaban compared to 0 to 0.4% LMWH, and a fatal PE rate of 0.1 to 0.13% apixaban compared to 0% LMWH[29,30]. Using dabigatran for prophylaxis after THA, the incidence for DVT was 5.1 to 8.0% vs. 6.4 to 8.6% for LMWH and a non-fatal PE rate of 0.1 to 0.4% for dabigatran vs. 0.2 to 0.3% for LMWH, and a fatal PE rate of 0.1% with dabigatran[31,32]. For TKA, the incidence of DVT was 29.9 to 40.1% for dabigatran vs. 24.6 to 37.3% for LMWH with a non-fatal PE rate of 0 to 1.0% for dabigatran vs. 0.8% for LMWH[33,34].

Aspirin (ASA) has been shown to be an effective prophylactic agent after THA and TKA with reported rates of DVT up to 2.6%, non-fatal PE rates of 0.14 to 0.6%, and a fatal PE rate of 0.7 to 0.2%[35-38]. A prospective randomized control trial comparing ASA to warfarin in standard-risk patients undergoing TKA or THA reported a DVT and a PE rate of 4.6% compared to 0.7% for ASA and warfarin, respectively[39]. For patients at "typical" risk of VTE after THA and TKA, the AAOS guidelines endorse ASA for VTE prophylaxis[40].

Non-pharmacologic interventions have also decreased the incidence of VTE after TJA. Regional anesthesia, hypotensive anesthesia, intermittent pneumatic compression devices, optimized blood loss management programs, rapid rehabilitation protocols, and risk stratification protocols have all contributed to the decrease in VTE over time[41-49]. However, even when combined with the most aggressive of pharmacologic interventions, the rates of PE and DVT are not zero. Genetic predispositions for thromboembolism have not been well-defined and are not yet identified easily in the laboratory[50-53]. Until that testing is available, VTE after TJA will not be a "never event".

Post-operative VTE has been a constant concern for orthopaedic surgeons performing TJA. Prior to prophylaxis, DVT and PE were common occurrences and a major source of fatality. Prophylaxis with warfarin, LMWH, and DOAC have decreased the rates of VTE, however, studies show persistent presence of VTE despite these investigated regimens. VTE Prophylaxis is a balance of reducing thromboembolic disease while mitigating surgical complications associated with anticoagulants[15,54-56]. Current strategies regarding the best prophylactic regimen for each individual patient remain under investigation[40,57]. With the continued presence of VTE for the currently available prophylactic regimens, VTE after THA and TKA should not be considered a "never event".

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2 - Is there a difference in VTE risk profile for patients undergoing total hip arthroplasty or total knee arthroplasty?

Response/Recommendation: Patients undergoing total knee arthroplasty (TKA) have a higher venous thromboembolism (VTE) risk than total hips arthroplasty (THA) patients. In addition, VTE tends to present earlier in TKA patients. There is no evidence for different risk profiles among patients undergoing THA or TKA. Also, there is also no clarity on whether it is necessary to stratify TKA differently than THA patients, or how to do it.

Strength of recommendation: Limited.

Delegates vote: Agree 93.04% Disagree 4.35% Abstain 2.61% (Strong Consensus).

Rationale: Modern surgical protocols and the use of thromboprophylaxis have reduced deep venous thrombosis (DVT) rates in both TKA and THA patients, but not pulmonary embolism (PE) rates[58-61]. However, differences in VTE risk persist between both procedures.

DVT rates after THA have varied over time. Dua et al., and Shahi et al., both studied the United States National Inpatient Sample (NIS) and found in-hospital VTE rates of 0.59% after THA (DVT 0.4% and PE 0.23%)[59]. DVT rates decreased from 2002 to 2011, from 0.55 to 0.24%, but PE rates did not[58]. However, other studies have found conflicting results. Using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database and analyzing 30-day VTE rates, Warren et al., found no changes between 2008 and 2016, and Grosso et al., found no changes

between 2006 and 2016[62,63]. Pedersen et al., found a slight increase in 90-day hospitalizations for venous thromboembolism between 1995 and 2006[7]. Lieberman et al., evaluated 21 randomized controlled trials of several VTE prophylaxis strategies in low-risk patients undergoing THA[61]. They found a PE rate of 0.21%, that did not change between 1997 and 2013, and suggested that PE even in a healthy population are not completely avoidable.

Similar findings regarding temporal changes in VTE rates have been found in TKA patients. However, thromboembolic risk continues to be higher than after THA[58,59,62-65]. Using the NIS, Dua et al., found a decrease in in-hospital DVT rates after TKA between 2001 to 2011, from 0.86 to 0.45%[58]. Shahi et al., found higher in-hospital incidence rates of VTE of 0.62% in patients undergoing TKA, versus 0.40% in THA, and similarly, DVT rates decreased during the studied period, but PE rates did not[59]. Using the NSQIP database, Sarpong et al., and Warren et al., found that 30-day VTE rates decreased between 2006 and 2016[62,65]. Sarpong et al., found a 0.87% 30-day DVT rate in 221,764 patients that decreased from 1.5% in the 2006 to 2009 period to 0.79% in the 2014 to 2016 period. Warren et al., found a 30-day VTE rate of 1.4% that decreased from 3% in 2008 to 1.4% in 2016[62]. However, mortality and PE rates did not experience changes. Other studies have also failed to find a decrease in PE rates after TKA. Cote et al., performed a meta-analysis including 18 studies with 27,073 patients that underwent TKA between 1996 and 2010[66]. They found a symptomatic PE rate of 0.37%, that did not change over time.

Patients undergoing revision THA appear to have a higher risk of VTE than primary THA. Studies using the NSQIP, and NIS databases show VTE, DVT, and PE rates in revision THA of 0.6 to 1.34%, 0.7 to 1.06%, and 0.3 to 0.4%, respectively[59,67,68]. Interestingly, revision TKA confers a VTE risk somewhat similar to that of a primary TKA. Shahi et al., found higher in-hospital VTE rates in revision TKA compared to primary TKA, using the NIS database[59]. Thirty-day rates of VTE, DVT, and PE, using the NSQIP and NIS databases, were 1.16 to 2%, 0.88 to 0.9%, 0.34 to 0.4%, respectively[59,62,67]. Contrarily, Boylan et al., found a higher VTE risk within 30 days after primary TKA (i.e., 2.24%, DVT 1.61%, and PE 0.82%) than revision TKA (i.e., 1.84%, DVT, 1.41%, and PE 0.52%), using the New York Statewide Planning and Research Cooperative System database[69]. Different from primary arthroplasties, VTE rates have not decreased over the last decades for revision surgeries.

Patients undergoing TKA not only have a higher risk of VTE, but they get a VTE earlier after surgery than THA patients. Pedersen et al., found a median time to VTE that was 20 to 22 days for patients undergoing THA, and 15 days for those who underwent TKA, using Danish registers[64,70]. Gill et al., found a median time for DVT of 16 days in THA and 14 days in TKA in a cohort of more than 13,000 patients in the United Kingdom[71]. Using United States data, several studies have confirmed these findings[68,72-74]. Bohl et al., found patients undergoing TKA had an earlier time to PE (day 3 vs. 5 in THA) and DVT (day 5 vs. 13)[72]. Johnson et al., reviewed 341,601 primary THA and TKA patients[73]. Of patients who had a PE, those who underwent a TKA had a PE earlier than those who underwent a THA (81,7% during the first 10 days, vs. 58.8%). Interestingly, Courtney et al., found no differences in time to DVT (12.9 vs. 14.8 days) or to PE (9.2 vs. 8.6 days) in patients undergoing primary or revision THA[68].

Most studies have investigated risk factors in both THA and TKA patients. As such, TKA has been identified as a risk factor, but most other risk factors appear to be similar between patients undergoing both procedures[68,75-83]. Zhang et al., performed a meta-analysis of ten risk factors for VTE after TKA and THA[84]. They included 14 retrospective case control or prospective cohort studies. They found that three risk factors were the most associated with VTE: history of VTE (odds Ratio [OR] > 10.6), varicose veins (OR > 2.7), and congestive heart failure (OR 2.03). Zhang et al., performed a systematic review on level I and II evidence on VTE risk factors after TJA between 2003 and 2013[85]. They included 54 studies. They found that several risk factors were associated with increased VTE risk. Increasing age, body mass index over 30, bilateral surgery, female patients, and surgery duration longer than two hours were identified as risk factors for both TKA and THA patients. Patients undergoing TKA surgery had a higher VTE risk, compared to those undergoing THA. In TKA patients, cemented fixation was identified as a risk factor and early mobilization was identified as a protective factor. In THA patients, a previous VTE conferred a higher risk for VTE.

Regional variability may also play a role in VTE rate differences. Several reports suggest lower VTE rates in Asian patients, both in THA and TKA[75-78,86-91]. Lee et al., performed a meta-analysis of the incidence of VTE in Asian patients undergoing TKA who did not use thromboprophylaxis[89]. They included 18 studies, totaling 1,838 patients. The rate of symptomatic PE was low (0.01%), similar between countries, and consistent in time. Seven studies reported symptomatic DVT, which was 1.9%. As such, the Asia-Pacific Venous Thromboembolism Consensus has agreed that the risk of VTE is lower in patients of Asian ethnicity[90]. These results differ markedly from those coming from other parts of the world. European studies have shown VTE, DVT, and PE rates of 0.79 to1.3%, 0.35 to 0.46%, and 0.35 to 0.57% for THA and 1.5%, 0.3 to 0.51%, and 0.51 to 1.47% for TKA, respectively[70,71,79,92,93]. Januel et al., performed a comparative study between patients who underwent THA in Canada, Switzerland, New Zealand, California, and France[94]. They found that VTE rates varied between countries (0.16 to 1.41%) during hospital stays. Length of stay and ultrasound screening strategies explained only partially these differences, but other factors like completeness of registration and validity of diagnoses may play a role.

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3 - What is the most optimal VTE prophylaxis following TKA/THA?

Response/Recommendation: Low-dose aspirin (ASA) is currently the most effective and safest method of prophylaxis against venous thromboembolism (VTE) in patients undergoing total joint arthroplasty (TJA). We recommend the use of low-dose ASA as the primary method of VTE prophylaxis in all patients undergoing TJA, including moderate-to high-risk patients.

Strength of Recommendation: Strong.

Delegates vote: Agree 76.92% Disagree 19.66% Abstain 3.42% (Strong Consensus).

Rationale: The risk of VTE in orthopaedic surgery patients is well established[95]. Patients undergoing elective total knee arthroplasty (TKA), or total hip arthroplasty (THA) are considered at high risk for the development of deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE)

TABLE I Studies, design, anticoagulation used, and size of sample

Author's Last Name	Year of Publication	Type of Design	Type of Surgery	Chemical Name	Sample Size
German Hip Arthroplasty Group[136]	1992	Classic RCT	Hip	Heparin	168
				LMWH	167
Laguardia[112]	1992	Classic RCT	Hip	LMWH (Pre-Op)	19
				LMWH (Post-Op)	21
Leyvraz et al.[137]	1992	Classic RCT	Hip	Heparin	139
				LMWH	145
Leyvraz et al.[138]	1991	Classic RCT	Hip	Heparin	175
				LMWH	174
Freick[139]	1991	Classic RCT	Hip	Heparin	48
				LMWH	52
Planès et al.[140]	1991	Classic RCT	Hip	LMWH	65
				LMWH (20 mg)	61
				LMWH (40 mg)	62
Levine et al.[120]	1991	Classic RCT	Hip	Heparin	263
				LMWH	258
Eriksson et al.[141]	1991	Classic RCT	Hip	Heparin	59
				LMWH	63
Planès et al.[142]	1988	Classic RCT	Hip	Heparin	112
				LMWH	107
Planès et al.[142]	1988	Classic RCT	Hip	Heparin	113
				LMWH	124
Josefsson et al.[123]	1987	Classic RCT	Hip	ASA	40
				Heparin	42
Planès et al.[143]	1986	Classic RCT	Hip	LMWH (60 mg)	50
				LMWH (30 mg)	28
				LMWH (40 mg)	50
				LMWH (20 mg)	100
RD Heparin Arthroplasty Group[144]	1994	Classic RCT	Total Joint	Heparin (Twice)	328
				Heparin (Once)	320
				Warfarin	321
Menzin et al.[145]	1994	Classic RCT	Hip	Heparin	209
				LMWH (30 mg)	195
				LMWH (40 mg)	203
Colwell Jr. Et al[146].	1994	Classic RCT	Hip	Heparin	209
				LMWH (30 mg)	195
				LMWH (40 mg)	203
Hull et al.[147]	1993	Classic RCT	Total Joint	LMWH	715
				Warfarin	721
Hull[148]	1997	Classic RCT	Total Joint	LMWH	590
				Warfarin	617
Francis et al.[149]	1997	Classic RCT	Hip	LMWH	192
				Warfarin	190
Eriksson et al.[116]	1997	Classic RCT	Hip	LMWH	1,023
				Thrombin Inhibitors	1,028

continued

TABLE I (*continued*)

Author's Last Name	Year of Publication	Type of Design	Type of Surgery	Chemical Name	Sample Size
Warwick et al.[150]	1998	Classic RCT	Hip	Mechanical	136
				LMWH	138
Colwell Jr. et al.[151]	1999	Classic RCT	Hip	LMWH	1,516
				Warfarin	1,495
Kakkar et al.[152]	2000	Classic RCT	Hip	Heparin	134
				LMWH	125
Hull et al.[113]	2000	Classic RCT	Hip	LMWH (Pre-Op)	152
				LMWH (Post-Op)	139
				Warfarin	133
Borghi et al.[117]	2002	Observational Retrospective	Hip	Heparin	192
				LMWH	457
Turpie et al.[118]	2002	Classic RCT	Hip	LMWH	797
				Thrombin Inhibitors	787
Eriksson et al.[153]	2002	Classic RCT	Total Joint	LMWH	308
				Thrombin Inhibitors	1,169
Eriksson et al.[154]	2003	Classic RCT	Total Joint	LMWH	1,184
				Thrombin Inhibitors	1,141
Colwell Jr. et al.[155]	2003	Classic RCT	Hip	LMWH	775
				Thrombin Inhibitors	782
Eriksson et al.[154]	2003	Classic RCT	Total Joint	LMWH	1,178
				Thrombin Inhibitors	1,138
Pitto et al.[156]	2004	Classic RCT	Hip	Mechanical	100
				LMWH	100
Enyart[157]	2005	Observational Prospective	Total Joint	LMWH	2,627
				Warfarin	770
Senaran et al.[158]	2006	Classic RCT	Hip	Heparin	50
				LMWH	50
Della Valle et al.[99]	2006	Observational Prospective	Hip	ASA (325 mg)	1,599
				Warfarin	348
Gelfer et al.[107]	2006	Classic RCT	Total Joint	ASA (100 mg)	61
				LMWH	60
Cohen et al.[159]	2007	Classic RCT	Total Joint	Thrombin Inhibitors	400
				Thrombin Inhibitors (with compression stocks)	395
Eriksson et al.[160]	2007	Classic RCT	Hip	Factor Xa Inhibitor (220 mg)	1,146
				Factor Xa Inhibitor (150 mg)	1,163
				LMWH	1,154
Tian et al.[109]	2007	Classic RCT	Total Joint	ASA (100 mg)	100
				LMWH	140
Eriksson et al.[122]	2008	Classic RCT	Hip	Rivaroxaban	2,209
				LMWH	2,224

continued

TABLE I (*continued*)

Author's Last Name	Year of Publication	Type of Design	Type of Surgery	Chemical Name	Sample Size
Kakkar et al.[121]	2008	Classic RCT	Total Joint	Rivaroxaban	1,228
				LMWH	1,229
Colwell Jr. et al.[108]	2010	Other	Hip	ASA (81 mg)	199
				LMWH	196
Raskob et al.[161]	2010	Other	Hip	Factor Xa Inhibitor	170
				Factor Xa Inhibitor	158
				LMWH	144
Lassen et al.[162]	2010	Classic RCT	Hip	Apixaban	1,949
				LMWH	1,917
Eriksson et al.[163]	2011	Other	Hip	Factor Xa Inhibitor	792
				LMWH	785
Intermountain Joint Replacement Center Writing Committee[127]	2011	Observational Prospective	Total Joint	ASA (325 mg)	152
				Warfarin	129
				Warfarin	415
Kwong[164]	2011	Other	Total Joint	Factor Xa Inhibitor	6,183
				LMWH	6,200
Khatod et al.[165]	2011	Observational Retrospective	Hip	ASA	934
				LMWH	7,202
				Warfarin	6,063
Jameson et al.[119]	2011	Observational Retrospective	Total Joint	ASA	22,942
				LMWH	85,642
Raskob et al.[166]	2012	Other	Total Joint	Apixaban	3,394
				LMWH	3,394
Nieto et al.[167]	2012	Other	Total Joint	Factor Xa Inhibitor	12,200
				LMWH	12,261
Vulcano et al.[126]	2012	Observational Retrospective	Total Joint	ASA (325 mg)	1,115
				Warfarin	426
Fuji et al.[168]	2012	Other	Total Joint	Factor Xa Inhibitor (Low)	136
				LMWH	82
				Factor Xa Inhibitor	134
Beyer-Westendorf et al.[169]	2012	Observational Retrospective	Total Joint	Rivaroxaban	1,043
				LMWH	1,495
Shoda et al.[114]	2015	Observational Retrospective	Total Joint	LMWH	11,049
				Thrombin Inhibitors	22,727
Charters et al.[170]	2015	Observational Retrospective	Total Joint	Rivaroxaban	649
				LMWH	1,113
Bonarelli et al.[171]	2015	Observational Prospective	Hip	Factor Xa Inhibitor	211
				LMWH	196
Heckmann et al.[172]	2015	Observational Prospective	Total Joint	Rivaroxaban	838
				LMWH	464
Özler et al.[173]	2015	Classic RCT	Total Joint	Rivaroxaban	60
				LMWH	60

continued

TABLE I (*continued*)

Author's Last Name	Year of Publication	Type of Design	Type of Surgery	Chemical Name	Sample Size
Ricket et al.[174]	2016	Observational Retrospective	Total Joint	Rivaroxaban	440
				LMWH	438
Kim[175]	2016	Other	Hip	Rivaroxaban	350
				LMWH	351
Huang et al.[125]	2016	Observational Retrospective	Total Joint	ASA	796
				Warfarin	6,723
Deirmengian[124]	2016	Observational Retrospective	Hip	ASA	534
				Warfarin	2,463
Yhim et al.[115]	2017	Observational Retrospective	Hip	ASA	3,654
				Rivaroxaban	4,843
				LMWH	13,653
				Thrombin Inhibitors	997
Yhim et al.[115]	2017	Observational Retrospective	Knee	ASA	24,612
				Rivaroxaban	64,859
				LMWH	55,181
				Thrombin Inhibitors	7,721
Lindquist et al.[176]	2018	Observational Retrospective	Total Joint	ASA (325 mg)	366
				Rivaroxaban	438
				LMWH	440
Senay et al.[177]	2018	Observational Prospective	Total Joint	Factor Xa Inhibitor	904
				LMWH	1,468
Tan et al.[178]	2019	Observational Retrospective	Total Joint	ASA	13,610
				LMWH	17,554
				Warfarin	29,303
Ghosh et al.[179]	2019	Observational Prospective	Total Joint	ASA	6,078
				Clopidogrel	56
				Factor Xa Inhibitor	40
				LMWH	995
				Warfarin	105
Kasina et al.[180]	2019	Observational Prospective	Hip	Rivaroxaban	5,752
				LMWH	26,881
Gage et al.[181]	2019	Classic RCT	Total Joint	Warfarin (Low)	804
				Warfarin	793
Cheallaigh et al.[182]	2020	Observational Retrospective	Total Joint	ASA	3,460
				Rivaroxaban	1,212
				LMWH	961
Matharu et al.[183]	2020	Observational Retrospective	Hip	ASA	35,904
				Factor Xa Inhibitor	29,522
				Thrombin Inhibitors	3,864
Matharu et al.[183]	2020	Observational Retrospective	Knee	ASA	42,590
				Factor Xa Inhibitor	30,697
				Thrombin Inhibitors	41,323
Rahman et al.[184]	2020	Other	Hip	Rivaroxaban	80
				LMWH	80

continued

TABLE I (*continued*)

Author's Last Name	Year of Publication	Type of Design	Type of Surgery	Chemical Name	Sample Size
Ren et al.[185]	2021	Observational Retrospective	Hip	ASA (100 mg)	34
				Rivaroxaban	36
Borton et al.[186]	2021	Observational Retrospective	Hip	ASA	2,560
				LMWH	1,049
				Warfarin	193
Uvodich et al.[111]	2021	Observational Retrospective	Total Joint	ASA (81 mg)	961
				ASA	2551
Hovik[110]	2021	Observational Prospective	Total Joint	ASA (81 mg)	1,084
				LMWH	5,010

RCT=Randomized clinical trial; LMWH=Low-molecular-weight heparin; mg=milligrams: ASA=Aspirin.

that can be fatal[96]. Historical estimates of the incidence of DVT without prophylaxis are between 40% and 84% after TKA and around 39% to 74% after THA[97]. Recent clinical practice guidelines (CPG) on effective and safe VTE prophylaxis, along with perioperative protocols regarding early post-operative mobilization and spinal anesthesia, have drastically reduced morbidity and mortality secondary to VTE[98,99]. Nevertheless, the National Institutes of Health (NIH) predicts that the number of patients undergoing TJA and consequently the number of thromboembolic complications is on the rise[100].

In 2008 the American Association of Hip and Knee Surgeons (AAHKS) conducted a survey of its members to explore current hospital guidelines for VTE prophylaxis following TJA. 99% of respondents said they routinely utilized either chemical or mechanical prophylaxis following both TKA/THA[101]. Despite not being able to recommend a specific agent, the 2011 American Academy of Orthopaedic Surgeons (AAOS) CPG advised that all patients undergoing TJA must receive some form of VTE prophylaxis[102]. However, the more recent American College of Chest Physicians (ACCP) guidelines of 2012 endorsed the use of ASA as an appropriate method of VTE prophylaxis following TJA[103]. Currently, the selection of a VTE prophylactic agent following arthroplasty is largely determined by individual surgeon preference[104]. Common anti-coagulants used for the prevention of VTE in orthopaedic patients include ASA, warfarin, injectable agents like low-molecular-weight heparin (LMWH), and the more recently approved Factor Xa inhibitors such as rivaroxaban and apixaban[105]. The decision of which anticoagulant to use entails achieving an ideal balance of agent efficacy, while also avoiding the adverse side effects brought on by drugs with higher risk profiles[106].

Comparative analyses were performed using Network Meta-Analyses (NMA) and odds ratio (OR) with 95% confidence intervals reported. Evaluation of all included studies, levels I-IV, showed that low-dose ASA (100 mg) demonstrated the lowest risk of VTE development[106-111]. Compared to low-dose ASA, LMWH (postop), LMWH (preop), and rivaroxaban did not significantly differ in their risk of developing VTE, with OR of 1.11 (0.33, 3.76), 1.36 (0.41, 4.50) and 1.38 (0.55, 3.45), respectively. Conversely, high-dose ASA (325 mg) showed the greatest risk of VTE with an OR of 7.90 (2.60, 24.05) followed by heparin (5.94 [2.28, 15.47]) and mechanical prophylaxis (5.76 [1.87, 17.73]), when compared to low-dose ASA. When assessing for bleeding events in all studies, low-dose ASA (81 mg) exhibited the lowest risk estimate and was used as a reference. Mechanical prophylaxis (1.97 [0.04, 94.52]), LMWH 20 mg (2.93 [0.20, 43.80]) and low-dose warfarin (4.32 [0.25, 75.41]) showed the next lowest estimates but did not significantly differ in risk from low-dose ASA. Thrombin inhibitors (23.91 [1.94, 295.06]) were the most likely to be associated with bleeding events, followed by LMWH (postop) (19.66 [1.53, 252.94]) and heparin (18.32 [1.45, 231.39])[112-118].

Limiting analysis to only level I (RCT) studies, rivaroxaban demonstrated the lowest risk of VTE development[99,119-122]. Low-dose ASA (100 mg), when compared to rivaroxaban, did not significantly differ in risk of VTE development with an OR of 1.61 (0.47, 5.54). Apixaban (2.70 [1.30, 5.62]) and direct thrombin inhibitors (3.49 [1.91, 6.39]) had the next lowest risk of VTE. Additionally, LMWH given post-operatively had an OR of 3.89 (1.38, 10.97). High-dose ASA when compared with rivaroxaban, was found to have the highest OR of VTE development at 26.11 (6.69, 101.90) followed by LMWH 30 mg (15.02 [1.98, 114.01] and low-dose warfarin (13.83 [6.13, 31.18]). LMWH (20 mg) demonstrated the lowest probability of bleeding events in level I studies and was used as a reference. Low-dose warfarin (1.37 [0.25, 7.58]), mechanical prophylaxis (0.69 [0.03, 15.53]), one dose of heparin (3.11 [0.98, 9.89]) and ASA (4.03 [1.02, 15.97]) had relatively low risk of bleeding when compared to LMWH 20 mg. 100 mg ASA (8.67 [2.32, 32.40]), thrombin inhibitors (7.01 [2.50, 19.64] and heparin (6.23 [2.39, 16.21]) increased the risk of bleeding, when compared with LMWH 20 mg[107-109,123,124].

The results of our meta-analysis are consistent with currently published scientific literature. We found that in level-

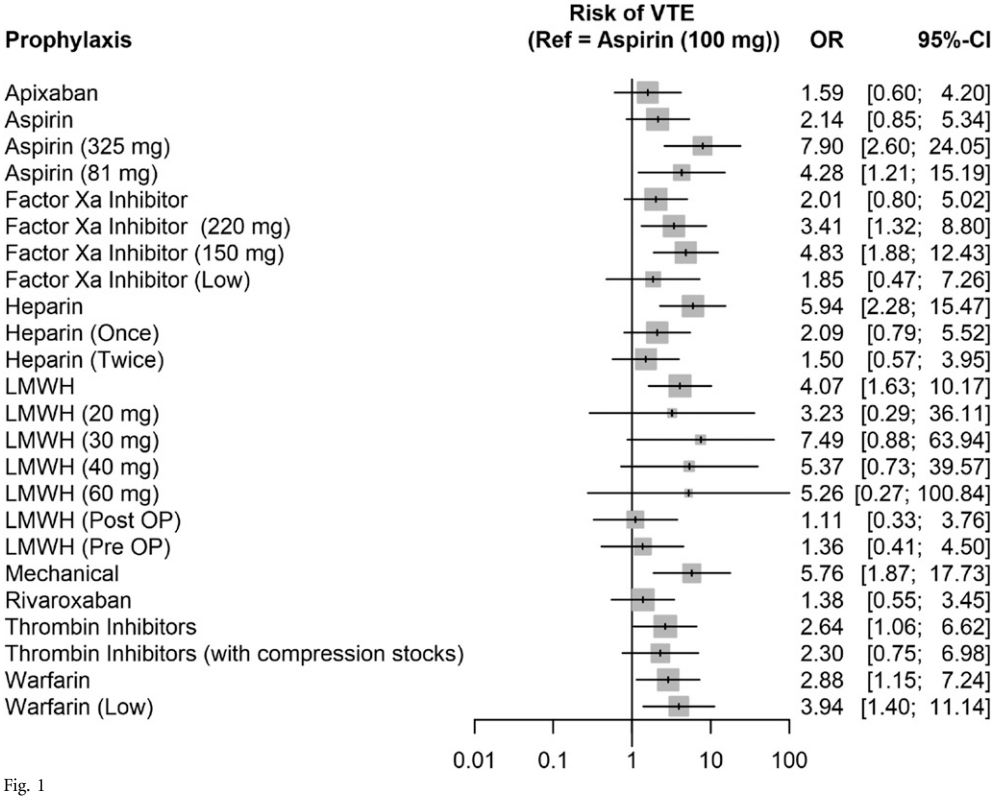

Fig. 1

Figs. 1 through 4 Level I-IV studies.

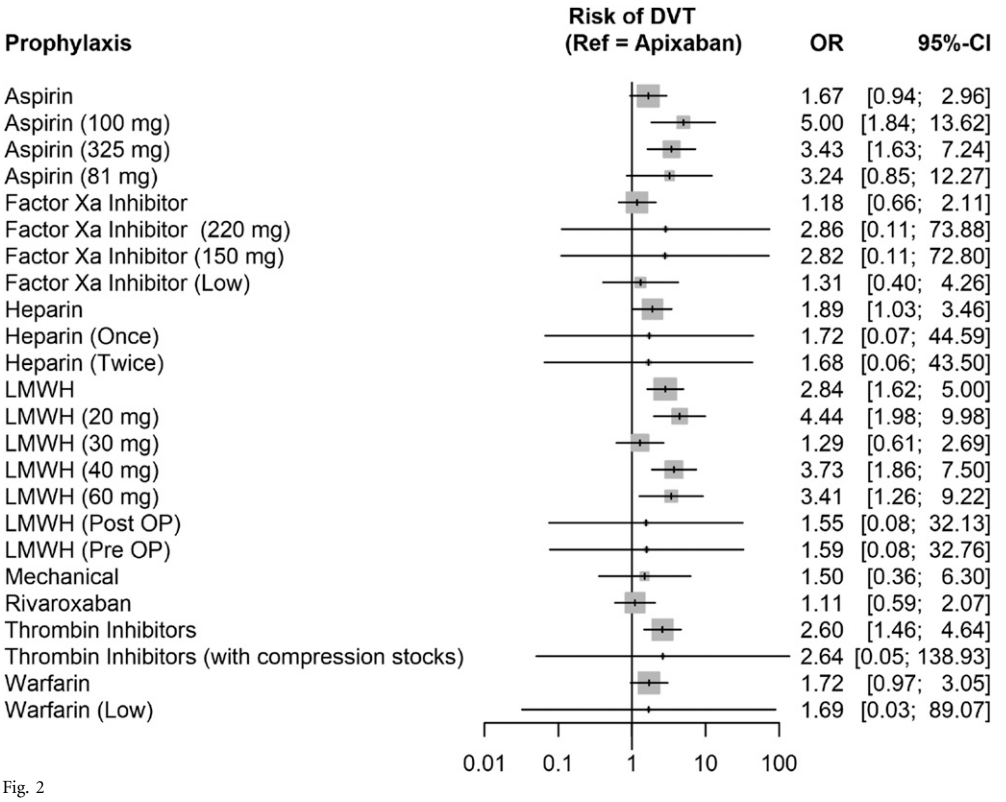

Fig. 2

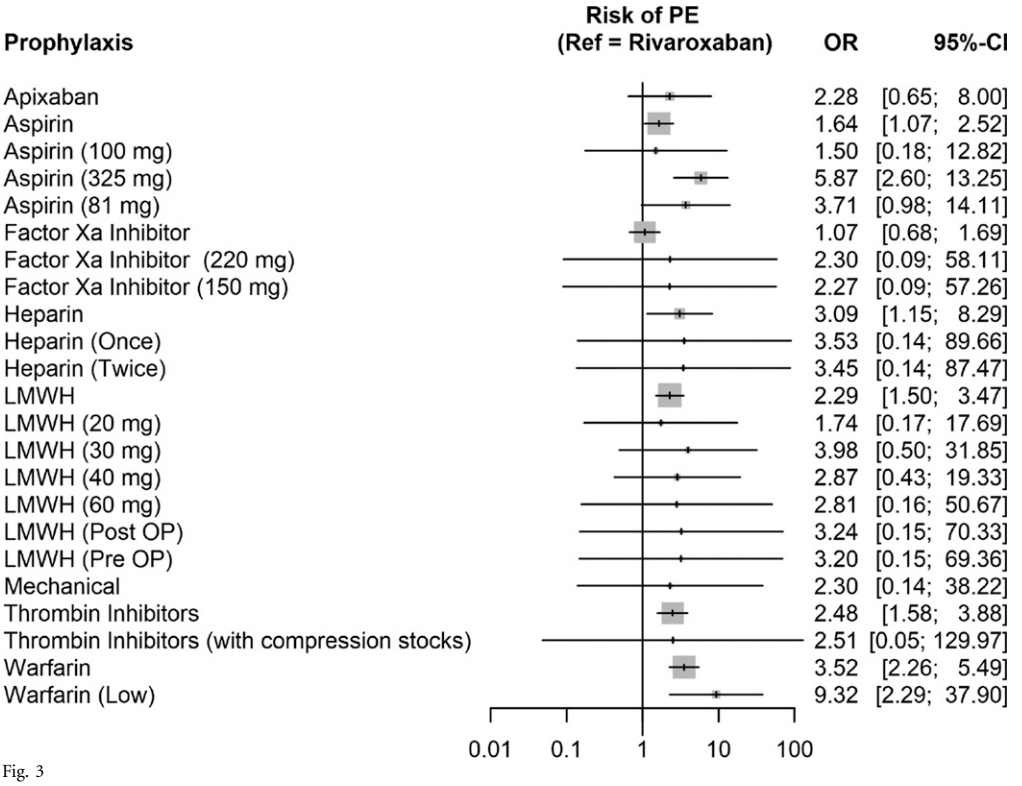
Prophylaxis
Risk of PE
(Ref = Rivaroxaban)
OR
95%-CI
Apixaban 2.28 [0.65; 8.00]
Aspirin 1.64 [1.07; 2.52]
Aspirin (100 mg) 1.50 [0.18; 12.82]
Aspirin (325 mg) 5.87 [2.60; 13.25]
Aspirin (81 mg) 3.71 [0.98; 14.11]
Factor Xa Inhibitor 1.07 [0.68; 1.69]
Factor Xa Inhibitor (220 mg) 2.30 [0.09; 58.11]
Factor Xa Inhibitor (150 mg) 2.27 [0.09; 57.26]
Heparin 3.09 [1.15; 8.29]
Heparin (Once) 3.53 [0.14; 89.66]
Heparin (Twice) 3.45 [0.14; 87.47]
LMWH 2.29 [1.50; 3.47]
LMWH (20 mg) 1.74 [0.17; 17.69]
LMWH (30 mg) 3.98 [0.50; 31.85]
LMWH (40 mg) 2.87 [0.43; 19.33]
LMWH (60 mg) 2.81 [0.16; 50.67]
LMWH (Post OP) 3.24 [0.15; 70.33]
LMWH (Pre OP) 3.20 [0.15; 69.36]
Mechanical 2.30 [0.14; 38.22]
Thrombin Inhibitors 2.48 [1.58; 3.88]
Thrombin Inhibitors (with compression stocks) 2.51 [0.05; 129.97]
Warfarin 3.52 [2.26; 5.49]
Warfarin (Low) 9.32 [2.29; 37.90]
0.01
0.1
1
10
100

Fig. 3

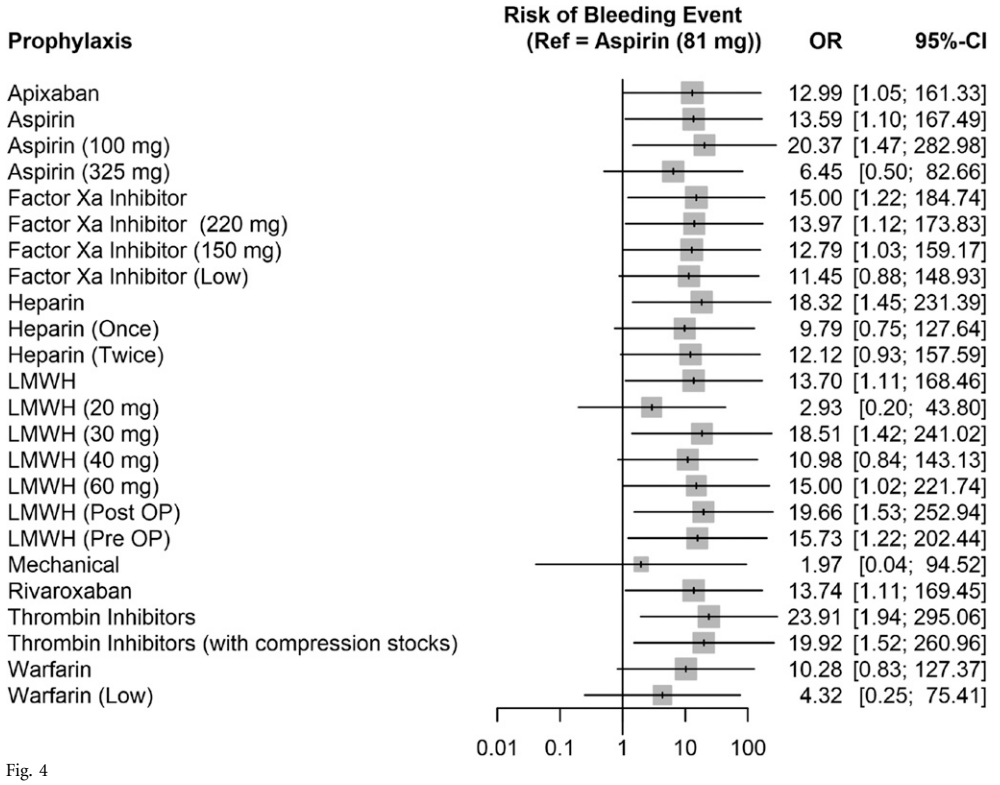
Prophylaxis
Risk of Bleeding Event
(Ref = Aspirin (81 mg))
OR
95%-CI
Apixaban 12.99 [1.05; 161.33]
Aspirin 13.59 [1.10; 167.49]
Aspirin (100 mg) 20.37 [1.47; 282.98]
Aspirin (325 mg) 6.45 [0.50; 82.66]
Factor Xa Inhibitor 15.00 [1.22; 184.74]
Factor Xa Inhibitor (220 mg) 13.97 [1.12; 173.83]
Factor Xa Inhibitor (150 mg) 12.79 [1.03; 159.17]
Factor Xa Inhibitor (Low) 11.45 [0.88; 148.93]
Heparin 18.32 [1.45; 231.39]
Heparin (Once) 9.79 [0.75; 127.64]
Heparin (Twice) 12.12 [0.93; 157.59]
LMWH 13.70 [1.11; 168.46]
LMWH (20 mg) 2.93 [0.20; 43.80]
LMWH (30 mg) 18.51 [1.42; 241.02]
LMWH (40 mg) 10.98 [0.84; 143.13]
LMWH (60 mg) 15.00 [1.02; 221.74]
LMWH (Post OP) 19.66 [1.53; 252.94]
LMWH (Pre OP) 15.73 [1.22; 202.44]
Mechanical 1.97 [0.04; 94.52]
Rivaroxaban 13.74 [1.11; 169.45]
Thrombin Inhibitors 23.91 [1.94; 295.06]
Thrombin Inhibitors (with compression stocks) 19.92 [1.52; 260.96]
Warfarin 10.28 [0.83; 127.37]
Warfarin (Low) 4.32 [0.25; 75.41]
0.01
0.1
1
10
100

Fig. 4

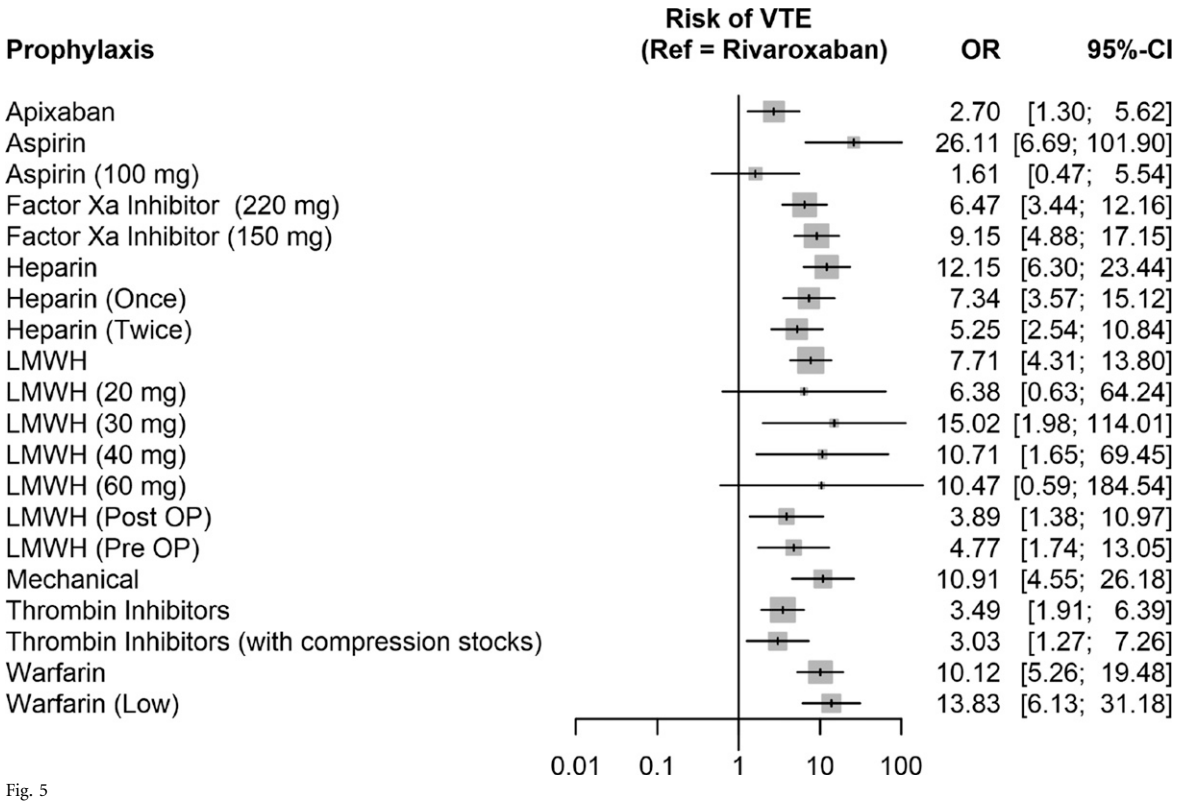

Fig. 5

Figs. 5 through 8 Only Level I studies.

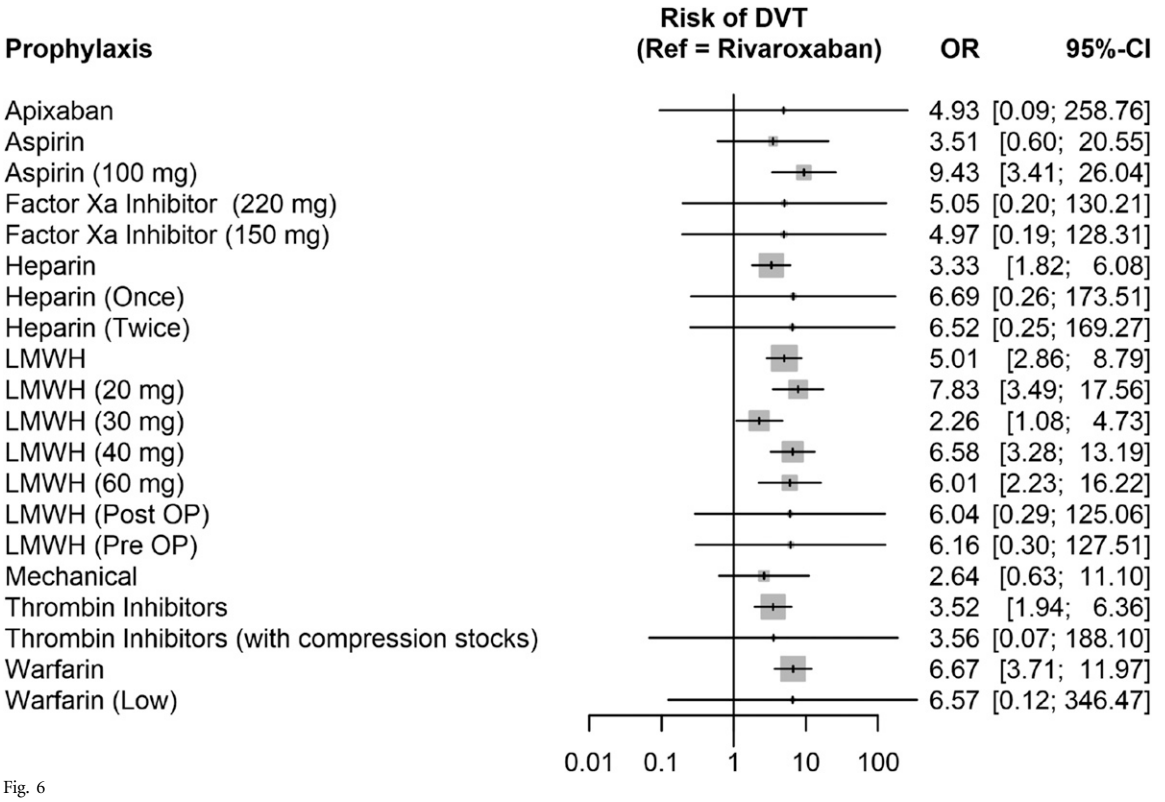

Fig. 6

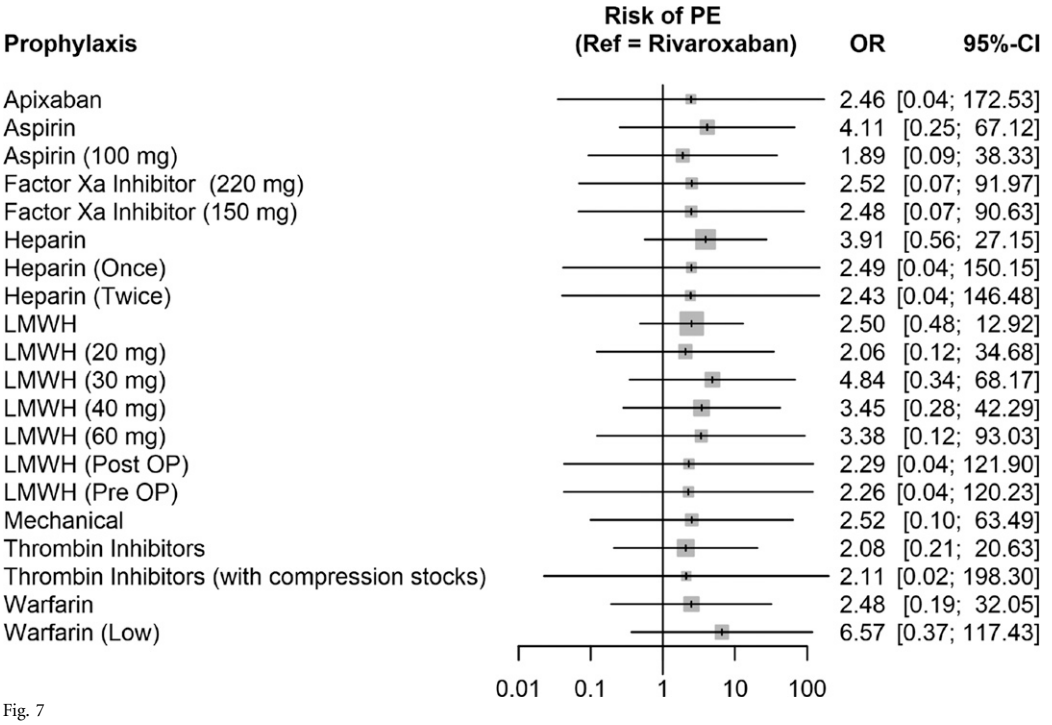

Fig. 7

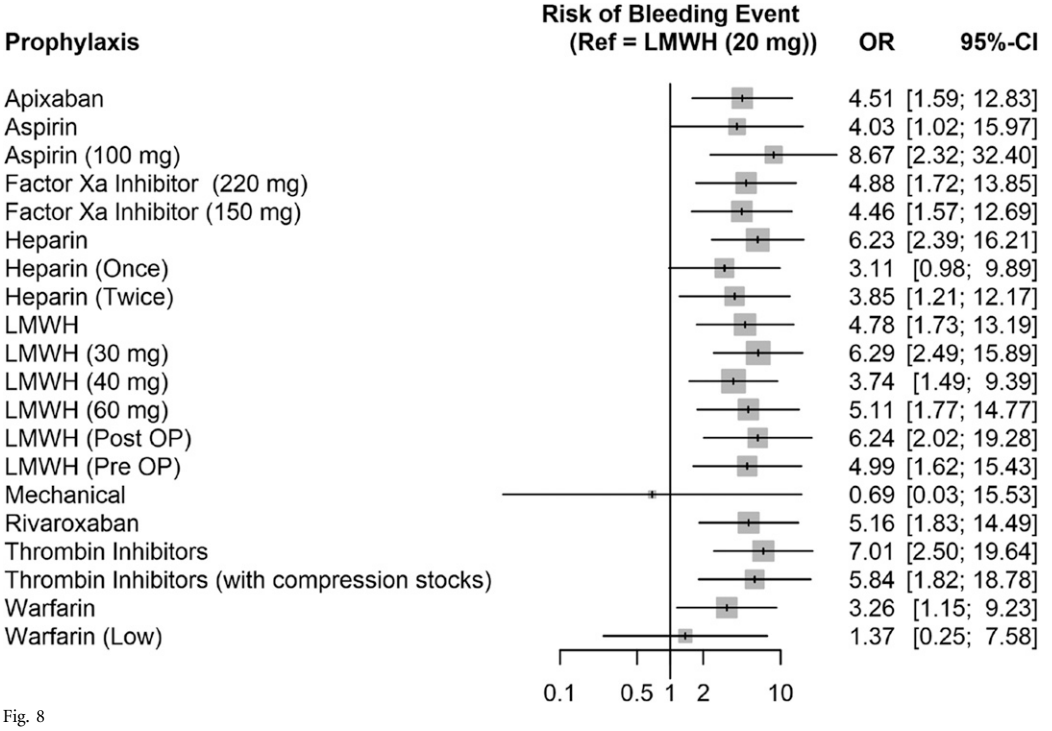

Fig. 8

I studies, rivaroxaban exhibited slightly lower rates of VTE occurrence when compared to ASA. However, the significance of this is limited, as only four such studies included ASA, none of which directly compared ASA to rivaroxaban[99,107,109,123]. Overall, we found that low-dose ASA was effective at preventing VTE when compared to other measures. In addition, it exhibited lower rates of bleeding when compared to more commonly used prophylactic agents[99,107,109,115,123-127].

In the United States, ASA has emerged as the most commonly used VTE prophylactic agent following TJA[101]. This widespread adoption of ASA for VTE prophylaxis in TJA has reinforced its standing as a safe and effective agent, that requires no blood test for monitoring[95]. In a recent meta-analysis of RCT, Matharu et al.[128], demonstrated that there was no difference in risk of developing VTE, in patients receiving ASA vs. other anticoagulants following TJA. Furthermore, Rondon et al.[129], showed that patients who received ASA, vs. those in the non-ASA cohort, had a 3-fold and 2-fold reduction in risk of death following TJA at 30-days and 1-year, respectively. In addition, ASA has a considerably more benign risk profile when compared to other more potent anticoagulants. Patients receiving ASA experience substantially lower rates of bleeding, hematomas, wound infection, and periprosthetic joint infection[95,130].

Recent literature has now discredited previously made determinations that high-dose ASA (325 mg twice a day [*bis in die* (bid)]) provides greater protection against cardiovascular and cerebrovascular events than low-dose ASA (75 - 100 mg bid)[131,132]. Likewise, the Pulmonary Embolism Prevention trial of 2001 showed that low-dose ASA significantly reduced the incidence of DVT and PE in patients undergoing TJA[133]. Despite the AAOS guidelines[102] recommending high-dose ASA (325 mg bid) for VTE prevention following TJA, Parvizi et al.[129,134], demonstrated that low-dose (81 mg bid) ASA was just as effective at VTE prevention as high-dose ASA, while also exhibiting no difference in mortality rates up to 1 year postoperatively. Moreover, low-dose ASA is also associated with lower rates of bleeding than high-dose ASA and may potentially reduce gastrointestinal toxicity[135].

Even with the advent of newer more potent anticoagulants, conventional low-dose ASA remains the most optimal method of VTE prophylaxis following TJA. The results of this meta-analysis, along with previously published literature, reiterate low-dose ASA's position as an effective, safe, widely available, and inexpensive agent.

Analysis and comparison between studies is shown in (Table I), and (Figure 1 to Figure 8).

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4 - What is the chemoprophylactic agent of choice for patients undergoing simultaneous bilateral total knee arthroplasty (SBTKA)?

Response/Recommendation: Patients undergoing SBTKA are at a higher risk of venous thromboembolism (VTE) compared to those undergoing unilateral total knee arthroplasty (TKA). Chemical prophylaxis should be considered for these patients.

Strength of Recommendation: Limited.

Delegates vote: Agree 94.83% Disagree 1.72% Abstain 3.45% (Strong Consensus).

Rationale: A SBTKA is an effective surgical option for patients with bilateral knee osteoarthritis as it imparts several benefits including a decreased cumulative operative time and lower economic burden[187-189]. Although SBTKA provides several advantages for the patient, it is associated with a higher rate of complications such as VTE.

A vast body of literature has reported an increased risk of VTE following SBTKA compared to unilateral TKA[190-197]. This heightened risk may be the result of increased operative time, blood loss, and longer recovery period associated with the operation. Current VTE prophylaxis guidelines presented by the American Academy of Orthopaedic Surgeons (AAOS) and American College of Chest Physicians (ACCP) do not provide guidance on the most appropriate prophylactic agent to prescribe to patients undergoing SBTKA[198,199]. Consequently, it is common practice for surgeons to prescribe more aggressive anticoagulation for these higher-risk patients.

Although aspirin has shown to be as effective as other chemoprophylactic agents with a more favorable safety profile for patients undergoing TKA[200-207], existing studies examined heterogenous cohorts containing both unilateral and bilateral

procedures[208-210]. Furthermore, other studies compared aspirin with potent anticoagulants only after risk-stratifying patients based on VTE risk, prescribing aspirin only to "low-risk" unilateral TKA and potent anticoagulants to "high-risk" bilateral TKA[211,212]. As a result, current literature still lacks consensus regarding the most appropriate VTE prophylactic agent for patients undergoing SBTKA.

Two retrospective studies compared the efficacy of various chemoprophylactic agents for the prevention of VTE following SBTKA[213,214]. Goel et al., evaluated the incidence of VTE in patients undergoing SBTKA and compared the efficacy of aspirin and warfarin for VTE prevention[213]. Employing a validated VTE risk calculator to control for confounding risk factors, the study found that aspirin was as protective as warfarin for these high-risk patients. Similarly, Nam et al., compared the efficacy of a multimodal regimen (mobile compression device with aspirin) and warfarin in patients undergoing SBTKA, reporting no symptomatic VTE events in the aspirin cohort compared to one in the warfarin cohort[214].

Although it is widely recognized that SBTKA is associated with an increased risk of VTE, current literature lacks robust data evaluating the optimal prophylactic agent for these higher-risk patients. In the absence of such data, it is the recommendation of this workgroup that chemical prophylaxis, which includes aspirin, should be considered for patients undergoing SBTKA.

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5 - What is the chemoprophylactic agent of choice for patients undergoing simultaneous bilateral total hip arthroplasty (SBTHA)?

Response/Recommendation: Patients undergoing SBTHA are at a higher risk of venous thromboembolism (VTE) compared to those undergoing unilateral total hip arthroplasty (THA). Chemoprophylaxis should be considered for these patients, although the optimal agent remains uncertain.

Strength of Recommendation: Limited.

Delegates vote: Agree 94.07% Disagree 1.69% Abstain 4.24% (Strong Consensus).

Rationale: A SBTHA has demonstrated several advantages in carefully selected patients, including the need for only one anesthetic, reduced length of stay and decreased perioperative costs[215-217]. Although one recent meta-analysis reported lower rates of major systemic complications and deep venous thrombosis (DVT) in SBTHA[218], and comparable rates of pulmonary embolism (PE) and mortality between simultaneous and staged procedures, there is ample evidence to suggest that single-stage bilateral THA is associated with a greater risk of VTE due to the an increased volume of procoagulants forced into the venous circulation from the intramedullary canal as well as the prolonged operative time causing venous stasis[219,220]. A vast body of literature has reported an increased risk of VTE following simultaneous bilateral compared to unilateral THA[221-227].

The most recent guidelines from the American Academy of Orthopaedic Surgeons (AAOS), the American College of Chest Physicians (ACCP) and the National Institute or Health and Clinical Excellence (NICE) do not specify the optimal VTE prophylactic agent for patients undergoing SBTHA[228-230]. While aspirin has been established as an effective chemoprophylaxis option with a favorable safety profile compared to more aggressive anticoagulants[231], it remains uncertain whether VTE prophylaxis selection should be individualized on the basis of the risk profile of the patient. The guidelines by the AAOS similarly emphasized the importance of risk stratification but was unable to offer guidance on such stratification[229].

Current literature lacks consensus regarding the most appropriate VTE prophylactic agent for patients undergoing simultaneous bilateral joint replacements. Previous studies comparing different agents examined heterogenous cohorts containing both unilateral and bilateral THA[232-234]. In addition, another study compared the efficacy of aspirin with that of other anticoagulants only after risk-stratifying unilateral cases into a "low-risk" group that received aspirin, and bilateral cases into a "high-risk" group that received potent anticoagulants, thus making it difficult to make a valid comparison[235]. While a few retrospective studies have examined the efficacy of different chemoprophylactic agents following simultaneous bilateral total knee arthroplasty[236,237], only one study has been performed in THA literature[238]. Beksaç et al., retrospectively analyzed 644 patients who underwent SBTHA followed by a multimodal prophylaxis protocol. Importantly, the authors found no significant difference in the rates of symptomatic VTE (6.2% vs. 5.7%), PE (1.4% vs. 1.1%), DVT (7.0% vs. 5.7%) between the warfarin (n = 292) and aspirin (n = 352) groups. There were two deaths in each group, neither of which were related to VTE[238].

While it is widely acknowledged that bilateral joint replacements are associated with a greater VTE risk, there is a paucity of evidence on the optimal prophylactic agent following these procedures. Therefore, we recommend that routine chemoprophylaxis, including aspirin as well as more potent anticoagulants, should be considered for all patients undergoing SBTHA. Future comparative trials are needed to address this issue.

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6 - Which VTE prophylactic agent used in patients undergoing TKA/THA has the highest bleeding rate?

Response/Recommendation: Patients undergoing total hip arthroplasty/total knee arthroplasty (THA/TKA) who received thromboprophylaxis are at an increased risk of bleeding. Higher bleeding rates were detected for low-molecular-weight heparin (LMWH) versus aspirin (ASA) and for rivaroxaban versus LMWH and other novel oral anticoagulants (NOAC), while the lowest bleeding rates in patients receiving NOAC were observed for apixaban. Drug dosage and patient characteristics (age, renal dysfunction) may complicate the data on bleeding risk as may changes in clinical practice (particularly with the wide use of tranexamic acid (TXA) currently).

Strength of Recommendation: Limited.

Delegates vote: Agree 95.73% Disagree 1.71% Abstain 2.56% (Strong Consensus).

Rationale: Thromboprophylaxis by different strategies has proven effective in decreasing the risk of venous thromboembolism (VTE)[239] associated with both THA, and TKA. VTE can include distal or proximal deep venous thrombosis (DVT) and occasionally pulmonary embolism (PE). The use of thromboprophylaxis trades off the decreased risk of VTE with the potential for increased bleeding.

Bleeding as a complication of THA/TKA surgery under pharmacological thromboprophylaxis is a safety issue usually incorporated into clinical trials, even if the definition and adjudication of bleeding outcomes may be inhomogeneous and therefore inconclusive[240]. Major bleeding may account for up to 8.9% of total perioperative deaths[241] following total joint arthroplasty (TJA) and therefore is a concerning complication. While major bleeding and hemorrhage is usually detected and reported in trials, minor bleeding remains subjective whilst occult blood loss may be underdiagnosed. Two large phase 4 trials reported a 0.1% major bleeding risk following TJA when rivaroxaban was used for thromboprophylaxis[242,243]. Heterogeneity increases when specific bleeding complications are investigated, such as gastrointestinal bleeding[244]. Furthermore, a meta-analysis with trial sequential analysis to test the robustness of findings related to rivaroxaban[245] concludes that major bleeding (not included as primary endpoint) did not reach the required information size and therefore more evidence may be needed to verify the risk. However, when surgical-site bleeding is incorporated in a risk-benefit analysis of NOAC, the clinical net benefit is not so clear in THA while maintained in TKA[246]. Despite these inconsistencies, efficacy and safety is universally confirmed and accepted for all thromboprophylaxis agents in clinical use today, after clinical trials and meta-analysis.

An important body of literature is available about the results of early and pivotal clinical trials for all pharmacological agents in the market. Individual trials may offer different reporting criteria for bleeding events, and therefore, comparative trials and meta-analysis should be preferred to define bleeding rates and risks, even if sometimes limited strength of the recommendations is observed, due to limited or conflicting evidence. Systematic reviews and particularly meta-analysis of these trials offer best evidence and data to conclude on some comparisons. But even those may be conflicting due to heterogeneity in reported bleeding, and in surgical or patient confounding factors. A recent meta-analysis with pooled analysis of bleeding events in the rivaroxaban trials[247] showed that the overall rate of major bleeding events, overt bleeding events associated with fall in hemoglobin (Hb) of > 2 g/dL, clinically overt bleeding events leading to transfusion of > 2 units of blood, clinically overt bleeding events leading to further surgeries, and non-major bleeding events were $< 1\%$, $< 1\%$, $< 1\%$, $< 1\%$, and 3%, respectively. Many procedural factors may apply. Differences in clinical practice such as the use of TXA and transfusion indications, means that conclusions are hard to establish.

Three major studies of safety comparisons were identified in the literature: LMWH versus ASA[248], non-vitamin-K oral anticoagulants (NOAC, including direct factor Xa inhibitors and other, such as rivaroxaban, dabigatran, apixaban, ximelagatran, etc.) versus LMWH[249-262] or ASA[263-265], and NOAC of different groups comparing to each other[252,266]. Bleeding rates are not always reported, and bleeding risks may be used as the surrogate. Rarely, meta-analysis have been published focusing on the surgical site bleeding risks[267], reporting higher relative risks for LMWH and rivaroxaban, and lower for apixaban. Network meta-analysis comparing all options[268] seem to confirm a decreased hemorrhage risk with oral anti-Xa compared with LMWH, also lower for both anti-Xa and LMWH to vitamin-K antagonists (VKA) with international normalized ratio (INR) between 2 and 3.

When comparing ASA and LMWH[248] in a meta-analysis (4 trials, 1507 patients), no significant difference in the bleeding risk was detected (major bleeding, relative risk [RR] = 0.84; minor bleeding, RR = 0.77).

NOAC comparisons report slightly different bleeding rates for each agent against LMWH (usually enoxaparin) and among them. A synthesis includes: major bleeding in 1.4% (220 mg) or 1.1% (150 mg) vs. 1.4% (3 trials and 8,135 patients in dabigatran vs enoxaparin[251],); major or non-major, clinically relevant bleeding RR vs. enoxaparin of 1.52 (ribaroxaban), 0.34 (betrixaban), 0.88 (apixaban), 0.85 (darexaban), 1.30 (edoxaban)[250]; better preventive effects on bleeding with apixaban[252]; RR of major bleeding of oral direct factor Xa inhibitors vs. enoxaparin, 1.27 (5 trials, 12,184 patients with THA) and 0.94 (5 trials, 13,169 patients with TKA) being non significantly different from enoxaparin[253]; less bleeding (and less efficacy) of

enoxaparin vs. immediately postop ximegalatran with hip odds ratio (OR) = 0.30 and knee OR = 0.71 (6 trials, 10,051 THA or TKA patients)[254]; compared to enoxaparin, the RR of clinically significant risk of bleeding was higher with rivaroxaban (RR = 1.25), similar with dabigatran (RR = 1.12) and lower with apixaban (RR = 0.82) in a meta-analysis of 16 trials, 38,747 THA or TKA patients[256]; compared with dabigatran, enoxaparin similarly efficacious and similar risk of bleeding (OR = 0.90), while compared with rivaroxaban, enoxaparin less efficacious but lower risk of bleeding (OR = 0.79) in a meta-analysis with 6 trials, 18,405 THA or TKA patients[257]; in a network meta-analysis with 19 trials and 43,838 THA or TKA patients, OR were also calculated against enoxaparin 30 mg twice a day (*bis in die* [bid]) or 40 mg daily, and bleeding (major/non-major clinically relevant) was significantly increased for fondaparinux (vs. 40 mg daily, OR = 0.67) and rivaroxaban (vs. 40 mg daily, OR = 0.77)[258], while apixaban as the comparator (2.5 mg bid) showed increased bleeding with enoxaparin 30 mg bid (OR = 0.75), dabigatran (OR = 0.73), fondaparinux (OR = 0.56), and rivaroxaban (OR = 0.65); a meta-analysis with 21 randomized control trials (RCT)[259] produced major bleeding rates with enoxaparin of 1.32%, dabigatran 1.25%, rivaroxaban 2.02%, apixaban 0.70%, ximegalatran 0.93%; a pooled analysis of 2 RCT with 8,464 THA or TKA patients comparing apixaban and enoxaparin showed a major bleeding rate of 0.7% and 0.8%, but when non-major clinically relevant bleeding was summed, the rates were 4.4% for apixaban and 4.9% for enoxaparin[260]. As a summary, major bleeding rates for enoxaparin were reported from 0.8 to 1.3%, for dabigatran 1.1 to 1.4%, for apixaban around 0.7, for rivaroxaban around 2%. Other clinically relevant bleeding may account for about 4%, but minor bleeding rates are difficult to establish.

When comparing ASA and NOAC, the former had less risk of blood transfusion than rivaroxaban (RR = 0.94)[264]. A large trial (3,424 patients) did not find significant differences between ASA and rivaroxaban in clinically important bleeding (1.29% vs. 0.99%) or major bleeding (0.47% vs. 0.29%)[263], and a recent meta-analysis[269] could not find any significant differences in any bleeding, major bleeding, minor bleeding, gastrointestinal tract bleeding or wound hematoma, between ASA or any other comparator.

Risks associated to dosage were studied between anti-Xa agents and LMWH[255,270]. With LMWH as a comparator, enoxaparin 30 mg bid may decrease the VTE risk but may increase the clinically significant hemorrhage (in[270] significantly, in[255] non-significantly). Of note, many clinical trials of NOAC have used enoxaparin 40 mg once daily, the standard in many centers at the time of trials. ASA dosage in thromboprophylaxis has been studied (81 mg bid vs. 325 mg bid) showing similar bleeding rates with an overall rate of 0.9%, although 325 mg produced more gastrointestinal symptoms[271]. Prolonged administration of thromboprophylaxis with LMWH was not associated with changes in major bleeding but there was an increase in minor bleeding (3.7% in long-term administration vs. 2.5% in short-term prophylaxis)[272], although a registry study[273] did not associate any increased bleeding risk. Again, definition and reporting may be different.

There is little contemporary literature with warfarin as a comparator and most studies compare different doses[274,275]. Early trials with warfarin and LMWH[276] seemed to highlight higher bleeding risks with LMWH vs. adjusted warfarin (2.8% vs. 1.2% incidence of major bleeding events).

Risks may be increased in case of renal dysfunction[277], and concomitant medications or age may also affect bleeding. Non-steroidal anti-inflammatory drugs[278,279] did not increase the risk of bleeding for dabigatran[278], and age older than 75[280] showed lower risk of bleeding with anti-Xa medications than with LMWH (OR = 0.71).

Fibrinolysis and antifibrinolytic agents (such as TXA) may have an impact on bleeding[281-284], and it is worth considering that many of the above-mentioned meta-analysis were based on trials performed without perioperative TXA. Today's standard-of-care incorporating TXA may have produced different bleeding rates. Hidden blood loss after TXA in patients receiving enoxaparin, rivaroxaban or nadroparin was not statistically significant in a trial with 150 patients[281], but this will need further investigation.

Although all investigated thromboprophylaxis agents have a reasonable safety profile, bleeding events are a matter of concern for all surgeons. Variability in patients and procedures may apply, but careful attention to outweigh risks and benefits, personalize the thromboprophylaxis regime and early detection of related bleeding complications is required to improve the standard of health care invasive measures such as anticoagulant prescription in the perioperative period of total joint replacement, particularly when no specific antidote is available for most NOAC[285], and anticoagulant overtreatment represents a serious risk of bleeding in our surgical patients.

Enrique Gómez-Barrena, Per Kjærsgaard Andersen

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7 - What is the incidence of readmission and re-operation for hematomas secondary to administration of chemoprophylaxis for VTE in patients undergoing total joint arthroplasty?

Response/Recommendation: The incidence of readmission and re-operation for hematomas secondary to chemoprophylaxis for venous thromboembolism (VTE) in patients undergoing total joint arthroplasty (TJA) is low and not definitively related to the choice of anti-coagulant. There is a trend toward increased incidence of hematomas requiring re-operation in patients on enoxaparin in comparison to warfarin or factor Xa inhibitors. Thirty-day readmission rates are higher for all chemotherapeutic agents (low-molecular-weight heparin [LMWH], direct-oral anticoagulant [DOAC], warfarin), in comparison to aspirin (ASA). However, risk stratification practices resulting in higher risk patients who have complex co-morbidities preferably receiving these more potent agents have not been eliminated as a confounding variable in existing studies.

Risk stratification can be done as per the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) guidelines and by further information found in the response to question # 24 of the 2021 International Consensus Meeting (ICM) on VTE - General section.

Strength of Recommendation: Limited.

Delegates vote: Agree 93.16% Disagree 3.42% Abstain 3.42% (Strong Consensus).

Rationale: The incidence of unplanned readmission following TJA has been reported to be 2.4 to 8.5% within 30 days and 5.3 to 11.9% at 90 days[286-289].

Hematoma has been reported to be between the 3rd to 7th most common reason for readmission following primary TJA[290,291], and accounts for up to 6.7% of readmissions following total hip arthroplasty (THA)[291] and 8.5% of readmissions for total knee arthroplasty (TKA)[287].

A variety of chemoprophylactic agents are used for VTE prevention following TJA including low- and high-dose ASA (81 mg or 325 mg, respectively), LMWH, warfarin, and newer DOAC such as factor Xa and thrombin inhibitors including rivaroxaban, apixaban, dabigatran. There is no universal consensus on the optimal strategy for risk stratification and choice of agent for VTE prevention following primary TJA. While DOAC have been demonstrated to be more effective and convenient for patients than injectable medications[292], there remain concerns about increased risk of complications related to bleeding such as wound healing problems and hematomas, which can lead to unplanned readmissions and reoperations.

Multiple randomized control trials have shown that while both enoxaparin and warfarin have good efficacy for VTE prevention in TJA, enoxaparin is associated with a trend towards increased risks of major and minor bleeding. This finding was consistently a trend, but not always statistically significant[293,294].

A meta-analysis comparing DOAC and LMWH for DVT prevention in TJA was performed using a dose-response model to evaluate the efficacy and safety of anticoagulation for the prevention of VTE in THA and TKA[295]. The therapeutic index was used to compare the safety and efficacy of a variety of chemoprophylactic agents. The therapeutic index-defined as a ratio of bleeding/efficacy using major bleeding (defined by the International Society on Thrombosis and Haemostasis) as the reference point for bleeding, and VTE as the reference point of efficacy, was found to be superior for factor Xa inhibitors (apixaban (5 mg/daily), rivaroxaban (10 mg daily), and edoxaban (30 mg daily) in comparison to both low- and high-dose LMWH (enoxaparin 40 mg daily or 30 mg twice a day [*bis in die* (bid)], respectively). Dabigatran was not found to be superior to enoxaparin for bleeding risk or efficacy. It was found that there is a difference in the efficacy and safety profile based upon regional variations of dosing of enoxaparin used: the 30 mg bid dosing (North American dosing) was associated with increased risk of major bleeding or clinically relevant bleeding compared to 40 mg once daily (European dosing)[295].

Conversely, in a retrospective analysis of a prospective database[296], use of factor Xa inhibitors was associated with a significantly higher rate of bleeding and wound complication in comparison to those on high-dose ASA in patients undergoing primary THA and TKA (18.7% vs. 0%, $p < 0.03$). Of the patients with bleeding and wound complications, however, only one developed a hematoma and two were readmitted. Another observational study assessed the incidence of post-operative complications in patients receiving either rivaroxaban or enoxaparin thromboprophylaxis for THA and TKA. There were no significant differences in the readmission rate between rivaroxaban and enoxaparin treated patients, nor in the incidence of minor bleeding (2.0% vs. 0%) and hemorrhagic wound complications (5.0% vs. 1.8%)[297].

In a large single center cohort of 17,784 patients undergoing TKA, the incidence of hematomas requiring re-operation within 30 days of surgery was 0.24%. Patients who had hematomas were compared to those who did not have hematomas (controls). A history of bleeding disorder (von Willebrand disease, or Hemophilia A, or B) was found to be associated with increased risk of hematomas requiring readmission and re-operation; pre-operative anticoagulation and type of post-operative

anticoagulant (i.e., no chemoprophylaxis, ASA, LMWH, warfarin) were not found to be risk factors for hematoma formation[298,299], although some studies revealed a higher rate of bleeding complications and reoperations following TKA using pre-operative warfarin management[300] and pre-operative dalteparin[301].

In a case control series comparing patients who had TJA that developed periprosthetic joint infection (PJI) and controls who did not develop a PJI[302], the authors found that patients who had international normalized ratio (INR) > 1.5 on warfarin chemoprophylaxis had an increased risk of PJI following TJA and patients who had PJI had higher rates of reoperation due to hematomas than those who had no infection, of whom the majority had an INR < 1.5.

In a retrospective review including 21,864 primary THA and TKA, it was found that 30-day readmission rates after primary THA were increased when the choice of VTE prophylaxis was any agent other than ASA. However, a major limitation of this study was that anticoagulant selection was mainly based on the discretion of the operative surgeon[290].

As for revision TJA, it is thought that it may expose patients to higher VTE risks and for developing bleeding and infection complications. In a retrospective review of a database including 3,178 patients who underwent revision TJA[303], administration of ASA to low-risk patients reached a higher efficacy than warfarin to reduce VTE events and reduced the incidence of reoperations for evacuation of postoperative hematomas. In a retrospective cohort study of 1,048 revision TJA[304], when administering LMWH (tinzaparin) compared to DOAC (rivaroxaban), higher readmissions (9 vs. 22, p = 0.046) and reoperation rates (0 vs. 9, p = 0.032) were found.

Using a multimodal approach in which the treatment regimen is selected according to patient risk factors may be the best strategy[305]. In a retrospective review of 1,179 consecutive TJA[303], reoperations and readmissions due to wound hematomas occurred only in patients being managed with warfarin or LMWH (p = 0.0001), either for prophylaxis (high-risk factors) or for treatment of VTE/pulmonary embolism (PE), compared to those receiving antiplatelet chemoprophylaxis.

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8 - Does the type of VTE prophylaxis influence the risk of subsequent surgical site infection (SSI) in patients undergoing orthopaedic procedures?

Response/Recommendation: The use of warfarin is associated with significantly higher surgical site infection (SSI) and periprosthetic infection (PJI) rates when used for venous thromboembolism (VTE) prophylaxis, especially in patients undergoing total joint arthroplasty (TJA). Limited evidence points to lower or similar rates of SSI using aspirin (ASA) as prophylaxis compared to more potent anticoagulants.

Strength of Recommendation: Limited.

Delegates vote: Agree 93.91% Disagree 2.61% Abstain 3.48% (Strong Consensus).

Rationale: The most suitable pharmacological agent for VTE prophylaxis in patients undergoing orthopaedic procedures is yet to be identified, given the need to balance clinical effectiveness and inherent bleeding risk[306-308]. Several studies have shown that increased rates of wound drainage and SSI are associated with chemical thromboprophylaxis use, most notably when more potent agents are favored[309-314].

Warfarin: Is one of the earliest thromboprophylaxis agents described, but its use in the perioperative orthopaedic setting remains controversial to this day[315-318]. A vast body of level one studies, prospective cohorts, and relevant retrospective studies have shown statistically higher rates of SSI associated with warfarin use when compared to ASA[306,312,315,319-322], low-molecular-weight heparin (LMWH)[315,319,323], and rivaroxaban[315,317]. Agaba et al., using a nationwide healthcare database in the US, analyzed 25,966 total hip arthroplasty (THA) patients without a previous history of VTE[315]. They compared the use of ASA, enoxaparin, warfarin, apixaban, fondaparinux and rivaroxaban. Warfarin use was associated with the highest number of 30- and 90-days complications, including SSI[315]. Huang et al., described prophylactic warfarin use as an independent risk factor for PJI following TJA, after a retrospective investigation and logistic regression analysis[324].

Low-molecular-weight heparin (LMWH): There is conflicting evidence regarding the rate of infectious complications following the use of LMWH. Using the Global Orthopaedic Registry, Wang et al., evaluated the 90-day postoperative complication rates in 3,755 patients undergoing primary THA and total knee arthroplasty (TKA) using LMWH or warfarin in the US[323]. Patients that received LMWH had significantly higher risk of SSI and reoperation. Turpie et al., performed a meta-analysis of four randomized controlled trials (RCT) comparing fondaparinux against enoxaparin in 7,344 patients undergoing THA, TKA and hip fracture surgery for 11 days after surgery[324]. An increased bleeding risk was associated with fondaparinux use, but no differences in infection rates were identified[324].

Factor Xa inhibitors and direct thrombin inhibitors: The published evidence pertaining to the effects of both factor Xa inhibitors and direct thrombin inhibitors on wound complications has been inconsistent. After rivaroxaban was approved, several observational studies found increased rates of wound complications when it was compared with LMWH[325-327]. Jensen et al., evaluated the infection and reoperation rates in 559 consecutive patients undergoing TKA or THA using rivaroxaban, compared to 489 consecutive patients using tinzaparin[325].A significant increase in wound complications and reoperation rates were found to be associated with rivaroxaban, especially in patients undergoing TKA. However, they did not find significant differences in infection rates. Jameson et al., found similar results, in a multicentric study evaluating 2,762 patients using rivaroxaban compared to a retrospective cohort of 10,361 patients using LMWH after TJA[326]. To further evaluate these concerns, a meta-analysis was performed, evaluating the 12,383 patients of the four Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trials, looking at their bleeding and infection rates[328]. They found an overall similar complication rate between patients using enoxaparin and rivaroxaban. However, in TKA patients specifically, higher infection rates were associated with enoxaparin use, and higher bleeding rates were associated with rivaroxaban use. Other studies have found similar results[308,322,329-334]. When directly compared with warfarin, rivaroxaban seems to have lower SSI rates[315,317]. Glassber et al., retrospectively studied patients undergoing elective THA from a US administrative database between 2010 and 2015[317]. They included 20,292 patients that received warfarin and 15,631 patients that received rivaroxaban and found significantly higher rates of PJI associated with warfarin use. Several observational studies have expressed concern about problems with wound discharge when using dabigatran[335-338]. However, pooled analysis of the two oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE) trials, which included 4,374 patients, found no differences in wound complications or infections between dabigatran and enoxaparin[339].

Aspirin (ASA): The last two decades have seen renewed interest in the use of ASA as a VTE chemoprophylactic agent, especially due to reports of lower surgical wound complications rates. Tan et al., published a multi-institutional, retrospective study on 60,467 primary and revision THA and TKA, performed between 2000 and 2015[321]. They compared the use of ASA, LMWH and warfarin over 90 days postoperatively. They found a significantly lower rate of PJI in patients that received ASA compared to those that received either warfarin or LMWH. This finding was consistent across all the VTE risk groups. However, Bozic et al., did not find such differences. They retrospectively analyzed 93,840 patients undergoing primary TKA between 2003 and 2005[307] and compared the use of ASA, warfarin, and injectable medications such as enoxaparin and fondaparinux. They found no differences in infection rates or mortality. Similar results were found in a meta-analysis done by Matharu et al., who studied 13 RCT including 6,060 THA and TKA patients[340]. In a pooled analysis, they found no differences in infection rates between ASA and other VTE prophylaxis agents but did not clarify further with a subgroup analysis.

Compared to ASA, prophylactic warfarin use has demonstrated an increased risk of SSI and PJI[306,312,315,319-322,341]. Huang et al., studied 3,156 patients undergoing THA or TKA[342]. As mentioned above, following logistic regression analysis, the use of warfarin was identified as an independent risk factor for PJI[342]. Huang et al., conducted a retrospective study including 30,270 THA and TKA patients who received ASA 81 mg or 325 mg bid, or warfarin with an INR goal of 1.8 - 2.0, for four weeks[320]. They compared patients considered high-risk to those considered low-risk for the development of VTE. High-risk patients that received warfarin had a higher risk of both PJI and

mortality than patients receiving ASA. However, other studies have not found differences in SSI rates[306,343,344].

When comparing ASA with LMWH, the data is less clear[345-348]. Kulshrestha, and Kumar, randomized patients undergoing TKA to receive either routine anticoagulation, consisting of enoxaparin 40 mg for two weeks postoperatively followed by ASA for two further weeks thereafter, or a risk stratified thromboprophylaxis strategy[345]. The risk stratified study group were identified as either being "high-risk", thus receiving enoxaparin and ASA as above, or "standard-risk", receiving ASA 325 mg only for four weeks. No difference was identified in infection rates between the two groups, but patients were nearly eight times more likely to experience a wound complication whilst receiving LMWH as opposed to ASA. Haac et al., recently conducted an open-label RCT of adult patients admitted to an academic trauma center with operative extremity fractures, or a pelvis or acetabular fracture, comparing ASA with LMWH[347]. Deep infections were identified in 4.3% of patients receiving ASA, and in 5.5% in those receiving LMWH. Given the significant heterogeneity in dosage, duration, and timing of VTE chemoprophylaxis initiation in different studies, Farey et al., performed a meta-analysis on the use of early postoperative thromboprophylaxis with ASA versus enoxaparin in TJA patients[348]. They included four trials, consisting of 1,507 patients, and found no difference in adverse event rates. However, they cautioned about the high risk of bias and low quality of available evidence.

Numerous studies have focused on comparing the use of ASA with direct oral anticoagulants. A recent meta-analysis included eight studies with 97,677 THA and TKA patients, three of which were RCT, comparing the use of rivaroxaban and ASA[349]. No difference was identified with regards to the rate of wound complications. Using data from the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man, Matharu et al., studied 218,650 patients undergoing TJA between 2003 and 2017[350]. They reviewed patients using ASA and compared to patients receiving either direct thrombin inhibitors or factor Xa inhibitors. They found no differences in either SSI or re-operations between either of the VTE chemoprophylactic classes.

Several issues limit the available evidence regarding VTE prophylaxis and SSI in orthopaedic procedures. Orthopaedic surgeries encompass interventions spanning the entire spectrum of operative invasiveness and duration, across a wide variety of anatomical locations, within both the elective and emergency settings. Routine VTE chemoprophylaxis use has not been universally adopted throughout all orthopaedic subspecialties, as controversy continues to exist in many domains. Most studies evaluating the association between infection risk and thromboprophylaxis modalities are of a retrospective design, and their heterogeneity reflects the persistent variety in thromboprophylaxis practices[351]. Furthermore, perioperative management has progressed dramatically in the last decade with a trend towards enhanced recovery programs, early mobilization, outpatient rehabilitation and ambulatory same-day procedures. As such, many of the simultaneous temporal changes in surgical technique and perioperative care over the last decade may confound the results. Also, thromboprophylaxis protocols vary in their doses and duration, making comparisons difficult. Infection risk is often reported as a secondary outcome in studies evaluating VTE rates and thus any attempted sub-analyses are often underpowered. Moreover, SSI definitions demonstrate variety across the studies in the literature, further compromising the comparisons of pooled results. Finally, most publications have investigated VTE prophylaxis within a specific subset of the orthopaedic population: those undergoing TJA surgery[347]. Considering that most of the relevant current published evidence demonstrates heterogeneity and a high risk of bias, additional level one studies are needed to truly evaluate the associations between VTE prophylaxis and SSI across all orthopaedic surgery subspecialties[350].

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9- Does the type of VTE prophylaxis influence the risk of subsequent periprosthetic joint infection in patients undergoing joint arthroplasty?

Response/Recommendation: Yes, the type of venous thromboembolism (VTE) prophylaxis influences the risk of subsequent periprosthetic joint infection (PJI). The strongest association is observed for vitamin-K antagonists (VKA) when compared to acetylsalicylic acid (Aspirin [ASA]).

Strength of Recommendation: Moderate.

Delegates vote: Agree 91.30% Disagree 5.22% Abstain 3.48% (Strong Consensus).

Rationale: Impaired hemostasis and bleeding in an arthroplasty wound, resulting in hematoma formation and persistent wound drainage, might favor bacterial growth and the subsequent development of PJI. Therefore, it is reasonable to assume that the risk to develop a PJI is influenced by the type of VTE prophylaxis used. We have conducted a literature search in PubMed and Embase according to the search strategy defined in the appendix. From the total of 107 articles, a final number of 23 articles met the predefined inclusion and exclusion criteria. The details of these studies are summarized in Table II.

Most of the included studies compared the infection risk between low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOAC)[352-361]. The largest analysis has been

TABLE II

Author	Year	Joint	VTE prophylaxis	Dose	Duration	Outcome	Infection rate/odds	p-value	Study design
Agaba et al.[360]	2017	Hip	ASA (n = 551) enoxaparin (n = 6,791) warfarin (n = 12,008) rivaroxaban (n = 5,403) fondaparinux (n = 876) apixaban (n = 337)	NP	≤ 30 days	PJI < 30 days*	OR 0.86 (0.54, 1.38) OR 0.53 (0.44, 0.65) OR 1.44 (1.26, 1.64) OR 0.36 (0.29, 0.46) OR 0.40 (0.24, 0.67) OR 1.58 (0.83, 3.01)	NP	Retrospective cohort
			ASA (n = 551) enoxaparin (n = 6,791) warfarin (n = 12,008) rivaroxaban (n = 5.403) fondaparinux (n = 876) apixaban (n = 337)	NP	≤ 30 days	PJI < 90 days*	OR 0.47 (0.25, 0.88) OR 0.34 (0.27, 0.44) OR 1.17 (1.01, 1.34) OR 0.27 (0.20, 0.35) OR 0.40 (0.24, 0.67) OR 0.77 (0.31, 1.87)	NP	Retrospective cohort
Brimmo et al.[371]	2015	Hip, Knee	Rivaroxaban (n = 159)	10 - 20 mg OD	≥ 2 weeks	Deep SSI (≥ 2 cultures)	2.5%	< 0.015	Retrospective cohort
			other (n = 480)†				0.2%		
Cafri et al.[361]	2017	Knee	ASA (n = 5,124) enoxaparin (n=13,318) fondaparinux (n=3,225) warfarin (n=8,832)	325 mg OD 40 - 60 mg OD 2.5 mg OD INR goal 1.8 – 2.0	NP	SSI: deep infection or revision surgery for infection related reasons < 90 days index procedure	0.39% / 1.00 0.39% / 0.90 (0.48 - 1.67) 0.41% / 0.84 (0.36 - 1.92) 0.46% / 0.80 (0.42 - 1.53) (OR: vs. ASA)	0.732 /0.148 0.674/ 0.172 0.500/ 0.089 (superiority /non-inferiority)	Retrospective cohort
Chahal et al.[352]	2013	Hip, knee	Enoxaparin (n = 227)	40 mg OD	6 weeks or stopped at discharge and continued on ASA	Infection defined as returning to theatre <12 months	0.88%	NP	Comparison with retrospective cohort after change in protocol
			rivaroxaban (n = 160)	10 mg OD	10 days for knees, 30 days for hips		1.88%		
Charters et al.[353]	2015	Hip, knee	Enoxaparin (n = 1,113)	30 mg bid for knees 40 mg OD for hips	14 days 21 days	Deep infection requiring DAIR	0.9%	0.99	Comparison with retrospective cohort after change in protocol
			rivaroxaban (n = 649)	10 mg OD for knees 10 mg OD for hips	12 days 35 days		0.9%		

continued

TABLE II (*continued*)

Author	Year	Joint	VTE prophylaxis	Dose	Duration	Outcome	Infection rate/odds	p-value	Study design
Di Benedetto et al.[372]	2017	Hip	Rivaroxaban (n = 145)	NP	35 days	PJI < 4 weeks	0%	1.00	Retrospective cohort
			other (n = 60)‡				0%		
Feldstein et al.[367]	2017	Hip, knee	ASA 325 mg bid (n = 282)	325 mg bid	1 month	PJI < 1 month	0%	1.00	Prospective cohort
			ASA 81 mg bid (n = 361)	81 mg bid			0%		
Glassberg et al.[373]	2019	Hip			*Community insured*				Retrospective cohort
			warfarin (n = 12,876)	NP	No info	PJI < 90 days	0.88%	0.02	
			rivaroxaban (n = 10,892)	NP			0.62% OR 1.57 (1.16, 2.13)		
					Medicare				
			warfarin (n = 7,416)	NP	No info	PJI < 90 days	0.85%	0.02	
			rivaroxaban (n = 4,739)	NP			0.49% OR 1.79, (1.14 - 2.81)		
Huang et al.[363]	2016	All joints	ASA low risk (n = 4,102) warfarin low-risk (n = 18,649)	81 or 325 mg bid INR goal 1.8 -2.0	4 weeks postop 4 weeks postop	PJI < 90 days (MSIS criteria)	0.2% 1.1%	< 0.001	Retrospective
			ASA high-risk (n = 796) warfarin high-risk (n = 6,723)	81 or 325 mg bid INR goal 1.8 – 2.0	4 weeks postop 4 weeks postop		0.1% 1.7%		
			warfarin high-risk (n = 6,723)	INR goal 1.8 – 2.0	4 weeks postop		An OR 13.7 (1.9, 98.5)	0.001	
Huang et al.[362]	2015	All joints	ASA (n = 1,456) warfarin (n = 1,700)	325 bid INR goal 1.8 – 2.0	6 weeks postop	PJI < 90 days	0.4% 1.5%	< 0.001	Comparison with retrospective cohort after change in protocol
			warfarin (n = 1,700)	INR goal 1.8 – 2.0			An OR 2.77 (1.19, 6.45)		
Jameson et al.[354]	2012	Hip, knee	LMWH (n = 10,361)	NP	14 days knees 21 days hips	SSI and PJI r equiring return to surgery < 30 days	0.53%	0.59	Comparison with retrospective cohort after change in protocol
			rivaroxaban (n = 2,762)				0.62%		
Jensen et al.[355]	2011	Hip, knee	LMWH (n = 489)	4500 U	28 days	Deep infection requiring DAIR < 30 days	1.0%	0.10	Comparison with retrospective cohort after change in protocol
			rivaroxaban (n = 559)	10 mg OD	14 days knees 28 days hips		2.5%		

continued

TABLE II (*continued*)

Author	Year	Joint	VTE prophylaxis	Dose	Duration	Outcome	Infection rate/odds	p-value	Study design
Kim et al.[356]	2015	Hip	Rivaroxaban (n = 350)	10 mg OD	7 - 12 days postop	PJI	0%	1.00	Randomized trial
			enoxaparin (n = 351)	40 mg OD			0%		
			placebo (n = 185)				0%		
Kulshrestha et al.[374]	2013	Knee	Routine LMWH (n = 450) Risk stratification	40 mg OD	2 weeks postop	PJI	0.9%		Randomized trial
			(ASA ± LMWH) (n = 450)	325 bid ± 40 mg OD	4 weeks postop ± 2 weeks postop		0.2%		
Lassen et al.[357]	2012	Hip, Knee	Rivaroxaban (n = 6,183)	10 mg OD	10 - 40 days	Wound infection < 30 days	0.16%		Randomized trial
			enoxaparin (n = 6,200)	40 mg OD or 30 mg bid			0.27%		
Matharu et al.[375]	2020	Hip	ASA ± LMWH (n = 28,049) direct thrombin inhibitor ± LMWH (n = 28,049)	NP	NP	SSI < 90 days	OR 1.04 (0.84, 1.28)		Retrospective (national joint registry)
			ASA ± LMWH (n = 19,021) factor Xa inhibitor ± LMWH (n = 19,021)				OR 0.91 (0.70, 1.17)		
		Knee	ASA ± LMWH (n = 34,161) direct thrombin inhibitor ± LMWH (n = 34,161)				OR 1.09 (0.93, 1.27)		
			ASA ± LMWH (n = 25,114) factor Xa inhibitor ± LMWH (n = 25,114)				OR 0.91 (0.75, 1.11)		
Parvizi et al.[368]	2017	Hip Knee	ASA 81 mg bid (n = 1,459)	81 mg bid	4 weeks	PJI < 90 days	0.2%	0.28	Prospective crossover study
			ASA 325 mg bid (n = 3,192)	325 mg bid			0.5%		
Singh et al.[364]	2020	Hip, Knee	ASA 325 mg bid (n = 2,183)	325 mg bid	6 weeks	PJI < 6 months	1.4%	0.23	Retrospective
			warfarin (n = 3,333)				1.8%		
Tan et al.[365]	2019	All joints§	LMWH (n = 17,554)	NP	4 - 6 weeks	PJI < 90 days	No absolute numbers or % reported		Retrospective
			warfarin (n = 29,303)	INR goal 1.8 – 2.0					
			ASA (13,610)	81 mg or 325 mg bid					

continued

TABLE II (*continued*)

Author	Year	Joint	VTE prophylaxis	Dose	Duration	Outcome	Infection rate/odds	p-value	Study design
Tang et al.[369]	2020	Knee#	ASA (n = 435)	81 mg bid	1 month	PJI < 90 days**	0.2%	0.36	Retrospective
			ASA (n = 1,003)	325 mg bid			0.6%		
Tang et al.[370]	2020	Hip#	ASA (n = 388)	81 mg bid	1 month	PJI <90 days**	0.77%	0.46	Retrospective
			ASA (n = 973)	325 mg bid			1.2%		
Yen et al.[358]	2014	Knee	Rivaroxaban (n = 61)	10 mg once	2 weeks	Need for I&D < 90 days	0%	1.00	Retrospective
			enoxaparin (n = 52)	20 mg bid			0%		
Zou et al.[359]	2014	Knee	Rivaroxaban (n = 102)	10 mg/day	14 days	Wound complications < 4 weeks	4.9%	0.027, 0.014	Prospective randomized controlled trial
			LMWH (n = 112)	0.4 ml/day			2.7%		
			ASA 100 mg (n = 110)	100 mg/day			1.8%		

performed by Jameson et al., a retrospective multicenter observational analysis in which the authors compared the incidence of several wound complications after total hip arthroplasty (THA) and total knee arthroplasty (TKA) in 12 hospitals in the United Kingdom before and after a change of VTE prophylaxis protocol from LMWH to rivaroxaban[354]. One of the primary endpoints of the study was deep infection in which early reoperation was necessary. A total of 13,123 patients were included in the study, in which the infection rate was 0.53% in the LMWH group and 0.62% in the rivaroxaban group (no significant difference [NS]). A major limitation of this study was the fact that it was not possible to discriminate between surgical wound irrigation for infection or hematoma.

In addition, two randomized trials comparing LMWH and DOAC were performed, in which one was too small a sample size to detect any infection complication[356]. The other, performed by Lassen et al., in patients undergoing THA or TKA (RECORD programme), a post-operative wound infection rate of 0.27% in the LMWH group was observed compared to 0.16% in the rivaroxaban group (NS)[357]. No differences were observed between THA and TKA. Again, no clear definition was provided for post-operative wound infection. Figure 9A depicts a forest plot of all studies comparing LMWH with DOAC with respect to their risk of developing an infection. Only the studies in which the absolute numbers were depicted by the authors are included. The analyzed studies showed low

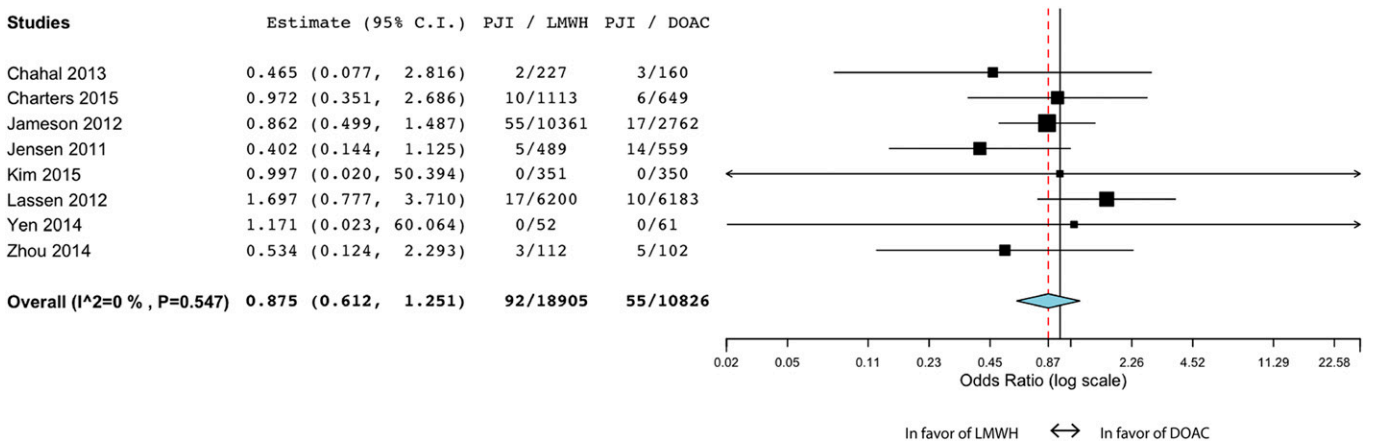

Fig. 9A

Forest plot. Depicting studies comparing LMWH with DOAC. LMWH=Low-molecular-weight heparin; DOAC=Direct oral anticoagulants; C.I.=Confidence interval; PJI=Periprosthetic joint infection.

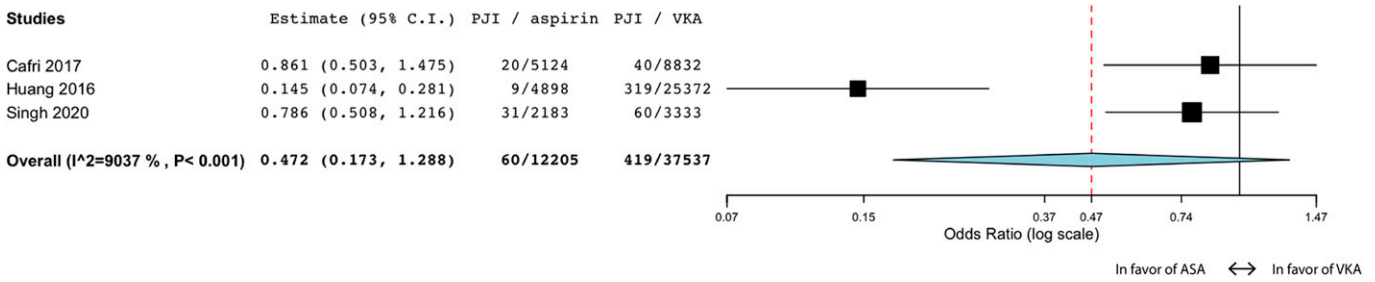

Fig. 9B

Forest plot. Depicting studies comparing ASA with VKA. ASA=Aspirin; VKA=Vitamin-K antagonist; C.I.=Confidence interval; PJI=Periprosthetic joint infection.

heterogeneity, and no differences between both types of VTE prophylaxis were observed.

The second most common comparison has been made between ASA and VKA[360-365]. All of these studies were retrospective analyses. The study performed by Huang et al., was the only one that defined PJI according to the Musculoskeletal Infection Society (MSIS) criteria[363]. In this study, the authors divided patients into those with a high-risk (n = 4,898) versus low-risk for VTE (n = 22,751), and consistently demonstrated a significantly lower PJI incidence in the ASA groups vs. the VKA groups (Table 2), with a PJI incidence of 0.18 versus 1.26% of the total cohort, respectively. The studies of Cafri et al., and Singh et al., showed a clear trend towards a lower infection rate in the ASA group, but this difference was NS[361,364]. Tan et al., also reported a lower risk for PJI when using ASA, but absolute numbers in this study were not provided[365]. In the study from Agaba et al., analyzing different VTE agents[360], warfarin, (VKA) was the only one significantly associated with the highest PJI risk, in particular in the early post-operative period, with an odds ratio (OR) of 1.44. An international normalized ratio (INR) greater than 1.5 was found to be more prevalent in patients who had post-operative wound complications and subsequent PJI[366]. Figure 9B depicts the forest plot of the three studies comparing ASA with VKA, including solely those studies in which the absolute numbers were depicted by the authors. With a high heterogeneity between studies, there was a significant difference observed in infection rate between the ASA and the VKA group in the pooled analysis. The dose of ASA (80 mg vs. 325 mg) does not seem to have any influence on the infection rate, either for THA or TKA when analyzed separately[367-370].

Unfortunately, only a few studies have directly compared infection rates between LMWH vs. ASA. In a retrospective analysis, Agaba et al., evaluated different types of VTE prophylaxis in 72,670 patients undergoing THA[360]. Rivaroxaban (DOAC), ASA, enoxaparin (LMWH), and fondaparinux had a significant protective effect on the development of PJI within 90 days after the index surgery, with OR of 0.27, 0.34, 0.40 and 0.47, respectively. For another DOAC, apixaban, a protective effect was not observed. With overlapping confidence intervals, the PJI risk for LMWH versus ASA was not significantly different. The largest analysis in which LMWH was directly compared to ASA is the study of Tan et al.[365]. In this study, 60,467 primary and revision total joint arthroplasties were retrospectively evaluated. The use of ASA was associated with a significantly lower risk for PJI development compared to LMWH and VKA (both $p < 0.001$). For LMWH vs. VKA, the PJI rate was lower for the high-risk VTE group only ($p < 0.001$). Unfortunately, no absolute numbers on PJI rates per type of VTE prophylaxis were provided in this study.

In conclusion, based on the literature review, VKA seem to be associated with the highest, and ASA (at least when compared to VKA) with the lowest risk for PJI. For LMWH and DOAC, no significant difference in PJI risk could be identified. Important limitations of the reviewed articles were the lack of a clear and adequate definition for (deep) infection and/or PJI. In addition, few studies performed multivariate analyses in which it remains unclear whether the type of VTE prophylaxis is an independent predictor for PJI.

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10 - Should the method for VTE prophylaxis be altered in patients undergoing revision for infection?

Response/Recommendation: Although infection is known to increase the risk of venous thromboembolism (VTE), there is no evidence to support a change in the approach to this group of patients. In general, aspirin (ASA) is safe and effective in revision surgery. Nevertheless, more potent anticoagulation strategies should be considered in the high-risk cases after risk stratification as determined by the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) guidelines and by further information found in the response to question # 24 of the 2021 International Consensus Meeting (ICM) on VTE - General section.

Strength of Recommendation: Limited.

Delegates vote: Agree 94.83% Disagree 2.59% Abstain 2.59% (Strong Consensus).

Rationale: Patients undergoing revision arthroplasty surgery have been shown to have higher rates of VTE when compared to primary arthroplasty[376]. However, revision alone is not considered an independent risk factor for VTE[377-379]. Variables such as infection, prolonged operative time, and decreased post-operative mobilization have been shown to increase the risk of VTE. Revision arthroplasty due to periprosthetic joint infection (PJI) is complex and challenging to manage, and much effort has been made to minimize its associated complications.

PJI is a rare, but devastating, complication of total joint arthroplasty (TJA) that place significant burden on both patients and health care systems. The incidence of PJI ranges from 1 - 2% in primary arthroplasty[380]. Data collected from joint registries demonstrates an overall weighted mean of 0.97% for total hip arthroplasty (THA) and 1.03% for total knee arthroplasty (TKA). The rate of revision due to PJI has increased by two-fold for primary THA and three-fold for revision THA[381]. Infection has been shown to be an independent risk factor for VTE[382]. A recent study demonstrated that the odds of developing VTE were more than double for revision TKA compared to aseptic revisions[383]. These findings suggest that the indication for septic revision arthroplasty should be considered when selecting post-operative VTE prophylaxis.

There are currently no specific guidelines addressing thromboprophylaxis for revision arthroplasty, and the current recommendations are extrapolated from primary arthroplasty procedures. In addition, many clinical trials have excluded revision arthroplasty when evaluating the efficacy and safety of anticoagulation modalities. Clinical apprehension of increased rates of VTE in revision arthroplasty stem from a more extensive and complex surgical exposure, longer operative times, larger systemic inflammatory response, and decreased post-operative mobilization. However, utilization of a more aggressive thromboprophylaxis regimen following revision arthroplasty could lead to poorer outcomes, as revision arthroplasty has been associated with increased rates of bleeding and complications[384]. Therefore, the decision of postoperative anticoagulation must weigh the risk of post-operative bleeding with that of VTE.

Traditionally, more potent anticoagulants such as vitamin-K antagonists (warfarin), low-molecular-weight heparin (LMWH), or direct-oral anticoagulants (DOAC) have been reserved for higher risk patients with established risk factors including obesity or prior history of VTE[385-388]. In the setting of PJI, patients undergoing revision arthroplasty are receiving antibiotics that have been shown to disrupt the gastrointestinal microbiome[389]. These antibiotics can harm the

vitamin-K producing gut flora causing agents like warfarin to be associated with supratherapeutic international normalized ratios (INR) and increased bleeding. Additionally, LMWH and DOAC have high potency and fast onset, but have been associated with higher rates of post-operative wound drainage[390].

In recent years, significant attention has been turned to using less potent antithrombotic agents such as ASA in both primary and revision arthroplasties. In a large retrospective study that looked at 2,997 patients, Deirmengian et al., evaluated whether ASA was as effective as warfarin for VTE prophylaxis in revision arthroplasty. They found a significantly higher incidence of symptomatic VTE in the warfarin group (1.75%) compared with the ASA group (0.56%). All other complication rates were similar except for the rate of bleeding events, which was also higher with the administration of warfarin. A limitation of the study included an analysis of confounders which revealed that patients in the warfarin group had higher rates of revision for PJI, higher Charlson comorbidity index scores, and longer procedural times.

Another recent retrospective study by Manista et al., analyzed various VTE prophylaxis regimens in 1,917 low-risk patients who underwent revision arthroplasty[377]. They found that the most commonly used prophylactic agent was rivaroxaban (40.6%), followed by warfarin (28.5%), and ASA (27.6%). There was no statistically significant difference in post-operative VTE, or complications observed. They concluded that ASA was just as effective as the other agents without the increased risk of bleeding in low-risk patients.

There has also been a trend towards using a lower dose ASA for VTE prophylaxis in revision arthroplasty compared to the traditional higher doses used in earlier regimens. Three retrospective studies within the past two years have cited low-dose ASA as a suitable chemoprophylactic agent in revision arthroplasty[391-393]. Tang et al., compared a prophylaxis protocol of 81 mg of ASA twice a day (*bis in die* [bid]) compared to 325 mg ASA bid in 1,361 revision THA patients and found no difference in total VTE, bleeding, or any other complication between the two groups[391]. A similar retrospective study was conducted for patients undergoing revision TKA and also observed no significant difference between low- and high-dose ASA for total VTE, bleeding, or any other complications[392]. Finally, Tang et al., reviewed the efficacy and safety of low-dose ASA in higher risk patients undergoing revision arthroplasty[393]. As prior studies have suggested that obesity may be associated with an increased risk of VTE, wound complications, and infections, these patients are routinely classified as high-risk and therefore traditionally prescribed a higher dose of ASA for prophylaxis. However, in their study, they found no difference in VTE rates or any other complications using low-dose ASA and observed similar complication rates to non-obese patients.

The management of revision arthroplasty in the setting of PJI is variable and challenging due to its complex nature. Patients with PJI represent a group at elevated risk for VTE following revision arthroplasty and these factors should be considered when tailoring VTE prophylaxis. Due to the lack of current evidence, it is difficult to recommend a specific VTE prophylaxis or any alterations to existing regimens. While there is data supporting ASA as a suitable thromboprophylaxis for most patients, patients at much higher risk of VTEs may require a more potent agent. However, there is recent literature to suggest that low-dose ASA may be safe for higher risk patients undergoing septic revision arthroplasty and is non-inferior at maintaining low rates of VTE. Further research is warranted to identify higher risk patients, stratify risk factors, and determine whether modifications to VTE prophylaxis are required. Future prospective studies should address the optimal approach to VTE prophylaxis in this high-risk population.

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11 - What is the optimal choice for VTE prophylaxis following two-stage or resection arthroplasty for treatment of knee and hip periprosthetic joint infection?

Response/Recommendation: Following explantation or reimplantation of components as part of a two-stage procedure or definitive resection arthroplasty for a hip or knee periprosthetic joint infection (PJI), patients should be stratified based on the risk of venous thromboembolism (VTE) events versus risk of post-operative complications associated with anticoagulation. Anticoagulation can be selected from established guidelines for primary total hip arthroplasty (THA) and total knee arthroplasty (TKA).

Strength of Recommendation: Moderate.

Delegates vote: Agree 93.97% Disagree 2.59% Abstain 3.45% (Strong Consensus).

Rationale: There are minimal clinical studies that directly focus on the risk and incidence of VTE during the treatment of PJI. There are a number of retrospective clinical studies comparing the incidence of VTE events between primary and revision arthroplasty surgery seeking to identify associated independent risk factors. Compared to primary arthroplasty, revision surgery has increased clinical concern for VTE events given the increased surgical exposure, surgical duration, and restricted weight bearing and mobilization post-operatively. However, the available clinical evidence suggests that revision surgery is not an independent risk factor for VTE, anticoagulation can be associated with post-operative complications, and that aspirin (ASA) can be non-inferior to other classes of anticoagulation when patients are appropriately selected. Combined, the limited available evidence suggests that patients should be stratified based on risk for thromboembolic events vs. the risk of post-operative complications associated with anticoagulation, and that this can then be selected from established guidelines for primary THA and TKA in patients being treated with a two-stage exchange or resection arthroplasty.

Predictors of VTE Events in Revision Arthroplasty Knee and Hip Surgery: Multiple studies have compared the incidence of VTE in primary and revision THA and TKA. Comparing direct VTE rates between revision and primary arthroplasty surgery, some studies have observed no difference in VTE rates[394-397], some have observed a decreased incidence[394], and others have observed an increased incidence[398-400]. In the studies that observed a higher incidence of VTE in revision vs. primary arthroplasty surgery, when the rates were adjusted for risk factors and comorbidities, revision surgery was either not associated with a higher risk of VTE[398], or had a lower difference based on risk stratification[401]. Only one of these studies, after adjusting for risk, still observed revision surgery as an independent factor for increase VTE. Combined evidence suggests that revision arthroplasty surgery is not an independent risk factor for VTE.

These studies also assessed independent risk factors of VTE in revision surgery. In a registry study of National Surgical Quality Improvement Program (NSQIP), independent risk factors for deep venous thrombosis (DVT) were age > 70 years, malnutrition, infection, operating time > 3 hours, the American Society of Anesthesiologist score > 4, kidney disease, and race. Independent risk factors for pulmonary embolism (PE) were age > 70 years, operating time > 3 hours, and race[398]. This was the only study in the literature that identified surgical infection as an independent risk factor of VTE with an odds ratio 4.1[398]. A separate retrospective institutional study identified independent VTE risk factors: body mass index (BMI) > 25kg/m^2, knee procedure, Charlson comorbidity index (CCI) > 2, chronic obstructive pulmonary disease (COPD), anemia, DVT, atrial fibrillation, and depression[395]. A multicenter retrospective study, in a high-risk group for VTE events, identified independent predictors for VTE, including a previous history of VTE, metastatic cancer, myeloproliferative disorder, transfusion, peripheral vascular disease, and age[394]. It should be emphasized that these are studies and not guidelines.

Restricted weight-bearing and limited mobility remains a unique risk factor for VTE events following revision as compared to primary THA and TKA surgery. Early mobilization, when clinically appropriate, remains a key tenant in orthopaedic fracture care and arthroplasty for preventing VTE events. In large part because of the unacceptable ethical concerns in conducting the clinical studies, there is minimal literature that can directly assess if weight-bearing restrictions are an independent predictor of VTE in fracture care and management. Nevertheless, there is strong consensus in orthopaedic surgery that early mobilization and weight-bearing are important at limiting VTE events. In non-operative fractures, literature from emergency medicine suggests that immobilization combined with non-weight-bearing are a risk factor for VTE events, but the quality of the evidence is low[402,403]. In orthopaedic trauma, limited evidence suggests that weight-bearing status is not a predictor of VTE events with fracture fixation[404,405].

VTE Prophylaxis in Revision THA and TKA: The use of aggressive anticoagulation in the prevention of VTE is associated with adverse events and does not have a benign safety profile. The incidence of VTE in arthroplasty surgery is well-established, but increased bleeding is associated with its own post-operative complications[406-408]. Revision procedures are associated with increased post-operative bleeding complications[397], potentially leading to poorer outcomes as revision arthroplasty is associated with higher rates of complications, especially infection[396]. A series of studies provide compelling evidence that reducing complications associated with bleeding reduces rates of PJI[394,409,410]. When patients were given a more aggressive anticoagulation regardless of VTE or bleeding risk, the incidence of post-operative wound complications increased with no change in overall VTE rates as compared to when a more nuanced approach was utilized that risk stratified patients[411].

ASA has an increased safety profile, and available evidence suggests it is non-inferior to other more aggressive anticoagulation. In revision arthroplasty surgery, the use of ASA had no difference in VTE rates as compared to other anticoagulants[412]. In an institutional registry that compared warfarin and ASA, no difference was observed in VTE rates, and warfarin was an independent predictor of mortality and PJI[413].

Based on these concerns, the American Academy of Orthopaedic Surgery (AAOS) recommends stratification of VTE risk balanced with risks associated with bleeding complications from anticoagulation[414]. The AAOS clinical practice guidelines (CPG) on VTE prophylaxis recommended early mobilization as a consensus recommendation for high-risk for VTE patients and those with a history of VTE. Furthermore, there was a consensus recommendation to consider both mechanical and pharmacologic treatment after surgery. In comparison, the previous American College of Chest Physicians (ACCP) guidelines recommend more aggressive prophylaxis with low-molecular-weight heparin (LMWH) or direct oral anticoagulants[415]. As discussed above, there is published evidence that ACCP guidelines with warfarin in particular lead to higher complication rates[411]. More recently, the ACCP guidelines have included the use of low dose ASA based on non-inferiority clinical studies to other anticoagulants in primary arthroplasty patients[416]. Surgeons should consider the guidelines for prophylaxis after hip and knee arthroplasty as recommended by the AAOS[414] and the ACCP[415] as well as information on stratification of risk discussed in the response to question # 24 of the 2021 International Consensus Meeting (ICM) on VTE - General section.

Without direct evidence in the literature regarding the optimum VTE prophylaxis strategy for this patient group, one should consider that revision surgery is not an independent risk factor for VTE, that aggressive anticoagulation has potential adverse events, that low dose ASA is non-inferior in the appropriate patient population, and the need to stratify VTE and bleeding risk factors when selecting anticoagulation agents for two-stage exchange and resection arthroplasty as per the AAOS[414] and the ACCP[415] guidelines with further information on stratification of risk discussed in the response to question # 24 of the 2021 ICM on VTE - General section.

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12 - Should the use of lower extremity tourniquet be avoided in patients at a high risk of VTE?

Response/Recommendation: Lower extremity tourniquets may be associated with an increased risk of venous

thromboembolism (VTE) post-operatively and should be used with caution in patients at a high risk of VTE.

Strength of Recommendation: Moderate.

Delegates vote: Agree 91.30% Disagree 7.83% Abstain 0.87% (Strong Consensus).

Rationale: Tourniquets are commonly used during total knee arthroplasty (TKA) to minimize blood loss and to improve visualization during surgery[417]. However, there is still controversy regarding the impact of tourniquets on postoperative pain, functional outcomes and complication rates after surgery[417-422]. Specifically, there are concerns that tourniquet use may be associated with an increased risk of VTE post-operatively[417-419].

Several meta-analyses investigating the association between tourniquet use and the incidence of VTE postoperatively have yielded mixed results[417-419,423-426]. Xie et al., in a meta-analysis of 14 randomized controlled trials reported that tourniquet use doubled the risk of postoperative VTE compared to no tourniquet use[418]. Similarly, Migliorini et al., in their meta-analysis including both randomized and non-randomized studies found that tourniquet use increased the risk of postoperative VTE four-fold, but this increase was of borderline statistical significance[426]. Two meta-analyses also reported an increased risk of postoperative VTE with use of a tourniquet[417,423].

In contrast, several meta-analyses have reported no difference in VTE rates between patients who had tourniquet use and no tourniquet use during TKA[424,426]. Cai et al., included 541 TKA from 11 randomized controlled trials and found no difference in VTE rates between patients who had tourniquets and those that did not[424]. However, one limitations of meta-analyses published to date is that the majority of these included a single study with a high rate of postoperative deep venous thrombosis (DVT) that was inconsistent with other studies. In a study of 103 patients who were not given chemoprophylaxis post-operatively and were screened for asymptomatic VTE, Mori et al., observed that 53% of patients with a tourniquet (n = 27) had a VTE post-operatively compared to 23% of patients without a tourniquet (n = 12)[427]. Including this study in a meta-analysis artificially inflates the rate of VTE, as most surgeons in contemporary practice provide chemoprophylaxis post-operatively and do not perform routine VTE screening in asymptomatic patients. A recent systematic review by Ahmed et al., excluded this study in a meta-analysis of 17 randomized controlled trials[419], noting an increased risk of VTE with the use of tourniquet compared to no tourniquet use, although this only approached statistical significance (Relative risk [RR] 1.95, 95% confidence interval [CI] 0.99 to 3.82).

An additional limitation of the literature is the heterogeneity in the way tourniquets are used, which may influence the rate of VTE post-operatively. Some surgeons use a tourniquet from incision to closure, others use it for cementation only, and the remainder use a tourniquet until the cement is dry and let it down prior to wound closure. Zhang et al., investigated the timing of tourniquet release and its impact on post-operative pain and complications in a meta-analysis of 11 randomized controlled trials[417]. In their series of 670 TKA, they found that early release of the tourniquet before wound closure was associated with fewer VTE post-operatively compared to late release after wound closure[417]. In addition to variation in the duration of tourniquet use, there is also variation in the cuff pressure selected among different surgeons. Consequently, it is unknown how different cuff pressures influence the rate of post-operative VTE.

With varied data on the influence of tourniquet use on the incidence of VTE post-operatively, it is recommended that surgeons use tourniquets with caution in patients who are at high risk of VTE or ischemia-related events post-operatively. Examples include patients with evidence of calcification of their popliteal or distal superficial femoral artery on radiographs, low ankle-brachial-index, history of VTE, peripheral vascular or arterial disease, or absent or asymmetrical pedal pulses. In these patients, avoidance of a tourniquet should be considered. However, if a tourniquet is used, minimizing the duration of tourniquet use and the cuff pressure could help to minimize complications postoperatively.

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13 - Considering the trend to ambulatory hip and knee arthroplasty, is there a role for the use of pneumatic compression devices?

Response/Recommendation: Pneumatic compression devices have been demonstrated to be effective prophylaxis against venous thromboembolism (VTE) following hip/knee

arthroplasty when used concurrently with chemoprophylaxis. However, their use in present-day ambulatory hip/knee arthroplasty is not clearly supported in current literature.

Strength of Recommendation: Limited.

Delegates vote: Agree 83.76% Disagree 13.68% Abstain 2.56% (Strong Consensus).

Rationale: Considering the serious consequences of VTE, arthroplasty surgeons are sensitive to the need for VTE thromboprophylaxis[428]. Clinical practice guidelines generally recommend either pharmacologic and/or mechanical VTE prophylaxis. Pharmacologic options include anticoagulation agents such as low-molecular-weight heparin (LMWH), warfarin, new oral anticoagulants, and aspirin (ASA). The issue with the administration of anticoagulation is the associated bleeding risk with some of the agents. The focus in VTE prevention after total knee arthroplasty (TKA) and total hip arthroplasty (THA) is shifting away from the use of high-risk medications towards ASA and mechanical prophylaxis in an effort to minimize symptomatic bleeding and wound-related complications. Despite advantages, controversy remains regarding the efficacy of pneumatic compression devices in preventing VTE[429]. The patient population with the greatest consensus for the use of mechanical prophylaxis with intermittent pneumatic compression devices (IPCD) are those patients at high risk for bleeding[430-432], due to well documented decreased risk of major bleeding and surgical site bleeding associated with IPCD[433-435].

Evidence in Total Knee Arthroplasty (TKA): Numerous studies have supported the use of pneumatic compression devices (including ambulatory devices) after undergoing hip and knee arthroplasty[433,436-442]. According to the AAOS[443] and the ACCP, pneumatic compression devices are effective against VTE after TKA as a part of multimodal VTE prophylaxis protocol[431,437]. Arsoy et al., reported no difference in the VTE rates in a cohort of patients receiving mobile compression devices and ASA compared with patients receiving LMWH, except that bleeding events and related complications were significantly lower in the compression device group ($p = 0.015$)[444].

Evidence in Total Hip Arthroplasty (THA): According to the AAOS and ACCP, there is less evidence for the effectiveness of mechanical prophylaxis after THA. Nonetheless, Colwell et al.[433], in a multicenter randomized controlled trial (RCT) compared IPCD against enoxaparin and found IPCD to be just as effective as enoxaparin in preventing proximal and distal deep venous thrombosis and pulmonary embolism (PE) events, with a significantly lower bleeding risk (1.3% IPCD vs. 4.3% LMWH). In over 400 patients, they found a significant decrease in major bleeding events in the mobile compression group (0%) compared with the LMWH group (6%) after THA ($p = 0.0004$). The symptomatic VTE rates using mechanical compression alone have been reported at 0.92%, in a series of patients with obesity undergoing THA[445]. In addition, in one RCT prolonged outpatient use of pneumatic compression devices further decreased the incidence of VTE compared to isolated inpatient use only[446].

In addition, IPCD have been shown to be effective in Asian population undergoing TKA and THA[439,442]. The prophylactic efficacy of IPCD against VTE, when used in combination with chemoprophylaxis, has been demonstrated in many other studies[447-449].

In a systemic review Pavon et al., identified 14 eligible RCT (2,633 subjects) and 3 eligible observational studies (1,724 subjects). IPCD were comparable to anticoagulation agents for major clinical outcomes (VTE: risk ratio, 1.39; 95% confidence interval, 0.73 - 2.64). Limited data suggest that concurrent use of anticoagulation with IPCD may lower VTE risk compared with anticoagulation alone and that IPCD alone compared with anticoagulation may lower major bleeding risk[429].

The use of IPCD alone or with ASA after lower extremity arthroplasty has shown similar VTE rates to more potent chemoprophylaxis in standard-risk patients. The use of a risk stratifying protocol with ASA/LMWH and portable pneumatic compression pumps as part of a multimodal VTE prophylaxis protocol resulted in a very low rate of symptomatic VTE events in patients undergoing outpatient primary TKA[438]. Higher DVT risk was observed in "high-risk patients" such as those with a prior history of VTE, active cancer, or others. As IPCD continue to evolve, it is important to consider the most appropriate prophylaxis while maximizing compliance. The proposed duration for the use of IPCD is > 18 - 20 hours a day, and with different periods of postoperative use - in hospital, for 10 days, and up to 20 days. Several studies show concerns with compliance, with many patients stopping the use of these devices upon discharge from hospital[438,450].

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14 - Should mechanical compressive devices be used routinely in patients undergoing total hip arthroplasty or total knee arthroplasty?

Response/Recommendation: Mechanical compressive devices can be used routinely in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) as venous thromboembolism (VTE) prophylaxis.

Strength of Recommendation: High.

Delegates vote: Agree 92.37% Disagree 7.36% Abstain 0.00% (Strong Consensus).

Rationale: Prevention of VTE following total joint arthroplasty (TJA) remains a priority for orthopaedic surgeons, and many modalities are currently available. The main advantage of compressive mechanical devices is that their use, unlike chemical prophylaxis, is not associated with increased bleeding after surgical procedures.

The VTE prevention Guidelines from the American Academy of Orthopaedic Surgeons (AAOS)[451] advocate for the use of mechanical compressive devices for the prevention of VTE in patients undergoing elective TJA and who, independent of the surgery, are not at an increased risk for VTE. In the consensus recommendation, the authors highlighted the benefit of mechanical compressive devices specifically for patients who are at a higher risk of bleeding, such as patients who have hemophilia, liver disease, and other bleeding disorders. The AAOS guidelines also endorse the use of mechanical compressive devices for patients with prior history of VTE who are undergoing THA or TKA[451]. Importantly, the AAOS recommendations are in agreement with the American College of Chest Physicians' (ACCP) recommendations in that mechanical compression devices can be used alone, without chemical prophylaxis, for the prevention of VTE particularly in low-risk patients[452]. The ACCP guidelines also propose that mechanical compressive devices may be used alone in TJA patients who are at an increased risk of bleeding[452].

Since the publication of AAOS and ACCP guidelines on prevention of VTE, there have been additional publications on this topic. A total of 21 studies were identified from the literature review, of these, nine reports were summaries/review articles and 12 were original studies. The study by Dietz et al., highlighted the low patient compliance (35%) with these devices[453]. A few other studies described the efficacy and safety of aspirin, low-molecular-weight heparin (LMWH), or direct-oral anticoagulants (DOAC) in combination with mechanical prophylaxis[454-457]. There are many different types of compressive devices in the market, with some of them being portable devices. The study by Dietz et al., described the efficacy of a portable pneumatic compression pump, while Arsoy et al., described the efficacy of a mobile compression device[453,458]. A meta-analysis by Pour et al., examined the issue of distal application of compression devices, namely foot pumps, and found current literature supported the efficacy of these distal devices[459]. Another study by Zhao et al., a quasi-randomized controlled design, compared the efficacy of plantar compression devices and calf compression devices in 121 patients, concluding that calf-thigh pneumatic compression was more effective than plantar compression for reducing thigh swelling during the early postoperative period[459,460]. The remaining studies supported the use of mechanical devices in patients undergoing THA or TKA[461-472].

The synergistic relationship between compression devices and chemical prophylaxis has been examined in a few studies. Kakkos et al., investigated the efficacy of combined mechanical compression and pharmacologic prophylaxis for the prevention of VTE in patients undergoing THA and TKA, performing a systematic review and meta-analyses that included a total of 22 trials (15 randomized controlled trials) and 9,137 patients[457]. The types of interventions studied were intermittent pneumatic leg compression devices, which

included calf sleeves as well as foot pumps, and pharmacologic prophylactic agents such as unfractionated heparin and LMWH. The authors provided specific data for the additive value of mechanical compression in combination with pharmacologic prophylaxis and reported a decrease in the incidence of symptomatic pulmonary embolism (PE) from 2.92% to 1.20% when comparing pharmacological prophylaxis alone to combined mechanical compression and pharmacological prophylaxis (95% confidence interval, 0.23 to 0.64). While Harrison-Brown et al., An et al., and Torrejon et al., also argued in support of the synergistic role of chemical prophylaxis in combination with mechanical compression, their reports did not demonstrate any additive value of mechanical compression in combination with pharmacologic prophylaxis[454-456].

Another issue regarding the use of mechanical compressive devices relates to the duration of use. As previously stated, guidelines from the AAOS did not give recommendations on the duration of use of mechanical compression devices[451], and only recommended that patients discuss the usage duration with their treating physician. The AACP on the other hand recommended that mechanical compressive devices should be used throughout the hospital stay and for a minimum of 10 to 14 days[452]. Since the publication of these two guideline reports, there have been 12 original studies evaluating various compression devices used from one day to three months postoperatively. Due to the large range, there appears to be no compelling evidence to suggest an optimal duration of mechanical compression amidst the current era of short-stay hospitalizations[453,458].

Another search was performed regarding VTE prophylaxis for ambulatory surgeries of the hip and knee. While several studies were found, the majority only studied pharmacological prophylaxis, and none provided compelling data on the duration of mechanical compression[473-478]. Further studies are needed to address this knowledge gap.

In summary, mechanical devices can be used as VTE prophylaxis in patients undergoing THA and TKA. Recent studies support prior established guidelines that recommend the use of mechanical compression devices. Further research should aim to clarify the most appropriate devices, duration of use, as well as synergistic relationship with pharmacological agents.

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15 - Should pneumatic compression devices (PCD) routinely be co-administered to patients receiving aspirin for VTE prophylaxis?

Response/Recommendation: It appears that coadministration of aspirin (ASA) with pneumatic compression devices (PCD) may be more effective than ASA alone in prevention of venous thromboembolism (VTE) following total joint arthroplasty (TJA).

Strength of Recommendation: Moderate.

Delegates vote: Agree 82.76% Disagree 12.93% Abstain 4.31% (Strong Consensus).

Rationale: Multiple studies in the literature have analyzed the concomitant use of ASA and PCD in prevention of VTE[479-495]. Two studies have specifically evaluated the question on hand[489,496].

The study by Snyder et al., was a randomized control trial (level II) that assessed the difference in the rate of deep venous thrombosis (DVT) following total knee arthroplasty (TKA) using ASA-based prophylaxis with or without extended use of mechanical PCD therapy. One hundred patients undergoing TKA, were placed on ASA for three weeks and were randomized to receive PCD during hospitalization only or extended use at home up to six weeks post-operatively. Lower extremity Duplex venous ultrasonography was used to diagnose DVT at different time intervals. The rate of DVT was significantly lower for patients receiving extended use of PCD at 0% compared to 23.1% for those with inpatient use of PCD ($p < 0.001$)[489].

Another study by Daniel et al., was a retrospective review (level III) of the clinical records of 463 consecutive patients undergoing primary total hip arthroplasty (THA) (487 procedures) to determine the incidence of DVT. In 258 procedures, (244 patients) PCD were not used, whereas, in 229 procedures (219 patients) bilateral PCD were utilized. Doppler ultrasound screening for DVT was performed in all patients between the fourth and sixth post-operative days. No symptomatic calf or DVT. Asymptomatic DVT was detected in 25 patients (10.2%) in the cohort not receiving PCD and ten patients (4.6%) receiving PCD ($p = 0.03$)[496].

In another study (Level II) Colwell Jr, et al., evaluated the effectiveness of a mobile compression device with or without ASA compared with current pharmacological protocols for prophylaxis against VTE in patients undergoing elective primary unilateral arthroplasty. Among 3,060 patients in the entire cohort, 28 patients (0.92%) had VTE of which 23 patients (0.72%) developed DVT, and five (0.16%) developed pulmonary embolism (PE). The rate of symptomatic VTE among the cohort receiving mobile compression device was similar in patients receiving mobile compression devices compared to those receiving chemoprophylaxis[484].

The study by Sharrock et al., (level III) performed a systematic review to determine the incidence of all-cause mortality and PE in patients undergoing TJA. They found that the incidence of all-cause mortality non-fatal PE was higher in patients receiving low-molecular-weight heparin (LMWH) compared to those receiving ASA and PCD. Group A than in Group B (0.41 vs. 0.19%) and (0.60 vs. 0.35%), respectively. The latter study provided further support for the use of PCD and ASA as VTE prophylaxis in patients undergoing TJA[488].

Crawford et al., retrospectively reviewed the incidence of symptomatic VTE in 1,131 patients undergoing outpatient primary TKA who used a portable PCD as part of their VTE prevention protocol. An ASA-based VTE prophylaxis was used in patients who had a standard-risk for VTE. High-risk patients received a stronger chemoprophylaxis for two weeks followed by ASA for four weeks. PCD were worn for 23 hours/day for 14 days. They concluded that the use of portable PCD as part of a multimodal VTE prophylaxis protocol led to a very low rate of symptomatic VTE events in patients undergoing outpatient primary TKA[483].

In another level III evidence study, Khatod et al., examined whether a best prophylactic agent exists for the prevention of postoperative PE and whether the type of anesthesia affects the rates of PE. Patients received either mechanical prophylaxis alone (n = 1,533), ASA alone (n = 934), warfarin (n = 6,063), LMWH (n = 7,202) with or without mechanical prophylaxis. No clinical differences were detected in the rate of VTE between different types of prophylaxis or the types of anesthesia. Notably in the ASA group, 874 patients also received PCD, and 60 patients did not have PCD. In this small cohort size, there was no difference in the rate of PE, or mortality between the two groups[480].

Based on the available literature, it appears that coadministration of PCD with ASA is likely to reduce the rate of VTE further in patients undergoing TJA.

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16 - Does the use of Continuous Passive Machine (CPM) reduce the risk of VTE following knee surgery?

Response/Recommendation: There is no conclusive evidence that continuous passive machine (CPM) reduces the risk of venous thromboembolism (VTE) following knee surgery. Three moderate quality studies demonstrate no difference in the risk of VTE in knee surgery with the use of continuous passive motion, with five low quality studies showing a potential reduced risk of VTE.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.69% Disagree 3.45% Abstain 0.86% (Strong Consensus).

Rationale: VTE is a well-established complication of lower limb surgery. This is attributable to the nature of the lower limb surgery, which facilitates Virchow's triad of venous stasis, endothelial damage, and hypercoagulability.

Since its invention in 1978, CPM has been used in total knee arthroplasty (TKA), septic arthritis, tendon repairs, and ligament reconstruction to improve range of motion and stimulate healing[497]. Studies have demonstrated that using CPM increases venous and lymphatic flow, thus reducing venous stasis and reducing risk for the development of VTE[497,498].

Two moderate quality randomized-controlled trials (Goll et al.[499], and Lynch et al.[500]), reported no statistically significant differences in the incidence of VTE following TKA with the use of CPM with concurrent aspirin (ASA) use, when compared to ASA alone.

Goll et al.[499], evaluated the incidence of VTE and pulmonary embolism (PE) in 102 TKA patients via venography on day 12, and ventilation perfusion (VQ) scanning on day 13. Their data demonstrated that 76% of venograms were positive for VTE in the control group, and 75% in the CPM group respectively. With regards to PE, 10 of the 50 patients in the control group and 8 of the 45 in the CPM group had positive VQ scans. Although no p-value was reported in this study, the authors have stated that there was no statistically significant difference in VTE outcomes between the groups.

Lynch et al.[500], serially randomized 150 TKA patients treated with ASA, performing venography on day seven post-operatively. They reported positive venograms in 28 of the 75 patients in the control group, and 34 of the 75 in the CPM group, representing no statistically significant difference between the groups (although no p-value was reported).

A cohort study comprised of 103 patients by Ververeli et al.[501], reported the incidence of PE as a secondary outcome in TKA patients on warfarin by the post-operative day seven. VQ scanning identified PE in two of the 52 control patients, and one of the 51 CPM patients. With regards to their reported VTE outcomes, this was low-quality evidence and although suggestive of no statistical difference, the authors did not explicitly comment on this.

Contradicting the findings of the above studies, Fuchs et al.[502], designed a randomized controlled trial (RCT) of 227 heparinized lower limb trauma patients allocated to control versus a method of ankle CPM. All patients were screened weekly with ultrasound and plethysmography. If suggestive of VTE, patients underwent venography for definitive diagnosis.

The data from Fuchs et al.[502], demonstrated a statistically significant reduction in incidence of VTE in patients receiving CPM, recording 29% positive venograms in the control group, compared to 3.6% in the CPM group ($p < 0.001$). With regards to their data on knee surgery in particular (six patients total), one of three patients in the control group developed a deep venous thrombosis (DVT), with none reported in the CPM group. Although a high-quality study with a relatively large sample size of trauma patients, the small number of patients undergoing knee surgery limited the ability to make conclusions specific to VTE outcomes in this patient group.

In a cohort study of 40 TKA patients receiving ASA, Lynch et al.[498], performed venography and VQ scanning on post-operative day five. In the control group, 50% had positive venograms and 30% had positive VQ scans. In the CPM group, 5% had positive venograms and none had a positive VQ scan. This represented a statistically significant difference in VTE incidence between groups in this low-quality study spanning 12-year, with $p < 0.0007$ for VTE and $p < 0.0057$ for PE respectively. This group had previously published[503] a very

similar study with almost identical patient numbers, representing likely duplication of data.

Vince et al.[504], analyzed 62 TKA patients using venography and VQ scans on post-operative days four and five, respectively. With regards to VTE, 75% of control patients had positive venograms compared to 45% of CPM patients. No PE were diagnosed in either group. However, it is not reported whether this difference is statistically significant, nor is it documented whether patients received any chemical VTE prophylaxis in this low-quality study.

A cohort study by Maloney et al.[505], in 111 TKA patients receiving ASA reported four positive VQ scans in the control group (73 patients), compared to no positive scans in the CPM group (38 patients). Patients were only scanned if there was clinical suspicion of PE, representing high risk of selection bias. Moreover, the authors have not commented on whether their data was statistically significant.

In a low-quality cohort study by Wasilweski et al.[506], 74 patients (91 TKAs) receiving ASA were screened for VTE on post-operative day three, six, eight, and twelve with phlebography and diagnosed using venography. PE was screened using clinical suspicion and diagnosed with VQ scanning. They reported five VTE and one PE in the control group (44 TKA), compared to no VTE and one fatal PE in the CPM group (47 TKA). Although suggestive, it was not reported whether this difference was statistically significant. Moreover, there are discrepancies in their number of patients in the study, and confounding data as they included both knees in bilateral TKA patients. For these reasons, this is a low-quality study.

The vast majority of published articles on CPM identified in the literature search included VTE as a secondary outcome, and of these papers only a small proportion[507-510] actually report raw data (often grouped within 'complications'). As a result, there is a high risk of bias of selectively reporting VTE, and most study designs preclude statistical analyses, thus rendering them low quality evidence with respects to VTE outcomes.

In conclusion, the heterogeneity of the low to moderate quality evidence suggests there is no evidence that CPM reduces the incidence of VTE in knee surgery. Our recommendation is limited, as the current literature varies immensely in terms of chemical VTE prophylaxis used, methods for screening for VTE, as well as CPM prescription (hours per day and endpoints). Therefore, we recommend that additional research be undertaken to provide higher-quality evidence. Further adequately powered RCT with larger sample sizes, standardized chemical VTE prophylaxis and CPM prescriptions, as well as VTE screening protocols pre- and post-operatively are necessary to answer the question.

We accept the risk of language bias in this systematic review, as studies not originally published in English were excluded.

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17 - Does the "enhanced recovery" concept, which includes early ambulation, reduce the risk of VTE in patients undergoing primary total hip or knee arthroplasty?

Response/Recommendation: The "enhanced recovery" concept including early mobilization is likely to reduce the risk of venous thromboembolism (VTE) in patients undergoing primary total hip arthroplasty (THA) or total knee arthroplasty (TKA). However, the literature lacks studies with a high level of evidence considering this topic.

Strength of Recommendation: Limited.

Delegates vote: Agree 96.58% Disagree 1.71% Abstain 1.71% (Strong Consensus).

Rationale: Data from The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database demonstrates a risk of VTE in patients undergoing THA of 0.6% within 30 days of surgery, and 1.4% in patients who undergo TKA[511]. Santana et al., report similar rates, highlighting that due to the total number of THA and TKA performed worldwide, a large number of patients suffer from VTE, which can be associated with marked morbidity and

mortality[512]. Therefore, it is of high importance to minimize complications in these patients.

The Enhanced Recovery After Surgery (ERAS) concept has been developed as a multidisciplinary and multimodal approach with the goal of improving clinical outcomes and maximizing efficiency of healthcare resource use. The utilization of the ERAS concept has been effective in reducing lengths of stay and complications[513]. However, no previous review has defined the effect of the ERAS concept on the incidence of VTE. The ERAS society issued a consensus statement for peri-operative care in THA and TKA in 2019, making evidence-based recommendations across 17 topic areas[514]. With regards to antithrombotic prophylaxis treatment, the ERAS society recommended that patients should be mobilized as soon as possible after surgery and receive VTE prophylaxis in accordance with local policies.

A summary of studies analyzed in this current recommendation is shown in Table III[515-526]. Studies were selected for inclusion if they compared the incidence of VTE in patients undergoing surgery using an ERAS protocol to a control group. In addition, comparative studies of 'early mobilization' were included. There were only 12 published studies meeting the inclusion criteria and the majority were retrospective in design.

One randomized controlled trial was identified, which showed no statistically significant difference in the incidence of deep venous thrombosis (DVT) between the ERAS and control group in patients undergoing THA for osteonecrosis[518]. However, the quality of this evidence was determined to be low due to the lack of a defined randomization process, allocation concealment, and the procedure for identification and diagnosis of DVT, with no blinding of assessors. In addition, the primary outcome of the trial was post-operative function, and the study is unlikely to have sufficient power to detect a difference in the incidence of symptomatic DVT. Two non-randomized, prospective cohort studies reported a lower frequency of DVT with the use of an ERAS protocol in both THA and TKA patients, and of both DVT and pulmonary embolism (PE) in TKA patients[516,519]. These differences were not statistically significant in either study. Venditolli et al., also observed a non-statistically significant decrease in the incidence of DVT in a prospective cohort of THA and TKA patients using an ERAS protocol, compared to a historical control[520].

In the majority of the remaining retrospective studies, VTE was less frequent in the group where the ERAS concept was utilized, but only two studies identified a statistically significant difference[515,522]. After full implementation of an ERAS pathway in a large cohort of both TKA and THA patients, Glassou et al., observed a reduction in the incidence of DVT from 0.8 to 0.5%[522]. Millar et al., observed a reduction in DVT from 1.5 to 0.7% and from 3.6 to 1.6% in both THA and TKA respectively, after the introduction of an ERAS pathway[515]. However, it is noted that the ERAS measures used were not clearly defined in the study and were introduced alongside a specific focus on VTE prophylaxis, in addition to the ERAS concept.

No comparative studies using 'early mobilization' as a specific intervention were identified in the systematic search. However, additional observational papers in the wider

TABLE III Data extracted from the literature

Author	Year	Sample Size	Prophylaxis Method	Mean Age (years)	Dosage	Duration	Major Bleeding	VTE Rate
Sugano et al.[549]	2009	70	Mechanical + ASA*	30.2	Unmentioned	2 weeks	No	0
Thawrani et al.[547]	2010	83	No Prophylaxis	15.6	Unmentioned	Unmentioned	No	0
Ito et al.[548]	2011	158	ASA**	32	Unmentioned	2 weeks	No	0.6%
Zaltz et al.[545]	2011	1067		24	Unmentioned	Unmentioned	No	0.94%
Polkowski et al.[551]	2014	134	Mechanical + ASA	30	2x325 mg per day	6 weeks	No	1.3%
Wassilew et al.[550]	2015	48	LMWH	31.7	Unmentioned	Unmentioned	No	0
Wingerter et al.[552]	2015	50	Mechanical + ASA	28	2x325 mg per day	6 weeks	No	0
Bryan et al.[553]	2016	75	Mechanical/ASA	28	2x325 mg per day	6 weeks	No	1.33%
Yamanaka et al.[554]	2016	144	Mechanical ± LMWH(Enoxoparin/ Edoxaban)	32.2	Unmentioned	Unmentioned	No	2.1%
Azboy et al.[557]	2018	87	ASA (High dose) / ASA (Low dose) / Warfarin	31.3	2x325mg ASA (High dose) 2x81mg (Low dose) Warfarin dose Unmentioned	4 weeks	No	1.1%

VTE=Venous thromboembolism; ASA=Aspirin; mg=milligrams; LMWH=Low-molecular-weight heparin. *Only few patients take chemical prophylaxis. **Given to patients at high-risk for thrombosis.

literature have been considered for the purpose of discussion. Immobility is a recognized risk factor for developing VTE[527,528]. However, Chindamo and Marques considered that there was currently insufficient evidence in the wider literature that early mobilization in isolation reduces the risk of VTE[529]. In the context of arthroplasty surgery, Lei et al., found an incidence of DVT of 0.71% in cohort of patients mobilized within 24 hours after TKA, compared to 1.41% in patients beginning mobilization beyond this time point[530]. This study was purely observational and there was no difference in the mobilization protocol between the two groups. Therefore, although baseline demographics were comparable for both groups, it is possible that the early mobilization group represented patients who have higher pre-operative mobility and performance status, which may predispose them to a lower risk of VTE. Chandrasekaran et al., reported that mobilization in the first 24 hours after TKA is an effective way to reduce the incidence of DVT[531]. However, the follow-up was at longest, seven days post-surgery. Furthermore, Husted et al., analyzed the importance of early mobilization within the ERAS concept for TKA and THA, highlighting that the incidence of VTE was lower in patients mobilized two to four hours post-surgery in comparison to patients mobilized six to eight hours post-surgery[532]. Therefore, it should be further investigated whether early mobilization per se or inclusion into an ERAS protocol reduces the risk of VTE in THA and TKA patients.

Limitations of this review include heterogeneity of the included studies, with major variations in mobilization and ERAS protocols, thus complicating the estimation of any intervention effect. Furthermore, as most of the studies are retrospective, reporting on multiple outcomes of the ERAS concept, and not focused specifically on VTE, it is likely that many are under-powered to detect any significant difference in rates of DVT and PE.

In summary, the data on VTE in the context of ERAS in the literature is limited. Two retrospective studies with a large number of patients, identified an association between the use of ERAS concept and a lower incidence of DVT in both TKA and THA. No studies demonstrated a statistically significant difference in the rate of PE in patients undergoing THA and TKA in an ERAS setting. Future interventional studies using well-defined ERAS protocols may provide greater insight into the effect of ERAS concept, including early mobilization, on the incidence of DVT and PE.

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18 - Do patients undergoing elective pelvic and/or femoral osteotomy require routine VTE prophylaxis?

Response/Recommendation: Given the low rate of venous thromboembolism (VTE) in patients undergoing elective pelvic and/or femoral osteotomy, as well as the absence of robust data in current literature, this workgroup recommends that aspirin (ASA) and/or mechanical prophylaxis should be used as VTE prophylaxis in this patient population. Only patients at a high risk of VTE should be given more potent or additional chemoprophylaxis.

Strength of Recommendation: Limited.

Delegates vote: Agree 86.32% Disagree 10.26% Abstain 3.42% (Strong Consensus).

Rationale: Periacetabular osteotomy (PAO) and/or femoral osteotomy are surgical options available to treat young patients with developmental dysplasia of the hip or other hip conditions[533-538]. Although isolated femoral osteotomy is performed in the pediatric patient population, femoral osteotomy is often combined with a pelvic osteotomy in adults. Patients undergoing these surgical procedures are often young and healthy[536,537,539]. However, the nature of the surgical procedure is such that these patients are often required to limit weight-bearing postoperatively[540], which could potentially increase the risk of VTE. The other aspect to consider is that these patients are also at increased risk for bleeding as the surgery involves multiple cuts through pelvic bone and/or femoral shaft. Thus, the use of an anticoagulant agent needs to be carefully considered, taking into account the potential risk for bleeding and VTE.

The issue of VTE after pelvic and/or femoral osteotomy has been evaluated previously. The incidence of VTE in patients undergoing PAO has been reported to be very low at 0% to 5%[541-546]. Although the incidence of VTE after osteotomy seems to be lower than that after total joint arthroplasty without prophylaxis, these values are not negligible and VTE prophylaxis should still be considered. Notwithstanding, there are no specific recommendations regarding the most appropriate method of VTE prophylaxis in patients undergoing pelvic and/or femoral osteotomy.

In a study by Thawrani et al., on 76 patients undergoing PAO (83 hips) with a mean age of 15.6 years, there was no detected VTE event without any VTE prophylaxis[547]. Ito et al., retrospectively reviewed the long-term outcomes of PAO in patients younger than 40 years of age (n = 103; mean age 27.1 years) and older patients (n = 36; mean age 47.2 years)[548]. Only high-risk patients with a previous history of VTE were given 2 weeks of ASA for VTE prophylaxis, although the dose of ASA administered is not disclosed in the study. One patient in the older cohort died of pulmonary embolism on day 4[548]. The latter patient was not receiving ASA for prophylaxis. In another retrospective study, Sugano et al., evaluated the role of mechanical prophylaxis for VTE in 70 patients with a mean age of 32.5 years who underwent pelvic and femoral osteotomy[549]. Epidural anesthesia, perioperative calf compression, early mobilization and intermittent pneumatic compression were used in the patient group. VTE was not observed in any patient at the 6-month follow-up[549].

In another study by Wassilew et al., weight-adjusted subcutaneous low-molecular-weight heparin (LMWH) was used in 48 patients, with a mean age of 31.7 years, undergoing PAO. LMWH was administered until patient was allowed to fully weight-bear at around 12 weeks, and no patients developed VTE[550].

Polkowski et al., studied 134 patients (149 hips) undergoing PAO at a mean age of 30 years. The patients received ASA 325 mg twice a day (*bis in die* [bid]) and compression stockings for 6 weeks, following which, proximal deep venous thrombosis (DVT) was detected in 2 patients (1.3%)[551]. Wingerter et al., evaluated 100 patients who underwent PAO with tranexamic acid (TXA) (50 hips) and without TXA (50 hips), analyzing the cohort for development of VTE and other complications. No VTE prophylaxis was administered to patients younger than 18 years of age in that study. Older patients were given contralateral mobile mechanical compression device intraoperatively and bilateral mechanical compression device for 10 days postoperatively. All patients older than 18 received 325 mg of ASA bid for 6 weeks, and none of the patients in either group developed VTE[552]. The issue of TXA and its influence on VTE was also studied by Bryan et al., in a study on 150 patients undergoing PAO[553]. Of these, 75 patients received intravenous TXA, and 75 patients did not receive TXA. All patients received mechanical prophylaxis in the hospital and 325 mg ASA bid for 6 weeks. The authors reported two VTE events (2.7%) in patients receiving TXA and 1 (1.3%) in the group that did not receive TXA[553]. Yamanaka et al., examined the incidence of VTE in patients who underwent a total of 820 major hip surgeries, including 144 PAO[554]. The mean age of these patients was 32.2 years. Mechanical prophylaxis and LMWH were used in combination in 79 patients, and mechanical prophylaxis only was used in 65 patients. VTE rate was 1.3% in patients who received mechanical prophylaxis and chemical prophylaxis together, and 3.1% in patients who received mechanical prophylaxis only ($p = 0.43$)[554].

Another study investigated the incidence of VTE after PAO in 1,067 patients with a mean age of 24 years (range, 13 - 56) who had surgery at six North American centers[545]. Multiple types of VTE prophylaxis were employed including mechanical, pharmacological, and combined mechanical and pharmacological methods. Pulmonary embolism (PE) was observed in four patients and DVT in seven patients, and the incidence of clinically symptomatic VTE was reported to be 0.94% (9.4/1,000). Two of the six participating hospitals used both chemoprophylaxis and mechanical prophylaxis for VTE, and the crude incidence of VTE per 1,000 patients after PAO were 6.73 (2/297) and 8.73 (2/297), respectively. In two other hospitals,

only pharmacological or mechanical prophylaxis were used, and the incidence of VTE was 9.37 (3/32) and 12.05 (3/249), respectively. These results suggested that the combination of pharmacological and mechanical prophylaxis methods was useful in preventing VTE after PAO. Conversely, two of the participating hospitals that treated younger patients had a lower incidence of VTE compared to the others, even though they did not adopt pharmacological nor mechanical prophylaxis or only used one of them. This suggested that the risk of postoperative VTE after PAO may be lower in children than in adolescents. However, Allahabadi et al.[555], noted that 9 patients among 1,480 operated joints in a cohort aged 10 - 18 years developed VTE within 90 days, concluding that pharmacologic prophylaxis had no effect on the incidence of VTE. Prevention of VTE after osteotomy in children remains controversial, and further research is necessary to address this knowledge gap. Although the risk of VTE after PAO in adolescents remains contentious, according to the report by Salih et al.[556], the incidence of grade IV complications according to the modified Dindo-Clavien grading system (which included PE) was higher in patients aged 40 years or older (odds ratio [OR] 3.126, $p = 0.012$), with body mass index > 30kg/m^2 (OR 2.506, $p = 0.031$) and joint laxity (Beighton's score of ≥ 6, OR). However, they focused not only on VTE, but also on other complications after PAO, and only one case (0.45%) of PE occurred among 223 patients treated with mechanical and pharmacological prophylaxis using LMWH and ASA on outpatient basis. Regarding the effectiveness of pharmacological prophylaxis, Azboy et al.[557], described the usefulness of ASA (325 mg bid) in 87 patients who underwent PAO, and only one patient developed uneventful DVT in the cohort.

Both the American College of Chest Physicians (ACCP) and the American Academy of Orthopedic Surgeons (AAOS) recognize ASA as a safe and effective prophylactic agent for total joint arthroplasty[558,559]. ASA has also been employed as VTE prophylaxis in patients undergoing joint preservation procedures[557]. A recent retrospective study investigating VTE prophylaxis methods in patients undergoing PAO included a total of 80 patients (87 hips; mean age 31.3 years). Three different chemical prophylaxis methods were used in the study. A total of 33 patients were given ASA 325 mg bid, 31 were given ASA 81 mg bid, and 23 were given warfarin. Uneventful PE developed in only 1 patient who was on 325 mg ASA. No significant difference in the incidence of VTE was seen among the three cohorts ($p = 0.516$)[557].

Our search of the literature did not reveal any high-quality studies related to VTE risk after pelvic and/or femoral osteotomy. In the absence of robust data and guidance from the ACCP and/or the AAOS, this workgroup recommends that mechanical prophylaxis and/or ASA may be sufficient to minimize the risk of VTE in adult patients undergoing pelvic and/or femoral osteotomy. Adolescent and children appear to be at extremely low risk of VTE after osteotomy. The issue of whether VTE prophylaxis should be administered to these patients is discussed in the Pediatric section of the International Consensus Meeting (ICM) on VTE.

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19 - What are the indications for Doppler ultrasound of the lower extremity to confirm or rule out DVT?

Response/Recommendation: In the absence of any specific guidance from the literature we would propose that in any patient who is within 6 weeks following a lower limb surgery that a Doppler scan should be requested when:

a. There is lower limb swelling that does not respond to elevation or after a night's rest in bed.
b. The lower extremity swelling worsens after a night spent recumbent.
c. There is a high index of suspicion for deep venous thrombosis (DVT) in patients with active cancer and/or history of prior venous thromboembolism (VTE).

Strength of Recommendation: Limited.

Delegates vote: Agree 89.57% Disagree 6.09% Abstain 4.35% (Strong Consensus).

Rationale: Having assessed the literature the presently available tools, such as the Well's score[560], are based predominantly on assessing the indications for Doppler in the situation of an unprovoked DVT. When using such scores, the majority of postoperative total joint arthroplasty (TJA) meet the criteria for a Doppler investigation and therefore such scores are unsuitable for this patient population.

There are no studies specifically assessing the indications for Doppler ultrasound in determining the presence of a DVT following TJA. In addition, there are no studies that have determined the positive or negative predictive value of clinical criteria used to trigger the use of a Doppler ultrasound to determine if a DVT has developed following TJA.

DVT occurring after lower limb TJA appears to follow a different and more benign pathway than unprovoked DVT[561,562], which has significantly reported morbidity and mortality. Postoperative DVT is largely asymptomatic with the reported incidence often being about 10% when every postoperative TJA has a Doppler[563]. The presence of DVT has not been shown to correlate with age, gender, race, presence of diabetes mellitus, history of malignancy, smoking status, fixation type, primary versus revision type of surgery, or operating time[564]. Although a symptomatic DVT may occur in the hospital, the assessment and diagnosis are more commonly an issue for patients who have been discharged and then present to the emergency room with lower limb pain and or swelling.

To highlight the present uncertainty about the indications for a Doppler scan following TJA, a study using data from Musgrave Park hospital in Belfast, Northern Ireland looked at over 10,000 TJA performed since 2016. This yet unpublished study found that over 8% of patients had at least one Doppler after TJA with < 5% having a proximal DVT. According to the British National Institute for Health and Care Excellence (NICE) guidelines[565], if a Doppler scan cannot be done within 4 hours of being requested then the patient should receive therapeutic anticoagulation. As a result, many of the patients with a negative scan received therapeutic anticoagulation. Furthermore, if the scan is negative then NICE recommends a further scan in the following 6 to 8 days[565]. As a result, many patients had a second Doppler.

The two major concerns about missing a DVT are propagation to the lung with a subsequent pulmonary embolism (PE) and risk of death and post thrombotic syndrome. With regard to the first concern, we are not aware of any literature that has demonstrated that propagation of a DVT to the lung occurs following TJA. With regard to the post thrombotic syndrome, this is clearly an important clinical issue with a reported incidence of between 20% and 50% following DVT[566] but again this would appear to be following unprovoked DVT with no published evidence about DVT as a consequence of TJA. It is generally considered that a venous clot will recanalize within 3 months and that this process is not aided by anticoagulation with the latter simply preventing extension locally or to the lung.

The rationale of focusing attention on postoperative swelling that doesn't respond to elevation is that these are the patients who are perhaps at higher risk from developing a post thrombotic syndrome and who may therefore benefit from anticoagulation to reduce the risk of local extension.

In the general population, it has been shown that when leg edema or calf tenderness was present, the incidence of acute DVT was significantly greater ($p < 0.0001$)[567]. Although these may be common symptoms after TJA, it is not unreasonable to consider that increased or sudden unilateral swelling after elevation or first thing in the morning after awakening may indicate the need for a Doppler ultrasound[568]. We recommend that once the scan has been ordered the patient should not normally be anticoagulated prior to a positive scan result unless the scan cannot be done for more than 24 hours. If the patient is on routine VTE prophylaxis this should continue as prescribed. If there is a distal or calf DVT, then the patient does not need to be anticoagulated, and the scan does not need to be repeated unless there is a further change in the symptoms. If the scan is negative, it does not need to be routinely repeated unless there is a further change in symptoms. If the patient has a proximal DVT, then the patient should be anticoagulated according to local protocols. Throughout this process and regardless of the diagnosis, the patient should continue with their normal rehabilitation program. If the investigations have not been ordered by the surgical team, they should be informed independently of the outcome.

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20 - Should the presence of a distal DVT in an extremity mandate repeat imaging of proximal veins?

Response/Recommendation: Based on current literature and recommendations from official bodies, patients with an isolated distal deep venous thrombosis (DVT) (in whom a proximal component was not detected at the initial scan) can be managed without anticoagulation but need to have a follow up ultrasound (US) of the proximal veins after 1 week to rule out DVT extension. It is reasonable to treat the patient empirically with anticoagulation, especially in situations where a follow-up ultrasound may not be possible.

Strength of Recommendation: Consensus.

Delegates vote: Agree 89.57% Disagree 6.09% Abstain 4.35% (Strong Consensus).

Rationale: Isolated distal DVT encompasses thromboses of the calf veins below the knee, with the popliteal vein not being involved. Most calf vein DVT are located in the posterior tibial and peroneal veins[569-573]. The rate of extension to the proximal veins and the rate of pulmonary embolism (PE) are highly variable. Studies have shown that 9% – 21.4% of isolated distal DVT may propagate proximally[570,572,574].

Venous compression ultrasound (US) is the standard imaging test for patients with suspected lower extremity DVT. Protocols recommended by the American College of Chest Physicians (ACCP)[575], the American Institute of Ultrasound in Medicine/American College of Radiology/Society of Radiologists in Ultrasound[576](p30), and the Intersocietal Accreditation Commission Vascular Technology[577] have been inconsistent with regards to the necessary components of the US. While scanning the proximal veins is agreed by all societies, the necessity of routine scanning of the distal calf veins remains debatable[570,578,579].

If the distal veins are imaged and isolated distal DVT is diagnosed, the two treatment strategies involve either treating the patient with anticoagulation or holding anticoagulation and following up with repeated US examination. Surveillance studies from non-orthopedic literature suggest that proximal DVT is diagnosed at the second US in 1.9% – 12.8% of patients[572,580,581].

The majority of orthopaedic literature that examined the rate of propagation of distal DVT was conducted in the context of total joint arthroplasty, and mainly total knee arthroplasty (TKA). Barrellier et al., conducted a randomized prospective study[582] comparing short vs. extended venous thromboembolism (VTE) prophylaxis. While not the main outcomes, the authors found that distal DVT progressed to the proximal veins in 27 of 141 patients (19.1%) who received short-term prophylaxis. In those who received extended VTE prophylaxis, the rate was significantly lower but still affected 9 of 144 patients (6.3%), suggesting the need for routine surveillance of the proximal veins regardless of prophylaxis modality. Several retrospective studies support these findings, although lower rates of propagation were reported; Oishi et al.[583], examined the clinical course of isolated DVT diagnosed with routine US at day 4 postoperatively. Out of 41 asymptomatic patients that were diagnosed with an isolated DVT and had serial US surveillance, seven (17%) developed a proximal DVT in the ipsilateral limb by the fourteenth postoperative day. Tateiwa et al.[584], retrospectively followed up 42 patients with an isolated DVT using consecutive US and reported a DVT exacerbation in five patients (11.9%), three of whom showed additional thrombus formation. The remaining two patients had thrombus elongation or propagation from the distal to proximal veins. More recently Omari et al.[585], retrospectively reviewed 445 patients who were diagnosed with isolated DVT following TKA. The authors reported propagation to the popliteal vein in 10 of 459 patients (2.2%). In contrast with these studies, Yun et al.[586], found no propagation in a 6-month computer tomography (CT) follow-up of 39 TKA patients with an isolated DVT. Notably, the methodology of that study had major flaws as half of the cohort (37 of 78 patients) that were diagnosed with isolated DVT on day 7 were not further evaluated and outcomes were not available.

While not intended specifically for orthopedic use, several official bodies have designed protocols for the follow-up of distal DVT, all of which support the continued surveillance of these patients through a serial US of the proximal veins in cases of distal DVT that are managed expectantly[573,574,587]. Current recommendations entail repeating the US at 1 week and then at 2 weeks if the distal DVT persists but does not extend[570]. No further imaging is required if the distal DVT resolves at 1 week or does not extend significantly at 2 weeks. Serial US is not indicated if the patient receives anticoagulation unless there is a change in the clinical condition of the patient that warrants a change in treatment[588].

Acknowledging the limited data available on the subject, especially in the field of orthopaedics, our literature review suggests that up to 19% of distal DVT may subsequently extend into the proximal veins. It is therefore recommended that anticoagulation be administered immediately, or serial US be performed as surveillance to detect thrombus extension[589-592]. The abovementioned protocols for surveillance of patients with

an isolated DVT should be followed. It should be noted, however, that compliance with repeat US imaging is inconsistent[593], so, if a repeat US cannot be done, it may be best to treat that patient with anticoagulation.

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21 - Do patients undergoing UKA, including patellofemoral joint arthroplasty, have a different VTE risk profile compared to TKA?

Response/Recommendation: The incidence of symptomatic venous thromboembolism (VTE) is low in both unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA) patients, deep venous thrombosis (DVT) and pulmonary embolism (PE) occur in up to 1.6% and 0.13% of UKA patients. Most studies had a trend of decreased VTE risk following UKA compared to TKA but were underpowered, only registry studies were sufficiently powered and showed a VTE risk ratio (RR) of 0.39 (0.27 - 0.57). There is a paucity of data on patellofemoral joint arthroplasty (PFJA) and VTE risk.

Strength of Recommendation: Moderate.

Delegates vote: Agree 96.49% Disagree 0.88% Abstain 2.63% (Strong Consensus).

Rationale: UKA is an alternative option to TKA for the surgical management of symptomatic osteoarthritis and accounted for 2.7% of all primary TKA reported in the American Joint Replacement Registry[594], 5.6% of the Australian Registry[595], 8% of the Swedish Register[596], and 9.1% of the British Registry[597].

A vast body of literature has reported comparable or better clinical UKA outcomes compared to TKA[598-600], fewer early postoperative complications[599,601-605], fewer early reoperations[601,603-605], and decreased mortality[599,601,606] but a greater revision rate compared to TKA[594,595,597,601,606]. VTE related to UKA is reported less frequently and symptomatic VTE occurs in 0.41 - 1.6%[607,608] of patients including symptomatic DVT in 0.28 – 1.6%[607-610], and PE in 0.13%[607]. Several large consecutive series report an absence of symptomatic VTE[610], or asymptomatic VTE following UKA[611]. Conversely, Koh et al., reported a consecutive series of 70 patients without VTE symptoms following UKA, but 26% had a VTE lesion identified with multidetector row computer tomography (CT), and all resolved without thromboprophylaxis nor thrombotic treatment[612].

There are no randomized controlled trials (RCT) powered to examine uncommon sentinel events such as VTE and mortality following UKA compared to TKA, but every study

has reported similar or improved complication rates, VTE incidence and mortality in UKA patients compared to TKA patients. Systemic review methodologies with meta-analysis remain underpowered to measure these events. Wilson et al., used a systemic review of RCT of more than 50 patients, nationwide databases, joint registries and large cohort studies to compare UKA to TKA[599]. In that review and meta-analysis the UKA/TKA VTE RR was 0.39 (0.27 – 0.57, p < 0.001) derived from the British Registry[601], and four American national databases[603,606,609,613], that include 32,711 UKA and 228,499 TKA patients.

Wilson et al., identified two RCT including 614 patients and four large cohort studies including 574 patients that were underpowered to compare VTE incidence in UKA and TKA[599]. Additionally Beard et al.[600], conducted a multicenter RCT of 528 patients with 2 VTE events in both cohorts, Schmidt-Braekling et al.[610], added a RCT of 112 patents to the literature and Brown et al.[614], examined 605 UKA and 22,235 TKA in an institutional database with a trend toward less VTE related to UKA.

Liddle et al.[601], used propensity matched UKA and TKA patients in the National Joint Registry for England and Wales from 2003 - 2012 and included 25,334 UKA and 75,996 TKA. The VTE RR was 0.42 (0.34 – 0.52, p < 0.001). Mortality risk was significantly decreased for UKR patients (0.23 (0.11 – 0.50) at 30 days and 0.47 (0.31 – 0.69) at 90 days). Mortality is multifactorial and may be related to fatal pulmonary embolism and other factors such as myocardial infarction and stroke which were both decreased in the UKA group; odds ratio 0.53 (0.31 – 0.90) and 0.37 (0.16, 0.86) respectively.

Di Martino et al.[604], reported on 6,453 UKA and 54,012 TKA from the Italian Registro Implantologia Protesica Ortopedica (RIPO) data base from 2000 - 2017; DVT was reported in 0.03% of UKA and 0.2% of TKA patients.

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) has been interrogated over three time periods. Duchman et al.[609], used propensity matched UKA and TKA patients in the ACS NSQIP database from 2005 to 2011 and included 1,588 UKA and 1,588 TKA; the VTE RR was 0.32 (0.16 – 0.66, p < 0.02). Drager et al.[603], examined 36,274 TKA and 1,340 UKA non-matched patients in the ACS NSQIP database from 2011 to 2012; the VTE RR was 0.33 (0.16 – 0.69). Courtney et al.[613], examined 49,136 TKA and 1,351 UKA non-matched patients in the ACS NSQIP database from 2014 to 2015; the VTE RR was 0.44 (0.24 – 0.82).

Bolognesi et al.[606], examined 65,505 TKA and 3,098 UKA American Medicare patients from 2000 - 2009; after multivariable adjustment, UKA patients had no significant risk differential of VTE (adjusted hazard ratio [HR] = 0.86; 95% confidence interval [CI] = 0.57 to 1.29) or mortality (adjusted HR = 0.75; 95% CI = 0.50 to 1.11). Hansen et al.[605], used propensity matched UKA and TKA patients in the 2002 - 2011 USA Medicare database and 2004 - 2012 MarketScan database and report on 4,414 matched UKA Medicare patients and 20,721 MarketScan patients. The VTE RR for TKA patients was 1.67 (1.16 - 2.38, p = 0.006) in the Medicare cohort and 1.69 (1.45 - 1.96, p < 0.001) in the MarketScan cohort and mortality RR was 2.63 (1.35 - 5.00), p = 0.004) in the Medicare cohort and 2.08 (1.96 - 2.022, p < 0.001) in the MarketScan cohort.

Enhanced recovery after surgery (ERAS) following TKA has potential to decrease VTE risk, potentially approximating the risk to UKA patients who typically have a rapid recovery pathway. UKA patients have similar prothrombotic serum markers following surgery[615] and the addition of rapid mobilization, decreased tourniquet use and multimodal analgesia protocols could diminish the prothrombotic potential of TKA compared to UKA. Petersen et al.[607], report a VTE incidence of 0.41% following 3,927 UKA which was comparable to 0.39% in fast-tracked TKA patients[616] over the same time period.

PFJA are used less frequently and account for 0.36 to 1.2% of knee arthroplasties[595,597], and the incidence of VTE related to PFJA is less well described. Tarassoli et al.[617], performed a meta-analysis of PFJA outcomes and identified only one study reporting one postoperative DVT in 56 PFJA (1.8%)[618]. No additional reports of VTE following PFJA were identified.

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Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G878).

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