

Table S1 - Characteristics of the 73 randomised controlled trials on the intravenous use of tranexamic acid in major orthopaedic surgery included in the meta-analysis.

First Author, year ^{ref.}	Cases (ivTXA/C)	Surgery	ivTXA dose	Controls	Thromboprophylaxis (duration)	VTE	VTE screening method (follow-up period)	Other TXA-related SAE
Benoni, 1996 ¹⁶	43/43	TKA	43 pts: 10 mg/kg intra and post	43 pts: saline	Dalteparin/enoxaparin (7-10 post days)	ivTXA: 3/43 (7%, 3 DVT) C: 5/43 (12%, 4 DVT, 1 PE)	None	0/43
Hippala, 1997 ¹⁷	39/38	TKA	39 pts: 15 mg/kg intra + 10 mg/kg (two doses) post	38 pts: saline	Enoxaparin 40 mg/day SC (NR)	ivTXA: 2/39 (5%, 2 DVT) C: 3/38 (8%, 2 DVT, 1 PE)	Clinical exam (hospital stay)	0/39
Jansen, 1999 ¹⁸	21/21	TKA	21 pts: 15 mg/kg intra and repeated every 8 h for 3 days	21 pts: saline	Fraxiparin (until discharge)	ivTXA: 0/21 C: 2/21 (9.5%, 2 DVT)	Clinical exam, D-dimer/ FDP (8-24-72 h post)	0/21
Eckback, 2000 ¹⁹	20/20	THA	20 pts: 10 mg/kg pre and intra + 1 mg/kg/h for 10 h post	20 pts:	Dalteparin (10 post days)	ivTXA: 1/20 (5%, 1 DVT) C: 1/20 (5%, 1 DVT)	US (3-21 post days)	NR
Engel, 2001 ²⁹	12/12	TKA	12 pts: 15 mg/kg intra + 10 mg/kg post	12 pts: none	Certoparin 3,000 IU/day SC (until discharge or mobility)	ivTXA 2/12 (17%, 2 DVT) C: 0/12	Clinical exam (hospital stay)	0/12
Ellis, 2001 ²¹	10/10	TKA	10 pts: 15 mg/kg intra + 10 mg/kg/h for 12 h post	10 pts: saline	Enoxaparin 40 mg/day SC (35 days)	ivTXA: 0/10 C: 0/10	D-dimer intra	0/10
Tanaka, 2001 ²²	73/26	TKA	24 pts: 20 mg/kg pre 22 pts: 20 mg/kg intra 27 pts: 10 mg/kg pre and intra	26 pts: saline	NR	ivTXA: 0/73 C: 0/26	Venography + PLS (7-14 post days)	0/73
Benoni, 2001 ²³	18/20	THA	18 pts: 10 mg/kg pre	20 pts: saline	Enoxaparin 40 mg/day SC (7-10 post days)	ivTXA: 1/18 (6%, 1 PE) C: 1/20 (5%, 1 PE)	Clinical exam (6 post weeks)	0/18
Veien, 2002 ²⁴	15/15	TKA	15 pts: 10 mg/kg intra and post	15 pts: saline	Dalteparin 5,000 IU/day SC (until discharge or mobility)	ivTXA: 0/15 C: 0/15	Clinical exam (hospital stay)	0/15
Good, 2003 ²⁵	27/24	TKA	27 pts: 10 mg/kg intra and post	24 pts: saline	Dalteparin 500 IU/day SC (10 post days)	ivTXA: 2/27 (7%, 2 DVT) C: 2/24 (8%, 2 DVT)	Clinical exam (NR)	0/27
Husted, 2003 ²⁶	20/20	THA	20 pts: 10 mg/kg pre + 1 mg/kg/h for 10 h	20 pts: saline	LMWH (until discharge)	ivTXA: 0/20 C: 0/20	Clinical exam (3 months)	NR
Zohar, 2004 ²⁷	40/20	TKA	20 pts: 15 mg/kg intra + 10 mg/kg/h for 12 h post 20 pts: 15 mg/kg intra + 10 mg/kg/h for 2 h post	20 pts: none	Enoxaparin 40 mg/day SC (until discharge)	ivTXA: 0/40 C: 0/20	Clinical exam (3 months) + DUS on 5 post day	0/40
Garneti, 2004 ²⁸	25/25	THA	25 pts: 10 mg/kg pre	25 pts: saline	Stockings + foot pumps (post period)	ivTXA: 1/25 (4%, 1 PE) C: 0/25	Duple x venogram (5 post day)	NR
Yamasaki, 2004 ²⁹	20/20	THA	20 pts: 1 g pre	20 pts: none	None	ivTXA: 0/20 C: 0/20	Clinical exam (4 post weeks)	NR
Lemay, 2004 ³⁰	20/19	THA	20 pts: 10 mg/kg pre + 1 mg/kg/h until wound closure	10 pts: saline	Dalteparin 5,000 IU/day SC (NR)	ivTXA: 0/20 C: 0/19	Clinical exam + US (5-7 post days)	NR
Niskanen, 2005 ³¹	19/20	THA	19 pts: 10 mg/kg pre and 10 mg/kg (two doses) post	20 pts: saline	Dalteparin (hospital stay)	ivTXA: 0/19 C: 0/20	Clinical exam (NR)	0/19

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Johansson, 2005 ³²	47/53	THA	47 pts: 15 mg/kg pre	53 pts: saline	Dalteparin 5,000 IU/day SC (until mobilization)	ivTXA: 0/47 C: 0/53	Clinical exam (6 post weeks)	NR
Open, 2006 ³³	15/14	TKA	15 pts: 15 mg/kg intra	14 pts: saline	Dalteparin (until discharge)	ivTXA: 0/15 C: 0/14	US (5 post day)	0/15
Camarasa, 2006 ³⁴	35/60	TKA	35 pts: 10 mg/kg intra and post	60 pts: saline	Dalteparin 5,000 IU/day SC (40 days)	ivTXA: 0/35 C: 0/60	Clinical exam (3 months)	0/35
Molloy, 2007 ³⁵	50/50	TKA	50 pts: 500 mg intra and post	50 pts: none	ASA 150 mg/day (6 weeks)	ivTXA: 0/50 C: 0/50	Clinical exam (NR)	0/50
Sadeghi, 2007 ³⁶	32/35	HFS	32 pts: 15 mg/kg pre	35 pts: saline	NR	ivTXA: 0/32 C: 0/35	Clinical exam (6 post weeks)	NR
Claeys, 2007 ³⁷	20/20	THA	20 pts: 15 mg/kg intra	20 pts: saline	Fraxiparine (10 post days)	ivTXA: 3/17 (18%, 3 DVT) C: 0/18	Clinical exam, US (10 post day)	NR
Alvarez, 2008 ³⁸	46/49	TKA	46 pts: 10 mg/kg intra + 10 mg/kg/h for 3 h post	49 pts: saline	Bemiparin 3500 IU/day SC (3-4 weeks after discharge)	ivTXA: 0/46 C: 0/49	Clinical exam (3 months)	0/46
Kakar, 2009 ³⁹	25/25	TKA	25 pts: 10 mg/kg intra + 1 mg/kg/h until wound closure	25 pts: saline	NR	ivTXA: 0/25 C: 0/25	Clinical exam (7 post day)	0/25
Zulferey, 2010 ⁴⁰	57/53	HFS	57 pts: 15 mg/kg pre and post	53 pts: saline	Fondaparinux 2.5 mg/day (35 days)	ivTXA: 5/57 (9%, 5 DVT) C: 3/53 (6%, 3 DVT)	Clinical exam (6 post weeks), US (7 post day)	3/57 (5%, 3 ACS)
Kazemi, 2010 ⁴¹	32/32	THA	32 pts: 15 mg/kg pre	32 pts: saline	Enoxaparin 40 mg/day SC (10 post days)	ivTXA: 0/32 C: 1/32 (3%)	Clinical exam (NR)	NR
MacGillivray, 2011 ⁴²	40/20	TKA	20 pts: 10 mg/kg intra and post 20 pts: 15 mg/kg intra and post	20 pts: saline	Warfarin (INR 2.5-5) (NR)	ivTXA: 2/40 (5%, 2 PE) C: 0/20	Clinical exam (hospital stay)	0/40
Charochohvanich, 2011 ⁴³	50/50	TKA	50 pts: 10 mg/kg intra and post	50 pts: saline	None	ivTXA: 0/50 C: 0/50	Clinical exam (3 months)	0/50
Malhotra, 2011 ⁴⁴	25/25	THA	25 pts: 15 mg/kg pre	25 pts: saline	LMWH (hospital stay)	ivTXA: 0/25 C: 0/25	D-dimer (pre and 24 h post), US (10 post day)	NR
McConnell, 2012 ⁴⁵	22/22	TKA	22 pts: 10 mg/kg pre	22 pts: saline	ASA 150 mg/day os (35 days)	ivTXA: 0/22 C: 0/22	NR	0/22
Charochohvanich, 2012 ⁴⁶	120/120	TKA	120 pts: 10 mg/kg intra and post	120 pts: saline	MAP	ivTXA: 0/120 C: 0/120	Clinical exam (hospital stay)	0/120
Maniar, 2012 ⁴⁷	160/40	TKA	40 pts: 10 mg/kg intra 40 pts: 10 mg/kg intra and post 40 pts: 10 m/kg pre and intra 40 pts: 10 mg/kg pre, intra and post	40 pts: none	LMWH (until discharge)	ivTXA: 0/160 C: 0/40	Clinical exam (3 months)	0/160

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Lin, 2012 ⁴⁸	101/50	TKA	52 pts: 10 mg/kg intra 49 pts: 10 mg/kg pre and intra	50 pts: saline	Enoxaparin 40 mg/day SC (until discharge)	ivTXA: 1/101 (1%, 1 DVT) C: 0/50	Clinical exam (3 months)	0/101
Ravitej, 2012 ⁴⁹	88/87	BL, TKA	88 pts: 10 mg/kg intra and 10 mg/kg/h for 3 h intra (second TKA)	87 pts: saline	Enoxaparin 40 mg/day SC (NR)	ivTXA: 0/88 C: 1/87 (1%, 1 DVT)	Clinical exam (post period)	0/50
Imai, 2012 ⁵⁰	95/22	THA	24 pts: 1 g intra 20 pts: 1 g intra and post 25 pts: 1 g pre 26 pts: 1 g pre and post	25 pts: saline	Enoxaparin 40 mg/day SC (10 post days)	ivTXA: 11/95 (12%, 10 DVT, 1 PE) C: 3/22 (14%, 3 DVT)	WBCT (7 post day)	NR
Gautam, 2013 ⁵¹	14/13	TKA	14 pts: 10 mg/kg intra and post	13 pts: none	NR	ivTXA: 0/14 C: 0/13	Clinical exam (post period), D-dimer (2 post day), DUS (5 post day)	0/14
Seo, 2013 ⁵²	50/50	TKA	50 pts: 1.5 g intra	50 pts: saline	NR	ivTXA: 0/50 C: 2/50 (4%, 2 DVT)	NR	0/50
Aguilera, 2013 ⁵³	44/43	TKA	44 pts: 1 g (two doses) intra	43 pts: none	LMWH (30 post days)	ivTXA: 0/44 C: 0/43	NR	1/44 (1 TIA)
Vijay, 2013 ⁵⁴	45/45	HFS	45 pts: 500 mg pre + 1 mg/kg/h during operation	45 pts: saline	NR	ivTXA: 0/45 C: 0/45	Clinical exam (hospital stay)	0/45
Lee, 2013 ⁵⁵	34/34	THA	34 pts: 15 mg/kg pre + 15 mg/kg CI (until wound closure)	34 pts: saline	NR	ivTXA: 0/34 C: 0/34	Clinical exam, US (7 post day)	NR
Kim, 2014 ⁵⁶	163/163	TKA	90 pts (UL, TKA): 10 mg/kg intra and post 73 pts (BL, TKA): 10 mg/kg intra and post + 10 mg/kg intra (second TKA)	163 pts: none	Standard risk: enoxaparin 40 mg/day SC (7-10 days) High risk: IPP (7-10 days) + ASA (6 weeks)	ivTXA: 0/163 C: 1/163 (0.6%, 1 PE)	Clinical exam (NR)	0/163
Huang, 2014 ⁵⁷	184/0	TKA	92 pts: 3 g intra 92 pts: 1.5 g intra	-	LMWH 6000 IU/day SC (until discharge) + rivaroxaban 10 mg/day os (10 post days)	ivTXA: 1/184 (0.5%, 1 DVT)	DUS (1-3 post days, at discharge, 1-3 months)	0/184
Patel, 2014 ⁵⁸	42/47	TKA	42 pts: 10 mg/kg intra	47 pts: 2 g IATA	LMWH (14 post days)	ivTXA: 0/42 C: 0/47	Clinical exam (hospital stay)	0/42
Soni, 2014 ⁵⁹	40/40	TKA	40 pts: 10 mg/kg pre, intra and post	40 pts: 3 g IATA	LMWH (until discharge)	ivTXA: 0/40 C: 0/40	NR (6 post weeks)	0/40
Sarzaeem, 2014 ⁶⁰	50/50	TKA	50 pts: 500 mg post	50 pts: none	NR	ivTXA: 0/50 C: 0/50	NR	0/50
Pachauri, 2014 ⁶¹	50/49	TKA	50 pts: 1 g pre and post	49 pts: none	LMWH (post period)	ivTXA: 0/50 C: 0/49	NP	NR
Gomez-Barrera, 2014 ⁶²	39/39	TKA	39 pts: 15 mg/kg intra and post	39 pts: IATA 3 g	Enoxaparin 40 mg/day SC (14 post days)	ivTXA: 0/39 C: 1/39 (3%, 1 DVT)	Clinical exam (hospital stay)	0/39

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Oremus, 2014 ⁶³	49/49	TKA, THA	49 pts: 1 g (two doses) intra	49 pts: saline	Enoxaparin 40 mg/day SC (28 post days for TKA, 35 post days for THA)	ivTXA: 0/49 C: 2/49 (4%, 1 DVT and 1 PE)	Clinical exam (hospital stay)	NR
Wei, 2014 ⁶⁴	101/100	THA	101 pts: 3 g pre	100 pts: saline	LMWH (NR)	ivTXA: 1/101 (1%, 1 DVT) C: 0/100	Clinical exam (3 months), US (discharge)	NR
Emara, 2014 ⁶⁵	20/20	HFS	20 pts: 10 mg/kg pre + 5 mg/kg/h during operation	20 pts: saline	Enoxaparin (NR)	ivTXA: 5/20 (25%, 5 DVT) C: 1/20 (5%, 1 DVT)	Clinical exam (4 post weeks)	1/20 (5%, 1 CVS)
Shinde, 2015 ⁶⁶	28/28	TKA	28 pts: 10 mg/kg intra + 10 mg/kg (two doses) post	28 pts: saline	Dalteparin 5,000 IU/day SC (5 days) or rivaroxaban 10 mg/day os (10 days) + MAP	ivTXA: 3/28 (11%, 3 DVT) C: 2/28 (7%, 2 DVT)	Clinical exam (hospital stay), DUS (5 post day)	0/28
Lin, 2015 ⁶⁷	40/40	TKA	40 pts: 1 g pre	40 pts: saline	Rivaroxaban 10 mg/day os (14 post days)	ivTXA: 0/40 C: 0/40	Clinical exam (3 months)	0/40
Karaaslan, 2015 ⁶⁸	41/40	BL, TKA	41 pts: 15 mg/kg intra + 10 mg/kg/h for 3 h post (second TKA)	40 pts: none	Enoxaparin 40 mg/day (NR)	ivTXA: 1/41 (2%, 1 DVT) C: 0/40	Clinical exam (hospital stay), DUS (7-14 post days)	0/41
Aguilera, 2015 ⁶⁹	50/50	TKA	50 pts: 1 g (two doses) intra	50 pts: none	LMWH (30 post days)	ivTXA: 0/50 C: 0/50	Clinical exam (2 months)	0/50
Shen, 2015 ⁷⁰	41/40	TKA	41 pts: 15 mg/kg intra	40 pts: saline	LMWH (NR)	ivTXA: 4/41 (10%, 4 DVT) C: 4/40 (10%, 4 DVT)	Clinical exam, DUS (1-2-4-12 post weeks)	0/41
Hsu, 2015 ⁷¹	30/30	THA	30 pts: 1 g pre and post	30 pts: saline	Enoxaparin 40 mg/day SC (until discharge)	ivTXA: 0/30 C: 0/30	Clinical exam (two weeks, 1-2 months)	0/30
Mohib, 2015 ⁷²	50/50	HFS	50 pts: 15 mg/kg pre and post	50 pts: saline	Enoxaparin 40 mg/day SC (NR)	ivTXA: 0/50 C: 0/50	NR	NR
Nielsen, 2016 ⁷³	60/0	TKA	60 pts: 1 g pre	-	Rivaroxaban 10 mg/day os (until discharge)	ivTXA: 0/60	Clinical exam (3 months)	0/60
Drosos, 2016 ⁷⁴	30/30	TKA	30 pts: 1 g intra	30 pts: none	NR	ivTXA: 0/30 C: 0/30	Clinical exam (30 days)	0/30
Chen, 2016 ⁷⁵	60/60	BL, TKA	60 pts: 10 mg/kg intra (first TKA)	60 pts: saline	Rivaroxaban 10 mg/day (14 post days)	ivTXA: 10/60 (17%, 10 CMVT) C: 9/60 (15%, 9 CMVT)	Clinical exam (6 post weeks), DUS (discharge and on 6 post weeks)	0/60
Xie, 2016 ⁷⁶	151/0	TKA	50 pts: 20 mg/kg pre 50 pts: 20 mg/kg pre + 10 mg/kg post 51 pts: 20 mg/kg pre + 10 mg/kg (two doses) post	-	IPP + enoxaparin 2,000 IU/day SC (until discharge) and rivaroxaban 10 mg/day os (10 post days)	ivTXA: 0/151	Clinical exam, DUS (at discharge and at 1 month follow-up)	0/151

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Tzatzairis, 2016 ⁷⁷	40/40	TKA	40 pts: 1 g pre	40 pts: none	LMWH (NR)	ivTXA: 0/40 C: 0/40	Clinical exam (6 post weeks)	0/40
Jain, 2016 ⁷⁸	119/0	TKA	119 pts: 15 mg/kg pre + 10 mg/kg (two doses) post	-	ASA 75 mg/day (6 weeks)	ivTXA: 0/119	Clinical exam (NR)	0/119
Xie, 2016 ⁷⁹	140/70	THA	70 pts: 1.5 g pre 70 pts: 1 g pre	70 pts: 2 g IATA	IPP + enoxaparin 4,000 IU/day SC (until discharge) + rivaroxaban 10 mg/day os (30 days)	ivTXA: 3/140 (2%, 3 DVT) C: 0/70	Clinical exam (hospital stay), DUS (at discharge and at 1-3 months follow-up)	0/140
Wu, 2016 ⁸⁰	84/0	THA	84 pts: 15 mg/kg pre	-	IPP + LMWH 4,000 IU/day SC (until discharge) + rivaroxaban 10 mg/day os (30 days)	ivTXA: 8/84 (9.5%, 1 DVT, 7 CMVT)	Clinical exam (3 months), DUS (5 post day)	0/84
Tengberg, 2016 ⁸¹	33/39	HFS	33 pts: 1 g pre + 3 g post (24-h infusion)	39 pts: saline	Dalteparin 5,000 IU/day SC (NR)	ivTXA: 0/33 C: 1/39 (3%, 1 DVT)	Clinical exam (3 months)	0/33
Yi, 2016 ⁸²	100/50	THA	100 pts: 15 mg/kg pre	50 pts: saline	Enoxaparin 2,000 IU/day SC (until discharge) + rivaroxaban 10 mg/day os (15 days)	ivTXA: 4/100 (4%, 4 DVT) C: 0/50	Clinical exam (3 months), DUS (3 post day)	NR
Zhang, 2016 ⁸³	25/25	THA	25 pts: 1 g pre	25 pts: none	LMWH 4,100 IU (2 post weeks)	ivTXA: 1/25 (4%, 1 DVT) C: 0/25	Clinical exam (1 month), DUS (7 post day)	0/25
Maniar, 2017 ⁸⁴	50/25	BL, TKA	25 pts: 10 mg/kg (two doses) intra 25 pts: 10 mg/kg pre + 10 mg/kg (two doses) post	25 pts: 3 g IATA (two doses)	Enoxaparin 40 mg/day SC (until discharge)	ivTXA: 0/50 C: 0/25	Clinical exam (3 months)	0/50
Lee, 2017 ⁸⁵	283/93	TKA	283 pts: 10 mg/kg intra and post	93 pts: 2 g IATA	IPP and/or rivaroxaban/ASA according to the risk (5 weeks)	ivTXA: 1/283 (0.3%, 1 PE) C: 0/93	Clinical exam (NR)	0/283
Lei, 2017 ⁸⁶	159/0	TKA	53 pts: 20 mg/kg pre + 10 mg/kg (two doses) post 49 pts: 20 mg/kg pre + 10 mg/kg (three doses) post 57 pts: 20 mg/kg pre + 10 mg/kg (four doses) post	-	IPP + enoxaparin 2,000 IU/day SC (until discharge) and rivaroxaban 10 mg/day os (10 post days)	ivTXA: 0/159	Clinical exam (hospital stay), DUS (at discharge and on 2 post weeks)	0/159
Wang, 2017 ⁸⁷	100/98	TKA	100 pts: 1 g TXA intra	98 pts: saline	Rivaroxaban 10 mg/day os (14 post days)	ivTXA: 10/100 (10%, 10 DVT) C: 10/98 (10%, 10 DVT)	Clinical exam (3 months), venography (16 post days)	0/100
Vera, 2017 ⁸⁸	53/49	TSA	53 pts: 10 mg/kg pre and intra	49 pts: saline	UFH 5,000 IU/day SC (until discharge) and ASA 325 mg/da (2 post weeks)	ivTXA: 0/53 C: 0/49	Clinical exam (6 post weeks)	0/53

ivTXA: intravenous tranexamic acid; IATA: intra-articular tranexamic acid; C: controls; h: hour; SAE: severe adverse events; TKA: total knee arthroplasty; THA: total hip arthroplasty; pre: preoperative; intra: intraoperative; post: postoperative; pts: patients; INR: international normalised ratio; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; NR: not reported; PLS: perfusion lung scan; US: ultrasound; DUS: doppler ultrasound; SC: subcutaneously; ASA: acetyl salicylic acid; UL: unilateral; BL: bilateral; IPP: intermittent pneumatic pump; MAP: mechanical ankle pumping; NP: not performed; TIA: transient ischaemic attack; HFS: hip fracture surgery; CMVT: calf muscle vein thrombosis; ACS: acute coronary syndrome; CVSS: cerebrovascular stroke; CI: continuous infusion; WBCT: whole body computed tomography; TSA: total shoulder arthroplasty; UFH: unfractionated heparin.