

1 **Title Page**

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3 **Title: A systematic review of Tranexamic acid in hip fracture surgery**

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19 **Keywords** = Bleeding, femoral neck fracture, hip fracture, meta-analysis, Orthopaedics,
20 surgery, systematic review, Tranexamic acid, transfusion, trauma.

21 **STRUCTURED SUMMARY**

22 **Aim:** To systematically examine and quantify the efficacy and safety of Tranexamic acid in
23 hip fracture surgery.

24 **Methods:** A systematic literature search was conducted using Medline, EMBASE, AMED,
25 CiNAHL, and the Cochrane Central Registry of Controlled Trials. Two assessors
26 independently screened search outputs for potentially relevant articles which met the
27 eligibility criteria. The primary outcome measure was requirement of post-operative blood
28 transfusion. Risk of bias assessment was performed using the Cochrane Collaboration's risk
29 of bias tool for RCT's and the ROBINS-I tool for observational studies. Meta-analysis was
30 performed to estimate risk ratio (RR), risk difference (RD) and mean difference (MD) values
31 for dichotomous and continuous data outcomes respectively. The interpretation of each
32 outcome was made using the GRADE approach.

33 **Results:** Of 102 studies identified, seven met the inclusion criteria including a total of 770
34 participants (TXA: 341; Control: 429). On meta-analysis, intra-venous TXA resulted in a 46%
35 risk reduction in blood transfusion requirement compared to a placebo/control group
36 (RR:0.54; 95% CI: 0.35 to 0.85; I²: 78%; Inconsistency (Chi²) p=<0.0001; N=750). There was
37 also a significantly higher post-operative haemoglobin for TXA versus placebo/control
38 (MD:0.81; 95% CI: 0.45 to 1.18; I²: 46%; Inconsistency (Chi²) p=0.10; N=638). There was
39 no increased risk of thromboembolic events (RD:0.01; 95% CI: -0.03, 0.05; I²: 68%;
40 Inconsistency (Chi²) p=0.007, N=683).

41 **Conclusion:** There is moderate quality evidence that TXA reduces blood transfusion in hip
42 fracture surgery, with low quality evidence suggesting no increased risk of thrombotic
43 events. These findings are consistent with TXA use in other orthopaedic procedures.

44

45 **Keywords:** Bleeding, femoral neck fracture, hip fracture, meta-analysis, Orthopaedics,
46 surgery, systematic review, Tranexamic acid, transfusion, trauma.

47

48 **PROSPERO Registration:** CRD42016036806

49

50 **INTRODUCTION**

51 Despite modern healthcare advances, hip fractures still remain a major risk group for in-
52 hospital mortality, with figures as high as 15% [1, 2]. These deaths typically happen early in
53 the post-operative period, with a mean of 11 days from admission [3].

54 Peri-operative blood loss is a common complication of hip fracture surgery that has been
55 linked to post-operative mortality [4]. Blood loss in people who undergo hip fracture surgery
56 is often significant [5], and is likely underestimated by standard intra-operative calculations
57 [6]. In addition post-operative anaemia has been linked to increased impairment of functional
58 ability, longer length of hospital stay and increased mortality [4, 7, 8].

59 Typical management of post-operative anaemia is through blood transfusion, Major
60 orthopaedic surgery has been identified as the commonest indication for blood transfusion in
61 surgical patients [9]. There is however concern regarding a significantly increased risk of
62 serious bacterial infection in hip fracture patients undergoing allogenic blood transfusion [10].
63 The most recent Serious Hazards of Transfusion report (SHOT) found evidence for 15
64 transfusion-related deaths and 169 incidences of major morbidity associated with blood
65 transfusion in 2014 within the UK alone [11].

66 One potential method of decreasing peri-operative blood loss and reducing post-operative
67 transfusion is through the use of Tranexamic acid (TXA). This is an anti-fibrinolytic agent
68 which blocks the lysine binding site of plasminogen [12]. Current evidence suggests that
69 TXA reduces peri-operative blood loss and transfusion rates across a range of surgical
70 disciplines without an increased risk of thrombosis [12-15].

71 Scientific rationale and supporting evidence suggests that TXA may be useful in reducing
72 blood loss and transfusion rates in hip fracture surgery. Studies into TXA and hip fracture
73 surgery have so far provided variable assessments of efficacy in reducing blood loss and
74 thromboembolic risk with no clear consensus [16-19]. This topic has yet to be investigated in
75 the form of a systematic review. The purpose of this study was to address this limitation

76 within the evidence and systematically examine the available literature regarding the
77 potential risks and benefits of TXA use in hip fracture surgery with quantification of effect
78 through meta-analysis of relevant data.

79

80 **METHODS**

81 A systematic review and meta-analysis of the use of TXA in hip fracture surgery was
82 performed and reported according to the Preferred Reporting Items for Systematic Reviews
83 and Meta-analyses (PRISMA) statement [20]. The review protocol was registered on the
84 international prospective register of systematic reviews (PROSPERO) prior to
85 commencement (Registration number CRD42016036806).

86 **Search Strategy**

87 Identification of relevant articles was undertaken through a search of Medline, EMBASE,
88 AMED, CiNAHL, and the Cochrane Central Registry of Controlled Trials. A search of
89 unpublished/grey literature databases was undertaken including: OpenGrey, Current Clinical
90 Trials, the WHO registry of clinical trials and clinaltrials.gov. All electronic searches were
91 undertaken from database inception to 18th June 2016. A full electronic search strategy for
92 MEDLINE is shown in Supplementary Table 1. This was adapted for each individual
93 database.

94 All reference lists from potentially eligible studies were reviewed. An additional online search
95 was undertaken using the Google search engine to identify any papers which may have
96 been omitted from the initial search and to cross-reference against the database search.

97 **Eligibility Criteria**

98 Studies were included if they: presented results evaluating the clinical outcomes and/or
99 complications regarding the use of TXA in hip fracture surgery. We considered any form of

100 hip fracture surgery including: open reduction internal fixation (cannulated screws, dynamic
101 hip screws, intramedullary devices), hemiarthroplasty and total hip arthroplasty (THA) for
102 trauma. We excluded papers which were review articles and studies that included
103 assessment of primary THA (elective), hip arthroscopy or any form of non-trauma hip
104 surgery. We excluded non-English language publications but did not exclude studies based
105 on study quality, age of publication or location of study origin.

106 **Study Identification**

107 Two assessors (LF, TS) independently screened the titles and abstracts of the search
108 outputs for potentially relevant articles which met the eligibility criteria. For those papers
109 which were deemed potentially eligible, their full-texts were evaluated to determine final
110 eligibility.

111 **Data Extraction**

112 Data were extracted onto a pre-defined data extraction sheet by one reviewer (LF) and
113 verified by a second (TS). Data included: study design, research aims, participants
114 characteristics (age, gender, type of hip fracture, medical morbidity, fracture fixation,
115 operative details), randomisation method (if applicable), intervention (TXA and control) and
116 outcome data. Trial authors were contacted for any missing relevant data.

117 **Outcome Measures**

118 The primary outcome measure was frequency of post-operative blood transfusion. The
119 secondary outcome measures were: post-operative haemoglobin, peri-operative blood loss,
120 frequency of thromboembolic events, length of hospital stay and complications within the
121 initial 90-days post-operatively. Outcomes were assessed as either intra-operative, short-
122 term (hospital admission) or longer-term (post-hospital discharge).

123 **Quality Assessment**

124 Risk of bias assessment was performed by two reviewer independently (LF, TS) using the
125 Cochrane Collaboration’s risk of bias tool for RCT’s [21] and the Risk of Bias in non-
126 randomised studies – of interventions (ROBINS-I) tool [22] for observational studies. The
127 ROBINS-I tool assesses bias across six domains including: confounding, participant
128 selection, intervention classification, departure from intended interventions, missing data,
129 measurement of outcomes and selection of reported results. For each domain an outcome of
130 low, moderate, serious, critical and no information for risk of bias is recorded. An overall risk
131 of bias judgement is then determined through combination of the six domains. The Cochrane
132 Collaboration’s risk of bias tool for RCT’s comprises seven domains including: random
133 sequence generation, allocation concealment, blinding of participants/personnel, blinding of
134 outcome assessment, incomplete outcome data, selective reporting and other bias. For each
135 domain an outcome of low risk, unclear risk or high risk is recorded. There is no overall
136 assessment of risk of bias.

137 During the study period any disagreements in quality assessment, study eligibility or data
138 extraction were resolved through discussion between two reviewers (LF, TS).

139 **Data Analysis**

140 An assessment of clinical heterogeneity was made by analysing the completed data
141 extraction form. When there was evidence of between-study heterogeneity in population
142 characteristics, surgical intervention or trial intervention (i.e. TXA), a meta-analysis was
143 deemed inappropriate and a narrative analysis of the evidence was undertaken. When there
144 was clinical homogeneity in respect to population characteristics, surgical intervention and
145 trial intervention, a meta-analysis was deemed appropriate and undertaken for those specific
146 outcomes. All reported values are for Intravenous TXA unless otherwise stated.

147 When meta-analysis was undertaken, statistical heterogeneity was assessed using the
148 inconsistency-value (I^2) and Chi-squared tests. When I^2 was $\leq 20\%$ and Chi-squared equated
149 to $p \geq 0.10$, a fixed-effects model meta-analysis was undertaken. When these were not

150 satisfied, a random-effects meta-analysis was undertaken [23]. For dichotomous outcomes
151 including frequency of post-operative blood transfusion, thromboembolic events and 90-day
152 complications, the relative risk (RR) or risk difference (RD) was estimated with 95%
153 confidence intervals (CI). A risk difference was calculated if a zero number of events was
154 reported for an outcome within an individual trial. The number needed to treat (NNT) was
155 calculated for the primary outcome of post-operative blood transfusion using the inverse of
156 the absolute risk reduction value. For all continuous outcomes including post-operative
157 haemoglobin level, peri-operative blood loss and length of hospital stay, the mean difference
158 (MD) was calculated with 95% CIs. In all analyses, $p < 0.05$ denoted statistical significance.
159 All analyses were undertaken by two reviewers (LF, TS) using Revman Version 5.3 [24]. All
160 meta-analysis results are presented in the text as: outcome (RR/RD/MD); 95% CI;
161 Inconsistency (I^2) value; Inconsistency (Chi^2) p value; Sample size (N).

162 A sensitivity analysis was conducted to analyse outcomes in trials without significant
163 methodological limitation i.e. ambiguity on hip fracture type or surgical intervention. *A priori*
164 subgroup analyses included comparison of the TXA intervention to control group on clinical
165 outcomes stratified by mean age (less than 75 years versus 76 years and over), BMI group
166 (less than or equal to BMI 40 versus BMI greater than 40), and hip fracture type
167 (intracapsular vs extracapsular). Assessment was performed by excluding data from studies
168 which did not meet the subgroup analysis requirements.

169 The analysis for each outcome was evaluated using the Grades of Recommendation,
170 Assessment, Development and Evaluation (GRADE) approach by two reviewers (LF, TS)
171 [25]. This was used to categorise the quality of evidence into four possible levels: high,
172 moderate, low or very low quality. This approach evaluates the quality of evidence for each
173 individual analysis (i.e. the body of the literature forming that particular analysis as opposed
174 to the whole evidence irrespective of whether it was used in an analysis or not).

175

176 **RESULTS**

177 **Search Results**

178 A summary of the search results are presented in Figure 1. A total of 102 studies were
179 identified. Sixteen of these underwent full-text assessment. Subsequently seven met the
180 eligibility criteria. Two abstract only publications [26, 27] were not included due to incomplete
181 data and lack of contact details in conference proceedings. A search of the grey/unpublished
182 literature identified four ongoing trials at various stages of completion [28-31].

183 **Characteristics of Included Studies**

184 A summary of included study characteristics are shown in Table 1. A total of 770 patients
185 were included in the analysis. The mean age was 72 years; 65% were female. Of these 341
186 patients received TXA (321 intravenous (IV) TXA; 20 topical TXA). There was a wide
187 variation in the frequency and dose of TXA given peri-operatively. Of the seven studies,
188 three did not differentiate fracture type or management; two studies examined patients
189 undergoing intracapsular hip fracture treatment (hemi-arthroplasty) alone [17, 19] and two
190 studies focused on extracapsular hip fractures (one utilised sliding hip screw fixation [18], the
191 other a short intramedullary nail device [32]).

192 **Quality Assessment**

193 The seven articles identified as suitable for systematic review consisted of six double-blind
194 RCTs [16-18, 32-34] and one retrospective cohort study [19]. Randomisation methods
195 included utilisation of opaque sealed envelopes [32, 33], random number techniques [34]
196 and a computer generated random number table [18]. One study [16] used a stratified
197 sampling technique via a computer generated randomisation list to ensure equal distribution
198 of patients undergoing osteosynthesis or hip arthroplasty. One study did not report their
199 method of randomisation [17].

200 Risk of bias assessment was performed for individual studies with the results shown in
201 Supplementary table 2. Determination of the risk of bias across studies was also performed
202 for each outcome measured.

203

204 **Synthesis of results**

205 Primary outcome: Post-operative blood transfusion requirement

206 All seven studies reported the requirement for post-operative blood transfusion [16-19, 32-
207 34]. Meta-analysis showed there was a 46% lower risk of blood transfusion requirement in
208 those who received intra-venous TXA compared to a placebo/control group (RR: 0.54; 95%
209 CI: 0.35 to 0.85; I^2 : 78%; Inconsistency (Chi^2) $p < 0.0001$; $N=750$; Figure 2). The NNT for
210 this primary outcome was 8. The funnel plot for the primary outcome is shown in Figure 3.

211 Secondary outcome: Post-operative haemoglobin level

212 Six studies reported the requirement for post-operative haemoglobin level [17-19, 32-34]. On
213 meta-analysis, post-operative haemoglobin was greater in those who received intra-venous
214 TXA compared to a placebo/control group (MD: 0.81; 95% CI: 0.45 to 1.18; I^2 : 46%;
215 Inconsistency (Chi^2) $p=0.10$; $N=638$; Figure 4).

216 Secondary outcome: Total post-operative blood loss within the initial post-operative day

217 Five studies reported the requirement for post-operative blood loss [16, 17, 32-34]. Data
218 were available to pool outcomes from three studies [17, 33, 34]. On this meta-analysis, post-
219 operative total blood loss was less in those who received intra-venous TXA compared to the
220 placebo/control group (MD: -341; 95% CI: -672 to -9.87; I^2 : 100%; Inconsistency (Chi^2)
221 $p < 0.00001$; $N=197$; Supplementary Figure 1).

222 There was insufficient data in Zuffery et al [16] to be included in the meta-analysis as post-
223 operative blood loss was only reported at Day 8. They reported no statistically significant

224 difference between TXA and placebo groups (444mls; 95% CI: 116 to 804 vs. 307mls; 95%
225 CI: 90 to 526; respectively; $p=0.07$). Tengberg et al [32] also only provided data for post-
226 operative blood loss at Day 4, where there was a statistically significant higher blood loss for
227 control versus TXA (MD: 571; 95% CI: 61.7 to 1080; $p=0.029$)

228 Secondary outcome: Peri-operative blood loss

229 Three studies reported peri-operative blood loss [16, 32, 34]. Meta-analysis showed a
230 significantly lower blood loss for TXA versus control (MD: -190; 95% CI: -495 to 115; I^2 : 91%;
231 Inconsistency (Chi^2) $p<0.00001$; $N=249$; Supplementary Figure 2).

232 Secondary outcome: Total Length of Hospital Stay

233 Two studies reported hospital length of stay [19, 34]. There was no significant difference
234 between the TXA and placebo/control groups for this outcome (MD: 0.26; 95% CI: -4.05 to
235 4.56; I^2 : 77%; Inconsistency (Chi^2) $p=0.04$; $N=338$; Supplementary Figure 3).

236 Post-operative complications

237 Meta-analysis was only possible for six post-operative complications: 30-day mortality; 90
238 day mortality; stroke; overall thromboembolic events; pulmonary embolism and deep vein
239 thrombosis. The results of these analyses are shown in table 2. The forest plot for
240 thromboembolic events is presented in Figure 5. All other forest plots for post-operative
241 outcomes are displayed in the supplementary material (Supplementary Figures 4 to 8).
242 There were no statistically significant differences comparing TXA to placebo across the six
243 analyses.

244 Zufferey et al [16] reported on a number of other post-operative complications. There were
245 no significant differences observed for TXA compared to placebo for major bleeding
246 (inclusion criteria not defined), bacterial infection, pneumonia, lower respiratory tract
247 infection, urinary tract infection, superficial wound infection, deep wound infection and acute
248 coronary syndrome.

249 **GRADE Assessment**

250 The quality of evidence for each eligible outcome was assessed using the GRADE
251 approach. The results of this are presented in Table 2. These indicated that whilst the quality
252 of evidence was high the outcome of post-operative haemoglobin level, it was moderate for
253 those of requirement of post-operative blood transfusion and 30-day mortality. All other
254 outcomes were either of low or very low quality.

255 **Subgroup analysis**

256 Subgroup analysis was performed as planned where data permitted. There were five
257 observed alterations to meta-analysis outcomes. This included a lack of statistical
258 significance in transfusion rate for TXA versus placebo in those age ≥ 76 (RR 0.67 (0.37,
259 1.22); I^2 : 84%; Inconsistency (Chi²) $p=0.002$; $N=453$), in those BMI ≤ 40 (RR 0.73 (0.49,
260 1.11); I^2 : 68%; Inconsistency (Chi²) $p=0.02$; $N=289$), and where extracapsular hip fractures
261 were examined alone (RR 0.67 (0.24, 1.87); I^2 : 88%; Inconsistency (Chi²) $p=0.004$; $N=172$).
262 When considering peri-operative blood loss there was a lack of significance for TXA versus
263 placebo in those age ≥ 76 (MD -47.6 (-127, 31.5); I^2 : 0%; Inconsistency (Chi²) $p=0.97$;
264 $N=182$). There was also a lack of significance in post-operative haemoglobin for TXA versus
265 placebo when examining intracapsular hip fractures alone (MD 0.93 (-0.04, 1.91); I^2 : 79%;
266 Inconsistency (Chi²) $p=0.06$; $N=309$). Results for all other subgroup analyses are presented
267 in Table 3.

268 A sensitivity analysis was undertaken removing the results of Lee et al [19] to examine the
269 influence of any bias inherent in the design of this study. Due to ambiguity regarding the
270 number of femoral shaft fractures included in their study a similar assessment was also
271 performed with Vijay et al [33] removed. There were no significant differences in meta-
272 analysis outcomes for either cohort. Results are again presented in Table 3.

273

274 **DISCUSSION**

275 Our systematic review and meta-analysis found moderate-quality evidence that the use of
276 TXA in hip fracture surgery reduces the absolute risk of requiring a post-operative blood
277 transfusion by 12%. The NNT for this primary outcome was low at 8.

278 There is associated high-quality evidence for a higher post-operative haemoglobin level with
279 TXA and moderate quality evidence for no difference in 30 day mortality. The use of TXA
280 was not associated with an increase in post-operative stroke, pulmonary embolus, DVT or
281 composite thromboembolic events. However, the quality of evidence was judged as low for
282 these outcomes. There is also low quality evidence to suggest a decreased level of post-
283 operative and peri-operative blood loss with TXA and very low quality evidence suggesting
284 no difference in length of hospital stay. These findings are in keeping with evidence from
285 other systematic reviews examining the use of TXA in hip and knee arthroplasty [12], as well
286 as other surgical procedures [13].

287 There is a potential financial benefit associated with the use of TXA in hip fracture surgery
288 when considering blood transfusion. Our estimates suggest that when considering two peri-
289 operative doses of 1g IV TXA, with a cost of £1.50 per 5ml (100mg/ml) for TXA , £635 per
290 transfusion , and an NNT of 8, this would equate to a saving of approximately £74.13 per
291 patient who undergo hip fracture surgery on transfusion costs alone. Further cost-benefit
292 analyses are warranted to estimate the potential value (or not) of TXA on the entire patient
293 pathway following hip fracture to test whether these suggested benefits are repeatedly
294 evident following hip fracture surgery.

295 Subgroup analysis was performed to identify any potential patient or external factors which
296 may have influenced study findings. A number of differences in the significance of outcome
297 results were identified. Firstly, a lack of significance was noted for TXA versus placebo
298 regarding the transfusion rate in those studies with mean age ≥ 76 . This finding could be
299 explained by previously acknowledged heightened levels of pre-operative anaemia with

300 increasing age [35] amplifying the likelihood of transfusion in both groups. Secondly, there
301 was a lack of significance in transfusion rate for those BMI ≤ 40 . One potential explanation for
302 this result could relate to greater blood loss in both groups influencing the difference in
303 transfusion rate. Such higher levels of blood loss of those with a lower BMI would be in
304 keeping with findings in other orthopaedic surgical procedures [36]. There was also a lack of
305 significance in transfusion rate with TXA identified for extracapsular hip fractures. Again this
306 could be explained by recognised greater blood loss and higher levels of pre-operative
307 anaemia compared to intracapsular fractures [5]. Finally there was a lack of significance for
308 peri-operative blood loss in those age ≥ 76 which was felt to relate to the very wide
309 confidence intervals of the studies used in this analysis.

310 Sensitivity analysis with data from Vijay et al [33] and Lee et al [19] excluded did not have a
311 significant effect on any of the results and therefore neither were felt to have a negative
312 impact on the overall study outcome.

313 A number of limitations identified with this study related to the current evidence-base. Firstly,
314 it was not possible to analyse the potential impact of variation in the dose and timing of TXA
315 across studies. This was poorly reported and may relate to a current paucity of data
316 regarding the optimum therapeutic regimen for TXA. The small number of trials presented
317 meant that sub-group analysis to establish differences between TXA protocols was not
318 possible. Secondly, major inter-study variation in the transfusion protocol used may explain
319 some of the differences in outcomes across studies. It is notable that both of the studies with
320 identified low transfusion thresholds (Hb $< 9-10$ g/dl) [16, 32] did not find a statistically
321 significant difference in post-operative transfusion rate between TXA and placebo. This is
322 compounded by the fact that in the Tengberg et al [32] study the TXA group had significantly
323 lower haemoglobin at admission than the placebo group (11.92 [SD 1.61] vs 12.89g/dl [SD
324 1.45] respectively; $p=0.024$). Finally, the GRADE analysis identified a number of the
325 secondary outcomes as having low or very low quality evidence. This was mainly due to high
326 heterogeneity across studies, low event numbers and wide confidence intervals. This

327 unfortunately limits the conclusions that can be drawn from the evidence and the identified
328 results for these outcomes must be interpreted with caution.

329 Four key aspects for future research have been highlighted by this study. Firstly,
330 understanding the thrombotic risk associated with TXA use in hip fracture surgery is of
331 paramount importance to determining its clinical utility. Future studies must ensure that
332 safety outcomes are assessed. Only large studies are likely to provide sufficient cohort size
333 to accurately determine thrombosis risk. Verification of the optimum timing and dosage of
334 Intravenous TXA to reduce study heterogeneity would likely be of benefit in this regard.

335 Secondly, the use of topical TXA in hip fractures is another potential research area of
336 interest. Only one study [17] examined topical TXA as a treatment option. Their results
337 indicated an efficacy similar to that of Intravenous TXA when compared to placebo, but with
338 an improved safety profile. A lack of systemic absorption with topical TXA is one suggested
339 reason for such an effect. Comparable results have previously been identified with topical
340 TXA in hip and knee arthroplasty [37-39]. Caution should however be taken when
341 considering use in hemiarthroplasty as recent research has identified a potential cytotoxic
342 effect on chondrocytes in an animal model [40]. There is however no suggestion for an
343 adverse effect with artificial joint materials [41].

344 Thirdly, evaluation of treatment effect differences between different hip fractures and
345 treatment options may also be of benefit. Extracapsular hip fracture management has
346 previously been shown to have a higher amount of blood loss than intracapsular hip
347 fractures [5, 6]. The complexity and length of THA for hip fracture compared to
348 hemiarthroplasty has also been shown to lead to a higher degree of blood loss [42]. The
349 beneficial effects of TXA may be more pronounced in such high-risk groups.

350 Finally the impact of TXA administration at hospital admission should also be examined. This
351 approach is already heavily utilised in trauma patients based on results of the landmark
352 CRASH-2 trial [43]. Hip fractures have been associated with a high initial blood loss that may

353 not be apparent on initial haemoglobin testing [5, 44]. Early TXA may provide one method of
354 reducing pre-operative anaemia, which has previously been identified as risk-factor for
355 mortality [45].

356

357 **CONCLUSIONS**

358 The clinical importance and financial impact of post-operative blood transfusion requirement
359 and post-operative anaemia in hip fracture surgery is already well established. Our
360 systematic review and meta-analysis confirms that TXA is effective at reducing both of these
361 adverse outcomes in this setting. The presence of an associated thromboembolic risk with
362 TXA use remains unclear.

363

364 **REFERENCES**

- 365 1. Keene GS, Parker MJ, Pryor GA. Mortality and morbidity after hip fractures. *BMJ* 1993; 307:
366 1248-50.
- 367 2. Alzahrani K, Gandhi R, Davis A, Mahomed N. In-hospital mortality following hip fracture care
368 in southern Ontario. *Can J Surg* 2010; 53: 294-8.
- 369 3. Chatterton BD, Moores TS, Ahmad S, Cattell A, Roberts PJ. Cause of death and factors
370 associated with early in-hospital mortality after hip fracture. *Bone Joint J* 2015; 97-B: 246-51.
- 371 4. Foss NB, Kristensen MT, Kehlet H. Anaemia impedes functional mobility after hip fracture
372 surgery. *Age Ageing* 2008; 37: 173-8.
- 373 5. Smith GH, Tsang J, Molyneux SG, White TO. The hidden blood loss after hip fracture. *Injury*
374 2011; 42: 133-5.
- 375 6. Foss NB, Kehlet H. Hidden blood loss after surgery for hip fracture. *J Bone Joint Surg Br* 2006;
376 88: 1053-9.
- 377 7. Lawrence VA, Silverstein JH, Cornell JE, Pederson T, Noveck H, Carson JL. Higher Hb level is
378 associated with better early functional recovery after hip fracture repair. *Transfusion* 2003; 43:
379 1717-22.
- 380 8. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, Noveck H, Strom BL. Effect of
381 anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; 348: 1055-60.
- 382 9. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic
383 review of the literature. *Anesthesiology* 2010; 113: 482-95.
- 384 10. Carson JL, Altman DG, Duff A, Noveck H, Weinstein MP, Sonnenberg FA, Hudson JI,
385 Provenzano G. Risk of bacterial infection associated with allogeneic blood transfusion among
386 patients undergoing hip fracture repair. *Transfusion* 1999; 39: 694-700.
- 387 11. Bolton-Maggs P, Poles D. et al. on behalf of the Serious Hazards of Transfusion (SHOT)
388 Steering Group. The 2014 Annual SHOT report. In, 2015.

- 389 12. Gandhi R, Evans HM, Mahomed SR, Mahomed NN. Tranexamic acid and the reduction of
390 blood loss in total knee and hip arthroplasty: a meta-analysis. *BMC Res Notes* 2013; 6: 184.
- 391 13. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding:
392 systematic review and cumulative meta-analysis. *BMJ* 2012; 344: e3054.
- 393 14. Esmaeelzadeh M, Amini S. The effect of Tranexamic acid on cardiac surgery bleeding. *Rev*
394 *Clin Med* 2014; 1: 7-11.
- 395 15. Song G, Yang P, Hu J, Zhu S, Li Y, Wang Q. The effect of tranexamic acid on blood loss in
396 orthognathic surgery: a meta-analysis of randomized controlled trials. *Oral Surg Oral Med Oral*
397 *Pathol Oral Radiol* 2013; 115: 595-600.
- 398 16. Zufferey PJ, Miquet M, Quenet S, Martin P, Adam P, Albaladejo P, Mismetti P, Molliex S,
399 tranexamic acid in hip-fracture surgery s. Tranexamic acid in hip fracture surgery: a randomized
400 controlled trial. *Br J Anaesth* 2010; 104: 23-30.
- 401 17. Emara WM, Moez KK, Elkhoully AH. Topical versus intravenous tranexamic acid as a blood
402 conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. *Anesth*
403 *Essays Res* 2014; 8: 48-53.
- 404 18. Mohib Y, Rashid RH, Ali M, Zubairi AJ, Umer M. Does tranexamic acid reduce blood
405 transfusion following surgery for inter-trochanteric fracture? A randomized control trial. *J Pak Med*
406 *Assoc* 2015; 65: S17-20.
- 407 19. Lee C, Freeman R, Edmondson M, Rogers BA. The efficacy of tranexamic acid in hip
408 hemiarthroplasty surgery: an observational cohort study. *Injury* 2015; 46: 1978-82.
- 409 20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic
410 reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
- 411 21. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks
412 L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G. The Cochrane
413 Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
- 414 22. Sterne JA, Higgins JP, Reeves BC. on behalf of the development group for ROBINS-I: a tool for
415 assessing Risk Of Bias In Non-randomized Studies of Interventions, Version 7 March In, 2016.
- 416 23. Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*
417 *Version 5.1.0 [updated March 2011]: The Cochrane Collaboration, 2011.*
- 418 24. Review Manager (RevMan) In, Version 5.3 Edition, Copenhagen, 2014: [Computer Program].
- 419 25. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P,
420 DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. GRADE guidelines: 1.
421 Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64:
422 383-94.
- 423 26. Moghaddam MJ, Darabi E, Sheikholeslami E. Effect of tranexamic acid in decreasing need to
424 transfusion in hip fracture surgery: 6AP4-5. In, *Eur J Anaesthesiol*, 2011: 89.
- 425 27. Angulo Tabernerero M, Aguilar Ezquerro A, Cassinello Ojea C, Ungria Murillo J, Martin
426 Hernandez C. Tranexamic acid in osteoporotic hip fracture surgery. In, *Osteoporos Int*, 2015.
- 427 28. Lau R, Topical Application of Tranexamic Acid and Postoperative Blood Loss in Femoral Neck
428 Fractures [UNPUBLISHED - NCT01727843]: *Clinicaltrials.gov*, 2012
429 <https://clinicaltrials.gov/show/NCT01727843> Accessed 17/03/16
- 430 29. Lorich DG, The Effect of Tranexamic Acid on Transfusion Rates in Intertrochanteric Hip
431 Fractures [UNPUBLISHED - NCT01940536]: *Clinicaltrials.gov*, 2013
432 <https://clinicaltrials.gov/show/NCT01940536> Accessed 17/03/16
- 433 30. Pagnano M, Does Tranexamic Acid Reduce the Need for Blood Transfusions in Patients
434 Undergoing Hip Fracture Surgery? [UNPUBLISHED - NCT01714336]: *Clinicaltrials.gov*, 2012
435 <https://clinicaltrials.gov/show/NCT01714336> Accessed 17/03/16
- 436 31. Shteinberg E, Tranexamic Acid in Hip Fracture Patients [UNPUBLISHED - NCT01326403]:
437 *Clinicaltrials.gov*, 2011 <https://clinicaltrials.gov/show/NCT01326403> Accessed 17/03/16

- 438 32. Tengberg PT, Foss NB, Palm H, Kallemsen T, Troelsen A. Tranexamic acid reduces blood loss
439 in patients with extracapsular fractures of the hip: results of a randomised controlled trial. *Bone*
440 *Joint J* 2016; 98-B: 747-53.
- 441 33. Vijay BS, Bedi V, Mitra S, Das B. Role of tranexamic acid in reducing postoperative blood loss
442 and transfusion requirement in patients undergoing hip and femoral surgeries. *Saudi J Anaesth* 2013;
443 7: 29-32.
- 444 34. Sadeghi M, Mehr-Aein A. Does a single bolus dose of tranexamic acid reduce blood loss and
445 transfusion requirements during hip fracture surgery? A prospective randomized double blind study
446 in 67 patients. *Acta Medica Iranica* 2007; 45: 437-42.
- 447 35. Patel KV. Epidemiology of anemia in older adults. *Semin Hematol* 2008; 45: 210-7.
- 448 36. Carling MS, Jeppsson A, Eriksson BI, Brisby H. Transfusions and blood loss in total hip and
449 knee arthroplasty: a prospective observational study. *J Orthop Surg Res* 2015; 10: 48.
- 450 37. Chen S, Wu K, Kong G, Feng W, Deng Z, Wang H. The efficacy of topical tranexamic acid in
451 total hip arthroplasty: a meta-analysis. *BMC Musculoskelet Disord* 2016; 17: 81.
- 452 38. Alshryda S, Sukeik M, Sarda P, Blenkinsopp J, Haddad FS, Mason JM. A systematic review and
453 meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement.
454 *Bone Joint J* 2014; 96-B: 1005-15.
- 455 39. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of
456 bleeding. *Cochrane Database Syst Rev* 2013; 7: CD010562.
- 457 40. Tuttle JR, Feltman PR, Ritterman SA, Ehrlich MG. Effects of Tranexamic Acid Cytotoxicity on
458 In Vitro Chondrocytes. *Am J Orthop (Belle Mead NJ)* 2015; 44: E497-502.
- 459 41. Alshryda S, Mason JM, Sarda P, Lou T, Stanley M, Wu J, Unsworth A. The effect of tranexamic
460 acid on artificial joint materials: a biomechanical study (the bioTRANX study). *J Orthop Traumatol*
461 2015; 16: 27-34.
- 462 42. van den Bekerom MP, Hilverdink EF, Sierevelt IN, Reuling EM, Schnater JM, Bonke H,
463 Goslings JC, van Dijk CN, Raaymakers EL. A comparison of hemiarthroplasty with total hip
464 replacement for displaced intracapsular fracture of the femoral neck: a randomised controlled
465 multicentre trial in patients aged 70 years and over. *J Bone Joint Surg Br* 2010; 92: 1422-8.
- 466 43. collaborators C-, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, Dewan Y, Gando S, Guyatt
467 G, Hunt BJ, Morales C, Perel P, Prieto-Merino D, Woolley T. The importance of early treatment with
468 tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised
469 controlled trial. *Lancet* 2011; 377: 1096-101, 101 e1-2.
- 470 44. Kumar D, Mbako AN, Riddick A, Patil S, Williams P. On admission haemoglobin in patients
471 with hip fracture. *Injury* 2011; 42: 167-70.
- 472 45. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the
473 association between preoperative anaemia and mortality after surgery. *Br J Surg* 2015; 102: 1314-
474 24.

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476 **COMPETING INTERESTS & FINANCIAL SUPPORT**

477 “All authors have completed the Unified Competing Interest form at
478 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and
479 declare: no support from any organisation for the submitted work; no financial relationships
480 with any organisations that might have an interest in the submitted work in the previous 3

481 years; no other relationships or activities that could appear to have influenced the submitted
482 work”

483 **AUTHOR CONTRIBUTIONS**

484 LF developed the research idea. He performed the review literature search as well as
485 primary data extraction and data analysis. He wrote the structured summary, introduction,
486 results, discussion and conclusion sections of the manuscript.

487 TS performed the review literature search as well as secondary data extraction and data
488 analysis. He provided guidance on design of the manuscript and wrote the methods section.
489 He also provided critical appraisal of the manuscript prior to submission.

490 GA provided expertise in the clinical interpretation and application of the results. He also
491 performed critical appraisal of the manuscript prior to submission.

492 PM oversaw development and design of the study as well as providing critical appraisal of
493 the manuscript prior to submission.

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495 **FIGURE LEGENDS**

496 **Figure 1.** Flow diagram depicting the study selection process

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498 **Figure 2.** Forest-plot of TXA versus control for requirement for blood transfusion

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500 **Figure 3.** Funnel plot of TXA versus control for requirement for blood transfusion.

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502 **Figure 4.** Forest-plot of TXA versus control for post-operative haemoglobin

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504 **Figure 5.** Forest-plot of TXA versus control for thromboembolic events

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506 **SUPPLEMENTARY FIGURE LEGENDS**

507 **Supplementary Figure 1.** Forest-plot of TXA versus control for total blood loss

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509 **Supplementary Figure 2.** Forest-plot of TXA versus control for Peri-operative blood loss

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511 **Supplementary Figure 3.** Forest-plot of TXA versus control for length of stay

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513 **Supplementary Figure 4.** Forest-plot of TXA versus control for 90 day mortality
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515 **Supplementary Figure 5.** Forest-plot of TXA versus control for Stroke
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517 **Supplementary Figure 6.** Forest-plot of TXA versus control for Pulmonary Embolus
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519 **Supplementary Figure 7.** Forest-plot of TXA versus control for DVT

520 **Supplementary Figure 8.** Forest-plot of TXA versus control for 30 day mortality
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522 **Table 1.** Characteristics of included studies

Paper	Study	N	Gender (M/F)	Mean age (years)	ASA grade (3 or 4)	Fracture type	Fracture surgical management	Duration of surgery (minutes)	Intervention	Control
Lee et al 2015 [19]	RCS	271	Interv: 32/52 Control: 53/134	Interv: 86.0 Control: 84.7	Interv: 57 Control: 137	Hip Fracture	Hemiarthroplasty: 271	Not documented	(N: 84) 1g IV TXA given at induction.	(N:187) No treatment control.
Sadeghi & Mehr - Aein 2007 [34]	DBL blind RCT	67	Interv: 17/15 Control: 24/11	Interv: 51.8 Control: 44.4	Not documented	Hip Fracture	Not documented	Not documented	(N:32) Single bolus of 15mg/kg IV TXA given at induction.	(N:35) Same volume of IV normal saline given to controls.
Zuffery et al. 2010 [16]	DBL blind RCT	110	Interv: 10/47 Control: 4/49	Interv: 81 Control: 82	Interv: 19 Control: 20	Cervical: 45 Trochanteric: 19 Unstable trochanteric/inter/su btrochanteric: 46	THR: 45 Hemiarthroplasty: 2 SHS: 41 IMN: 22	Interv: 64.0 Control: 64.0	(N:57) Two doses of IV TXA – 15mg/kg given at induction then another 3 hours later.	(N:53) Control group received 2 doses of IV placebo at same intervals.
Emara 2014 [17]	DBL blind RCT	60	Interv (IV): 12/8 Interv (Topical): 10/10 Control: 14/6	Interv (IV): 56.5 Interv (Topical): 55 Control: 56	Not documented	Hip Fracture	Hemiarthroplasty: 60	Interv (IV): 2.3 hrs Interv (Topical): 2.3 hrs	(N:20) IV TXA 10mg/kg as bolus pre incision then 5mg/kg/h infusion until end (N:20) Topical TXA 100mls NS with 1.5g TXA poured into surgical field for 5 mins	(N:20) Control received 20ml of normal saline pre-incision and 80ml/h of normal saline until end. 100ml of normal saline poured into surgical field for 5 mins
Mohib et al. 2015 [18]	DBL blind RCT	100	Interv: 21/29 Control: 24/26	Interv: 69.0 Control: 70.0	Not documented	Intertrochanteric: 100	SHS: 100	Interv: 112.9 Control: 112.3	(N: 50) Two doses of IV 10mg/kg TXA at induction and 3 hours later.	(N:50) Controls: same amount saline.
Vijay et al 2013 [33]	DBL blind RCT	90	Interv: 10/35 Control: 10/35	Interv: 49.3 Control: 48.8	Interv: 0 Control: 0	Hip and Femoral fracture. No further details provided.	ORIF; hemiarthroplasty; THR. Frequencies not documented.	Interv: 118.7 Control: 117.3	(N: 45) 10mg/kg body weight IV TXA given 15min prior to incision.	(N:45) Controls: 1mg/kg body weight IV saline.
Tengberg et al 2016 [32]	DBL blind RCT	72	Interv: 7/26 Control: 14/25	Interv: 79.8 Control: 75	Interv: 5 Control: 12	Extracapsular (AO type 31-A2.2 to 31-A3): 72	Short intramedullary nail: 72	Not documented	(N: 33) 1g IV TXA as bolus pre incision then post-op 24hr infusion of 3g TXA	(N: 39) Controls: 5ml saline given pre incision and then 24 hour infusion of 1litre IV saline

523 Abbreviations: DBL = Double; RCT = Randomised controlled trial; RCS = Retrospective cohort study; Interv = Intervention group; THR = Total Hip replacement; SHS = Sliding
524 hip screw; IMN = Intramedullary nail; ORIF = Open reduction internal fixation

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Table 2. Synthesis of results for all outcomes & GRADE assessment: summary of findings

Outcomes	Intervention	Control	Relative effect (95% CI)	Inconsistency value (I ²)	Inconsistency (Chi ²) p value	Number of participants [Studies]	Quality of evidence	Comments
Post-operative blood transfusion	85 of 321	166 of 429	RR 0.54 (0.35, 0.85)	78%	p<0.0001	750 [16-19, 32-34]	Moderate	Serious imprecision
Post-operative haemoglobin	10.5 g/dl	10.0 g/dl	MD 0.81 (0.45, 1.18)	46%	p=0.10	638 [17-19, 32-34]	High	
Blood loss on 1 st post-operative day	467mls	780mls	MD -341 (-672, -9.87)	100%	p<0.0001	197 [17, 31, 34]	Low	Serious inconsistency & serious imprecision
Peri-operative blood loss	415mls	568mls	MD -190 (-495, 115)	91%	p<0.0001	249 [16, 32, 34]	Low	Serious inconsistency & serious imprecision
Length of hospital stay	16.4 days	16.1 days	MD 0.26 (-4.05, 4.56)	77%	p=0.04	338 [19, 34]	Very low	Serious risk of bias, serious inconsistency & serious imprecision
Post-operative complications: 30 day mortality	9 of 206	11 of 314	RR 1.33 (0.53, 3.34)	0%	p=0.48	520 [16,19, 32, 34]	Moderate	Serious risk of bias
Post-operative complications: Stroke	2 of 110	1 of 112	RR 1.49 (0.24, 9.25)	0%	p=0.60	222 [16, 17, 32]	Low	Very serious imprecision
Post-operative complications: Thromboembolic events	16 of 289	10 of 394	RD 0.01 (-0.03, 0.05) *	68%	p=0.007	683 [16-19, 32, 31]	Low	serious inconsistency & serious imprecision
Post-operative complications: Pulmonary embolus	0 of 205	0 of 207	RD 0.00 (-0.02, 0.02) *	0%	p=1.00	412 [16-18, 32, 33]	Low	Very serious imprecision
Post-operative complications: DVT	10 of 172	4 of 168	RD 0.01 (-0.03, 0.04) *	43%	p=0.13	412 [16-18, 32, 33]	Low	Serious inconsistency & serious imprecision

526 Abbreviations: GRADE = Grading of Recommendations Assessment, Development and Evaluation;

527 CI =Confidence interval; RR =Relative risk; RD = Risk difference; MD = Mean difference. * risk difference calculated given zero-events were reported in some

528 studies.

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Table 3. Subgroup & Sensitivity analysis

Subgroup Analysis	Variable [Studies]	Transfusion	Post-operative haemoglobin	Day 1 post-operative blood loss	Peri-operative blood loss	Total Length of Hospital Stay	Thromboembolic events	30 day mortality	90 day mortality	PE	DVT	Stroke
Age	≥76 [16,19,32]	RR 0.67 (0.37, 1.22); I ² : 84%; Inconsistency Chi ² p=0.002; N=453 *	MD 0.50 (0.10, 0.89); I ² : 0%; Inconsistency Chi ² p=0.87; N=341		MD -47.6 (- 127, 31.5); I ² : 0%; Inconsistency Chi ² p=0.97; N=182 *		RD 0.00 (-0.07, 0.08); I ² : 69%; Inconsistency Chi ² p=0.04; N=453	RR 1.61 (0.64, 4.03); I ² : 0%; Inconsistency Chi ² p=0.41; N=453		RD 0.00 (- 0.03, 0.03); I ² : 0%; Inconsistency Chi ² p=1.00; N=182	RD 0.01 (- 0.06, 0.07); I ² : 9%; Inconsistency Chi ² p=0.29; N=182	RD 0.04 (- 0.04, 0.04); I ² : 0%; Inconsistency Chi ² p=0.32; N=182
	≤75 [17,18,33,34]	RR 0.48 (0.33, 0.72); I ² : 10%; Inconsistency Chi ² p=0.35; N=297	MD 1.03 (0.46, 1.60); I ² : 64%; Inconsistency Chi ² p=0.0004; N=297				RD 0.03 (-0.06, 0.12); I ² : 84%; Inconsistency Chi ² p=0.002; N=230					
BMI	≤40 [16,17,32,34]	RR 0.73 (0.49, 1.11); I ² : 68%; Inconsistency Chi ² p=0.02; N=289 *	MD 1.34 (0.76, 1.93); I ² : 0%; Inconsistency Chi ² p=0.79; N=179	MD: -461 (- 478, -444); I ² : 0%; Inconsistency Chi ² p=0.43; N=107			RD 0.08 (-0.10, 0.26); I ² : 82%; Inconsistency Chi ² p=0.003; N=222	RR 2.26 (0.48, 10.63); I ² : 0%; Inconsistency Chi ² p=0.42; N=247		RD 0.00 (- 0.03, 0.03); I ² : 0%; Inconsistency Chi ² p=1.00; N=222	RD 0.04 (- 0.02, 0.11); I ² : 65%; Inconsistency Chi ² p=0.20; N=222	
	>40											
Hip fracture type	Intracapsular [17,19]											
	Extracapsular [18,32]	RR 0.67 (0.24, 1.87); I ² : 88%; Inconsistency Chi ² p=0.004; N=172 *	MD 1.40 (- 0.79, 2.01); I ² : 0%; Inconsistency Chi ² p=0.85; N=212				RD -0.02 (-0.07, 0.04); I ² : 40%; Inconsistency Chi ² p=0.20; N=172			RD 0.00 (- 0.03, 0.03); I ² : 0%; Inconsistency Chi ² p=1.00; N=172	RD -0.01 (- 0.05, 0.03); I ² : 0%; Inconsistency Chi ² p=0.49; N=172	

Subgroup Analysis	Variable [Studies]	Transfusion	Post-operative haemoglobin	Total post-operative blood loss	Peri-operative blood loss	Total Length of Hospital Stay	Thromboembolic events	30 day mortality	90 day mortality	PE	DVT	Stroke
Vijay et al. 2013 removed	[16-19,32,34]	RR 0.58 (0.36, 0.92); I ² : 78%; Inconsistency Chi ² p=0.0003; N=660	MD 1.01 (0.50, 1.51); I ² : 43%; Inconsistency Chi ² p=0.14; N=548	MD: -461 (-478, -444); I ² : 0%; Inconsistency Chi ² p=0.43; N=107			RD 0.02 (-0.04, 0.08); I ² : 75%; Inconsistency Chi ² p=0.0003; N=593			RD 0.02 (-0.02, 0.02); I ² : 0%; Inconsistency Chi ² p=1.00; N=322	RD 0.03 (-0.02, 0.08); I ² : 58%; Inconsistency Chi ² p=0.07; N=322	
Lee et al. 2015 removed	[16-18,32-34]	RR 0.60 (0.39, 0.92); I ² : 76%; Inconsistency Chi ² p=0.001; N=479	MD 1.00 (0.47, 1.54); I ² : 53%; Inconsistency Chi ² p=0.08; N=369				RD 0.02 (-0.04, 0.09); I ² : 77%; Inconsistency Chi ² p=0.001; N=412		RR 2.26 (0.48, 10.63); I ² : 0%; Inconsistency Chi ² p=0.42; N=479			

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Abbreviations: CI = confidence intervals; I² = inconsistency value; N = number of cases; RR = Risk ratio; RD = risk difference (calculated given zero-events were reported in some studies). * denotes result that has ceased to become statistically significant after subgroup analysis.

534 **Supplementary Table 1.** Search strategy

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1. Tranexamic acid
2. hip fracture
3. femoral fracture
4. neck of femur
5. extracapsular
6. intracapsular
7. subcapital
8. transcervical
9. basicervical
10. intertrochanteric
11. subtrochanteric
12. hemiarthroplasty
13. total hip arthroplasty
14. sliding hip screw
15. dynamic hip screw
16. intramedullary nail
17. femoral nail
18. cannulated screws
19. open reduction internal fixation
20. OR/1-11
21. OR/12-19
22. AND/1,20,21

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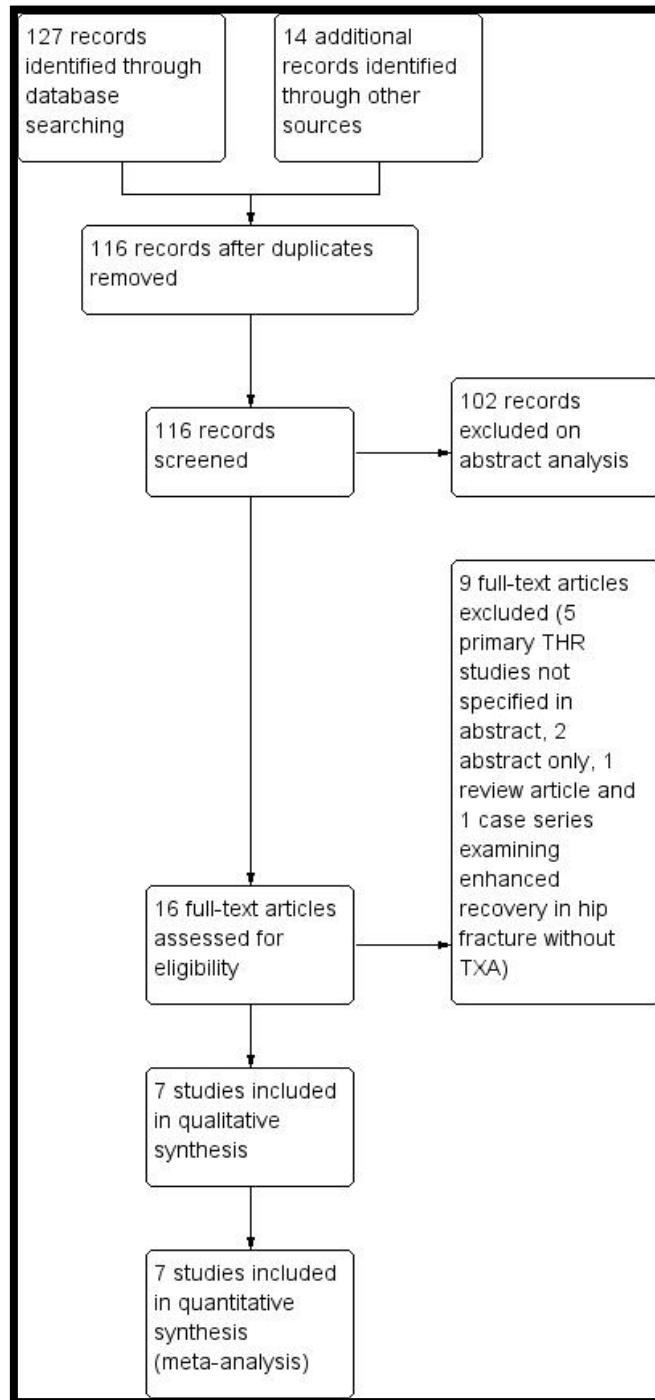
Supplementary table 2. Risk of bias assessment for individual studies

<i>RCT Studies</i>	Random sequence generation	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Other bias explanation
Emara et al 2014 [17]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	High risk	Low risk	
Mohib et al 2015 [18]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Sadeghi et al 2007 [34]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	
Vijay et al 2013 [33]	High risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk	unclear frequency of distal or proximal femoral fracture
Zufferey et al 2010 [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Tengberg et al 2015 [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Significant baseline differences in treatment groups
<i>Observational studies</i>	Bias due to confounding	Bias in participant selection	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Lee et al 2015 [19]	Serious risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk	Moderate risk	Serious risk

547 Risk of bias assessment was performed using the Cochrane Collaboration's risk of bias tool for RCT's. Each domain was classified as either unclear, low or high risk. The Risk
548 of Bias in non-randomised studies – of interventions (ROBINS-I) tool was used for observational studies. Each domain was classified as low risk, moderate risk, serious risk,
549 and critical risk or not interpretable. An overall bias assessment was then made using the same scale.

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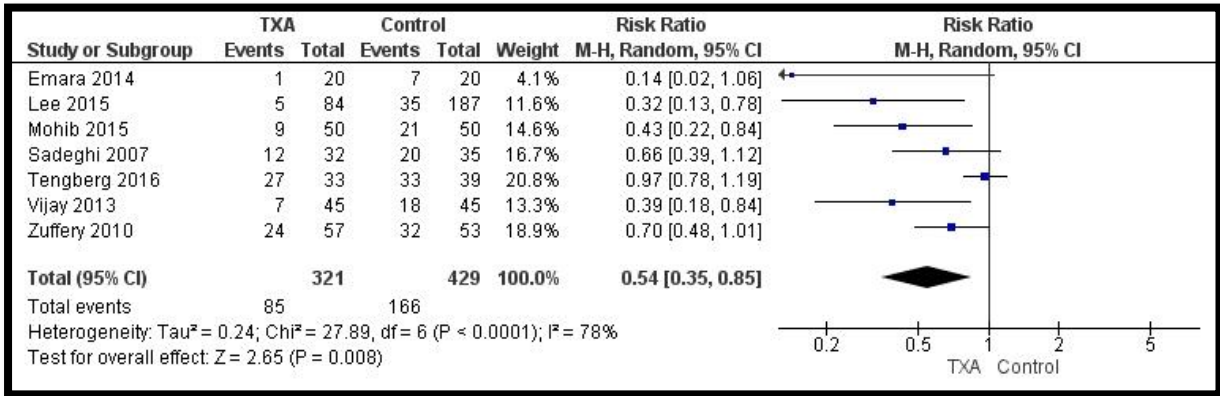
551 **Figure 1.** Flow diagram depicting the study selection process
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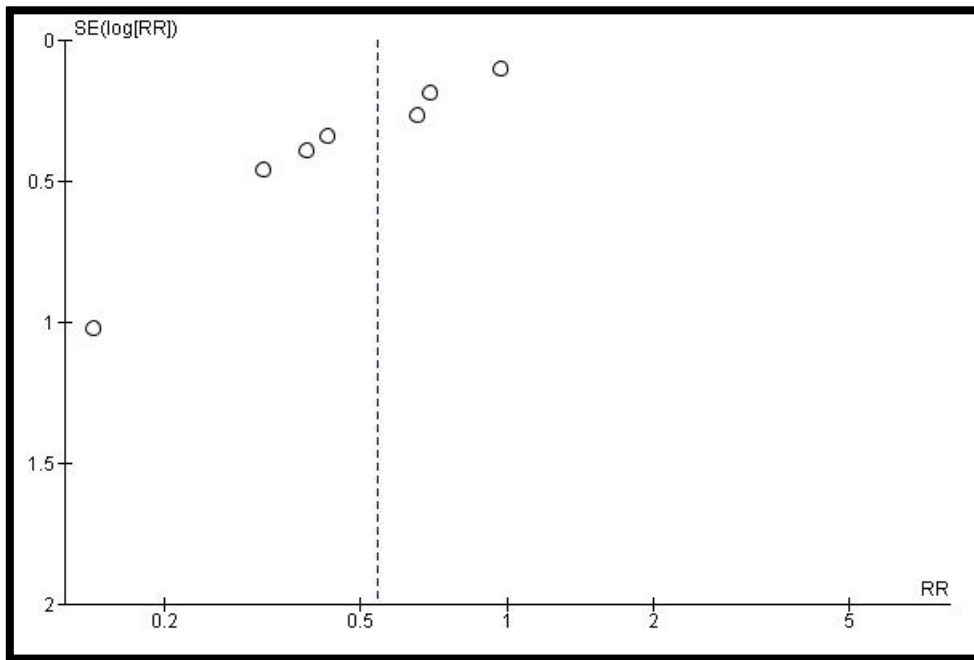
Figure 2. Forest-plot of TXA versus control for requirement for blood transfusion



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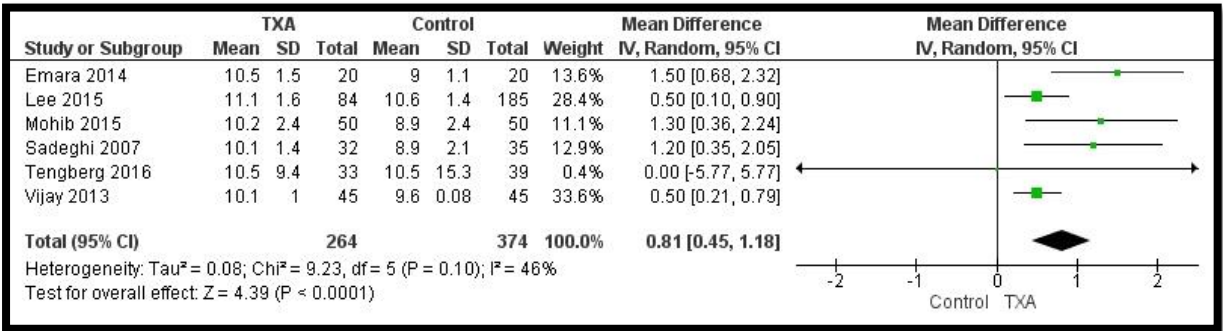
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561 **Figure 3.** Funnel plot of TXA versus control for requirement for blood transfusion.
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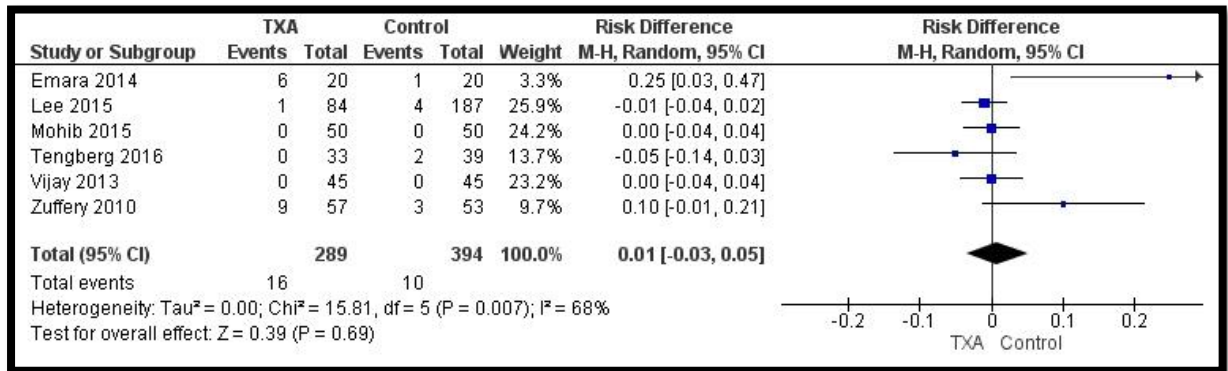
565 **Figure 4.** Forest-plot of TXA versus control for post-operative haemoglobin
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569 **Figure 5.** Forest-plot of TXA versus control for thromboembolic events
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