We conducted a systematic review and meta-analysis of randomised controlled trials evaluating the effect of tranexamic acid (TXA) upon blood loss and transfusion in primary total knee replacement. The review used the generic evaluation tool designed by the Cochrane Bone, Joint and Muscle Trauma Group. A total of 19 trials were eligible: 18 used intravenous administration, one also evaluated oral dosing and one trial evaluated topical use. TXA led to a significant reduction in the proportion of patients requiring blood transfusion (risk ratio (RR) 2.56, 95% confidence interval (CI) 2.1 to 3.1, p < 0.001; heterogeneity I² = 75%; 14 trials, 824 patients). Using TXA also reduced total blood loss by a mean of 591 ml (95% CI 536 to 647, p < 0.001; I² = 78%; nine trials, 763 patients). The clinical interpretation of these findings is limited by substantial heterogeneity. However, subgroup analysis of high-dose (> 4 g) TXA showed a plausible consistent reduction in blood transfusion requirements (RR 5.33; 95% CI 2.44 to 11.65, p < 0.001; I² = 0%), a finding that should be confirmed by a further well-designed trial. The current evidence from trials does not support an increased risk of deep-vein thrombosis (13 trials, 801 patients) or pulmonary embolism (18 trials, 971 patients) due to TXA administration.

Since its introduction in the late 1960s, total knee replacement (TKR) has become one of the most common operations in orthopaedic practice. In 2008, 64 924 TKRs were performed in England and Wales,1 which may underestimate the actual number, as recording procedures in the National Joint Registry was not mandatory for that period.

Undergoing TKR may necessitate allogeneic blood transfusion2,3 and patients remain concerned about the potentially serious complications of transfusion, although serological screening has reduced the risk for viral infection.4,5 Allogeneic blood transfusion may be associated with other non-infectious complications, such as haemolysis, immunosuppression, transfusion-related acute lung injury and even death.6 Technologies to minimise the need for blood transfusion include the use of antifibrinolytic drugs such as aprotinin, tranexamic acid (TXA) and aminocaproic acid (EACA).7,8 However, the use of these drugs remains controversial and in many centres is not routine.

The purpose of this review was to investigate the effect of TXA on peri-operative blood loss and blood transfusion after TKR, as well as changes in adverse clinical outcomes such as re-operation or increases in complications such as deep-vein thrombosis (DVT), pulmonary embolism (PE), infection, ischaemic heart disease and mortality.

Materials and Methods
The review was conducted in accordance with guidelines described in the Cochrane handbook for systematic review and meta-analysis of interventions.9 We confined this review to the examination of randomised controlled trials (RCTs) in adult patients who underwent a primary TKR regardless of the type or size of prosthesis used. Synchronous or sequential bilateral primary TKR and revision TKR were excluded.

The intervention considered was the use of TXA. Control groups could be a placebo or no treatment. Administration of study drugs could be by intravenous, oral or topical routes. The primary outcome measure in the review was the proportion of patients who were transfused with allogeneic blood, autologous blood or both. The secondary outcome measures were the number of units transfused; the amount of peri-operative blood loss; length of hospital stay; functional knee outcome measures; general quality of life outcome measures; and complications such as death, non-fatal myocardial infarction, stroke, DVT, PE, any thrombosis, renal failure and re-operation due to bleeding.
Search methods. The following exploded Medical Subjects Heading (MeSH) terms were used for the initial literature search: Antifibrinolytics, Tranexamic acid, Cyklokapron, Aprotinin, Trasylol, E-Aminocaproic acid and Amicar. Text searches of key fields were included. A MEDLINE search was then refined to clinical trials and RCTs in human adults. The search was extended to other databases, namely EMBASE, the Cochrane Controlled Trials Register, HealthSTAR and CINAHL, Google and Google Scholar for trials of antifibrinolytics and TKR published in any language from 1966 to December 2007. The bibliographies of retrieved trials and other relevant publications, including reviews and meta-analyses, were examined for additional articles. The following websites were searched to identify unpublished and ongoing studies: Current Controlled Trials (www.controlled-trials.com); Centre Watch (www.centerwatch.com); Trials Central (www.trialscentral.org/ClinicalTrials.aspx); The United Kingdom National Research Register (www.nrr.nhs.uk). The Journal of Bone and Joint Surgery (British and American volumes) and the American Academy of Orthopaedic Surgeons were searched manually.

Data collection and analysis. Study selection. Two authors (SA, JB) independently applied the search strategy to select references from the above-mentioned databases. The article titles and abstracts were then reviewed independently by two authors (SA, MS). When there was an issue requiring clarity, the full article was retrieved for further scrutiny. The two authors independently assessed each full study report to see whether it met the reviewers’ inclusion criteria. Where necessary, authors were contacted for more information and clarification of data. If there was a disagreement regarding inclusion, the senior authors (AN, JMM) would compare findings, and when no consensus could be reached the study was excluded.

Assessment of methodological quality of included studies. The review authors used a modification of the generic evaluation tool used by the Cochrane Bone, Joint and Muscle Trauma Group.10 Two authors (SA, MS) assessed the methodological quality of each study. Disagreement was resolved by consensus between the senior authors (AN, JMM). The total quality assessment score (QAS) was reported for each study to give an overall impression of the study, but was not used to weight studies in meta-analyses.

Data extraction and management. A data extraction form was designed and agreed by the review team. A pilot test using five articles was performed to ensure the form’s consistency. The form was then refined accordingly. Initially, three authors (SA, MS and PS) extracted data independently and reviewed the extracted data jointly. Disagreements were resolved by consensus or consultation with the senior reviewers (AN, JMM). If necessary, authors of individual trials were contacted directly to provide clarification.

Measures of treatment effect. Continuous data were recorded as mean, standard deviation (SD) and group size for each trial arm, with treatment effect being reported as the mean difference. We used the weighted mean difference to summarise findings across the trials, as outcomes were measured consistently in the trials (without recourse to using standardised mean differences). Dichotomous data were expressed as proportions or risks, with the treatment effect reported as a relative risk or risk ratio (RR) with 95% confidence intervals (CI). Statistical significance was set at p < 0.05.

Subgroup analysis. The following subgroup analyses were prospectively planned: 1) diagnosis (rheumatoid arthritis vs osteoarthritis); 2) gender (male vs female); 3) cementing technique (cemented vs uncemented); 4) use of transfusion protocols; and 5) dose and mode of administration. Data on the first three subgroups were lacking and it was not possible to conduct these analyses.

Data considerations. Missing data were sought from the authors. Where this was not possible or data were missing through loss to follow-up, intention-to-treat principles were used. No attempts at imputation were made. Trials with multiple arms (using different doses of TXA) were conflated to a single comparator of TXA or placebo. Review Manager (RevMan 5, The Nordic Cochrane Centre, Copenhagen, Denmark), was used to present the study findings and combine the estimates of the effect of treatments. Summary estimates of the overall effect of treatment are provided in the form of a forest plot. The Mantel-Haenszel (M-H) method was used to combine studies using a fixed effects model. The presence of statistical heterogeneity was assessed through Q and I² statistics, a value > 50% being considered substantial heterogeneity.

Results

Description of studies. A total of 323 citations were identified as potentially relevant studies. Subsequent scrutiny led to the exclusion of 290 of these. Full publications were obtained for 33 citations. These were assessed, and seven further citations were excluded11-17 (Fig. 1).

The remaining 26 citations referred to 19 placebo-controlled RCTs, 18 of which involved intravenous administration of TXA. One study18 also evaluated oral administration and another examined topical application of TXA.19 A total of 18 trials were placebo-controlled RCTs and one compared TXA with normo-volaemic haemodilution (NVHD).20 Most trials were small, with participant numbers ranging from 24 to 136 (Table I). However, trials were relatively well designed and QAS were generally high. The mode was 24 (the highest possible score) and the range was 14 to 24. Five studies scored < 20.

Different doses and modes of delivery were used. The dose ranged from approximately 700 mg to 10 500 mg.21-22 All studies used low-molecular-weight heparin (LMWH) as DVT prophylaxis, apart from two studies,23,24 the former of which did not use any chemical prophylaxis and the latter used aspirin. The transfusion trigger was an important design consideration, and all trials apart from one23 clearly specified their transfusion triggers (Table I).
Effects of intravenous TXA. Blood transfusion. In 14 trials (824 participants) usable data were available on the effect of TXA on blood transfusion after TKR.\textsuperscript{3,18,21,22,24-33} TXA led to a reduction in the proportion of patients who required blood transfusion (RR 2.56; 95% CI 2.10 to 3.11; p < 0.001) (Fig. 2). Although trials consistently suggested benefit, there was significant heterogeneity between findings (Q p < 0.001; I\textsuperscript{2} = 75%).

There are various ways to measure of the influence of each study on the overall meta-analytical findings. In our review, we used standard error as a measure for study size, as recommended by Sterne and Egger.\textsuperscript{34} The funnel plot (Fig. 3) shows trials scattered asymmetrically around the pooled RR, with small trials having greater effect. This might be due to smaller trials of lower quality tending to overestimate the true effect, although there was no evidence of significantly lower-quality scores in smaller trials. The funnel plot might also reflect clinical or methodological variations between studies. The pattern suggests potential publication bias, where small negative trials are less likely to be published than small positive ones. This is partially explored within the planned subgroup analyses.

Amount of blood transfusion. In 13 trials including a total of 791 participants, usable data on the amount of blood transfused in units were available, although these data do not capture variations in use between patients. Crude pooled data indicate a fourfold rise in the number of units transfused when TXA is not used.

Blood loss. In 12 trials (769 participants) usable data on blood loss were provided. Studies measured external blood loss as the volume contained in the drain, total blood loss, or a combination of both.

Post-operative blood loss. In eight trials data on post-operative blood loss (draining) were available.\textsuperscript{18,23,25-27,29,35,36} Using TXA significantly reduced post-operative blood loss (mean difference 245 ml, 95% CI 213 to 278; p < 0.001). However, there was significant heterogeneity in the finding (Q p < 0.001; I\textsuperscript{2} = 89%) (Fig. 4). The reduction in blood loss contained in the drain is a statistically robust finding, but the magnitude is poorly described by the fixed effect model owing to heterogeneity among the trial findings.

Total blood loss. A total of nine trials provided data on the effect of TXA on total blood loss. TXA had a more
A profound effect on total blood loss than blood loss recorded in the drain: a mean of 591 ml (95% CI 536 to 647; p < 0.001). Again, there was significant heterogeneity in the finding (Q p < 0.001; I² = 78%) (Fig. 5).

### Table I. Characteristics of included studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number</th>
<th>Intervention*</th>
<th>BT† trigger</th>
<th>Thromboprophylaxis‡</th>
<th>QAS§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>95</td>
<td>1) TXA 10 mg/kg IV then 1 mg/kg/h infusion for 6 h. 2) Control: normal saline</td>
<td>Hb &lt; 8 g/l</td>
<td>LMWH</td>
<td>22</td>
</tr>
<tr>
<td>Benoni and Fredin&lt;sup&gt;24&lt;/sup&gt;</td>
<td>86</td>
<td>1) TXA 10 mg/kg IV before tourniquet deflation then 10 mg/kg after 3 h (an extra dose of 10 mg/kg given if blood loss &gt; 500 ml within 1 h or 1000 ml within 4 h) 2) Control: normal saline</td>
<td>Hb &lt; 85 g/l to 100 g/l</td>
<td>LMWH</td>
<td>22</td>
</tr>
<tr>
<td>Camarasa et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>136</td>
<td>1) TXA 10 mg/kg IV before tourniquet deflation then 10 mg/kg after 3 h 2) EACA 100 mg/kg then 3 g/h for 3 h 3) Control: normal saline</td>
<td>Hb &lt; 80 g/l</td>
<td>LMWH</td>
<td>24</td>
</tr>
<tr>
<td>Ellis et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>30</td>
<td>1) TXA 15 mg/kg IV before tourniquet deflation then 10 mg/kg/h infusion for 12 h 2) Desmopressin 0.3 mcg/kg IV before tourniquet deflation then IV saline over 12 h 3) Control: normal saline</td>
<td>Hct &lt; 27%</td>
<td>LMWH</td>
<td>22</td>
</tr>
<tr>
<td>Engel et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>36</td>
<td>1) TXA 15 mg/kg IV before tourniquet deflation then 10 mg/kg after 3 h 2) Aprotinin 1 million units before tourniquet deflation then 0.5 million units/h for 4 h 3) Control: None</td>
<td>Hb &lt; 100 g/l</td>
<td>LMWH</td>
<td>18</td>
</tr>
<tr>
<td>Good et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>51</td>
<td>1) TXA 10 mg/kg IV before tourniquet deflation then 10 mg/kg after 3 h 2) Control: normal saline</td>
<td>Hb &lt; 90 g/l</td>
<td>LMWH</td>
<td>24</td>
</tr>
<tr>
<td>Hiippala et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>28</td>
<td>1) TXA 15 mg/kg IV before tourniquet deflation 2) Control: normal saline</td>
<td>Hb &lt; 100 g/l</td>
<td>LMWH</td>
<td>19</td>
</tr>
<tr>
<td>Hiippala et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>77</td>
<td>1) TXA 15 mg/kg IV before tourniquet deflation then two additional doses of 10 mg/kg after 3 to 4 h and 6 to 7 h 2) Control: normal saline</td>
<td>Hb &lt; 100 g/l</td>
<td>LMWH</td>
<td>22</td>
</tr>
<tr>
<td>Ido et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>43</td>
<td>1) TXA 1 g IV before tourniquet deflation then 1 g after 3 h 2) Control: None</td>
<td>None</td>
<td>None</td>
<td>14</td>
</tr>
<tr>
<td>Kakar et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>24</td>
<td>1) TXA 10 mg/kg IV before tourniquet inflation and 1 mg/kg/h until wound closure 2) Control: normal saline</td>
<td>Hb &lt; 8 g/l</td>
<td>LMWH</td>
<td>22</td>
</tr>
<tr>
<td>Jansen et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>42</td>
<td>1) TXA 15 mg/kg IV before surgery then 15 mg/kg 8 hourly for 3 days 2) Control: normal saline</td>
<td>PCV &lt; 26%</td>
<td>LMWH</td>
<td>24</td>
</tr>
<tr>
<td>Molloy et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>150</td>
<td>1) TXA 500 mg IV before tourniquet deflation and 500 mg after 3 h 2) Fibrin 10 ml spray 3) Control: None</td>
<td>Hct &lt; 26%</td>
<td>Aspirin</td>
<td>22</td>
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<tr>
<td>Orpen et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>29</td>
<td>1) TXA 15 mg/kg at cementing 2) Control: normal saline</td>
<td>Hb &lt; 100 g/l</td>
<td>LMWH</td>
<td>24</td>
</tr>
<tr>
<td>Tanaka et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>99</td>
<td>1) Pre-operatively: TXA 20 mg/kg 10 min before surgery and saline 10 min before tourniquet deflation 2) Intra-operatively: Saline 10 min before surgery and TXA 20 mg/kg 10 min before tourniquet deflation 3) Peri-operatively: TXA 10 mg/kg 10 min before surgery and 10 mg/kg 10 min before tourniquet deflation 4) Control: normal saline</td>
<td>Hb &lt; 70 g/l to 100 g/l</td>
<td>None</td>
<td>24</td>
</tr>
<tr>
<td>Veien et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>30</td>
<td>1) TXA 10 mg/kg IV before tourniquet deflation then 10 mg/kg after 3 h 2) Control: None</td>
<td>Hct &lt; 28%</td>
<td>LMWH</td>
<td>22</td>
</tr>
<tr>
<td>Wong et al&lt;sup&gt;19&lt;/sup&gt;</td>
<td>99</td>
<td>1) TXA 3 g topical 2) TXA 1.5 g topical 3) Control: normal saline</td>
<td>Hb &lt; 80 g/l to 100 g/l</td>
<td>LMWH</td>
<td>23</td>
</tr>
<tr>
<td>Zhang, Gao and Yi&lt;sup&gt;36&lt;/sup&gt;</td>
<td>102</td>
<td>1) TXA 1 g IV before tourniquet deflation then 1 g after 3 h 2) Control: normal saline</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zohar et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>80</td>
<td>1) TXA 15 mg/kg IV before tourniquet deflation then 10 mg/kg/h infusion for 12 h 2) Normovolemic haemodilution group bleeds to target 26%, IV volume maintained with Ringer's lactate and all the autologous blood was transfused 3) Control: None</td>
<td>Hct &lt; 27%</td>
<td>LMWH</td>
<td>18</td>
</tr>
<tr>
<td>Zohar et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>80</td>
<td>1) TXA long 15 mg/kg IV before tourniquet deflation then 10 mg/kg/h infusion for 12 h 2) TXA short as above but infusion for 2h then oral 1 g at 6 h and 12 h 3) TXA oral, 1 g 6 h pre-operatively then 1 g every 6 h for 18 h 4) Control: None</td>
<td>Hct &lt; 28%</td>
<td>LMWH</td>
<td>16</td>
</tr>
</tbody>
</table>

* TXA, tranexamic acid; IV, intravenous  
† BT, blood transfusion  
‡ LMWH, low-molecular-weight heparin; NA, not available  
§ QAS, quality assessment score
Length of stay. Two studies including 60 participants presented data on length of stay. Patients receiving TXA spent a mean of 0.76 days (95% CI 0.32 to 1.85) less in hospital, but this finding was not statistically significant (p = 0.17).

Deep-vein thrombosis. In all, 13 trials including 801 patients provided useful data on DVT (Fig. 6). The use of TXA was not associated with an increased risk of DVT (p = 0.98). There was no evidence of heterogeneity between trials (Q p = 0.98; I² = 0%). A similar finding was shown by Henry et al and Zufferey et al.

Pulmonary embolism. In all, 19 trials including 971 patients reported five cases of pulmonary embolism (PE). There was one PE in a patient receiving TXA and four in the control group, but the finding was not statistically significant (p = 0.5).
Mortality. Although seldom reported by trials, there were two reported deaths. Hiippala et al.\textsuperscript{3} reported one death caused by PE in the control group. Camarasa et al.\textsuperscript{27} reported one death in a patient who had received TXA and died six months later from an unrelated condition (author communication). However, there was no statistical significance in the risk of mortality among the study groups ($p = 0.89$).

Subgroup analysis. There was significant heterogeneity in the study findings. Subgroup analysis according to transfusion protocol (haemoglobin level, haematocrit or packed cell volume triggers), mode of administration or timing of administration did not adequately explain the variation in outcomes. However, subgroup analysis exploring the dose of TXA and blood transfusion rate was informative. A larger, homogenous treatment effect was found in trials that used higher doses (> 4000 mg) of TXA (RR 5.33; 95% CI 2.44 to 11.65, $p < 0.001$; $I^2 = 0\%$); a smaller, heterogeneous effect was apparent for lower doses (Fig. 7).

**Oral and topical TXA administration.** Zohar\textsuperscript{18} compared three different modes of TXA administration with placebo in 80 patients (Table I). The first group received only intravenous TXA, the second group intravenous and oral TXA, and the third group received oral TXA only. Wong et al.\textsuperscript{19} compared topical TXA with placebo using a dose of either 1.5 g or 3 g TXA. Both oral and topical routes showed an overall reduction of blood loss and transfusion rates in the TXA groups.

**Discussion**

A recent study showed that TXA reduces both blood loss and transfusion in total hip replacement without apparently increasing the risk of harm from adverse events such as DVT or PE blood.\textsuperscript{37} This study showed that intravenously administered TXA, used as a single treatment modality, produces similar effects in total knee replacement.\textsuperscript{37} These findings help to resolve some controversy, possibly originating from individual small trials, other
In trials, which would be adequate only to find changes of about 3% in DVT or PE rates. To find an increase in risk of 1%, which clinicians might consider unacceptable, would require trials with about 5000 patients.

The review identified only one small trial each of orally and topically administered TXA; consequently, there is inadequate evidence to inform the evidence-based use of these modalities.

The review identified a number of randomised and non-randomised studies that were not included but which nonetheless correlated with our findings. Zohar et al\textsuperscript{20} compared intravenous TXA with normovolaemic haemodilution, and Zohar et al\textsuperscript{17} compared intravenous TXA with desmopressin. Both studies showed that TXA is a superior blood sparing agent.

There are other meta-analyses that studied the relationship between TXA and blood loss and/or transfusion after TKR. Zufferey et al\textsuperscript{8} analysed the effect of intravenous antifibrinolytics, including TXA, aprotinin and EACA, on blood transfusion in various orthopaedic procedures. Only studies with a transfusion protocol were included, which resulted in 11 studies of TXA only being analysed. Results on blood transfusion were similar to those of our study, especially when considering a multiple-dose regimen of TXA. However, the effect of TXA on blood loss was briefly discussed as part of ‘other efficacy endpoints’ and was evaluated as a single group under ‘peri-operative blood loss’, although blood loss was not clearly defined.

Ho and Ismail\textsuperscript{15} studied the effect of TXA on reducing blood transfusion after total hip replacement (THR) and TKR. In all, nine trials involving knee replacement were included in the analysis. Blood loss was again collectively
defined as ‘peri-operative blood loss’, despite including the results of total blood loss as well as post-operative blood loss under this definition when studies were analysed.

Kagoma et al., in a recent meta-analysis, reviewed the evidence for using TXA, EACA and aprotinin on total blood loss and transfusion rates in TKR and THR. Despite similar trends to our study, all three antifibrinolytics were either analysed as a single group or the effects of each of them were evaluated for both THR and TKR. There are two other small meta-analyses, one by Cid and Lozano39 published in 2005 with nine studies only, and another by Zhang et al40 published in 2009 with eight studies only. Both reached similar conclusions.

Comparing these published reviews, where standard deviations were not reported in the original studies but were imputed using varying formulae, resulted in discrepancies in the outcomes reported. We have only included studies where standard deviations for continuous outcomes were reported or obtained from authors.

There are several strengths of this meta-analysis. First, we conducted a rigorous literature search of RCTs, including publications in any language as well as unpublished abstracts. Second, the QAS was high for most of the studies included, which contributes to the validity of estimates and conclusions drawn from the meta-analysis. Third, careful subgroup analysis was conducted, which potentially addresses the heterogeneity in blood transfusion estimates between the studies. There are too many potentially confounding influences to provide a definitive understanding, but variations in dosing, measurement and mode of administration may be important.

Limitations of this meta-analysis include the lack of sufficient data to support our intention to analyse functional outcome or quality of life outcome measures. Trials included in our study were designed to assess efficacy as the primary outcome and were underpowered to assess the safety of TXA in TKR. However, pooled data in this review do not support the view that TXA increases the rate of adverse complications.
In conclusion, intravenous TXA significantly reduces peri-operative blood loss and blood transfusion requirements after TKR, without an apparent increase in harm. Findings from a subgroup of trials evaluating high-dose (> 4 g) TXA need to be confirmed by well-designed trials.

Supplementary material

Tables showing the quality assessment items and possible scores and the studies reporting the amount of blood transfusion are available with the electronic version of this article on our website http://www.jbis.org.uk.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References