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Do Antifibrinolytics Reduce Allogeneic Blood Transfusion in Orthopedic Surgery?

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Studies have shown that antifibrinolytic (aprotinin, tranexamic acid, or ε-aminocaproic acid) reduce blood loss in orthopedic surgery. However, most lacked sufficient power to evaluate the efficacy and safety on clinical outcomes. This meta-analysis aims to evaluate whether intravenous antifibrinolytics, when compared with placebo, reduce perioperative allogeneic erythrocyte transfusion requirement in adults undergoing orthopedic surgery and whether it might increase the risk of venous thromboembolism. From MEDLINE, EMBASE, and the Cochrane Controlled Trials Register, the authors identified 43 randomized controlled trials in total hip and knee arthroplasty, spine fusion, musculoskeletal sepsis, or tumor surgery performed to July 2005 (for aprotinin, 23 trials with 1,268 participants; tranexamic acid, 20 with 1,084; ε-aminocaproic acid, 4 with 171). Aprotinin and tranexamic acid reduced significantly the proportion of patients requiring allogeneic erythrocyte transfusion according to a transfusion protocol. The odds ratio was 0.43 (95% confidence interval, 0.28–0.64) for aprotinin and 0.17 (0.11–0.24) for tranexamic acid. Results suggest a dose–effect relation with tranexamic acid. ε-Aminocaproic acid was not efficacious. Unfortunately, data were too limited for any conclusions regarding safety. Although the results suggest that aprotinin and tranexamic acid significantly reduce allogeneic erythrocyte transfusion, further evaluation of safety is required before recommending the use of antifibrinolytics in orthopedic surgery.

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ORTHOPEDIC surgery may be associated with substantial blood loss requiring transfusion of erythrocytes. Transfusion of allogeneic erythrocytes is not free of adverse events and has been associated with transmission of infectious diseases, increased postoperative bacterial infection, immune sensitization, and transfusion-related acute lung injury.[1,2] Measures taken to allay concerns about the safety of blood transfusions have translated into the increasing cost of allogeneic blood units. Blood banks regularly undergo blood shortages. For these reasons, there is a need to reduce allogeneic blood transfusions. A number of effective interventions have been developed, such as preoperative autologous donation, cell salvage, or the use of erythropoietin.[3–5] Pharmacologic agents such as aprotinin, tranexamic acid, or ε-aminocaproic acid (EACA) could reduce perioperative blood loss by interfering with fibrinolysis.[6] A previous meta-analysis showed that aprotinin or tranexamic acid, compared with placebo, was protective in allogeneic erythrocyte transfusion without significantly increasing the risk of adverse effects, including thromboembolic events.[7] However, most of the trials included in this review were performed in cardiac surgery (88% of included trials). Since the publication of this review, numerous small trials have evaluated the use of antifibrinolytics in orthopedic surgery and have shown them to be effective at reducing blood loss. Unfortunately, they were underpowered to detect efficacy on more relevant clinical outcomes. Furthermore, there remains a concern that these agents may promote a hypercoagulable state in settings of surgery at high risk of venous thromboembolism, such as orthopedic surgery.[6] Therefore, using the techniques of meta-analysis, we studied whether the use of intravenous antifibrinolytics in orthopedic surgery, when compared with placebo, reduces the requirement for perioperative allogeneic erythrocyte transfusion in adults and whether it might increase the risk of venous thromboembolism.

Materials and Methods

Literature Search

An exhaustive literature search, both manual and computer assisted (MEDLINE, EMBASE, and Cochrane Con-

trolled Trials Register), was conducted to identify all randomized studies performed to the end of July 2005 comparing an intravenous prophylactic antifibrinolytic regimen (aprotinin, tranexamic acid, or EACA) with no treatment, placebo, or such regimen. Orthopedic surgery was defined as surgery for primary hip arthroplasty, primary knee arthroplasty, and major orthopedic procedures, which included revision or bilateral arthroplasty, spinal fusion or posterior spinal fixation, musculoskeletal sepsis, or musculoskeletal tumors. Only the key words *aprotinin*, *tranexamic acid*, and *ε-aminocaproic acid* were used. All identified articles were analyzed unless it was clear from the summary that the study was not performed in an orthopedic setting. There was no restriction on the language of the article. Abstracts of meetings were searched, and reference lists in reviews, studies, and previous meta-analyses were checked. Particular attention was paid to duplicate reports; when studies were published as an abstract and an original article, only the latter was considered. When more than one article was available from a single study, an attempt was made to extract the information required from all relevant publications.

Study Selection

From these articles, open-label and single- or double-blind randomized studies evaluating an antifibrinolytic agent were selected. Only studies with a control group, either untreated or treated with a placebo or another antifibrinolytic agent, were considered. Studies that included another method in addition to antifibrinolytic administration for reducing allogeneic blood transfusion were eligible for selection if this other method was used in both the active and control groups. To be selected, studies also had to have evaluated the efficacy and/or safety of the antifibrinolytic using at least one of the following endpoints: proportion of patients receiving at least one unit of allogeneic erythrocyte transfusion according to a transfusion protocol, proportion of patients receiving any kind of erythrocyte transfusion (*i.e.*, comprising allogeneic and/or preoperative autologous blood donation and/or cell salvage blood) according to a transfusion protocol, number of units of allogeneic blood transfused per patient according to a transfusion protocol, total volume of blood loss in milliliters (perioperative and postoperative), venous thromboembolism documented by an objective test (ultrasound, fibrinogen uptake test, or venography for deep venous thrombosis, ventilation–perfusion lung scanning, pulmonary angiography, or spiral computed tomography for pulmonary embolism), or arterial thrombosis (myocardial infarction, stroke, or limb ischemia).

To limit evaluation bias on transfusion criteria, it was considered necessary that selected studies had to have a transfusion protocol that defined at which point a transfusion of allogeneic and/or autologous erythrocytes was considered necessary. The protocol had to be identical across treatment arms within a study but could differ between studies. Trials that lacked or did not mention the use of a transfusion policy meeting these requirements were not considered for the analyses of the proportion of patients requiring erythrocyte transfusion. For example, no trials were selected where autologous blood was systematically reinfused, whatever the value of hemoglobin or the hematocrit.

Studies were excluded if they were not or were not clearly stated to have been randomized. Studies conducted in pediatric patients were also excluded. Dose-ranging studies without a control group given placebo or no treatment for comparison were excluded.

Predefined data from individual trials were initially extracted independently by two authors (F.M., P.Z.). In the event of a discrepancy with regard to either study selection or data extraction, the decision of a third author (S.M.) was final. The authors of the selected trials were contacted to confirm the accuracy of the extracted data and/or to supply missing information or clarification. When more than one active treatment group was compared with a single control group (*e.g.*, dose-ranging studies), the experimental groups were combined and then compared collectively with the control group.**

Statistical Analysis

The results from each trial were summarized on an intention-to-treat basis.

For binary outcomes such as the proportion of patients requiring allogeneic or any kind of erythrocyte transfusion or having postoperative venous thromboembolism, the meta-analyses were performed using various methods, namely, logarithm of the relative risk, logarithm of the odds ratio (OR), and rate difference. Association and heterogeneity tests were performed for each meta-analysis. A value of $P \leq 0.05$ in an association test and a value of $P \leq 0.10$ in a heterogeneity test were considered to be statistically significant. For each binary outcome, the method with the lowest heterogeneity is presented. In the absence of a clear explanation for heterogeneity, a random-effects model was planned. The results of these meta-analyses are presented with 95% confidence intervals. The meta-analysis was performed according to the drug (aprotinin, tranexamic acid, and EACA).

Sensitivity analyses were conducted to explore the robustness of the results. We first examined the effect of the study design by separating double-blind studies (primary analysis) from open-label studies (secondary analysis). To identify any study that may have exerted a disproportionate influence on the summary treatment effect, we deleted studies one at a time. When trials

** The Cochrane Collaboration open learning material: Meta-analysis of continuous data. Available at: http://www.cochrane-net.org/openlearning/HTML/modA1.htm. Accessed June 24, 2006.

presented a per-protocol analysis, a sensitivity analysis imputed the missing data by choosing the worst-case scenario for treatment. We checked for publication bias using the funnel plot technique.[8]

In the absence of major bias suggesting that the study quality of one or a subgroup of studies may have exaggerated the treatment effect, all studies were combined. Then, exploratory analyses were performed according to the type of surgery (primary hip or knee arthroplasty *vs.* major orthopedic surgery), the type of anesthesia, the dose regimen, and the number of bolus doses (single *vs.* continuous infusion or repeated boluses).

To assess the transfusion risk with the use of antifibrinolytics according to the underlying transfusion risk, *i.e.*, how the transfusion rate in the antifibrinolytic group varies when the rate in the control group increases, an effect model analysis was performed using a weighted linear regression.[9] The transfusion risk was defined as the proportion of patients receiving at least one unit of allogeneic erythrocyte transfusion according to a transfusion protocol within a trial. A value of $P < 0.05$ was considered as statistically significant when testing the slope of the linear regression.

For continuous outcomes such as number of units of allogeneic blood transfused per patient and total volume of blood loss in milliliters, the meta-analyses were performed using a random-effects model of the standardized mean difference. The mean number of units of allogeneic blood transfused per patient or total volume of blood loss of each group (treated and control group), and the corresponding SDs were collected for each trial. For each continuous outcome, standardized mean difference was calculated as the mean difference between groups divided by the common within-group SD and adjusted according to the weight of individual studies. Methods for the meta-analysis of continuous data assume that data are normally distributed. It follows that conclusions based on outcomes that are not normally distributed may be erroneous. Measures were taken to avoid this: When analyzing continuous outcomes, trials were not considered if they did not summarize normal data, *i.e.*, trials having skewed distribution with an SD larger than the mean. When median and range were reported rather than mean and SD, assumptions were made to estimate these values: The median was designated as the mean, and the SD was estimated as $(0.95 \times \text{range})/4$. The results of the standardized mean difference from these meta-analyses are presented with 95% confidence intervals. A value of $P \leq 0.05$ in an association test was considered to be statistically significant.

Meta-analyses were performed using the software Comprehensive Meta Analysis (Biostat, Englewood, NJ), whereas linear regressions were calculated using the software S-PLUS 2000 (MathSoft, Seattle, WA).

Results

Study Selection

The literature search identified 762 studies, 63 of which remained potentially relevant after reading through titles and abstracts. Articles were excluded for several reasons: uncertainty regarding randomization (2 articles),[10,11] lack of a control group (3),[12–14] duplication (3),[15–17] subgroup analysis of previous study (1),[18] antifibrinolytic not administered intravenously (1),[19] conducted in pediatric patients (5).[20–24] All trialists were contacted; 23 confirmed the accuracy of the extracted data or supplied missing information (see acknowledgments). However, 5 studies were further withdrawn because data were not available on any outcome.[25–29] Therefore, 43 trials were selected for analysis: 23 with aprotinin,[30–52] 20 with tranexamic acid,[47,53–71] and 4 with EACA[48,50,52,72]; 4 trials studied two different antifibrinolytics compared with placebo.[47,48,50,52]

Study Design

Tables 1 to 3 show the design of the studies.

Aprotinin. Twenty-three studies using aprotinin and comprising a total of 1,268 patients were selected.[30–52] Trials were small; only 2 randomized more than 100 patients. Nine involved major orthopedic surgery (revision or bilateral arthroplasty, spinal fusion or posterior spinal fixation, musculoskeletal sepsis, or musculoskeletal tumor surgery), 12 involved primary hip arthroplasty, and 2 involved knee arthroplasty. In each study, patients received a loading dose of aprotinin before surgery, which was followed by continuous infusion or repeated boluses in 17 studies. The mean total perioperative dose of aprotinin was variable but was lower than 4 million kallikrein inactivator units in all except 2 studies.[49,50] Fifteen studies reported the use of a transfusion protocol but did not comment on the extent to which these protocols were followed. The transfusion trigger threshold differed between trials. Prophylaxis of deep venous thrombosis, where described, varied between studies according to the country and the year of the study. Venous thrombosis screening was done by an objective test in 8 studies.[31,34,35,39,45,49,50,52] Type of anesthesia varied between trails. Finally, 14 of the 22 studies were double-blind, and one open study reported a proper generation of the treatment allocation sequences (random number–generated table).[48]

Tranexamic Acid

Twenty studies using tranexamic acid and comprising a total of 1,084 patients were selected.[47,53–71] As with aprotinin, trials were small, and only one randomized more than 100 patients. Trials only involved primary hip or knee arthroplasty (10 and 11, respectively). Mean total perioperative dose of tranexamic acid was variable and ranged from 10 to 135 mg/kg. In hip arthroplasty,

Table 1. Aprotinin *versus* Placebo or No Treatment: Description of Studies

Reference	Year	Type of Surgery	Aprotinin and Intravenous Dose	Transfusion Protocol of Erythrocyte Units	DVT Prophylaxis	Screening of DVT	Type of Anesthesia	Double-blind	Patients Randomized
Wendt[30]	1982	THA	0.02 million KIU/kg	NA	UFH	Clinical	NA	Yes	32
Haas[31]	1985	THA	1.5 million KIU	NA	UFH-DHE	FUT	MA	NA	120
Janssens[32]	1994	THA	2 million KIU + 0.5 million KIU/h during surgery	Ht < 30%	LMWH	Clinical	GA	Yes	40
Thorpe[33]	1994	TKA	0.5 million KIU + 0.5 million KIU before deflation of tourniquet + 1 million KIU/h for 2 h	Depending on patient's condition	UFH	NA	GA	No	17
Murkin[34]	1995	Complex THA	2 million KIU + 0.5 million KIU/h during surgery	Hb < 8 g/dl or blood loss > 15% of blood volume	Warfarin or UFH	Ultrasound	GA	Yes	53
Hayes[35]	1996	THA	2 million KIU	Blood loss > maximum tolerated blood loss	LMWH	Venography	RA	Yes	40
Llau[36]	1996	Spine	2 million KIU + 2 bolus of 0.5 million KIU	NA	NA	NA	GA	Yes	20
Compostella[37]	1997	THA	2 million KIU + 0.5 million KIU/h during surgery	Ht < 27%	NA	NA	RA	NA	100
Utada[38]	1997	THA	2 million KIU	NA	NA	NA	RA and GA	NA	21
Capdevila[39]	1998	MOS	1 million KIU + 0.5 million KIU/h during surgery	Ht < 25%	Intravenous UFH	Ultrasound	GA	Yes	23
Garcia-Enguita[40]	1998	Complex THA	2 million KIU + 0.5 million KIU/h during surgery	Defined prospectively	NA	NA	RA	NA	30
Llau[41]	1998	THA	2 million KIU	Hb < 9 g/dl	LMWH	Clinical	GA	NA	20
D'Ambrosio[42]	1999	THA	0.5 million KIU + 0.5 million KIU/h during surgery	CS systematically reinfused	LMWH	Clinical	RA or GA	Yes	60
Lentschener[43]	1999	Spine	2 million KIU + 0.5 million KIU/h during surgery	Ht < 26%	LMWH	Clinical	GA	Yes	72
Langdown[44]	2000	THA	1.5 million KIU	NA	NA	NA	RA	Yes	60
Murkin[45]	2000	THA	0.5 million KIU or 1 million KIU + 0.25 million KIU/h during surgery or 2 million KIU + 0.5 million KIU/h during surgery	Ht < 18%	Warfarin	Ultrasound	RA or GA	Yes	301
Cvachovec[46]	2001	THA	1 million KIU + 1 million KIU during 1 h	Hb < 9-10 g/dl	LMWH	Clinical	RA or GA	No	42
Engel[47]	2001	TKA	1 million KIU before deflation of tourniquet + 0.5 million KIU/h for 4 h	Hb < 10 g/dl	LMWH	Clinical	RA	No	24
Urban[48]	2001	Spine	1 million KIU + 0.25 million KIU/h during surgery	Hb < 8 g/dl or Ht < 25%	NA	Clinical	GA	No	40
Samama[49]	2002	MOS	4 million KIU + 1 million KIU/h during surgery or 2 million KIU + 0.5 million KIU/h during surgery	Ht < 24%	LMWH	Venography	GA	Yes	58
Amar[50]	2003	Cancer	2 million KIU + 0.5 million KIU/h during surgery	Hb < 8 g/dl or Ht < 24%	IPC	Ultrasound	GA	Yes	47
Jeserschek[51]	2003	MOS	1 million KIU + 0.5 million KIU/h during surgery	Ht < 25–30%	LMWH	Clinical	NA	Yes	18
Ray[52]	2005	THA	2 million KIU + 0.5 million KIU/h for 3 h	Depending on patient's condition	FPC + aspirin	Ultrasound	GA	Yes	30

First dose of aprotinin was started before surgery, otherwise stated. Trials that systematically reinfused autologous blood, whatever the value of hemoglobin (Hb) or hematocrit (Ht) was, were not considered to have used a transfusion protocol.

Complex THA = revision or bilateral primary total hip arthroplasty; CS = cell savage blood; DHE = dihydroergotamine; Double-blind = patients and investigators were blinded to treatment allocation; DVT = deep vein thrombosis; FPC = foot pump compression; FUT = fibrinogen uptake test; GA = general anesthesia; IPC = intermittent pneumatic compression; KIU = kallikrein inactivator units; LMWH = low-molecular-weight heparin; MOS = major orthopedic surgery such as revision arthroplasty, musculoskeletal sepsis, or tumors; NA = data not available; RA = regional anesthesia; Spine = spine fusion or posterior spinal fixation surgery; THA = total hip arthroplasty; TKA = total knee arthroplasty; UFH = unfractionated heparin.

Table 2. Tranexamic Acid *versus* Placebo or No Treatment: Description of Studies

Reference	Year	Type of Surgery	Tranexamic Acid and Intravenous Dose	Transfusion Protocol of Erythrocyte Units	DVT Prophylaxis	Screening of DVT	Type of Anesthesia	Double-blind	Patients Randomized
Hiippala[53]	1995	TKA	15 mg/kg	Hb < 10 g/dl	LMWH	Clinical	RA	Yes	29
Benoni[54]	1996	TKA	10 mg/kg + 10 mg/kg 3 h after	Hb < 8.5–10 g/dl	LMWH	Clinical	RA	Yes	86
Hiippala[55]	1997	TKA	15 mg/kg + 10 mg/kg 3 and 6 h after	Hb < 10 g/dl	LMWH	Clinical	RA	Yes	77
Duquenne[56]	1999	THA	15 mg/kg	PAD systematically reinfused	NA	Ultrasound	GA	Yes	70
Jansen[57]	1999	TKA	15 mg/kg + 15 mg/kg every 8 h for 3 days	Ht < 26%	LMWH	Clinical	GA	Yes	42
Benoni[58]	2000	THA	10 mg/kg end of surgery + 10 mg/kg 3 h after	Hb < 8.5–10 g/dl	LMWH	Clinical	RA or GA	Yes	40
Ekbäck[59]	2000	THA	10 mg/kg + 1 mg · kg^{-1} · h^{-1} during surgery + 10 mg/kg 3 h after	PAD systematically reinfused	IPC	Ultrasound	RA	Yes	40
Ido[60]	2000	THA/TKA	1,000 mg + 1,000 mg 3 h after surgery	NA	NA	Clinical	NA	No	83
Benoni[61]	2001	THA	10 mg/kg	Hb < 8.5–10 g/dl	LMWH	Clinical	RA or GA	Yes	40
Ellis[62]	2001	TKA	15 mg/kg + 10 mg · kg^{-1} · h^{-1} for 12 h	Ht < 27%	LMWH	NA	GA	No	20
Engel[47]	2001	TKA	15 mg/kg + 10 mg/kg 3 h after	Hb < 10 g/dl	LMWH	Clinical	RA	No	24
Tanaka[63]	2001	TKA	20 mg/kg before surgery or 20 mg/kg before deflation of tourniquet or 10 mg/kg before surgery + 10 mg/kg before deflation of tourniquet	Hb < 7–10 g/dl	NA	Radioisotope venography	NA	Yes	99
Veien[64]	2002	TKA	10 mg/kg + 10 mg/kg 3 h after	Ht < 28%	LMWH	Clinical	RA	No	30
Good[65]	2003	TKA	10 mg/kg + 10 mg/kg 3 h after	Hb < 9 g/dl	LMWH	Clinical	RA	Yes	55
Husted[66]	2003	THA	10 mg/kg + 1 mg · kg^{-1} · h^{-1} for 10 h	Reduction in Hb > 25% and clinical symptoms	LMWH	Clinical	RA	Yes	40
Yamasaki[67]	2003	THA	1,000 mg	PAD systematically reinfused	None	Clinical	RA	No	40
Garneti[68]	2004	THA	10 mg/kg	None	IPC	Ultrasound or venography	RA	Yes	50
Lemay[69]	2004	THA	10 mg/kg + 10 mg · kg^{-1} · h^{-1} during surgery	Hb < 7 g/dl	LMWH	Ultrasound	RA	Yes	40
Zohar[70]	2004	TKA	15 mg/kg + 10 mg · kg^{-1} · h^{-1} for 12 h or 15 mg/kg + 10 mg · kg^{-1} · h^{-1} for 2 h + 1 g oral TA 6 and 12 h after	Ht < 28%	LMWH	Ultrasound	GA	No	60
Johansson[71]	2005	THA	15 mg/kg	Hb < 9 g/dl	LMWH	Clinical	RA	Yes	119

First dose of tranexamic acid was started before surgery in total hip arthroplasty (THA) and before deflation of tourniquet in total knee arthroplasty (TKA), otherwise stated. Trials that systematically reinfused autologous blood, whatever the value of hemoglobin (Hb) or hematocrit (Ht) was, were not considered to have used a transfusion protocol.

Double-blind = patients and investigators were blinded to treatment allocation; DVT = deep vein thrombosis; GA = general anesthesia; IPC = intermittent pneumatic compression; LMWH = low-molecular-weight heparin; NA = data not available; PAD = preoperative autologous blood donation; RA = regional anesthesia.

treatment was started preoperatively except in one study in which it was initiated at the end of surgery.[58] In knee arthroplasty, tranexamic acid was initiated before tourniquet deflation except in two treatment arms of one study in which the drug was started preoperatively.[63] The loading dose was followed by a continuous infusion or repeated boluses in 14 studies; in most cases, the second bolus was 3 h later. The transfusion trigger threshold varied between trials and was reported in 15 of them. As with aprotinin, the authors did not comment on the extent to which the transfusion protocols were followed. Short-term prophylaxis of deep venous throm-

Table 3. ε-Aminocaproic Acid *versus* Placebo or No Treatment: Description of Studies

Reference	Year	Type of Surgery	EACA and Intravenous Dose	Transfusion Protocol of Erythrocyte Units	DVT Prophylaxis	Screening of DVT	Type of Anesthesia	Double-blind	Patients Randomized
Urban[48]	2001	Spine	5 g + 15 mg · kg^{-1} · h^{-1} during surgery	Hb < 8 g/dl or Ht < 25%	NA	Clinical	GA	No	40
Harley[72]	2002	THA	150 mg/kg + 12.5 mg · kg^{-1} · h^{-1} for 5 h	Hb < 8 g/dl or Ht < 24%	UFH until INR > 2 with warfarin	Clinical	RA and/or GA	Yes	55
Amar[50]	2003	Cancer	150 mg/kg + 15 mg · kg^{-1} · h^{-1} during surgery	Hb < 8 g/dl or Ht < 24%	IPC	Ultrasound	GA	Yes	46
Ray[52]	2005	THA	10 g + 5 g over 3 h	Depending on patient's condition	FPC + aspirin	Ultrasound	GA	Yes	30

First dose of ε-aminocaproic acid (EACA) was started before surgery.

Double-blind: patients and investigators were blinded to treatment allocation; DVT = deep vein thrombosis; FPC = foot pump compression; GA = general anesthesia; Hb = hemoglobin; Ht = hematocrit; INR = international normalized ratio; IPC = intermittent pneumatic compression; LMWH = low-molecular-weight heparin; NA = data not available; RA = regional anesthesia; THA = total hip arthroplasty; UFH = unfractionated heparin.

bosis with low-molecular-weight heparin was the most common form of prophylaxis. Venous thrombosis screening was done by an objective test in 6 studies.[56,59,63,68,69,70] The majority of trials were performed in Scandinavia; therefore, regional anesthesia (epidural or spinal anesthesia) was favored over general anesthesia. Finally, 14 of the 20 studies were double-blind, 3 open studies reported a proper generation of the treatment allocation sequences (computer-generated randomization table),[62,64,70] and 3 open studies reported a proper concealment of the treatment allocation.[62,64,67]

ε-Aminocaproic Acid

There were only four selected studies using EACA, comprising a total of 171 patients.[48,50,52,72] Two involved hip arthroplasty, and two involved major orthopedic surgery. All studies used a single bolus before surgery followed by a continuous infusion. Transfusion of erythrocytes was predefined by a transfusion protocol in three studies. In one study, the regimen of deep venous prophylaxis was unavailable. Venous thrombosis screening was done by an objective test in two studies.[50,52] Three studies were double-blind, and the open study reported a proper generation of the treatment allocation sequences (random number–generated table).[48]

Results Regarding Requirement for Transfusion of Allogeneic Erythrocytes

Lack of a transfusion protocol, as defined in the Materials and Methods section, was the reason for excluding eight studies from the evaluation of this criterion (three with aprotinin,[33,42,52] four with tranexamic acid,[56,59,67,68] and one with EACA[52]). The other reason was nonavailable data of this criterion (five trials with aprotinin[32,35,37,40,48]) and nonavailable data on the use of a transfusion protocol (five with aprotinin[30,31,36,38,44] and one with tranexamic acid[60]).

We used the logarithm of the OR instead of the logarithm of the relative risk or the rate difference because it was the more conservative method. Treatment with aprotinin and tranexamic acid led to a significant reduction in the proportion of patients requiring at least one unit of allogeneic erythrocyte transfusion according to a transfusion protocol. Results were significant in double-blind studies for aprotinin (OR, 0.42 [95% confidence interval, 0.27–0.66]; $P < 0.01$) and for tranexamic acid (OR, 0.18 [0.12–0.28]; $P < 0.01$) (fig. 1). EACA did not lead to a significant reduction in the proportion of patients requiring allogeneic erythrocyte transfusion: The OR was 0.71 (0.29–1.73; $P = 0.45$; fig. 1).

Sensitivity analyses were not suggestive of major bias. Similar estimates of treatment effect for aprotinin and tranexamic acid were achieved in open-label studies: Heterogeneity test between open and double-blind subgroups was $P = 0.92$ for aprotinin and $P = 0.22$ for tranexamic acid (fig. 1). Deletion of individual studies one at a time did not significantly alter the primary outcome. After contacting the authors, data of excluded patients were unavailable in three per-protocol studies.[65,69,72] Imputing these missing data by choosing the worst-case scenario for treatment did not modify the direction or magnitude of treatment effect. Funnel plots for each drug did not suggest that low-quality studies (open-label studies) and/or publication bias (absence of studies showing no significant beneficial effect) exaggerated the magnitude of the estimated treatment effect (fig. 2).

Because these sensitivity analyses did not suggest major bias due to study quality, open-label and double-blind studies were pooled. The pooled estimate revealed a statistically significant reduction in allogeneic erythrocyte transfusion for aprotinin compared with placebo (OR, 0.43 [0.28–0.64]; $P < 0.01$) and for tranexamic acid compared with placebo (OR, 0.17 [0.11–0.24]; $P < 0.01$; fig. 1).

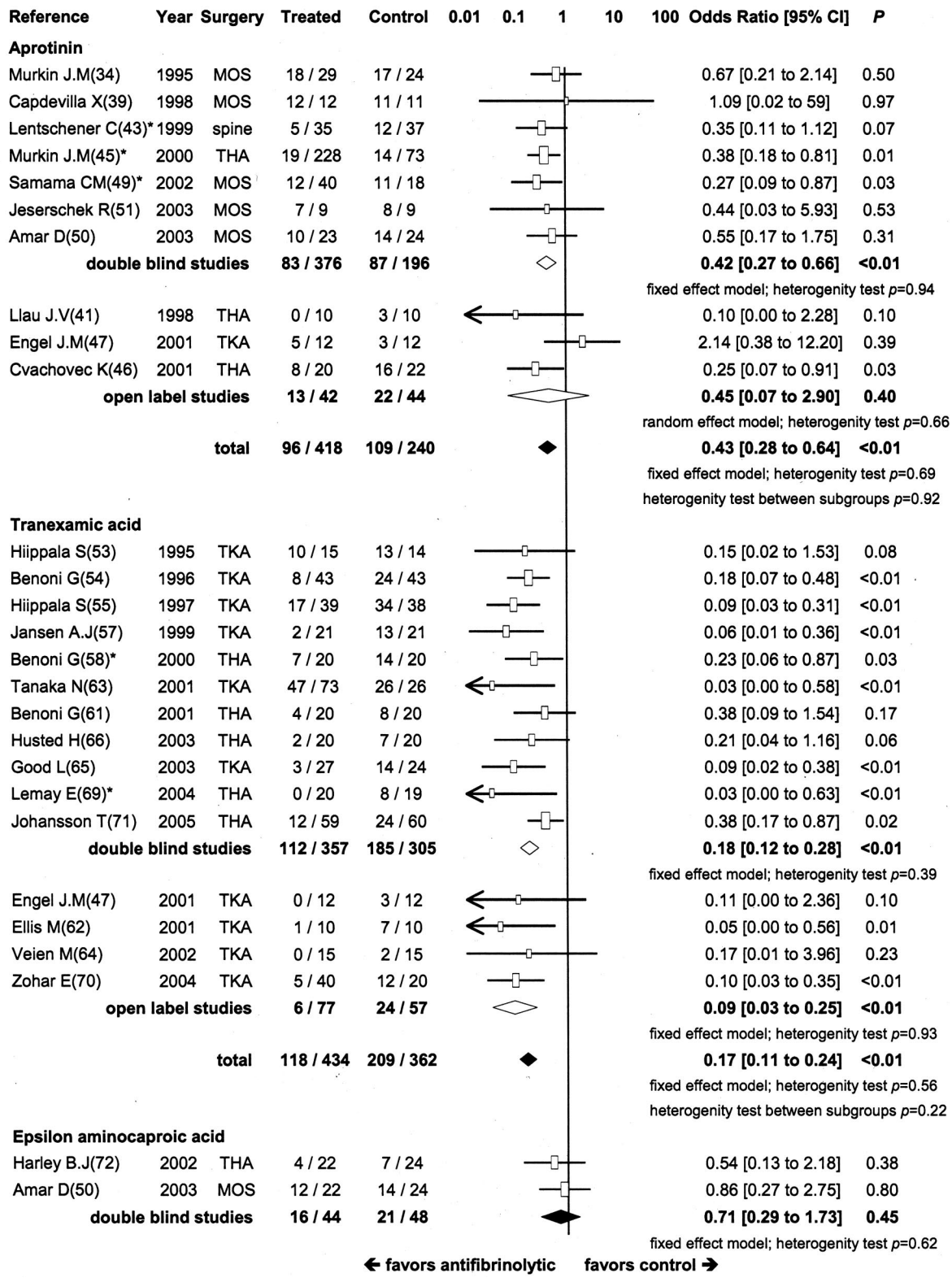

Fig. 1. Meta-analysis of use of antifibrinolytic compared with placebo or no treatment on the proportion of patients requiring allogeneic erythrocyte transfusion according to a transfusion protocol. The odds ratio for the individual studies is represented as a *square* within a *bar* representing the 95% confidence interval (CI). Symbol size is proportional to the study weight. The odds ratio for summaries is represented as a *diamond*. The width of the diamonds corresponds to the 95% CI. An odds ratio less than 1 indicates that the antifibrinolytic is more effective than placebo. If the value of 1 is included within the 95% CI, the result is not significant ($P > 0.05$). MOS = major orthopedic surgery; spine = spine fusion or posterior spinal fixation surgery; THA = total hip arthroplasty; TKA = total knee arthroplasty. * Trials used autologous blood before allogeneic blood when possible and according to a transfusion protocol. Data shown are allogeneic erythrocyte transfusion.

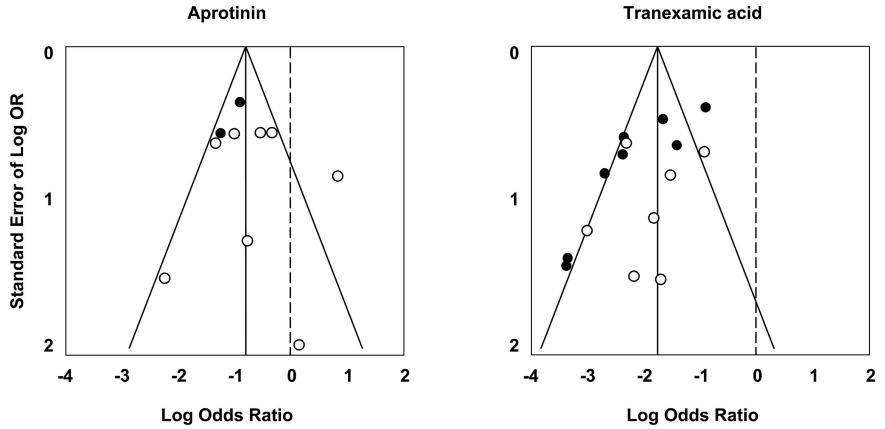

Fig. 2. Funnel plot of use of antifibrinolytic compared with placebo or no treatment on the proportion of patients requiring allogeneic erythrocyte transfusion according to a transfusion protocol. A funnel plot is a scatter plot of the treatment effect estimated from individual studies (logarithm of odds ratio [OR], *horizontal axis*) against a measure of study size (SE of logarithm of OR, *vertical axis*). *Solid line* is pooled OR; *dashed line* is null effect. Effect estimates from small studies should scatter more widely at the bottom of the graph, with the spread narrowing among larger studies. In the absence of bias, studies are symmetrically distributed around the pooled OR, and the plot resembles a symmetric inverted funnel. Asymmetric funnel plots may indicate publication bias or be due to exaggeration of treatment effects in small studies of low quality. *Solid circles* are double-blind studies; *open circles* are open-label studies and/or studies showing no significant beneficial effect.

Exploratory analyses did not find any influence of the type of anesthesia, the type of surgery, or the dose regimen for aprotinin. For example, the OR for aprotinin compared with placebo was 0.41 (0.22–0.74) in primary hip or knee arthroplasty and 0.44 (0.25–0.77) in major orthopedic surgery (heterogeneity test between subgroups; $P = 0.85$; fig. 3). Exploratory analyses did not suggest that the type of anesthesia modified the results for tranexamic acid. Trials with this latter drug were only performed in primary hip or knee arthroplasty. Although the results were not qualitatively influenced by the type of surgery, in quantitative terms, the results support a higher efficacy in knee arthroplasty for tranexamic acid compared with placebo (knee arthroplasty OR, 0.11 [0.06–0.18] *vs.* hip arthroplasty OR, 0.29 [0.17–0.52]; heterogeneity tests between subgroups $P < 0.01$; fig. 3). Furthermore, the efficacy of tranexamic acid in terms of requirement for transfusion of allogeneic erythrocytes seems to be modified by the regimen used. First, the efficacy *versus* placebo was greater with a dose regimen of more than 30 mg/kg tranexamic acid (OR, 0.08 [0.04–0.17]) than with a lower dose regimen (OR, 0.21 [0.14–0.33]; fig. 3). The heterogeneity test between these two dose regimens is significant ($P = 0.03$). Second, the results seem to favor the use of more than one single bolus dose of tranexamic acid (single bolus *vs.* placebo: OR, 0.32 [0.17–0.63]; bolus followed by continuous infusion or repeated bolus *vs.* placebo: OR, 0.12 [0.07–0.19]; heterogeneity tests between subgroups, $P = 0.01$; fig. 3).

The efficacy of aprotinin and tranexamic acid were also evaluated using a regression model. The linear regression revealed a significant correlation between the event rates (defined as the proportion of patients requiring allogeneic erythrocyte transfusion according to a transfusion protocol) in the active and control groups observed in the studies. This relation was evident not only for aprotinin ($R^2 = 0.83$, test of slope; $P < 0.01$), but also for tranexamic acid ($R^2 = 0.75$, test of slope; $P < 0.01$; fig. 4).

Other Efficacy Endpoints

Aprotinin and tranexamic acid led to a significant decrease in the proportion of patients requiring any kind of erythrocyte transfusion (*i.e.*, comprising allogeneic and/or preoperative autologous blood donation and/or cell salvage blood) according to a transfusion protocol (OR, 0.49 [0.33–0.73], $P < 0.01$ for aprotinin; 0.17 [0.12–0.25], $P < 0.01$ for tranexamic acid). The total perioperative blood loss was also significantly reduced with the use of aprotinin and tranexamic acid (standardized mean difference: 0.79 [0.64–0.94], $P < 0.01$ for aprotinin; 1.06 [0.68–1.43], $P < 0.01$ for tranexamic acid). EACA did not lead to a significant reduction in the

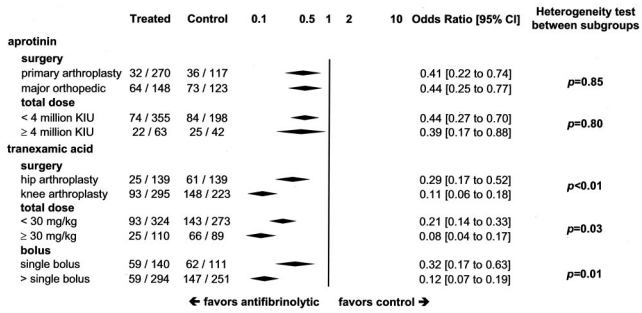

Fig. 3. Exploratory analyses of efficacy of aprotinin or tranexamic acid on allogeneic erythrocyte transfusion. The odds ratio for summaries is represented as a *diamond*. The width of the diamonds corresponds to the 95% confidence interval (CI). An odds ratio less than 1 indicates that the antifibrinolytic is more effective than placebo. If the value of 1 is included within the 95% CI, the result is not significant ($P > 0.05$).

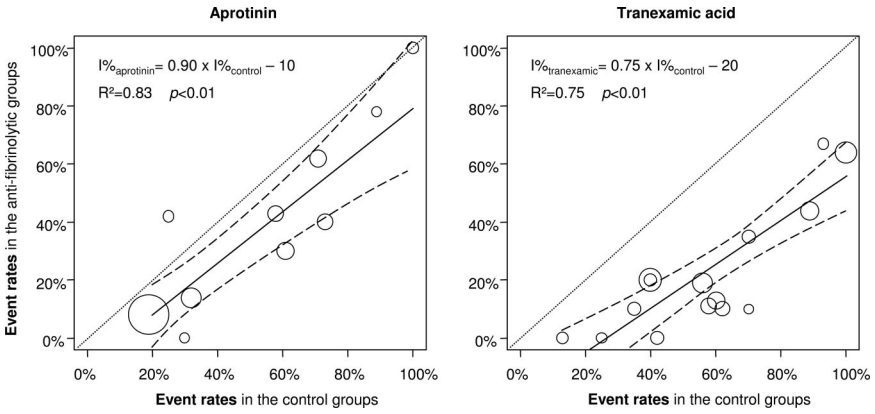

Fig. 4. Linear regression analysis of the transfusion rate with the use of aprotinin or tranexamic acid according to the underlying transfusion rate. All studies included in the meta-analysis are represented by a *circle*. The size of each circle is proportional to the size of the trials. Event rates: proportion of patients transfused with allogeneic erythrocyte according to a transfusion protocol. The *solid lines* are calculated linear regressions weighted by the number of patients included in each study. The *dashed lines* are 95% confidence intervals of the regression lines. R^2 is the coefficient of linear correlation; P is the probability that the slope of regression differs significantly from zero. The *dotted lines* represent equivalence. Studies below these dotted lines are in favor of the efficacy of the antifibrinolytic.

proportion of patients requiring any kind of erythrocyte transfusion (OR, 0.71 [0.29–1.73], $P = 0.45$) or in total blood loss (standardized mean difference: 0.38 [−0.39 to 1.16], $P = 0.33$).

Analysis for the outcome "number of units of allogeneic blood transfused per patient" was not performed for any drug because almost no trials summarized normal data.

Venous Thromboembolism

This meta-analysis did not show a statistically significant increase risk of venous thromboembolism for antifibrinolytics. In double-blind randomized trials that screened systematically for deep venous thrombosis using an objective test at the end of the study period or earlier if clinically suspected, adjusted pooled incidence of venous thromboembolism was 8.6% *versus* 12% for aprotinin compared with placebo, 20.8% *versus* 20.9% for tranexamic acid compared with placebo, and 8.1% *versus* 10.3% for EACA compared with placebo. The OR was 0.67 (0.36–1.27; $P = 0.22$) for aprotinin, 1.08 (0.49–2.39; $P = 0.84$) for tranexamic acid, and 0.82 (0.18–3.67; $P = 0.79$) for EACA (fig. 5). Similar estimates of treatment effect for antifibrinolytics were achieved in open-label studies and/or studies that only screened for symptomatic venous thrombosis: Heterogeneity test between open and double-blind subgroups was $P = 0.59$ for aprotinin, $P = 0.61$ for tranexamic acid, and $P = 0.87$ for EACA (fig. 5). Therefore, all studies were pooled, and the estimate of treatment effect did not reveal a statistically significant increase in venous thrombosis for each antifibrinolytic compared with placebo (fig. 5).

Other Safety Endpoints

Analysis for other adverse events that may be related to the use of antifibrinolytics was not performed because these events were seldom reported. Seven hundred twenty-three patients received aprotinin, and there was 1 case of non–ST-elevation myocardial infarction[54] and 1 case of lower limb ischemia[35]; 1 patient died of septic shock, rhabdomyolysis, and acute kidney failure[47]; and 2 had a nonfatal anaphylactic reaction.[51,52] With tranexamic acid (575 patients), there was 1 case of myocardial infarction.[55] One patient with EACA (76 patients) reported a rash postoperatively,[74] and 3 reported a non–ST-elevation myocardial infarction.[54] Finally, in the placebo-treated patients (1,057 patients), 1 had a postoperative cerebral vascular accident,[36] and another had a myocardial infarction.[47]

Discussion

Meta-analysis is a retrospective examination that is subject to the quality of the data of the included studies. To minimize the possibility of bias, for an accurate estimate of efficacy, we chose to perform a primary analysis by including only double-blind randomized trials. Results showed that the use of either aprotinin or tranexamic acid in orthopedic surgery significantly reduced the proportion of patients requiring erythrocyte transfusion according to a transfusion protocol (as has been previously shown in cardiac surgery or orthotopic liver transplantation).[7,73,74] With EACA, we did not find any significant reduction of hemorrhagic risk, probably due to the small number of trials included (2 trials with 101 participants).

Besides, to perform an exhaustive review of the use of antifibrinolytics in orthopedic surgery and to increase the power of the analysis, we extended our selection to open trials. To reduce bias we chose for our primary outcome not to consider trials that did not use or did not mention the use of a transfusion policy. Unfortunately, because none of the trials included comment on the extent to which the transfusion protocols were followed, this could be a source of bias in open-label studies. Therefore, we explored the robustness of our findings through sensitivity analyses.[75] Because these analyses did not suggest that the open-label trials or any individual trial exaggerated the magnitude of the estimated treatment effect of aprotinin or tranexamic acid,

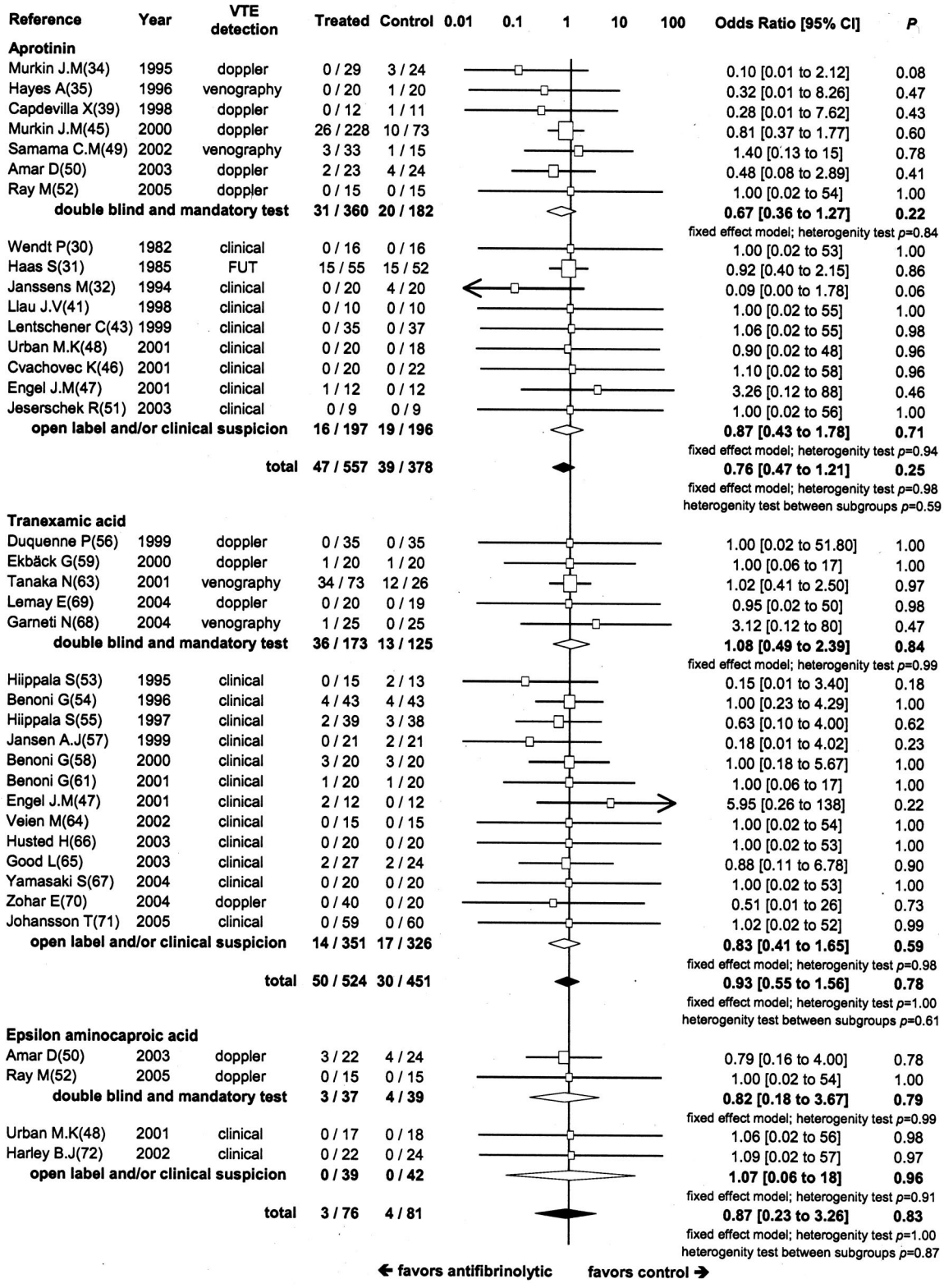

Fig. 5. Meta-analysis of use of antifibrinolytic compared with placebo or no treatment on venous thromboembolism. The odds ratio for the individual studies is represented as a *square* within a *bar* representing the 95% confidence interval (CI). Symbol size is proportional to the study weight. The odds ratio for summaries is represented as a *diamond*. The width of the diamonds corresponds to the 95% CI. An odds ratio greater than 1 indicates that the antifibrinolytic is at risk compared with placebo. If the value of 1 is included within the 95% CI, the result is not significant ($P > 0.05$). FUT = fibrinogen uptake test; VTE = venous thromboembolism.

open-label and double-blind studies were pooled. This permitted exploratory analyses for additional assessment of the use of antifibrinolytics in orthopedic surgery.

The regimen of antifibrinolytics used varied from one study to another. Because the optimal regimen in orthopedics had not previously been defined in randomized control studies, we explored the efficacy of aprotinin or tranexamic acid according to different covariables. With tranexamic acid, results showed a significant reduction of erythrocyte transfusion requirement whatever the regimen used. However, the effect was greater with the higher dosage. The OR was 0.21 (0.14–0.33) with a total dose lower than 30 mg/kg and 0.08 (0.04–0.17) with the higher dose. This may explain the discrepancy of results between knee and hip arthroplasty (fig. 3). In this latter surgical setting, which showed a lower efficacy than in knee arthroplasty, only the lower dose of tranexamic acid was used. With aprotinin, the exploratory analyses did not find any influence of any covariable analyzed; in particular, there was no significant dose–effect relation. It is noteworthy that the regimens of aprotinin used in orthopedic surgery were based on those used in cardiac surgery, with a primary preoperative loading dose followed, in most cases, by a continuous infusion limited to the intraoperative period. In orthopedic surgery, time taken for individual patients to achieve physiologic hemostasis in the postoperative period is uncertain. Besides, continual intraoperative bleeding may be responsible for partial washout of antifibrinolytics because reinfusion is not done immediately after blood loss, as in cardiac bypass surgery. This could explain the results observed with tranexamic acid that seem to favor administration of more than one single bolus limited to the intraoperative period (fig. 3). However, because the trials were not randomized with respect to the dose administered, the duration of treatment, and the timings of first administration, our evaluation of the different regimen of antifibrinolytics is evidently tentative and must be confirmed in further well-designed trials.

The efficacy of antifibrinolytics according to the underlying transfusion rate has not yet been investigated in clinical settings that are characterized by varying baseline risks of blood loss or transfusion.[7] With this in mind, we performed a linear regression analysis. Results revealed a significant correlation between the transfusion rates in the antifibrinolytic and control groups (fig. 4). Although this linear regression is a *post hoc* analysis, it proposes an estimation of the efficacy of antifibrinolytics in different clinical settings and according to varying baseline risks of transfusion. Furthermore, this linear model is suggestive of a mixed-effects model, a combination of a multiplicative and additive model.[9] Therefore, the number needed to treat for aprotinin or tranexamic acid to avoid transfusing one patient varies according to the different transfusion rates in the control group. For example, our linear regression suggests that with the use of tranexamic acid, the number needed to treat is five for a 20% transfusion rate in the control group and less than three for a 70% transfusion rate. We agree with Ho *et al.*[76] that tranexamic acid is likely to be more useful in the clinical setting of a high transfusion rate: The higher the transfusion rate is, the lower the number needed to treat (multiplicative model) is. However, the magnitude of efficacy may not be as variable as they previously suggested (additive model).[76]

There are several issues that must be addressed. Summarized data on transfusion of fresh frozen plasma or platelets in the individual trials were insufficiently reported to perform a meta-analysis. Therefore, the reduction in transfusion observed in our review is limited to erythrocyte transfusion and is not predictive for other allogeneic blood elements. The included trials did not compare the efficacy and cost of antifibrinolytics to other effective interventions designed to minimize allogeneic erythrocyte transfusion, such as preoperative autologous blood donation, perioperative cell salvage, or the use of erythropoietin.[77,78] Finally and more importantly, the safety of the use of antifibrinolytics remains a matter of concern. As previously suggested in cardiac surgery,[7] our review did not demonstrate a statistically significant excessive risk of thromboembolic events with the use of antifibrinolytics. However, great care should be taken regarding the safety results. Trials selected for our analysis were designed to assess efficacy but were inadequate for the detection of adverse events. The small sample size of the trials was not sufficient to detect relatively infrequent, but clinically serious, safety events such as arterial thrombosis, renal failure, or rhabdomyolysis.[6] Most studies lacked a prospective monitoring of safety outcomes, and due to enrollment criteria, patients at high risk of thromboembolic events, *e.g.*, patients with a history of ischemic heart disease, were often excluded. As a consequence, the reported rate of adverse events is underestimated in our review. For example, there were only 2 cases of myocardial infarction among 2,431 patients (0.08% [95% confidence interval, 0–0.2%]), a lower frequency than previously reported in orthopedic arthroplasty surgery (0.4%).[79] Besides, it seems that the different antifibrinolytics may not have the same frequency of serious adverse events.[80] The evaluation of venous thromboembolic events was less limited because several double-blind randomized trials prospectively and systematically assessed this endpoint with an objective test. Furthermore, the observed incidence of venous thrombosis was much higher than arterial thrombosis, allowing a more precise estimation (fig. 5). The lack of any significant excessive risk of venous thromboembolism with the use of antifibrinolytics could be due to the systematic use of venous thrombosis prophylaxis in these studies. Nevertheless, due to the wide confidence intervals of the summary estimate for venous thromboembolic events, this review cannot determine whether

the administration of these agents increases the incidence or severity of venous thrombosis. Therefore, no definite conclusions regarding venous thromboembolic events can be drawn from this review. Finally, there are concerns about the safety of aprotinin because it is a polypeptide derived from bovine lungs and possesses antigenic properties.[6] Among the 723 patients who received aprotinin in our analysis, 2 had a nonfatal anaphylactic reaction.[49,50]

In conclusion, this analysis suggests that the use of aprotinin and tranexamic acid in orthopedic surgery significantly reduces the risk of allogeneic erythrocyte transfusion. However, results were too scarce for the evaluation of safety. Therefore, no definite conclusions regarding the clinical benefit–risk ratio of the use of antifibrinolytics in orthopedic surgery can be derived from our review. Larger prospective trials are required to define the optimal regimen, to assess the safety and cost-effectiveness of antifibrinolytics before recommending their use in orthopedic surgery.

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