Aus dem Fachbereich Medizin der
Johann Wolfgang Goethe-Universität
Frankfurt am Main

betreut an der
Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie
Direktor: Prof. Dr. Dr. Kai Zacharowski

Erhöht die Gabe intravenöser Tranexamsäure die Wahrscheinlichkeit für thromboembolische Ereignisse?

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vorgelegt von
Isabel Natalie Taeuber

aus Langen

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Dekan:	Prof. Dr. Stefan Zeuzem
Referent:	Prof. Dr. Patrick Meybohm
Korreferent:	Prof. Dr. Ferdinand M. Gerlach
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2. Zusammenfassung

2.1 Hintergrund

Tranexamsäure (TXA) ist ein Antifibrinolytikum, welches Blutungen effizient reduzieren kann. Auf Grund des Wirkmechanismus bestehen jedoch Bedenken, dass TXA zu einem erhöhten Risiko für thromboembolische Ereignisse (TE) führen könnte.

2.2 Zielsetzung

Ziel dieser Arbeit ist die Untersuchung eines möglichen Zusammenhanges zwischen der Applikation intravenöser (iv) TXA und dem Auftreten von TE sowie der Mortalität. Ebenfalls soll ein möglicher Dosis-abhängiger Effekt untersucht werden.

2.3 Methoden

Es erfolgte eine systematische Suche der *MEDLINE* Datenbank und des *Cochrane Central Register of Controlled Trials*. Berücksichtigt wurden alle randomisiert kontrollierten Studien bis inklusive 2020, welche iv TXA mit Placebo oder einer Kontrollgruppe ohne Intervention verglichen. Die eingeschlossenen Studien sind in englischer, deutscher, spanischer oder französischer Sprache publiziert. Übergeordnete Endpunkte waren die Summe aller TE sowie die Gesamtmortalität. Zusätzlich wurden die Endpunkte venöse Thrombosen, Lungenembolien, venöse thromboembolische Ereignisse (VTE), Myokardinfarkte, Schlaganfälle oder transitorische ischämische Attacken, Mesenterialischämien, arterielle Verschlüsse, blutungsassoziierte Mortalität sowie nicht-blutungsassoziierte Mortalität untersucht. Anhand der „*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*“ (PRISMA) wurden die vorliegende Metaanalyse, Subgruppen- und Sensitivitätsanalyse erstellt. Als Effektstärkemaß wurde die Risikodifferenz (RD) berechnet. Für den primären Endpunkt der Summe aller TE erfolgten zusätzliche Sensitivitätsanalysen zur Berechnung des Risikoquotienten (RR). Eine Metaregressionsanalyse wurde zur Untersuchung eines dosisabhängigen Effektes durchgeführt. Das Bias-Risiko der eingeschlossenen Studien wurde anhand des *Cochrane Risk of Bias Tool* bewertet.

2.4 Ergebnisse

Insgesamt wurden 216 Studien in die vorliegende Metaanalyse eingeschlossen. Die Summe aller TE betrug 1020 (2,1%) in der TXA-Gruppe und 900 (2,0%) in der Kontrollgruppe. Es fand sich kein Zusammenhang zwischen iv TXA und dem Risiko für die Summe aller TE (RD = 0,001; 95%-Konfidenzintervall (CI): -0,001 bis 0,002; P = 0,49) sowie für venöse Thrombosen, Lungenembolien, VTE, Myokardinfarkte oder -ischämien und Schlaganfälle oder transitorische ischämische Attacken. Die Sensitivitätsanalyse für die Summe aller TE zur Berechnung des RR zeigte keine Assoziation mit iv TXA, weder unter Ausschluss der Studien ohne TE (RR = 1,03; 95%CI: 0,95 bis 1,12; P = 0,52) noch unter Einschluss dieser Studien (RR = 1,02; 95%CI: 0,94 bis 1,11; P = 0,56). Die Sensitivitätsanalyse der Studien mit einem geringen Selektionsbias zeigte ein vergleichbares Ergebnis. Die Sensitivitätsanalyse mit Patienten mit einem erhöhten Thromboembolie-Risiko fand keine Assoziation zwischen iv TXA und TE (RD = 0,000; 95%CI: -0,008 bis 0,009; P = 0,95). Die Subgruppenanalyse von Studien mit bis zu 99 Patienten, 100 bis 999 Patienten und 1.000 oder mehr Patienten zeigte keine Assoziation zwischen iv TXA und der Summe aller TE. Die Gabe von iv TXA war mit einer signifikanten Reduktion der Gesamtmortalität (RD = -0,007; 95%CI: -0,012 bis -0,004; P < 0,001) und der blutungsassoziierten Mortalität verbunden. Für die nicht-blutungsassoziierte Mortalität zeigte sich kein signifikanter Zusammenhang. Eine Metaregression mit 143 Interventionsgruppen fand keinen Zusammenhang zwischen der TXA-Dosierung und dem Risiko für VTE.

2.5 Diskussion

Die vorliegende Arbeit konnte zeigen, dass keine Assoziation zwischen iv TXA und TE besteht. Die Sensitivitätsanalysen konnten dieses Ergebnis bestätigen. Die Metaregressionsanalyse fand keinen dosisabhängigen Zusammenhang zwischen iv TXA und VTE. Gleichzeitig wird die Gesamtmortalität durch TXA signifikant reduziert. Die vorliegende Analyse unterstützt die sichere Anwendung von iv TXA und legt einen wahrscheinlichen Überlebensvorteil nahe. Die Subgruppenanalysen der neurologischen Patienten lieferten uneindeutige Ergebnisse, weshalb der Nutzen von iv TXA für dieses Patientenkollektiv unklar bleibt.

3. Summary

3.1 Background

Tranexamic acid (TXA) is an antifibrinolytic agent which efficiently reduces bleeding. However, due to its mechanism of action, concerns remain whether TXA could lead to an increased risk of thromboembolic events.

3.2 Aim of the Study

The aim of this study is to examine a possible association between the application of intravenous tranexamic acid and thromboembolic events and mortality in patients of any medical discipline and of all ages.

3.3 Methods

We systematically searched *MEDLINE* and *Cochrane Central Register of Controlled Trials* for eligible randomized controlled trials until 2020 that compared intravenous TXA with placebo or no treatment and were published in English, German, Spanish or French. The main endpoints were total thromboembolic events and overall mortality. Additional endpoints were venous thrombosis, pulmonary embolism, venous thromboembolic events, myocardial infarction or ischaemia, cerebral infarction or ischaemia, mesenteric ischemia, limb ischaemia, hepatic artery thrombosis, bleeding mortality and non-bleeding mortality. This metaanalysis was carried out according to the *"Preferred Reporting Items for Systematic Reviews and Meta-Analyses*" (PRISMA). We assessed the risk difference (RD) using the fixed-effect model. Sensitivity analyses were conducted using the random-effects model. We additionally assessed the risk ratio (RR) as a sensitivity analysis of the main endpoint of total thromboembolic events. To investigate a dose-dependent effect we conducted a metaregression analysis. The risk of bias was assessed using the *Cochrane Risk of Bias Tool*.

3.4 Results

In total, 216 studies were included in this metaanalysis. We found 1020 (2.1%) and 900 (2.0%) total thromboembolic events in the TXA group and control group.

No association was found between intravenous TXA and total thromboembolic events (RD = 0.001; 95% confidence interval (CI): -0.001 to 0.002; P = 0.49), venous thrombosis, pulmonary embolism, venous thromboembolic events, myocardial infarction or ischaemia, cerebral infarction or ischaemia, mesenteric ischaemia, limb ischaemia or hepatic artery thrombosis. A sensitivity analysis of total thromboembolic events using the risk ratio (RR) as an effect measure with (RR = 1.02; 95% CI: 0.94 to 1.11; P = 0.56) and without (RR = 1.03; 95% CI: 0.95 to 1.12; P = 0.52) studies with double-zero events showed robust results. Sensitivity analysis of studies judged at low risk for selection bias showed a robust result. A sensitivity analysis of patients with an increased risk for thromboembolic events showed no association between intravenous TXA and thromboembolic events (RD = 0.000; 95% CI: -0.008 to 0.009; P = 0.95). Comparison of studies with up to 99 patients, 100 to 999 and 1,000 or more patients showed no association between intravenous TXA and total thromboembolic events. Administration of intravenous TXA was associated with a significantly reduced overall mortality (RD = -0.007; 95% CI: -0.012 to -0.004; P < 0.001) and bleeding mortality. There was no significant association between intravenous TXA and nonbleeding mortality. Metaregression of 143 intervention groups found no association between dosing of intravenous TXA and the risk for venous thromboembolic events.

3.5 Discussion

This analysis of all medical disciplines and ages found no association between intravenous TXA and thromboembolic events. Sensitivity analyses showed robust results. Metaregression found no dose-dependent association between intravenous TXA and venous thromboembolic events. Additionally, overall mortality is significantly reduced by intravenous TXA. Overall, our results promote the safety of intravenous TXA and suggest a survival benefit by intravenous TXA, with uncertain benefit for the subgroup of neurological patients.

4. Abkürzungsverzeichnis

CI	Konfidenzintervall (*Confidence Interval*)
CII	Schlaganfall (-anfälle) oder Transitorische Ischämische Attacke(n) (*Cerebral Infarction or Ischaemia*)
FEM	Modell der fixen variablen Regressionskonstanten (*Fixed-Effect Model*)
g	Gramm
iv	Intravenös
kg	Kilogramm
mg	Milligramm
MI	Myokardinfarkt(e) oder –ischämie(n)
PE	Lungenembolie(n) (*Pulmonary Embolism*)
RCT	Randomisiert kontrollierte Studie(n) (*Randomised Controlled Trial*)
RD	Risikodifferenz (*Risk Difference*)
REM	Modell der zufälligen variablen Regressionskonstanten (*Random-Effects Model*)
RR	Risikoquotient (*Risk Ratio*)
TE	Thromboembolische(s) Ereignis(se)
TXA	Tranexamsäure
VT	Venöse Thrombose(n)
VTE	Venöse(s) Thromboembolische(s) Ereignis(se)

5. Übergreifende Zusammenfassung

Im Folgenden wird die Originalpublikation, auf der diese Promotionsarbeit basiert, übergreifend zusammengefasst. Personenbezogene Bezeichnungen im generischen Maskulinum beziehen sich auf alle Geschlechter in gleicher Weise.

5.1 Einleitung

Die Zahl der chirurgischen Eingriffe wächst stetig. Im Jahr 2004 wurden rund 230 Millionen chirurgische Eingriffe verzeichnet[1]. Diese Zahl stieg binnen acht Jahren auf weltweit über 310 Millionen chirurgische Eingriffe im Jahr 2012[2]. Neben Geburten oder Unfällen sind auch chirurgische Eingriffe häufig mit einem erhöhten Blutungsrisiko assoziiert. Eine internationale, multizentrische Studie mit über 40.000 nicht herzchirurgischen Patienten[3] konnte zeigen, dass ein relevanter Blutverlust, definiert als tödlicher oder transfusionspflichtiger Blutverlust oder Hämoglobinabfall auf unter 7g/l, die Ursache für 17% der Todesfälle innerhalb der ersten 30 Tage nach einer Operation ist und somit die häufigste operationsassoziierte Todesursache darstellt. Die Autoren schätzen, dass die perioperative 30-Tage-Mortalität weltweit für etwa 1,8 Millionen Todesfälle pro Jahr verantwortlich ist. Aus diesem Grund sollte es der Anspruch einer jeden medizinischen Einrichtung sein, einen lebensbedrohlichen Blutverlust der Patienten als eine der führenden Ursachen perioperativer Mortalität so gering wie möglich zu halten.

Tranexamsäure (TXA) ist ein hochpotentes Antifibrinolytikum und somit wirksam in der Therapie und Prophylaxe schwerer Blutungen[4]. TXA blockiert die Lysinbindungsstellen für den Gewebeplasminogenaktivator im Plasminogen, womit dieser gehindert wird an Fibrin zu binden[5]. Bereits formierte Fibrinnetze können somit weniger abgebaut werden. Eine Hyperfibrinolyse wird verhindert und bestehende Blutgerinnsel werden stabilisiert[5]. In den letzten Jahrzehnten wuchs das Interesse an TXA[6], da es nicht nur zur Eindämmung bereits bestehender Blutungen und nachweisbarer Hyperfibrinolyse wirksam ist, sondern auch zur Prophylaxe einer Hyperfibrinolyse und damit zur Prophylaxe eines erhöhten Blutverlustes sinnvoll sein kann[7-9]. Durch den Einsatz von TXA können Blutungen und Gerinnungsstörungen reduziert[10] und wertvolle Fremdblutressourcen geschont[8] werden. Ker und Kollegen konnten in ihrer Metaanalyse aus dem Jahr 2011 mit 129 eingeschlossenen Studien zeigen, dass

TXA die Wahrscheinlichkeit für Patienten, eine Bluttransfusion zu erhalten, um 37% reduziert[11].

Neben der allgemein anerkannten Wirksamkeit von TXA besteht jedoch trotz des immer liberaleren Einsatzes[6] eine gewisse Skepsis bezüglich unerwünschter Arzneimittelwirkungen. Die Frage, ob TXA als Gegenspieler der Fibrinolyse das Auftreten thromboembolischer Ereignisse begünstigen könnte, ist im wissenschaftlichen Diskurs sehr präsent.

Während Untersuchungen aus dem Bereich der Orthopädie keinen signifikanten Zusammenhang von TXA und thromboembolischen Ereignissen (TE) fanden[12,13], fehlen bislang aktuelle umfassende Metaanalysen über alle medizinischen Disziplinen. In früheren Metaanalysen[11,14] wurde zur Auswertung der Studien der Risikoquotient (RR) berechnet, was zur Folge hat, dass Studien mit null thromboembolischen Ereignissen in Interventions- und Kontrollgruppe automatisch aus der Analyse ausgeschlossen wurden. Da TE durch eine regelhafte postoperative Thromboseprophylaxe selten sind, machen eben diese Studien einen bedeutenden Anteil der Evidenz aus und sollten daher entsprechend berücksichtigt werden.

Zusätzlich variieren die Dosisregime zwischen den Studien stark. So reicht die Gesamtdosis von iv TXA von 0,5 bis 16,6g, beziehungsweise von 5,5mg/kg bis 135mg/kg Körpergewicht. Bislang liegen keine Daten vor, welche eine Auswirkung von unterschiedlichen TXA-Dosierungen auf das Thromboembolierisiko prüfen.

Die vorliegende Arbeit untersucht einen möglichen Zusammenhang von TE und iv TXA bei Patienten mit verschiedenen Blutungsereignissen oder einem erhöhten Risiko eines Blutungsereignisses, beispielsweise im Rahmen chirurgischer Eingriffe, von Geburten oder Unfällen. Hierbei wurden Studien aller medizinischen Fachdisziplinen, unabhängig von der Ereignisrate, berücksichtigt. Zur Untersuchung eines möglichen Zusammenhanges zwischen TXA-Dosierung und TE wurde eine Metaregressionsanalyse in die vorliegende Arbeit integriert. Diese Daten werden helfen, die Sicherheit von iv TXA zu evaluieren und einen möglichen Dosierungseffekt aufzuzeigen.

5.2 Methoden

5.2.1 Suchstrategie und Studienselektion

Die vorliegende Studie wurde im *PROSPERO Register* registriert (CRD42020147359).

Da ausschließlich publizierte Daten für die vorliegende Arbeit verwendet wurden, war die Prüfung durch eine Ethikkommission nicht notwendig.

Zur Identifikation potentiell geeigneter Studien wurde im Juli 2018 eine systematische Suche der *MEDLINE Datenbank* via *PubMed* durchgeführt. Hierbei wurde der Suchterm „tranexamic acid intravenous*“ verwendet. Die Suche wurde durch eventuelle Filter nicht weiter eingeschränkt. Anschließend wurden alle Studien anhand von Titel und Abstract nach passenden randomisiert kontrollierten Studien (RCT) durchsucht. War eine Entscheidung anhand von Titel und Abstract allein nicht möglich, wurde der Volltext herangezogen. Als passend definiert wurden hierbei zunächst alle Studien, die in mindestens einer Studiengruppe TXA iv verabreichten und in englischer, deutscher, französischer oder spanischer Sprache verfasst wurden.

Um eine möglichst umfassende Darstellung der zur Verfügung stehenden Studienlage zu gewährleisten, wurden zusätzlich die Referenzlisten aller in der Suche vorkommenden systematischen Reviews und Metaanalysen auf weitere einzuschließende RCT gescreent. Ebenfalls wurde das *Cochrane Central Register of Controlled Trials* durchsucht und die Referenzlisten der Studien auf gleiche Weise händisch durchsucht.

Nach Abschluss der manuellen Suche im September 2019 wurden die Volltexte untersucht und die Daten mittels Excel extrahiert. Hierbei wurden jene Studien berücksichtigt, welche die iv Gabe von TXA mit einer Placebo-Gruppe oder einer Kontrollgruppe ohne Intervention verglichen. Die Studienteilnehmer mussten randomisiert eingeteilt worden sein.

Bei Unklarheiten wurden die Autoren per E-Mail kontaktiert. Dies konnte beispielsweise notwendig sein, wenn in einem eingeschlossenen Artikel die Summe von venösen Thrombosen und Lungenembolien als venöse thromboembolische Ereignisse (VTE) kumuliert berichtet wurden. Für den Fall, dass diese Informationen nicht getrennt voneinander zur Verfügung gestellt werden konnten, wurden VTE als venöse Thrombosen gewertet.

Um zum Zeitpunkt der Publikation im April 2021 eine aktualisierte Datenlage anbieten zu können, wurde eine zusätzliche *MEDLINE*-Suche via *PubMed* durchgeführt. Hier wurde gezielt nach RCT zwischen Juli 2018 und Dezember 2020 gesucht. Diese Studien wurden in die aktualisierte Metaanalyse integriert.

5.2.2 Endpunkte und Datenextraktion

Folgende Endpunkte wurden extrahiert: Venöse Thrombosen (VT), Lungenembolien (PE), Myokardinfarkte (MI), Schlaganfälle oder transitorische ischämische Attacken (CII), Mesenterialischämien, arterielle Verschlüsse, Gesamtmortalität, blutungsassoziierte Mortalität sowie nicht-blutungsassoziierte Mortalität. VT und PE wurden zusätzlich zu dem Endpunkt VTE zusammengefasst. Der übergeordnete Endpunkt war die Summe aller thromboembolischen Ereignisse.

Des Weiteren wurden die Anzahl der Studienteilnehmer der zu berücksichtigenden Studiengruppen und die TXA Dosierung extrahiert.

5.2.3 Statistische Analyse

Die vorliegende Metaanalyse wurde anhand der „*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*“ (PRISMA)[15] erstellt. Da viele der eingeschlossenen Studien sowohl in der Interventionsgruppe als auch in der Kontrollgruppe keine TE verzeichneten, nutzten wir die Risikodifferenz (RD) zur Analyse der Ergebnisse, um diesen wichtigen Anteil an Evidenz mit einschließen zu können.

Die oben genannten Endpunkte wurden unter Verwendung des Modells der fixen variablen Regressionskonstanten (FEM) mittels Forest Plots analysiert. Um die Stabilität der Ergebnisse zu überprüfen, wurden für alle Endpunkte Sensitivitätsanalysen unter Verwendung des Modells der zufälligen variablen Regressionskonstanten (REM) durchgeführt. Der primäre Endpunkt „Summe aller thromboembolischen Ereignisse“ wurde zusätzlich mittels Risikoquotient (RR) unter der Verwendung von FEM und REM untersucht. Dieses Verfahren wurde sowohl unter Einschluss der Studien mit null Ereignissen in beiden

Gruppen als auch unter Ausschluss dieser Studien durchgeführt. Die statistische Auswertung wurde mittels *Review Manager* (RevMan Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) und „*R*“ (R Studio, A Language and Environment for Statistical Computing. Version 3.6.1, Vienna, Austria; 2016) durchgeführt.

Das Bias-Risiko wurde unter Verwendung des *Cochrane Risk of Bias Tool* beurteilt. Hierbei wurden für alle Studien folgende Parameter bewertet: Selektionsbias (Generation einer Zufallsfolge, verdeckte Zuordnung), Verblindung von Teilnehmern und Personal, Verblindung der Auswertung, inkomplette Ergebnisdaten, selektiver Ergebnisbericht und sonstige Ursachen. Die Bewertung eines möglichen Publikationsbias erfolgte mittels Funnel-Plots.

5.3 Ergebnisse

Die elektronische Suche der MEDLINE Datenbank ergab 704 Treffer, die manuelle Suche zusätzliche 78. Nach Reduktion der Duplikate blieben 778 Artikel, welche nach Ausschluss nicht randomisierter Studien, Tierversuchsstudien und solcher RCT ohne Interventionsgruppe mit iv TXA 377 Artikel zum Screening der Volltexte ließen. Hierbei wurden 158 Artikel auf Grund fehlender Kontrollgruppen, unpassenden Studiendesigns, fehlender Volltexte oder Übersetzungen ausgeschlossen. Dies ließ 219 RCT, von denen 192 Studien[16-207] mindestens einen Endpunkt adressierten und somit eingeschlossen werden konnten.

5.3.1 Studiencharakteristika

Die eingeschlossenen Studien wurden zwischen 1976 und 2018 publiziert. 117 Studien wurden im Jahr 2010 oder später veröffentlicht. Das Durchschnittsalter der Patienten in den eingeschlossenen Studien reichte von 6 Monaten bis hin zu 70 Jahren. Die medizinischen Fachrichtungen wurden für jeden Endpunkt in Subgruppen analysiert. Hierbei wurde zwischen thoraxchirurgischen, gynäkologischen, orthopädischen, polytraumatisierten, mund-kiefer-gesichtschirurgischen, pädiatrischen, neurologischen und „weiteren“ Patienten (urologische und nephrologische Patienten sowie Patienten mit

Lebertransplantation oder -resektion, Operation der Schilddrüse, gastrointestinaler Blutung oder diabetischer Hämorrhagie) unterschieden.

5.3.2 Summe aller thromboembolischen Ereignisse

Aus den eingeschlossenen Studien lieferten 176 Studien (eAppendix 11 des Online Supplements) Daten zu mindestens einem TE und konnten so für den Endpunkt der Summe aller TE berücksichtigt werden. Dies umfasste 65.900 Patienten, 33.487 Patienten in der TXA-Gruppe und 32.413 in der Kontrollgruppe. Insgesamt wurden 779 Ereignisse in der TXA-Gruppe und 706 in der Kontrollgruppe erfasst. Die Gabe von iv TXA war nicht mit einem erhöhten Risiko für TE assoziiert (RD = 0,001; 95% CI: -0,002 bis 0,003; P = 0,66).

Die Ergebnisse für die Subgruppe der neurologischen Patienten waren nicht robust. Bei Verwendung des FEM schienen signifikant mehr Patienten der TXA-Gruppe ein TE erlebt zu haben (RD = 0,026; 95% CI: 0,007 bis 0,045; P = 0,01). Unter Verwendung des REM zeigte sich jedoch kein signifikanter Anstieg (RD = 0,018; 95% CI: -0,013 bis 0,048; P = 0,26). Gleichzeitig ist zu beachten, dass die Heterogenität innerhalb der neurologischen Studien mit I^2=57% als hoch einzuschätzen ist. Auch nach Ausschluss der stark gewichteten Studien mit über 1.000 Patienten blieb die Heterogenität hoch (I^2=73%).

Die Sensitivitätsanalyse zur Berechnung des Risikoverhältnisses zeigte für den primären Endpunkt der Summer aller TE robuste Ergebnisse sowohl bei Ausschluss der Studien mit null TE (RR = 1,02; 95% CI: 0,93 bis 1,12; P = 0,71) als auch bei Einschluss dieser Studien (RR = 1,01; 95% CI: 0,92 bis 1,11; P = 0,77). Um auszuschließen, dass die Summe der TE in TXA- und Kontrollgruppe von der Studiengröße abhängen, wurde hier ebenfalls eine Sensitivitätsanalyse durchgeführt. Bei gegenüberstellender Betrachtung der Studien mit bis zu 99 Patienten, mit 100 bis 999 Patienten und solcher mit 1.000 Patienten oder mehr, fand sich kein signifikanter Unterschied in der Summe aller TE zwischen TXA- und Kontrollgruppe. Die Ergebnisse der Sensitivitätsanalysen blieben unter Verwendung des REM robust.

5.3.3 Venöse Thrombosen

Aus den eingeschlossenen Studien lieferten 163 Studien (eAppendix 12 des Online Supplements) Daten zu VT. Dies umfasste 59.666 Patienten, 30.334 Patienten in der TXA-Gruppe und 29.332 in der Kontrollgruppe. Insgesamt wurden 272 VT in der TXA-Gruppe und 213 in der Kontrollgruppe erfasst. Die Applikation von iv TXA war nicht mit einem erhöhten Vorkommen von VT assoziiert (RD = −0,000; 95% CI: −0,002 bis 0,002; P > 0,99). Die Ergebnisse blieben unter Verwendung des REM robust (RD = −0,000; 95% CI: −0,001 bis 0,000; P = 0,26).

5.3.4 Lungenembolien

Aus den eingeschlossenen Studien lieferten 129 Studien (eAppendix 13 des Online Supplements) Daten zu PE. Dies umfasste 61.562 Patienten, 31.155 Patienten in der TXA-Gruppe und 30.407 in der Kontrollgruppe. Insgesamt wurden 152 PE in der TXA-Gruppe und 153 in der Kontrollgruppe erfasst. Die Applikation von iv TXA war nicht mit einem erhöhten Vorkommen von PE assoziiert (RD = −0,000; 95% CI: −0,001 bis 0,001; P = 0,89). Die Ergebnisse blieben unter Verwendung des REM robust (RD = −0,000; 95% CI: −0,001 bis 0,001; P = 0,68).

5.3.5 Venöse thromboembolische Ereignisse

Zur Berechnung der VTE wurden VT und PE zusammengefasst. Hier lieferten 123 Studien (eAppendix 14 des Online Supplements) Daten zu beiden Endpunkten. Dies entsprach 56.126 Patienten, 28.438 Patienten in der TXA-Gruppe und 27.688 in der Kontrollgruppe. Insgesamt wurden 348 VTE in der TXA-Gruppe und 304 in der Kontrollgruppe erfasst. Die Applikation von iv TXA war nicht mit einem erhöhten Vorkommen von VTE assoziiert (RD = −0,000; 95% CI: −0,002 bis 0,002; P = 0,71). Die Ergebnisse blieben unter Verwendung des REM robust (RD = −0,001; 95% CI: −0,002 bis 0,001; P = 0,39).

5.3.6 Myokardinfarkt oder -ischämie

Aus den eingeschlossenen Studien lieferten 27 Studien[21,30,42,53,60,68,70,74,75,81,82,89,102,106,117,129,132,133,140,147,174,178,183,186,193,199,204]

Daten zu MI. Dies umfasste 45.379 Patienten, 22.700 Patienten in der TXA-Gruppe und 22.679 in der Kontrollgruppe. Die Subgruppe der thoraxchirurgischen Patienten wurde bei diesem Endpunkt ausgeschlossen, da auf Grund des Patientenkollektives nicht klar unterschieden werden könnte, ob ein MI vor oder nach der Applikation von iv TXA auftrat. Insgesamt wurden 70 MI in der TXA-Gruppe und 77 in der Kontrollgruppe erfasst. Die Applikation von iv TXA war nicht mit einem erhöhten Vorkommen von MI assoziiert (RD = −0,000; 95% CI: −0,001 bis 0,001; P = 0,56). Die Ergebnisse blieben unter Verwendung des REM robust (RD = 0,000; 95% CI: -0,001 bis 0,000, P = 0,42). Für die Subgruppe der polytraumatisierten Patienten zeigte sich bezüglich der MI sowohl bei Verwendung des FEM (RD = -0,002; 95% CI: -0,004 bis -0,000, P = 0,03) als auch bei Verwendung des REM (RD = -0,002; 95% CI: -0,004 bis -0,000; P = 0,03) ein signifikanter Vorteil für Patienten, die TXA iv erhalten hatten.

5.3.7 Schlaganfall oder transitorische ischämische Attacke

Aus den eingeschlossenen Studien lieferten 33 Studien[20,30,42,60,68,75,82,89,96,100,102,117,129,132,133,140,152,154-156,158,160-164,166,167,172,173,189,193,199] Daten zu CII. Dies umfasste 48.433 Patienten, 24.301 Patienten in der TXA-Gruppe und 24.132 in der Kontrollgruppe. Die Subgruppe der neurologischen Patienten wurde bei diesem Endpunkt ausgeschlossen, da auf Grund des Patientenkollektives nicht klar unterschieden werden könnte, ob CII vor oder nach der Applikation von iv TXA auftraten. Insgesamt wurden 114 CII in der TXA-Gruppe und 115 in der Kontrollgruppe erfasst. Die Applikation von iv TXA war nicht mit einem erhöhten Vorkommen von CII assoziiert (RD = -0,000; 95% CI: -0,001 bis 0,001; P = 0,90). Die Ergebnisse blieben unter Verwendung des REM robust (RD = 0,001; 95% CI: -0,001 bis 0,001; P = 0,79).

5.3.8 Weitere thromboembolische Ereignisse

Aus den eingeschlossenen Studien lieferten sechs Studien[41,46,82,102,163,195] Daten zu weiteren TE. Eine Extremitätenischämie wurde in vier Studien[41,46,82,102] erfasst, eine Mesenterialischämie[163] und eine Thrombose der Leberarterie[195] in jeweils einer Studie. Dies umfasste insgesamt 5.138 Patienten, 2.569 Patienten in den TXA-Gruppen und 2.569 in den Kontrollgruppen. Die Applikation von iv

TXA war nicht mit einem erhöhten Vorkommen von Ischämien der Extremitäten (RD = -0,004; 95% CI: -0,023 bis 0,015; P = 0,66) oder des Mesenteriums (RD = 0,002; 95% CI: -0,001 bis 0,005; P = 0,13) sowie Thrombosen der Leberarterie (RD = 0,063; 95% CI: -0,094 bis 0,22; P = 0,44) assoziiert. Die Ergebnisse blieben unter Anwendung des REM robust.

5.3.9 Gesamtmortalität

Aus den eingeschlossenen Studien lieferten 63 Studien (eAppendix 15 des Online Supplements) Daten zur Gesamtmortalität. Dies umfasste 55.305 Patienten, 27.865 Patienten in der TXA-Gruppe und 27.440 in der Kontrollgruppe. Insgesamt starben 2.218 Patienten in der TXA-Gruppe und 2.456 in der Kontrollgruppe. Bei Verwendung des FEM ergab sich ein signifikanter Überlebensvorteil für die Patienten der TXA-Gruppe (RD = −0,011; 95% CI: −0,015 bis −0,007; P < 0,001). Dieser konnte unter Anwendung des REM jedoch nicht bestätigt werden (RD = −0,004; 95% CI: −0,008 bis 0,000; P = 0,05). Die Subgruppe der polytraumatisierten Patienten verzeichnete unter Verwendung beider Modelle signifikante Überlebensvorteile für die TXA-Gruppe (RD = −0,015; 95% CI: −0,022 bis −0,008; P = 0,004). Die Subgruppe der „weiteren“ Patienten zeichnete sich durch eine hohe Heterogenität (I^2 = 78%) aus und lieferte inhomogene Ergebnisse bei Vergleich des FEM (RD = −0,038; 95% CI: −0,06 bis −0,015; P = 0,001) mit dem REM (RD = −0,024; 95% CI: −0,058 bis 0,009; P = 0,15).

5.3.10 Nicht-blutungsassoziierte Mortalität

Aus den eingeschlossenen Studien lieferten 48 Studien (eAppendix 16 des Online Supplements) Daten zur nicht-blutungsassoziierten Mortalität. Dies umfasste 46.619 Patienten, 23.458 Patienten in der TXA-Gruppe und 23.161 in der Kontrollgruppe. Insgesamt starben 1.180 Patienten in der TXA-Gruppe und 1.228 in der Kontrollgruppe. Die Applikation von iv TXA war nicht mit einem erhöhten Auftreten nicht-blutungsassoziierter Sterbefälle assoziiert (RD = −0,002; 95% CI: −0,006 bis 0,002; P = 0,29). Auch unter Verwendung des REM stellte sich dieses Ergebnis als robust dar (RD = −0,000; 95% CI: −0,002 bis 0,001; P = 0,92). Bei Betrachtung der Subgruppen zeigte sich bei Anwendung

des FEM für die neurologischen Patienten ein signifikanter Überlebensnachteil nach iv TXA-Gabe (RD = 0,044; 95% CI: 0,007 bis 0,081; P = 0,02), während sich für thoraxchirurgische Patienten ein signifikanter Überlebensvorteil nach iv TXA-Gabe abzeichnete (RD = −0,025; 95%CI: −0,045 bis −0,005; P = 0,02). Die Ergebnisse beider Subgruppen blieben bei Anwendung des REM jedoch nicht signifikant.

5.3.11 Blutungsassoziierte Mortalität

Aus den eingeschlossenen Studien lieferten 49 Studien (eAppendix 17 des Online Supplements) Daten zur blutungsassoziierten Mortalität. Dies umfasste 46.702 Patienten, 23.501 Patienten in der TXA-Gruppe und 23.201 in der Kontrollgruppe. Insgesamt starben 692 Patienten in der TXA-Gruppe und 874 in der Kontrollgruppe. Die Applikation von iv TXA war mit einem signifikanten Überlebensvorteil in Bezug auf die blutungsassoziierte Mortalität assoziiert (RD = −0,008; 95% CI: −0,011 bis −0,005; P < 0,001). Dieses Ergebnis erwies sich unter Verwendung des REM als robust (RD = −0,004; 95% CI: −0,008 bis −0,001; P = 0,02).

In der Subgruppenanalyse zeigte sich für neurologische (RD = −0,071; 95% CI: −0,102 bis −0,041; P < 0,001) sowie polytraumatisierte Patienten (RD = −0,008; 95% CI: −0,015 bis −0,002; P = 0,008) ein signifikanter Überlebensvorteil bezüglich der blutungsassoziierten Mortalität, welcher sich für die Sensitivitätsanalyse mittels REM als robust erwies. Es muss jedoch darauf hingewiesen werden, dass die Subgruppe der neurologischen Patienten einer hohen Heterogenität (I^2 = 60%) unterliegt. Für die Subgruppe der „weiteren“ Patienten konnte dieser Vorteil lediglich bei Anwendung des FEM verzeichnet werden (RD = −0,018; 95% CI: −0,033 bis −0,004; P = 0,02), nicht aber bei Anwendung des REM (RD = −0,01; 95% CI: −0,028 bis −0,009; P = 0,30).

5.3.12 Patienten mit erhöhtem Risiko für thromboembolische Ereignisse

Unter allen eingeschlossenen Studien haben 56 Studien[18,21,27,29,40,44,45,47,50,52,53,55,57,75,80,81,86,87,93,98,105,130,145,148,149,152-159,162,164,166-174,182-184,188,189,191,192,194,195,198,201,202] Patienten mit einem erhöhten Risiko für TE

in ihrer Rekrutierung berücksichtigt. Aus diesen Studien lieferten 49 Studien[18,21,27,29,40,44,45,47,50,52,53,55,57,75,80,81,86,87,93,98,105,130,145,148,149,152,154-156,158,162,164,166,167,169,171-174,182,183,188,189,191,194,195,198,201,202] Daten zu mindestens einem TE (42 zu VT, 26 zu PE, 25 zu VTE) und 20 Studien[27,86,152-154,156,158,159,162,166-168,170,172,174,183,184,188,192,195] Daten zur Gesamtmortalität. Die Applikation von iv TXA war weder für die Summe aller TE (RD = 0,000; 95% CI: −0,008 bis 0,009; P = 0,95), noch für VT (RD = 0,003; 95% CI: −0,007 bis 0,013; P = 0,57), PE (RD = −0,001; 95% CI: −0,009 bis 0,007; P = 0,73) oder VTE (RD = −0,000; 95% CI: −0,012 bis 0,01; P = 0,89) mit einem signifikant erhöhten Risiko assoziiert. Diese Ergebnisse blieben bei Anwendung der REM robust. Des Weiteren verzeichnete die TXA-Gruppe bei Anwendung des FEM einen signifikanten Überlebensvorteil (RD = −0,038; 95% CI: −0,057 bis −0,018; P < 0,001), welcher unter Anwendung des REM jedoch nicht bestätigt werden konnte (RD = -0,018, 95% CI: -0,043 bis 0,007; P = 0,15).

5.3.13 Metaregression

In die Metaregression zur Untersuchung eines potenziellen Zusammenhangs zwischen der Dosierung von iv TXA und dem Risiko für VTE konnten insgesamt 143 Interventionsgruppen eingeschlossen werden. Für die Einfachgabe variierten die Dosierungen zwischen 10 bis 30 mg/kg Körpergewicht, beziehungsweise für die nicht-gewichtsadaptierte Gabe zwischen 0,5 und 10g. Bei der Mehrfachgabe variierte die Gesamtdosis zwischen 5,5 bis 135 mg/kg Körpergewicht, beziehungsweise 1 bis 16,6g.

Bei Betrachtung der gewichtsadaptierten iv Gabe von TXA (117 Interventionsgruppen) konnte weder für die Einfachgabe (RD = 0,018; 95% CI: -0,053 bis 0,09; P = 0,6) noch für die Mehrfachgabe (RD = -0,005; 95% CI: -0,021 bis 0,011; P = 0,53) ein signifikanter Zusammenhang von Dosierung und dem Auftreten von VTE nachgewiesen werden. Bei Betrachtung der nicht-gewichtsadaptierten iv Gabe von TXA (56 Interventionsgruppen) konnte ebenso weder für die Einfachgabe (RD = -0,001; 95% CI: -0,327 bis 0,325; P > 0,99) noch für die Mehrfachgabe (RD = -0,017; 95% CI: -0,168 bis 0,134; P = 0,82) ein signifikanter Zusammenhang von Dosierung und dem Auftreten von VTE nachgewiesen werden. Um eine übergreifende Aussage treffen zu können,

wurde dort wo möglich die nicht-gewichtsadaptierte Dosierung mit Hilfe der Gewichtsangabe der Interventionsgruppe in mg/kg konvertiert. So konnten zusätzlich 142 Interventionsgruppen in einer übergreifenden Metaregressionsanalyse ausgewertet werden. Auch hier konnte kein Zusammenhang zwischen der verabreichten iv TXA-Dosis und dem Auftreten von VTE nachgewiesen werden (RD = -0,005; 95% CI: -0,013 bis 0,003, P = 0,21).

5.3.14 Bias-Risiko

Aus allen eingeschlossenen Studien wurden 139 mit einem geringen und 10 Studien mit einem hohen Bias-Risiko für die Generation einer Zufallsreihenfolge bewertet. Bei 43 Studien war das Risiko hinsichtlich der Generation einer Zufallsreihenfolge unklar. Bei 68 Studien war die verdeckte Zuordnung mit einem geringen Bias-Risiko behaftet, bei 4 Studien mit einem hohen. Da TE als postoperative Komplikation im klinischen Alltag, unabhängig von Studien, eine große Aufmerksamkeit erfahren, wurde davon ausgegangen, dass eine fehlende oder inkomplette Verblindung in diesem Fall nicht zu einem erhöhten Bias führen würde. Aus diesem Grund wurde das Bias-Risiko für die Verblindung von Teilnehmern und Personal sowie für die Verblindung der Auswertung für alle Studien als gering bewertet. Bei 191 Studien wurde das Bias-Risiko bezüglich inkompletter Ergebnisdaten als gering bewertet. Für 188 Studien wurde das Risiko eines selektiven Ergebnisberichtes als unklar eingeschätzt. Das Bias-Risiko für sonstige Ursachen war für 191 Studien unklar.
Die Analyse der Funnel-Plots ergab für die Endpunkte der Summe aller TE, VT, CII und nicht-blutungsassoziierte Mortalität keinen Anhalt für einen Publikationsbias. Eine leichte Rechtsverschiebung zeigte sich für die Endpunkte PE, VTE und MI, eine leichte Linksverschiebung für Gesamtmortalität und Blutungsassoziierte Mortalität. Die Verschiebung kam im Wesentlichen durch die Subgruppe der neurologischen Patienten zustande.

Für den primären Endpunkt der Summe aller TE wurde eine Sensitivitätsanalyse der 59 Studien mit einem geringen Selektionsbias-Risiko durchgeführt. Die oben präsentierten Ergebnisse erwiesen sich sowohl unter Anwendung des FEM (RD

= -0,001, 95% CI: -0,002 bis 0,003; P = 0,89) als auch unter Anwendung des REM (RD = -0,001, 95% CI: -0,002 bis 0,001; P = 0,89) als robust. Die Applikation von iv TXA war in der Gruppe der Studien mit einem geringen Selektionsbias nicht mit einem erhöhten Vorkommen von TE assoziiert.

5.3.15 Aktualisierte Metaanalyse

Die gezielte Suche nach den Einschlusskriterien entsprechenden RCT zwischen Juli 2018 und Dezember 2020 ergab 72 Treffer. Nach Durchsicht der Volltexte blieben 24 Studien[208-231] , die zusätzlich eingeschlossen werden konnten. Hiermit konnten nun insgesamt 216 RCT[16-231] für die Endpunkte der Summe aller TE, VT, PE und VTE sowie der Gesamtmortalität berücksichtigt werden. Diese aktualisierte Metaanalyse zeigte, dass die Applikation von iv TXA nicht mit einem erhöhten Risiko für VT (RD = −0,000; 95% CI: −0,001 bis 0,001; P = 0,85), PE (RD = 0,000; 95% CI: −0,001 bis 0,001; P = 0,74), VTE (RD = 0,000; 95% CI: −0,001 bis 0,002; P = 0,85) oder der Summe aller TE assoziiert (RD = 0,001; 95% CI: −0,001 bis 0,002; P = 0,49) war. Des Weiteren war die Gabe von iv TXA mit einem signifikanten Überlebensvorteil assoziiert (RD = −0,007; 95% CI: −0,012 bis −0,004; P < 0,001). Die Berechnungen blieben auch unter Anwendung des REM robust. Für den Endpunkt der Summe aller TE wurde zudem eine Sensitivitätsanalyse zur Berechnung des RR durchgeführt. Sowohl unter Berücksichtigung von Studien mit null Ereignissen in beiden Gruppen (RR = 1,02; 95% CI: 0,94 bis 1,11; P = 0,56) als auch unter Ausschluss dieser Studien (RR = 1,03; 95% CI: 0,95 bis 1,12; P = 0,52) konnte keine Assoziation zwischen iv TXA und TE nachgewiesen werden.

5.4 Diskussion

Tranexamsäure wirkt als Antifibrinolytikum einer potenziellen Hyperfibrinolyse und damit einem erhöhten Blutverlust effizient entgegen[11]. Bei rechtzeitiger Gabe kann so die Mortalität von schwer blutenden Patienten signifikant reduziert werden. Eine multizentrische internationale randomisiert kontrollierte Studie an 10.127 polytraumatisierten Patienten[232] konnte zeigen, dass die Mortalität der TXA-Gruppe bei Applikation von iv TXA innerhalb der ersten drei Stunden nach dem Unfallereignis im Vergleich zur Placebo-Gruppe signifikant reduziert werden

konnte. Auf Grundlage dieser Ergebnisse setzte die Weltgesundheitsorganisation (WHO) TXA 2011 auf die Liste der essenziellen Medikamente[233]. Im Jahr 2012 konnte durch die WOMAN Studie (World Maternal Antifibrinolytic Trial) ein Überlebensvorteil durch iv TXA für Frauen unter der Geburt eindrucksvoll bestätigt werden[234]. Bei unumstritten reduziertem Blutverlust unter iv TXA und vermehrter Anwendung wurden jedoch Bedenken bezüglich der Sicherheit, insbesondere in Bezug auf TE, laut. In der Literatur finden sich kontroverse Ergebnisse, variierend zwischen keinem[234] bis hin zu einem zwölffach erhöhten[235] Thromboserisiko.

Bisherige Metaanalysen nahmen sich dieser Problematik vor allem im Bereich der orthopädischen Patienten an[12,13,108,236]. So konnten beispielsweise Franchini und Kollegen 2018 zeigen, dass iv TXA nicht mit einem erhöhten Risiko für VTE assoziiert ist. Da viele der eingeschlossenen Studien null Ereignisse verzeichneten, berechneten die Autoren sowohl RR (RR = 1,07; 95% CI: 0,76 bis 1,50; P = 0,98) als auch RD (RD = 0,00; 95% CI: −0,00 bis 0,01; P = 1,00), um einen hierdurch bedingten Bias zu verringern[13].

Yates und Kollegen führten 2019 eine Metaanalyse mit 161 Studien verschiedener medizinischer Fachrichtungen durch. Die Untersuchung von 20.679 Patienten zeigte keine Assoziation zwischen iv TXA und VTEs (RR = 0,95; 95% CI: 0,78 bis 1,15). Da die Autoren den RR berechneten, wurden Studien mit null Ereignissen von der Berechnung ausgeschlossen. Eine Subgruppenanalyse wurde nicht durchgeführt[14].

5.4.1 Zusammenfassung und Einordnung der Ergebnisse

Um eine Assoziation von Thromboembolierisiko und iv TXA zu untersuchen, führten wir eine Metaanalyse mit Studien aller medizinischen Fachrichtungen, die Daten zu TEs erhoben und zur Verfügung gestellt haben, durch. Für die Analyse nutzten wir die RD als primäre Berechnungsgröße. Auch wenn die Verwendung der RD zu weiten Konfidenzintervallen führte, bietet sie die Möglichkeit, alle verfügbare Evidenz zu berücksichtigen und somit eine allgemeingültige Schlussfolgerung zuzulassen. Zusätzlich führten wir eine Sensitivitätsanalyse mittels RR durch, welche robuste Ergebnisse zeigte. Alle Analysen wurden in

einem 164 Seiten umfassenden Online Supplement zusätzlich zur Verfügung gestellt.

Insgesamt konnten 216 Studien zwischen 1976 und 2020 in die vorliegende Metaanalyse eingeschlossen werden. In der TXA-Gruppe fanden sich 1.020 (2,1%) und in der Kontrollgruppe 900 (2,0%) TEs. Es konnte keine Assoziation zwischen iv TXA und einem erhöhten Risiko für TEs gefunden werden. Bezüglich der blutungsassoziierten Mortalität zeigte sich ein signifikanter Überlebensvorteil der TXA-Gruppe gegenüber der Kontrollgruppe. Dieser zeigte sich insbesondere in der Subgruppe der polytraumatisierten und der neurologischen Patienten. Es ist zu erwähnen, dass unsere Suche nur eine Studie[232] mit polytraumatisierten Patienten, die iv TXA im Vergleich mit Placebo oder keinem Medikament erhalten haben, ergab. Für die nicht-blutungsassoziierte Mortalität fand sich kein signifikanter Unterschied zwischen den Gruppen. Eine aktualisierte Metaanalyse wurde durchgeführt, um kürzlich veröffentlichte RCTs zu berücksichtigen. Die Ergebnisse für die Summe der TEs, VTs, PEs, VTEs und die Gesamtmortalität blieben bei Einschluss der Studien von Juli 2018 bis Dezember 2020 robust.

Die Analyse der Subgruppen ergab für die neurologischen Patienten, im Gegensatz zu den Studien der anderen Fachdisziplinen, keine eindeutigen Ergebnisse. Die mittels des FEM errechneten Ergebnisse für die Endpunkte Summe aller TEs und nicht-blutungsassoziierte Mortalität blieben bei Verwendung des REM nicht robust. Insgesamt lieferten zwölf Studien mit neurologischen Patienten Daten zu TEs. Die Studiengröße variierte zwischen 24 und 2.325 eingeschlossenen Patienten. Die Heterogenität in dieser Subgruppe blieb auch bei einem Ausschluss der Studien mit mehr als 1.000 Patienten hoch. Zusammenfassend lässt sich sagen, dass die hohe Heterogenität und die Asymmetrie in den Funnel-Plots darauf hinweisen, dass weitere Studien an neurologischen Patienten, zum Beispiel nach Subarachnoidalblutung, nach Schädel-Hirn-Trauma, notwendig wären, um die Sicherheit von iv TXA in diesem speziellen Patientenklientel einordnen zu können.

Es wird oft diskutiert, dass Studien mit einer geringen Patientenzahl möglicherweise eine unzureichende Teststärke haben, um einen Interventionseffekt zu erkennen[237]. Um diesem Problem zu begegnen, führten wir eine Sensitivitätsanalyse durch und stellten fest, dass die Gabe von iv TXA in

Studien mit ≤99, 100 bis 999 und ≥1.000 Patienten nicht mit einem erhöhten thromboembolischen Risiko assoziiert war.

Patienten mit einem erhöhten Thromboembolierisiko werden häufig von Studien zu TXA ausgeschlossen. Die Halbwertszeit von iv TXA ist mit 1,9 bis 2,7 Stunden[238,239] sehr kurz, sodass diese Patienten von einer iv TXA-Gabe in der akuten Blutungssituation ebenfalls profitieren. Die vorliegende Arbeit adressiert diese Frage mittels einer Sensitivitätsanalyse von Studien, welche diese Risikopatienten einschlossen. Auch hier konnte kein Zusammenhang von TEs oder Mortalität und iv TXA festgestellt werden. Dieses Ergebnis legt nahe, dass auch Patienten mit einem erhöhten Risiko für TEs von iv TXA profitieren können. Die verabreichte Dosis von iv TXA im vorliegenden Studienkollektiv variiert stark von 0,5 g bis 5 g oder 10 mg/kg bis 100 mg/kg. Die breite Anwendung von iv TXA mit einer standardisierten Dosis posttraumatisch und postpartal bis hin zu einer gewichtsadaptierten Gabe im perioperativen Setting könnte zu der Fülle an unterschiedlichen Behandlungsschemata geführt haben. Es ist jedoch darauf hinzuweisen, dass die in dieser Arbeit integrierte Metaregressionsanalyse keinen dosisabhängigen Effekt zwischen iv TXA und VTEs aufzeigen konnte.

5.4.2 Limitationen

Diese Metaanalyse liefert wichtige und neue Daten für die tägliche Patientenversorgung. Dennoch sind einige Limitationen aufzuzeigen: Es ist nicht auszuschließen, dass unsere Suche, trotz der ausführlichen zusätzlichen händischen Recherche, nicht alle Studien erfasst hat, die unseren Einschlusskriterien entsprochen hätten. Da unsere Ergebnisse bei Einbeziehung der jüngeren Studien zwischen Juli 2018 und Dezember 2020 jedoch unverändert blieben, ist es unwahrscheinlich, dass der Einschluss weiterer Studien die Ergebnisse dieser Analyse grundlegend verändern würde.

Die Nachbeobachtungszeit in den einzelnen Studien variierte stark von 24 Stunden bis hin zu mehreren Monaten. Da iv TXA jedoch eine kurze Halbwertszeit von 1,9 bis 2,7 Stunden hat[238,239] und die Mehrzahl der thrombotischen Ereignisse sechs bis acht Tage postoperativ auftreten[240], kann davon ausgegangen werden, dass TXA bedingte Nebenwirkungen bereits in einem kurzen Beobachtungszeitraum registriert werden können.

Darüber hinaus wurde die Diagnostik von TEs nicht standardisiert, beispielsweise durch Ultraschall-Screening, sodass möglicherweise nicht in allen Fällen asymptomatische Thrombosen nachgewiesen wurden und die Inzidenz der TE in einigen Studien unterschätzt worden sein könnte. Viele der eingeschlossenen Studien lieferten zudem keine ausreichenden Informationen über die Durchführung einer Thromboseprophylaxe, sodass der Zusammenhang von Thromboseprophylaxe und thromboembolischen Ereignissen unter iv TXA nicht weiter untersucht wurde. Da venöse Thrombosen, unabhängig vom Einschluss in eine Studie, eine wichtige postoperative und postpartale Komplikation darstellen, ist davon auszugehen, dass auch bei lückenhafter Verblindung Thrombosen in der Kontrollgruppe ebenso wie in der Interventionsgruppe aufgefallen sind.

5.4.3 Schlussfolgerung

Die Analyse von 216 RCTs aus allen medizinischen Fachrichtungen ergab, unabhängig von der verwendeten Dosierung, kein signifikant erhöhtes Risiko für TEs bei Patienten, die iv TXA erhalten haben, im Vergleich zu einer Kontrollgruppe. Die vorliegenden Ergebnisse unterstützen die sichere Anwendung von iv TXA und legen einen wahrscheinlichen Überlebensvorteil nahe.

5.4.4 Offene Fragen und zukünftige Forschung

Die hohe Heterogenität in der Subgruppe der neurologischen Patienten und die Asymmetrie in deren Funnel-Plots unterstreicht die Notwendigkeit weiterer Forschung zur Sicherheit von iv TXA für diese Patientengruppe.

Die Sensitivitätsanalyse von Studien mit Risikopatienten legt nahe, dass auch diese von iv TXA profitieren könnten. Um eine gültige Aussage hierzu treffen zu können, braucht es jedoch zukünftige Studien, die iv TXA an diesen Patienten zielgerichtet untersuchen.

6. Übersicht des zur Veröffentlichung angenommenen Manuskripts

Taeuber I, Weibel S, Herrmann E, et al. Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Surg.* 2021;156(6):e210884. doi:10.1001/jamasurg.2021.0884

Reply Letter:

Taeuber I, Choorapoikayil S, Meybohm P. Importance of the Assessment Time Window for Intravenous Tranexamic Acid and Thromboembolic Events—Reply. *JAMA Surg.* Published online September 01, 2021. doi:10.1001/jamasurg.2021.4141

7. Das Manuskript

JAMA Surgery | Original Investigation

Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality

A Systematic Review, Meta-analysis, and Meta-regression

Isabel Taeuber; Stephanie Weibel, PhD; Eva Herrmann, PhD; Vanessa Neef, MD; Tobias Schlesinger, MD; Peter Kranke, MD; Leila Messroghli, MD; Kai Zacharowski, MD, PhD; Suma Choorapoikayil, PhD; Patrick Meybohm, MD

IMPORTANCE Tranexamic acid (TXA) is an efficient antifibrinolytic agent; however, concerns remain about the potential adverse effects, particularly vascular occlusive events, that may be associated with its use.

OBJECTIVE To examine the association between intravenous TXA and total thromboembolic events (TEs) and mortality in patients of all ages and of any medical disciplines.

DATA SOURCE Cochrane Central Register of Controlled Trials and MEDLINE were searched for eligible studies investigating intravenous TXA and postinterventional outcome published between 1976 and 2020.

STUDY SELECTION Randomized clinical trials comparing intravenous TXA with placebo/no treatment. The electronic database search yielded a total of 782 studies, and 381 were considered for full-text review. Included studies were published in English, German, French, and Spanish. Studies with only oral or topical tranexamic administration were excluded.

DATA EXTRACTION AND SYNTHESIS Meta-analysis, subgroup and sensitivity analysis, and meta-regression were performed. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

MAIN OUTCOMES AND MEASURES Vascular occlusive events and mortality.

RESULTS A total of 216 eligible trials including 125 550 patients were analyzed. Total TEs were found in 1020 (2.1%) in the group receiving TXA and 900 (2.0%) in the control group. This study found no association between TXA and risk for total TEs (risk difference = 0.001; 95% CI, −0.001 to 0.002; $P = .49$) for venous thrombosis, pulmonary embolism, venous TEs, myocardial infarction or ischemia, and cerebral infarction or ischemia. Sensitivity analysis using the risk ratio as an effect measure with (risk ratio = 1.02; 95% CI, 0.94-1.11; $P = .56$) and without (risk ratio = 1.03; 95% CI, 0.95-1.12; $P = .52$) studies with double-zero events revealed robust effect size estimates. Sensitivity analysis with studies judged at low risk for selection bias showed similar results. Administration of TXA was associated with a significant reduction in overall mortality and bleeding mortality but not with nonbleeding mortality. In addition, an increased risk for vascular occlusive events was not found in studies including patients with a history of thromboembolism. Comparison of studies with sample sizes of less than or equal to 99 (risk difference = 0.004; 95% CI, −0.006 to 0.014; $P = .40$), 100 to 999 (risk difference = 0.004; 95% CI, −0.003 to 0.011; $P = .26$), and greater than or equal to 1000 (risk difference = −0.001; 95% CI, −0.003 to 0.001; $P = .44$) showed no association between TXA and incidence of total TEs. Meta-regression of 143 intervention groups showed no association between TXA dosing and risk for venous TEs (risk difference, −0.005; 95% CI, −0.021 to 0.011; $P = .53$).

CONCLUSIONS AND RELEVANCE Findings from this systematic review and meta-analysis of 216 studies suggested that intravenous TXA, irrespective of dosing, is not associated with increased risk of any TE. These results help clarify the incidence of adverse events associated with administration of intravenous TXA and suggest that TXA is safe for use with undetermined utility for patients receiving neurological care.

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Invited Commentary

Supplemental content

Author Affiliations: Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt am Main, Germany (Taeuber, Neef, Messroghli, Zacharowski, Choorapoikayil, Meybohm); Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Wuerzburg, Germany (Weibel, Schlesinger, Kranke, Meybohm); Institute of Biostatistics and Mathematical Modelling, Goethe University Frankfurt, Frankfurt, Germany (Herrmann).

Corresponding Author: Patrick Meybohm, MD, Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Oberduerrbacher Str 6, 97080 Wuerzburg, Germany (meybohm_p@ukw.de).

Major surgery is commonly associated with substantial blood loss, subsequent anemia, and the need for blood transfusion. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study investigators[1] reported that among 40 004 patients undergoing noncardiac surgical procedures, the most common complications leading to death were major bleeding followed by myocardial injury and infection. Tranexamic acid (TXA) is an antifibrinolytic agent and widely used for prophylaxis and treatment of bleeding caused by hyperfibrinolysis. Poeran and colleagues[2] reported that the use of TXA increased in orthopedic surgery from almost 0% in 2006 to 11.2% in 2012, and the effectiveness to reduce surgical blood loss and associated complications has been reported.

Ker and colleagues[3] performed a meta-analysis including 129 trials encompassing more than 10 000 patients suggesting that administration of TXA is associated with reductions in allogeneic blood transfusion by 38% and that further trials assessing this effect are unlikely to add new insights. However, TXA is only applied with caution because antifibrinolytic therapy may be associated with an increased risk of seizures,[4,5] myocardial infarction,[6] and other thrombotic complications.[7-9] Nevertheless, the association of vascular occlusive events with TXA administration is controversial. Overall, vascular occlusive events are rare, and studies with 0 events are often excluded from meta-analysis because the assumption is that these studies may not be relevant to the treatment effect. Of 115 investigated trials in the meta-analysis by Ker and colleagues,[3] 72 examined the rate of pulmonary embolism (PE) and 66 studies examined the rate of deep vein thrombosis (DVT). However, trials with 0 events were excluded from analysis. Overall, TXA was not associated with an increased risk of PE in 10 trials (risk ratio [RR] = 0.61; 95% CI, 0.25-1.47) (event rate in TXA group: 4 of 449 vs control: 8 of429) and DVT in 19 trials (RR = 0.86; 95% CI, 0.53-1.39) (event rate in TXA group: 25 of 785 vs control: 29 of 785). Based on the low number of included event rates, the issue of use of TXA and vascular occlusive events remains unaddressed.[3] Several guidelines recommend the use of TXA in patients with excessive bleeding.[10-13] However, little is known about the incidence of vascular occlusive events in patients with substantial comorbidities or a history of thromboembolic events (TEs). In addition, debate is ongoing about the optimal perioperative dosing of intravenous TXA, which varies widely, ranging from 0.5 to 5 g or 10 to 100 mg/kg and might also explain the different observed incidences of vascular occlusive events.

To further explore the possible associations between intravenous TXA and vascular occlusive events in patients undergoing surgery or experiencing bleeding, we performed a comprehensive meta-analysis. We included randomized clinical trials (RCTs) irrespective of event rate and dosing regimen comparing intravenous TXA with a control group (placebo or no treatment) in our analysis. These data might help to clarify the safety of intravenous TXA and elucidate a possible dosing effect.

Key Points

Question Is intravenous administration of tranexamic acid associated with thromboembolic events in patients of all ages and of any medical discipline?

Findings In this systematic review and meta-analysis of 216 studies of 125 550 patients undergoing surgical procedures and receiving either intravenous administration of tranexamic acid or placebo or no treatment, 1020 (2.1%) thromboembolic events in the tranexamic acid group and 900 (2.0%) total thromboembolic events in the control group were found. There was no increased risk of any thromboembolic event in patients of all medical disciplines.

Meaning These results clarify whether vascular occlusive events are associated with administration of tranexamic acid.

Methods

Search Strategy and Study Selection

We systematically searched Cochrane Central Register of Controlled Trials and MEDLINE via PubMed for eligible RCTs investigating the effect of intravenous TXA on postinterventional outcome published between 1976 and 2018, followed by a manual search through September 20, 2019. To identify RCTs published after completion of the meta-analysis, another systematic review was performed for eligible studies published between July 1, 2018, and December 31, 2020. Search terms used and additional details are available in eAppendix 1 in the Supplement.

Outcome Measures

End points were venous thrombosis (VT), PE, venous thromboembolic events (VTEs), myocardial infarction or ischemia (MI), cerebral infarction or ischemia (CII), limb ischemia, mesenteric ischemia, hepatic artery thrombosis, and composite of all vascular occlusive events (total thromboembolic events [total TEs]). In addition, we assessed overall mortality, bleeding mortality, and any nonbleeding mortality rate (eAppendix 2 in the Supplement).

Data Extraction and Statistical Analyses

This study was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline for cohort studies.[14] Because many studies showed 0 events in both groups, we assessed the risk difference (RD) to provide accurate results. The fixed-effect analysis was used for meta-analysis because we assumed that the true effect size was the same in all studies because TEs are rare and the only reason the effect size varied between studies could be caused by the number of recruited patients. However, we performed sensitivity analysis using a random-effects model to estimate whether our results were robust. Furthermore, we performed a sensitivity analysis using the RR as an effect size measure with either including (continuity correction of 0.5) or excluding studies with 0 cell frequencies. An additional analysis of

total TEs with subgroups by study size was conducted. Heterogeneity was assessed by using I^2 statistics. A meta-regression was performed to investigate a relation between the event rate and the dosage of intravenous TXA.

We also investigated whether intravenous TXA was associated with increased risk for TE, VT, PE, VTEs, and overall mortality in patients with risks for TEs. Therefore, secondary analyses were performed only with studies including patients with a history of any TE, coronary artery disease, thrombophilia, or contraindication for TXA. Two of us (I.T. and S.C.) independently assessed the methodologic quality of included studies based on the Cochrane Risk of Bias tool. A sensitivity analysis with studies judged at low risk of selection bias was assessed for total TEs. Funnel plots were generated to detect possible evidence for small-study bias. Discrepancies were resolved by group discussion (I.T., S.C., P.M., E.H., and S.W.). Two-sided $P < .05$ was considered statistically significant. The Review Manager (RevMan) program, version 5.3 (The Nordic Cochrane Centre) and R software, version 3.6.1 (R Foundation for Statistical Computing) were used for analysis and graphic illustrations. Continuity corrections were performed with the R package, meta version 4.12-0. Further details appear in eAppendix 3 in the Supplement.

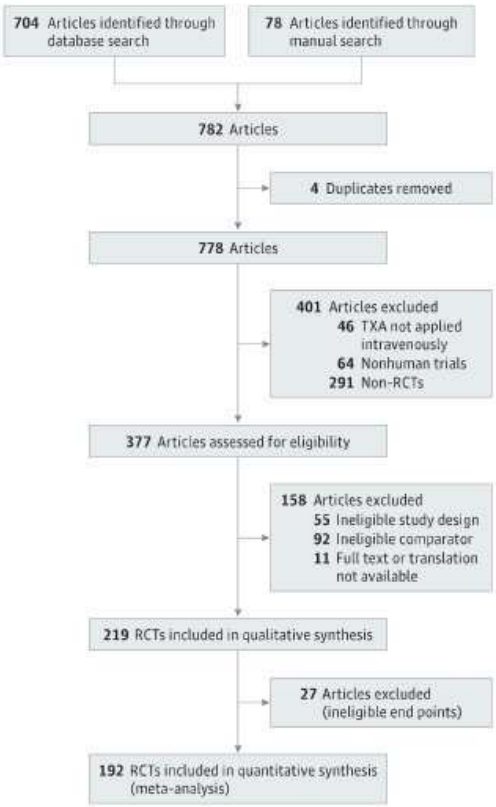
Results

The electronic database and manual search yielded a total of 782 studies published between 1976 and 2018. In total, 381 articles were considered for full-text review, of which 189 were excluded because of ineligible study designs (n = 55) or control groups (n = 92), ineligible end points (n = 27), missing or nontranslatable full text (n = 11), and duplicates (n = 4), leaving 192 RCTs[6,15-205] for final analysis (**Figure**). Included studies were published in English, German, French, and Spanish. Twenty-three authors were contacted, of whom 2 provided clarification[113] or data,[185] whereas 21 did not reply. In total, 68 118 patients of this search were included in this meta-analysis (34 610 TXA group and 33 508 control group). Demographic data and subgroup characteristics are reported in eTable 1 and eAppendix 4 in the Supplement.

Total Thromboembolic Events

In total, 176 studies (eAppendix 11 in the Supplement) provided data on total TEs in 65 900 patients (n = 33 487 TXA group vs n = 32 413 control group). We found 779 total TEs (2.3%) in the TXA group and 706 total TEs (2.2%) in the control group. Overall, administration of intravenous TXA was not associated with an increased risk for total TEs (RD = 0.001; 95% CI, −0.002 to 0.003; $P = .66$) (**Table 1**; eFigure 1 in the Supplement). However, the subgroup analysis showed that TXA was associated with a significantly increased risk for total TEs in the group of patients with neurological conditions (RD = 0.026; 95% CI, 0.007-0.045; $P = .007$). Sensitivity analysis using a random-effects model showed robust effect estimates for total TEs (RD = −0.001; 95% CI, −0.002 to 0.001; $P = .39$), but no significantly increased risk for total TEs in the subgroup of patients with neurological conditions was shown (RD = 0.018; 95% CI, −0.013 to 0.048; $P = .26$) (Table 1; eFigure 2 in the Supplement). Analysis of patients with neurological conditions showed a significant heterogeneity (I^2 = 57%). To investigate whether the heterogeneity was associated with sample size, we performed a sensitivity analysis including studies with sample sizes with more than 1000 patients. Overall, the heterogeneity remained high (I^2 = 73%). A sensitivity analysis was performed using the RR as an effect measure with and without studies with double-zero events revealed robust effect estimates for all subgroups (RR = 1.01; 95% CI, 0.92-1.11; $P = .77$ and RR = 1.02; 95% CI, 0.93-1.12; $P = .71$) (eFigure 3 and eFigure 4 in the Supplement). To elucidate whether incidence of total TEs increases with sample size, we performed a sensitivity analysis of studies including less than or equal to 99 patients, 100 to 999 patients, or greater than or equal to 1000 patients. Overall, administration of intravenous TXA was not associated with an increased risk for total TEs in studies with less than or equal to 99 patients

Figure. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram Showing Study Selection



The database search was conducted for articles published between 1976 and 2018, and the manual search was conducted through September 20, 2019. An updated search for studies published between July 1, 2018, and December 31, 2020, resulted in 72 potential additional studies of which 48 studies were excluded leaving 24 additional studies. Overall, 216 eligible studies underwent analysis. RCT indicates randomized clinical trial; TXA, tranexamic acid.

Table 1. TXA and Total Thromboembolic Events

Medical discipline	TXA		Control		Model	Risk difference (95% CI)	P value	I^2, %
	No. of included studies	Events	No. of included patients	Events	No. of included patients			
Cardiothoracic	16	72	3171	74	3009	Fixed effect	−0.001 (−0.009 to 0.007)	.83	0
						Random effects	−0.001 (−0.007 to 0.008)	.91	
Neurological	12	282	2007	230	2000	Fixed effect	0.026 (0.007 to 0.045)	.01	57
						Random effects	0.018 (−0.013 to 0.048)	.26	
Gynecological	26	35	12 356	41	12 286	Fixed effect	−0.001 (−0.002 to 0.001)	.53	0
						Random effects	−0.001 (−0.002 to 0.001)	.50	
Orthopedic	101	172	4787	113	4149	Fixed effect	0.001 (−0.007 to 0.009)	.79	0
						Random effects	0.001 (−0.004 to 0.007)	.64	
Major trauma	1	204	10 060	233	10 067	Fixed effect	−0.003 (−0.007 to 0.001)	.16	NA
						Random effects	−0.003 (−0.007 to 0.001)	.16	
Maxillofacial	6	0	265	0	192	Fixed effect	0.000 (−0.023 to 0.023)	>.99	0
						Random effects	0.000 (−0.019 to 0.019)	>.99	
Pediatric	2	0	42	0	40	Fixed effect	0.000 (−0.067 to 0.067)	>.99	0
						Random effects	0.000 (−0.064 to 0.064)	>.99	
Other	12	14	799	15	670	Fixed effect	−0.004 (−0.021 to 0.013)	.62	0
						Random effects	−0.004 (−0.018 to 0.011)	.63	
Total	176	779	33 487	706	32 413	Fixed effect	0.001 (−0.002 to 0.003)	.66	0
						Random effects	−0.001 (−0.002 to 0.001)	.39	

Abbreviations: NA, not applicable; TXA, tranexamic acid.

(RD = 0.004; 95% CI, −0.006 to 0.014; P = .40), 100 to 999 patients (RD = 0.004; 95% CI, −0.003 to 0.011; P = .26), and greater than or equal to 1000 patients (RD = −0.001; 95% CI, −0.003 to 0.001; P = .44) (eFigure 5 in the Supplement). The results remained robust using a random-effects model (eFigure 6 in the Supplement).

Venous Thrombosis, Pulmonary Embolism, and Venous Thromboembolic Events

In total, 163 studies (eAppendix 12 in the Supplement) provided data on VTs in 59 666 patients (n = 30 334 TXA group vs n = 29 332 control group). We found 272 VTs (0.9%) in the TXA group and 213 VTs (0.7%) in the control group. Overall, administration of intravenous TXA was not associated with an increased risk for VT (RD = −0.000; 95% CI, −0.002 to 0.002; P > .99) (eTable 2, eFigure 7 in the Supplement). Sensitivity analysis using a random-effects model showed robust effect estimates for PE (RD = −0.000; 95% CI, −0.001 to 0.000; P = .26) (eTable 2; eFigure 8 in the Supplement).

In total, 129 studies (eAppendix 13 in the Supplement) provided data on PE events in 61 562 patients (n = 31 155 TXA group vs n = 30 407 control group). We found 152 PE events (0.5%) in the TXA group and 153 PE events (0.5%) in the control group. Overall, administration of intravenous TXA was not associated with an increased risk for PE (RD = −0.000; 95% CI, −0.001 to 0.001; P = .89) (eTable 3; eFigure 9 in the Supplement). Sensitivity analysis using a random-effects model showed robust effect estimates for VT (RD = −0.000; 95% CI, −0.001 to 0.001; P = .68) (eTable 3; eFigure 10 in the Supplement).

To assess the total number of VTEs, PE and VT were combined and analyzed. In total, 123 studies (eAppendix 14 in the Supplement) provided data on VTEs in 56 126 patients (n = 28 438 TXA group vs n = 27 688 control group). We found 348 VTEs (1.2%) in the TXA group and 304 VTEs (1.1%) in the control group. Overall, administration of intravenous TXA was not associated with an increased risk for VTEs (RD = −0.000; 95% CI, −0.002 to 0.002; P = .71) (eTable 4; eFigure 11 in the Supplement). Sensitivity analysis using a random-effects model showed robust effect estimates for VTE (RD = −0.001; 95% CI, −0.002 to 0.001; P = .39) (eTable 4; eFigure 12 in the Supplement).

Myocardial Infarction or Ischemia, Cerebral Infarction or Ischemia, and Other Thromboembolic Events

Overall, administration of intravenous TXA was not associated with an increased risk for MI (RD = −0.000; 95% CI, −0.001 to 0.001; P = .56) (eTable 5; eFigure 13 and eFigure 14 in the Supplement). Detailed analyses are reported in eAppendix 5 in the Supplement.

Overall, administration of intravenous TXA was not associated with an increased risk for CII (RD = −0.000; 95% CI, −0.001 to 0.000; P = .90) (eTable 6; eFigure 15 in the Supplement) or other TEs (eFigures 16-18 in the Supplement). Detailed analyses are reported in eAppendix 6 in the Supplement.

Overall Mortality

In total, 63 studies (eAppendix 15 in the Supplement) assessed the overall mortality in 55 305 patients (n = 27 865 TXA group vs n = 27 440 control group). Death occurred in 2218 patients (8%) in the TXA group and 2456 patients (9%) in the control group. Overall, administration of intravenous TXA was

Table 2. TXA and Overall Mortality

Medical discipline	No. of included studies	TXA		Control		Model	Risk difference (95% CI)	P value	I^2, %
		Events	No. of included patients	Events	No. of included patients				
Cardiothoracic	15	32	3006	46	2970	Fixed effect	−0.005 (−0.011 to 0.002)	.12	0
						Random effects	−0.003 (−0.009 to 0.003)	.30	
Neurological	13	426	2017	449	2002	Fixed effect	−0.013 (−0.032 to 0.005)	.31	27
						Random effects	−0.016 (−0.041 to 0.02)	.28	
Gynecological	8	227	10 871	256	10 814	Fixed effect	−0.003 (−0.007 to 0.001)	.17	0
						Random effects	−0.002 (−0.005 to 0.002)	.31	
Orthopedic	16	18	844	17	652	Fixed effect	0.001 (−0.018 to 0.019)	.94	0
						Random effects	−0.002 (−0.015 to 0.011)	.76	
Major trauma	1	1463	10 060	1613	10 067	Fixed effect	−0.015 (−0.022 to −0.008)	.004	NA
						Random effects	−0.015 (−0.022 to −0.008)	.004	
Pediatric	1	0	40	0	42	Fixed effect	0.000 (−0.046 to 0.046)	>.99	NA
						Random effects	0.000 (−0.047 to 0.047)	>.99	
Other	9	52	1027	75	893	Fixed effect	−0.038 (−0.06 to −0.015)	.001	78
						Random effects	−0.024 (−0.058 to 0.009)	.15	
Total	63	2218	27 865	2456	27 440	Fixed effect	−0.011 (−0.015 to −0.007)	<.001	16
						Random effects	−0.004 (−0.008 to 0.000)	.05	

Abbreviations: NA, not applicable; TXA, tranexamic acid.

associated with significant reductions in overall mortality in patients of the TXA group (RD = −0.011; 95% CI, −0.015 to −0.007; $P < .001$) (**Table 2**) (eFigure 19 in the Supplement). Subgroup analysis showed a significantly decreased overall mortality in patients with trauma (RD = −0.015; 95% CI, −0.022 to −0.008; $P = .004$) and patients receiving care from other disciplines (RD = −0.038; 95% CI, −0.06 to −0.015; $P = .001$) for the TXA groups, whereas no significant differences could be detected within the remaining medical disciplines. Sensitivity analysis using a random-effects model did not show robust effect estimates for overall mortality (RD = −0.004; 95% CI, −0.008 to 0.000; $P = .05$) and for the subgroup of patients receiving care from other disciplines (RD = −0.024; 95% CI, −0.058 to 0.009; $P = .15$) (Table 2; eFigure 20 in the Supplement). Analysis of patients of other disciplines showed a significant heterogeneity ($I^2 = 78\%$).

Nonbleeding Mortality and Bleeding Mortality

In total, 48 studies (eAppendix 16 in the Supplement) assessed nonbleeding mortality in 46 619 patients (n = 23 458 TXA group vs n = 23 161 control group). Death occurred in 1180 patients (5%) in the TXA group and 1228 patients (5%) in the control group. Overall, administration of intravenous TXA was not associated with a decreased risk for nonbleeding mortality (RD = −0.002; 95% CI, −0.006 to 0.002; $P = .29$) (eTable 7; eFigure 21 in the Supplement). However, subgroup analysis showed a significant increase for nonbleeding mortality in patients with neurological conditions of the TXA group (RD = 0.044; 95% CI, 0.007-0.081; $P = .02$), whereas the subgroup analysis of cardiothoracic surgery showed a significant decrease for nonbleeding mortality in patients of the TXA group (RD = −0.025; 95% CI, −0.045 to −0.005; $P = .02$). Sensitivity analysis using a random-effects model showed robust effect estimates for nonbleeding mortality (RD = −0.000; 95% CI, −0.002 to 0.001; $P = .92$) but not for the subgroup of patients with neurological conditions (RD = 0.021; 95% CI, −0.014 to 0.057; $P = .24$) and cardiothoracic surgery (RD = −0.015; 95% CI, −0.031 to 0.002; $P = .10$) (eTable 7; eFigure 22 in the Supplement).

In total, 49 studies (eAppendix 17 in the Supplement) assessed the bleeding mortality in 46 702 patients (n = 23 501 TXA group vs n = 23 201 control group). Death occurred in 692 patients (3%) in the TXA group and 874 patients (4%) in the control group. Overall, administration of intravenous TXA was associated with an overall significant decrease of bleeding mortality (RD = −0.008; 95% CI, −0.011 to −0.005; $P < .001$) (**Table 3**; eFigure 23 in the Supplement). Subgroup analysis showed a significantly decreased bleeding mortality in patients with neurological conditions (RD = −0.071; 95% CI, −0.102 to −0.041; $P < .001$), patients with trauma (RD = −0.008; 95% CI, −0.015 to −0.002; $P = .008$), and patients of any other disciplines of the TXA group (RD = −0.018; 95% CI, −0.033 to −0.004; $P = .02$), whereas no significant differences could be detected within the remaining medical disciplines (cardiothoracic, gynecological, orthopedic, and pediatric). Sensitivity analysis using a random-effects model showed robust effect estimates for bleeding mortality (RD = −0.004; 95% CI, −0.008 to −0.001; $P = .02$) but not for the subgroup of other disciplines (RD = −0.01; 95% CI, −0.028 to −0.009; $P = .30$) (Table 3; eFigure 24 in the Supplement). Significant heterogeneity was detected for patients with neurological conditions ($I^2 = 60\%$).

Patients With Risks for Thromboembolic Events

Overall, administration of intravenous TXA was not associated with an increased risk for total TEs (RD = −0.000; 95% CI, −0.008 to 0.009; $P > .99$) (eFigure 25 in the Supple-

Table 3. TXA and Bleeding Mortality

Medical discipline	No. of included studies	TXA Events	TXA No. of included patients	Control Events	Control No. of included patients	Model	Risk difference (95% CI)	P value	I^2, %
Cardiothoracic	12	0	543	1	478	Fixed effect	−0.002 (−0.016 to −0.012)	.77	0
						Random effects	−0.004 (−0.012 to 0.011)	.94	
Neurological	8	43	685	91	678	Fixed effect	−0.071 (−0.102 to −0.041)	<.001	60
						Random effects	−0.056 (−0.11 to −0.002)	.04	
Gynecological	8	155	10 871	191	10 814	Fixed effect	−0.003 (−0.007 to −0.000)	.05	0
						Random effects	−0.002 (−0.005 to 0.001)	.12	
Orthopedic	13	0	647	0	461	Fixed effect	0.000 (−0.014 to 0.014)	.77	0
						Random effects	0.000 (−0.013 to 0.013)	>.99	
Major trauma	1	489	10 060	574	10 067	Fixed effect	−0.008 (−0.015 to −0.002)	.01	NA
						Random effects	−0.008 (−0.015 to −0.002)	.01	
Pediatric	1	0	40	0	42	Fixed effect	0.000 (−0.046 to 0.046)	>.99	NA
						Random effects	0.000 (−0.046 to 0.046)	>.99	
Other	6	5	655	17	661	Fixed effect	−0.018 (−0.033 to −0.004)	.02	53
						Random effects	−0.01 (−0.028 to −0.009)	.30	
Total	49	692	23 501	874	23 201	Fixed effect	−0.008 (−0.011 to −0.005)	<.001	9
						Random effects	−0.004 (−0.008 to −0.001)	.02	

Abbreviations: NA, not applicable; TXA, tranexamic acid.

ment), for VT (RD = 0.003; 95% CI, −0.007 to 0.013; P = .57) (eFigure 26 in the Supplement), for PE (RD = −0.001; 95% CI, −0.009 to 0.007; P = .73) (eFigure 27 in the Supplement), or for VTEs (RD = −0.000; 95% CI, −0.012 to 0.01; P = .89) (eFigure 28 in the Supplement). Administration of intravenous TXA was associated with significant reductions in overall mortality (RD = −0.038; 95% CI, −0.057 to −0.018; P < .001). Detailed analyses are reported in eAppendix 7, eFigure 29 and eFigure 30, and eTable 8 in the Supplement.

Meta-regression

A meta-regression of 143 intervention groups was conducted to assess a possible association between different intravenous dosages of TXA and VTE rate. Results from this analysis showed no association between total dosing (RD = −0.005; 95% CI, −0.021 to 0.011; P = .53), single dosing (RD = 0.018; 95% CI, −0.053 to 0.09; P = .60), or any dose of intravenous TXA (RD = −0.005; 95% CI, −0.013 to 0.003; P = .21) and incidence of VTEs. Detailed analyses are reported in eAppendix 8 in the Supplement.

Risk of Bias

Overall, 139 studies (72%) were judged with low risk and 10 (5%) at high risk for random sequence generation. The risk of bias in the remaining 43 studies (22%) was unclear because of insufficient information. Allocation was adequately concealed in 68 studies (35%), whereas 4 studies (2%) were judged at high risk because patients were not randomly assigned to intravenous TXA or the control group. Sensitivity analysis with studies judged at low risk for selection bias was performed for total TEs and showed that results remained robust (RD = -0.001, 95% CI, −0.002 to 0.003, P = .89) (eFigure 33 in the Supplement). Detailed analysis including funnel plots is reported in eAppendix 9 and in eFigures 31-36 in the Supplement.

Updated Meta-analysis

A systematic search was performed to identify RCTs published between July 1, 2018, and December 31, 2020. In total, 72 studies were considered for full-text review, of which 48 were excluded because of ineligible study designs or control groups (n = 35), ineligible end points (n = 5), missing or nontranslatable full text (n = 4), and duplicates (n = 4), leaving 24 RCTs[206-229] including 27 888 patients (14 242 TXA group and 13 646 control group) for analysis (eTable 9 in the Supplement).

Of all trials (n = 216) comprising 125 550 patients, we found 1020 total TEs (2.1%) in the TXA group and 900 total TEs (2.0%) in the control group. The addition of 24 trials published after our analysis was completed showed that effect estimates for total TEs (RD = 0.001; 95% CI, −0.001 to 0.002; P = .49), VT (RD = −0.000; 95% CI, −0.001 to 0.001; P = .85), PE (RD = 0.000; 95% CI, −0.001 to 0.001; P = .74), VTE (RD = 0.000; 95% CI, −0.001 to 0.002; P = .85), and overall mortality (RD = −0.007; 95% CI, −0.012 to −0.004; P < .001) remained robust (eTables 10-14; eFigures 37-46 in the Supplement). Sensitivity analysis for total TEs using the RR as an effect measure including studies with (RR = 1.02; 95% CI, 0.94-1.11; P = .56) and without (RR = 1.03; 95% CI, 0.95-1.12; P = .52) double-zero events showed similar results.Detailed analyses are reported in eAppendix 10 and eFigures 37-48 in the Supplement.

Discussion

Tranexamic acid is efficient to reduce bleeding by inhibiting the enzymatic breakdown of existing fibrin blood clots and is therefore widely used in anesthesia and surgery. The utility of TXA was supported by the results of 3 trials (CRASH-2,

WOMAN and CRASH-3), reporting its efficiency in reducing bleeding-associated deaths in patients with trauma,[41] postpartum hemorrhage,[40] and traumatic brain injury.[206] However, a significant survival benefit was achieved only when TXA was administered within the first 3 hours after injury or delivery.[40,41] On the basis of the CRASH-2 results, intravenous TXA was included in the World Health Organization list of essential medicine in 2011.[230] Along with the positive effect, concerns about potential adverse effects, in particular vascular occlusive events, were raised. Controversial results were published, reporting from no incidence of TE[40] up to 12-fold higher rates for DVT[7] after intravenous TXA administration. Yates and colleagues[231] performed a meta-analysis including RCTs with different application methods of TXA. Analysis of 20 679 patients revealed no increased risk for VTEs after administration of intravenous TXA compared with placebo or no intervention. No subgroup analysis was performed by the authors. In orthopedic patients undergoing surgery with or without intravenous TXA, a systematic review by Franchini and colleagues[232] encompassing 67 RCTs revealed no significant difference of VTEs measured as RD including studies with 0 events (RD, 0.0008) and RR excluding these studies (RR, 1.0411).

To assess any risk of TEs associated with administration of intravenous TXA, we performed a meta-analysis including studies from all medical disciplines that assessed and provided data for TEs. Analyses were performed using RD including studies with 0 events to allow a general conclusion. Although this method yields wide 95% CIs when events are rare, this approach provides precise information when analyzing all available evidence instead of excluding a large proportion of studies that provided double-zero events. Excluding these trials from analysis generates the risk of inflating the magnitude of the pooled treatment effect. However, we performed a sensitivity analysis using the RR as an effect measure with and without studies with double-zero events and revealed robust effect estimates. In total, 216 studies published between 1976 and 2020 encompassing 125 500 patients were included in the meta-analysis, and overall we found 1020 total TEs (2.1%) in the TXA group and 900 total TEs (2.0%) in the control group. There was no association between intravenous TXA and increased risk for vascular occlusive events. The bleeding-associated mortality was significantly reduced in intravenous TXA–treated patients compared with controls, whereas no difference in nonbleeding mortality was detected. Particularly, the use of intravenous TXA in patients experiencing major trauma and in patients with neurological conditions was associated with significant survival benefit concerning bleeding-related mortality. Notably, we found only 1 study providing data for patients with major trauma treated with intravenous TXA. An updated meta-analysis was performed to identify RCTs published recently. Our results remain unchanged when data from these trials for total TEs, VT, PE, VTE, and overall mortality were included in the meta-analysis.

Of all investigated subgroups, we found inconclusive results for patients with neurological conditions. In this subgroup, results obtained with the fixed-effect model did not remain robust when using the random-effects model for the end points of TE and nonbleeding mortality. However, we found a decrease in bleeding-associated mortality in patients of the TXA group compared with the control group. In total, 12 studies provided data for total TEs in patients with neurological conditions; study size varied between 24 and 2235. Heterogeneity remained high after omitting studies with more than 1000 patients. Overall, increased heterogeneity and asymmetry in funnel plots indicate that further trials are necessary to solve the uncertainty for patients with neurological conditions.

It is commonly held that trials with low numbers of recruited patients might be underpowered to detect an intervention effect. To address this possibility, we performed a sensitivity analysis and found that administration of intravenous TXA was not associated with an increased risk for total TEs in studies with less than or equal to 99 patients, 100 to 999 patients, and greater than or equal to 1000 patients. Patients with an increased risk for thromboembolism were often excluded from RCTs. Given the short elimination half-life of intravenous TXA, patients with a risk factor may benefit from treatment during surgery. We found that the risk for vascular occlusive events or overall mortality rate was not increased in studies including patients with increased risks for thromboembolism. To assess a possible effect of study size or risk of bias, we conducted sensitivity analyses for the primary endpoint of total TEs, with results remaining robust.

Overall, the administration dose of intravenous TXA varied widely from 0.5 to 5 g or 10 to 100 mg/kg. Moving away from one-dose-fits-all to weight-adapted dosing might be associated with the different treatment regimens applied worldwide in the context of trauma and surgery. Notably, we did not detect any dose-dependent association of TEs.

Limitations

Although this meta-analysis provides substantial data, this study has limitations. We cannot exclude that additional references might have been missed by our systematic search of databases. However, we believe that inclusion of further studies had no impact on our main findings regarding vascular occlusive events. The follow-up varied between trials, ranging from 24 hours to several months. However, the half-life of intravenous TXA is 1.9-2.7 hours.[233,234] Considering that postoperative thrombotic events occur 6 to 8 days after surgery,[235] we hypothesized that intravenous TXA–related adverse events would be detected within even in a short period of follow-up. Furthermore, TEs were not examined using ultrasonographic screening; therefore, asymptomatic thrombosis might not have been detected in all cases, and the incidence of TEs might be underestimated in some studies. Low incidence of VTEs with an approximate rate of 1 per 1000 patients[236] and the routine use of postoperative thrombosis prophylaxis might also be associated with a low detection rate in patients with and without administration of intravenous TXA. Many of the included studies did not provide sufficient information about thrombosis prophylaxis; therefore, the association of postoperative care and vascular occlusive events was not analyzed further.

Conclusions

Taken as a whole, this systematic review and meta-analysis did not find that intravenous treatment with TXA in patients of any medical discipline was associated with a significant increased risk for TEs irrespective of administered dose. The results of this study suggest that use of intravenous TXA may have utility in all medical fields, with some uncertainty for patients with neurological conditions.

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Concept and design: Taeuber, Neef, Kranke, Choorapoikayil, Meybohm.
Acquisition, analysis, or interpretation of data: Taeuber, Weibel, Herrmann, Schlesinger, Kranke, Messroghli, Zacharowski, Choorapoikayil, Meybohm.
Drafting of the manuscript: Taeuber, Kranke, Choorapoikayil, Meybohm.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Taeuber, Weibel, Herrmann, Kranke, Choorapoikayil, Meybohm.
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7.1 Reply Letter

Importance of the Assessment Time Window for Intravenous Tranexamic Acid and Thromboembolic Events - Reply

In Reply We thank Sentilhes and colleagues for their comment on our systematic review and meta-analysis of the association of tranexamic acid (TXA) with thromboembolic events and mortality[1] and their important perspective on a sufficient follow-up period.

Sentilhes et al[2] recently performed a randomized clinical trial among women undergoing cesarean delivery with an outstanding long-term follow-up of more than 3 months after delivery. Overall, TXA was associated with a significant reduction of postpartum hemorrhage or red blood cell transfusion (adjusted risk ratio, 0.84; 95% CI, 0.75-0.94; $P = .003$). Venous thromboembolic events are rare with an incidence of approximately 1 per 1000 patients. Of the included patients in the trial by Sentilhes and colleagues,[2] thromboembolic events occurred in 0.1% (2 of 2056) and 0.4% (8 of 2049) of patients in the placebo and TXA group, respectively (adjusted risk ratio, 4.01; 95% CI, 0.85-18.92; $P = .08$).[2] The authors raised an important point concerning the follow-up after discharge in trials included in our meta-analysis assessing the adverse events after TXA administration. Particularly, women with delivery have an increased risk of developing thromboembolic events. In our meta-analysis, 19 trials addressed cesarean delivery or postpartum hemorrhage, of which 8 trials (cited in our meta-analysis[1]) including 22 388 patients provided a detailed follow-up period: Ducloy-Bouthors et al, 6 weeks; Gungorduk et al, 6 weeks; WOMAN trial, 6 weeks; Maged et al, 4 weeks; Gungorduk et al, 3 weeks; Ahmed et al, 1 week; Abdel-Aleem et al, hospital stay; and Goswami et al, 24 hours. Overall, we found no association of intravenous TXA and thromboembolic events (risk difference, 0; 95% CI, 0; $P = .41$). Furthermore, our analysis revealed that the risk for vascular occlusive events (49 trials including 4753 patients) or overall mortality rate (20 trials including 2266 patients) was not increased in studies including patients with increased risks for thromboembolism. However, several risk factors such as age, metabolic syndrome, smoking, cancer, hormone therapy, or immobilization promote the development of thromboembolic events and should be assessed in future studies. As pointed out by Sentilhes and colleagues, future research should also focus on an extended assessment and follow up the included patients for at least 3 months to assess the thromboembolic events throughout a longer period. Moreover, a risk adjustment for multifactorial causes of thromboembolic events should be considered. Innovative tools such as telemedicine could help to collect these comprehensive data in future.

Isabel Taeuber
Suma Choorapoikayil, PhD
Patrick Meybohm, MD

Author Affiliations: Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Frankfurt am Main, Germany (Taeuber, Choorapoikayil); Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Wuerzburg, Germany (Meybohm).

Corresponding Author: Patrick Meybohm, MD, Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Oberduerrbacher Str 6, 97080 Wuerzburg, Germany (meybohm_p@ukw.de).

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1. Taeuber I, Weibel S, Herrmann E, et al. Association of intravenous tranexamic acid with thromboembolic events and mortality: a systematic review, meta-analysis, and meta-regression. *JAMA Surg*. 2021;156(6):e210884. doi:10.1001/jamasurg.2021.0884

2. Sentilhes L, Sénat MV, Le Lous M, et al; Groupe de Recherche en Obstétrique et Gynécologie. Tranexamic acid for the prevention of blood loss after cesarean delivery. *N Engl J Med*. 2021;384(17):1623-1634. doi:10.1056/NEJMoa2028788

7.2 Online Supplement

Supplemental Online Content

Taeuber I, Weibel S, Herrmann E, et al. Association of intravenous tranexamic acid with thromboembolic events and mortality: a systematic review, meta-analysis, and meta-regression. *JAMA Surg*. Published online April 14, 2021. doi:10.1001/jamasurg.2021.0884

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix-1:

Search Strategy

In this systematic review and meta-analysis, we systematically searched Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE via PubMed for eligible studies investigating the impact of iv TXA on post-interventional outcome, published between 1976 and 2018.

Hand-search of all meta-analyses and reviews identified through our electronic search was conducted to identify randomized controlled studies (RCTs) that were not found in the primary search. Additionally, we hand-searched reviews and meta-analyses from the Cochrane Database to identify missing trials. The manual search was concluded on 09/20/2019.

Search Terms

PubMed was searched to identify RCTs with at least one intervention group, that used iv TXA. The following search terms were used without any restriction:

- ("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) AND (“intravenously”[All Fields] NOT “intravenous”[All Fields])
- ("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) AND “intravenous”[All Fields]

Search Strategy for Updated Meta-Analysis

To identify RCTs published after completion of the meta-analysis a systematic review was performed. MEDLINE via PubMed was searched for eligible studies investigating the impact of iv TXA on post-interventional outcome, published between 2018/07/01 -2020/12/31.

Search Terms for Updated Meta-Analysis

PubMed was searched to identify RCTs with at least one intervention group, that used iv TXA. The following search terms were used with restriction (*Randomized Controlled Trial, Humans from 2018/07/01 -2020/12/31*):

- ("tranexamic acid"[MeSH Terms] OR ("tranexamic"[All Fields] AND "acid"[All Fields]) OR "tranexamic acid"[All Fields]) AND ("intravenous*"[All Fields])

Study Selection

Studies were screened by two independent reviewers (IT and SC). Discrepancies were solved through discussion or by contacting a third reviewer (PM). Assessment of eligibility was based on title and abstract. If necessary full text was screened. Non-relevant studies were excluded, and the remaining articles were examined in full. Studies with at least one intervention group (iv TXA) compared to a control group (placebo or no treatment) were included in our analysis. We included studies published in English, German, French and Spanish. Studies with only oral or topical administration were excluded.

Ethical Review

We only used published statistical data and therefore ethical approval was not required in our meta-analysis.

Registration

The present study has been registered at PROSPERO register (https://www.crd.york.ac.uk/prospero/, registration number: CRD42020147359).

eAppendix-2:

Outcome Measure

Authors were contacted via e-mail, if clarification of data or additional information were required. For example, if a study mentioned only venous thromboembolic events (VTE), the author was contacted to provide numbers of VT and PE separately. If no answer was provided, all VTE were counted as VT. Discrepancies were resolved through discussion with a third author (PM).

eAppendix-3:

Statistical Analyses

The Review Manager (RevMan) program (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and "R" (R Studio, A Language and Environment for Statistical Computing. Version 3.6.1, Vienna, Austria; 2016) were used for analysis and graphical illustrations. Continuity corrections were performed with the R package meta version 4.12-0. Since many studies showed zero-events in both groups, we assessed the Risk Difference (RD) to provide accurate results. The fixed-effect analysis was used for meta-analysis because we assumed that the true effect size is the same in all studies since TE events are rare and the only reason the effect size varies between studies could be caused by sampling error. However, we performed sensitivity analysis using random-effects model to estimate whether our results were robust. Furthermore, we performed a sensitivity analysis using the risk ratio (RR) as effect measure with either including (continuity correction of 0.5) or excluding studies with zero cell frequencies. An additional analysis of total TEs with subgroups by study size was conducted. Heterogeneity was assessed by using I^2 statistics. A meta-regression was performed to investigate a relation between the event rate and the dosage of iv TXA. We also investigated whether iv TXA was associated with increased risk for TE, VT, VTE and overall mortality in patients with risks for TE. Therefore, secondary analyses were performed only with studies including patients with: history of any TE, coronary artery disease, thrombophilia or contraindication for TXA. Two authors (IT, SC) independently assessed the methodological quality of included studies based on the Cochrane Risk of Bias tool. A sensitivity analysis with studies judged at low risk of selection bias was assessed for total TEs. Funnel plots were generated to detect a possible evidence for small study bias. Discrepancies were resolved by group discussion (IT, SC, PM, EH and SW). A meta-regression was performed with R package metaphor version 2.1-0. Analyses were performed with studies providing data for single or total dose and for fixed or weight adjusted dose. Fixed doses were converted to the equivalent milligram per kilogram dose, when average body weight of the TXA group was indicated, to provide one overall analysis.

eAppendix 4:

Demographic Data

Publication date ranged from 1976 to 2018, with 117 studies (61%) published in 2010 or later. Patient mean age varied from 6 months in paediatric studies up to 70 years. Comparator groups included placebo in 150 (78%) and no treatment in 42 (22%) studies (eTab.1).

Subgroup Characteristics

Subgroup analysis was performed in the surgical fields of cardiothoracic, gynaecology, orthopaedic, major trauma, maxillo-facial, paediatric, in neurological patients, and other (urological or nephrological patients, liver transplantation, liver tumour resection, gastrointestinal-tract bleeding, surgery of the thyroid gland, diabetic haemorrhage).

eAppendix-5:

Effect of Tranexamic Acid on Myocardial Infarction or Ischaemia

In total, 27 studies[6, 21, 40, 41, 48, 53, 62, 67, 74, 77, 78, 80, 85, 97, 111, 114, 117, 119, 123, 142, 149, 177, 182, 186, 191, 201, 203] provided data on MI in 45,379 patients (n=22,700 TXA-group vs. n=22,679 control-group). Cardiac patients were excluded from this analysis because we could not assess whether a MI or ischaemia occurred prior to the administration of TXA. We found 70 (0.3%) and 77 (0.3%) MI in the TXA- and control-group, respectively. Overall, administration of iv-TXA was not associated with an increased risk for MI (RD=-0.000, 95% CI: -0.001 to 0.001, P=.56) (eTab.5 and eFig.13-14). Subgroup analysis showed a significantly decreased MI or ischemia in trauma patients of the TXA-group (RD=-0.002, 95% CI: -0.004 to -0.000, P=.03). SA using random-effects model showed robust effect estimates for overall MI (RD=-0.000, 95% CI: -0.001 to 0.000, P=.42) and for the subgroup of trauma patients (RD=-0.002, 95% CI: -0.004 to -0.000, P=.03) (eTab.5 and eFig.14).

eAppendix 6:

Effect of Tranexamic Acid on Cerebral Infarction or Ischaemia

In total, 33 studies[21, 40, 41, 67, 77, 78, 80, 91, 99, 111, 114, 117, 119, 123, 142, 149, 152, 153, 155-157, 159, 161, 162, 164, 166-169, 172, 189, 191, 201] provided data on CII in 48,433 patients (n=24,301 TXA group vs. n=24,132 control group). Neurological patients were excluded from this analysis because we could not assess whether CII occurred prior to the administration of TXA. We found 114 (0.5%) and 115 (0.5%) total CII in the TXA and control group, respectively. Overall, administration of iv TXA was not associated with an increased risk for CII (RD=-0.000, 95% CI: -0.001 to 0.001, P=.90) (eTab.6 and eFig.15). Sensitivity analysis using random-effects model showed robust effect estimates (data not shown).

Effect of Tranexamic Acid on Other Thromboembolic Events

In total, 6 studies[31, 46, 67, 78, 172, 197] provided data on other TE. Limb ischaemia was assessed in four studies[31, 46, 67, 78] including 475 patients (n=242 TXA group vs. n=233 control group) (eFig.16), mesenteric ischaemia was assessed in one study[172] with 4,631 patients (n=2,311 TXA group vs. n=2,320 control group) (eFig.17) and hepatic artery thrombosis was assessed in one study[197] including 32 patients (n=16 TXA group vs. n=16 control group) (eFig.18). Spinal ischaemia and bypass graft redo were not investigated in any of the studies. Administration of iv TXA was not associated with an increased risk for limb ischaemia (RD=-0.004, 95% CI: -0.023 to 0.015, P=.66), mesenteric ischaemia (RD=0.002, 95% CI: -0.001 to 0.005, P=.13), and hepatic artery thrombosis (RD=0.063, 95% CI: -0.094 to 0.22, P=.44) (eFig.16-18). Overall, iv TXA was not associated with an increased risk for other TE. Sensitivity analysis using random-effects model showed robust effect estimates (data not shown).

eAppendix-7:

Effect of Tranexamic Acid in Patients with risks for Thromboembolic Events

In total, 56 studies included patients with risks for TE (eTab.1) of which 49 assessed TE[15, 19, 21, 29, 35, 42-44, 48-50, 52-55, 61, 63, 69, 76, 89, 103, 108, 117, 144, 148, 152-154, 156, 157, 159, 161-164, 166, 168, 169, 174, 175, 182, 185, 188, 189, 193, 195, 197, 198, 202], 42 VT[15, 19, 21, 29, 35, 42-44, 48-50, 52-55, 61, 63, 69, 76, 89, 103, 108, 117, 144, 148, 152, 154, 156, 161, 163, 174, 175, 182, 185, 188, 189, 193, 195, 197, 198, 202], 26 PE[15, 21, 35, 42-44, 49, 50, 54, 61, 63, 76, 103, 117, 144, 148, 154, 161, 163, 164, 168, 182, 185, 188, 189, 202], 25 VTE[15, 21, 35, 42-44, 49, 50, 54, 61, 63, 76, 103, 117, 144, 148, 154, 161, 163, 164, 182, 185, 188, 189, 202], and 20 overall mortality rate[29, 50, 151, 156, 157, 159, 160, 162, 164-166, 168-170, 173-175, 182, 192, 197]. We found 45 (1.8%) and 43 (1.9%) TE, 35 (1.8%) and 29 (1.5%) VT, 2 (0.1%) and 4 (0.3%) PE, 17 (1.3%) and 18 (1.3%) VTE, 44 (3.9%) and 86 (7.7%) death events in the TXA- and control-group, respectively. The subgroup analysis showed significantly decreased overall mortality in neurological patients (RD= -0.11, 95% CI: -0.19 to -0.04, P=.002) and patients of other disciplines (RD= -0.06, 95% CI: -0.11 to -0.02, P=.01) (eFig.29 and eTab.8). Sensitivity analysis using random-effects-model showed robust effect estimates for TE, VT, PE, and VTE (data not shown), but not for overall mortality (RD=-0.02, 95% CI: -0.04 to 0.01, P=.15) (eFig.30).

eAppendix 8:

Meta-Regression

TXA was either administered as a single dose varying from 10 to 30 mg/kg and 0.5 to 10 g or multiple times with dose varying from 5.5 to 135 mg/kg or 1 to 16.6 g (eTab.1). 91 studies[15, 17, 22, 25, 29, 31, 34, 38, 42-62, 64-69, 72, 74-78, 80-85, 88-90, 92-94, 97-100, 105, 107-109, 112-119, 123, 126, 128, 130, 132-139, 142, 144, 147, 150, 152, 156, 163, 188, 202, 203] including 117 intervention groups administrated TXA weight adapted with total dose of 5.5 to 135 mg/kg of which 41 studies[15, 22, 25, 29, 31, 34, 42, 43, 45-48, 54, 57, 61, 65, 68, 69, 77, 81, 83, 85, 88, 97, 105, 107, 109, 115, 117-119, 123, 126, 128, 133, 136-138, 147, 163, 202] including 51 intervention groups administrated TXA in single dose. Results from this analysis showed no association of total dosing (-0.005, 95% CI: -0.021 to 0.011, P=.53) or single dosing (0.018, 95%CI: -0.053 to 0.09, P=.6). 53 studies[6, 16, 18-21, 23, 24, 26-28, 30, 32, 33, 35-37, 39, 41, 63, 70, 87, 91, 95, 101, 102, 104, 106, 111, 120-122, 124, 125, 129, 140, 141, 143, 148, 155, 161, 164, 167, 168, 182, 183, 185, 186, 193, 198, 200, 201, 204] including 56 intervention groups administrated TXA with total dose of 0.5 to 16.6 g of which 35 studies[16, 18, 19, 21, 23, 24, 26-28, 30, 32, 33, 35-37, 39, 63, 87, 95, 102, 104, 120-122, 124, 125, 129, 140, 141, 143, 148, 155, 168, 186, 198] including 36 intervention groups administrated TXA in single dose of 0.5 to 10 g. Results from this analysis showed no association of total dosing (-0.017, 95% CI: -0.168 to 0.134, P=.82) or single dosing (-0.001, 95 % CI: -0.327 to 0.325, P>.99). To assess a possible relation of dose dependent association between iv TXA and VTE of all studies, we converted fixed dose to the equivalent milligram per kilogram dose in 23 trials. Results from the analysis of 113 studies including 142 intervention groups showed no association of any dose of iv TXA and incidence of VTE (-0.005, 95% CI: -0.013 to 0.003, P=.21). Overall, our analysis showed no association between TXA dosage and total VTE.

eAppendix-9:

Risk of Bias

Overall, 139 (72%) studies were judged to be at low risk and 10 (5%) at high risk for random sequence generation. The risk of bias in the remaining 43 (22%) studies were unclear because of insufficient information. Allocation was adequately concealed in 68 (35%) studies, whereas 4 (2%) studies were judged at high risk, because patients were not randomly assigned to iv TXA or control group. Thromboembolism is as a typical postoperative complication and assessed in all hospitalized patients and the lack of blinding is highly unlikely to influence outcome assessment. Therefore, blinding of participants and outcome assessment were judged at low risk in 192 (100%) studies. Incomplete outcome data was judged at low risk in 191 (99%) studies, since most studies routinely assessed TEs. In total 188 (98%) and 191 (99%) studies were judged to be of unclear risk at reporting and of other sources of bias owing to lack of information (eFig.31 and eFig.32). Sensitivity analysis with studies judged at low risk for selection bias was performed for total TEs and showed that results remained robust with fixed-effect-model (RD=-0.001, 95% CI: -0.002 to 0.003, P=.89) (eFig33) and random-effects-model (RD=-0.001, 95% CI: -0.002 to 0.001, P=.89).

Inspection of the funnel plots showed no indications of small study effects for the outcomes total TE, VT, CII and non-bleeding mortality (eFig.34). We found a slight right shift in funnel plots for the outcomes PE, VTE, and MI (eFig.35) caused by few small studies including neurological and orthopaedic patients and a slight left shift for the outcomes overall and bleeding mortality (eFig.36) caused by studies including neurological patients.

eAppendix-10:

Updated Meta-Analysis

Of the 24 trials, 13 included orthopaedic patients, 4 neurological patients, 3 gynaecologic patients, 1 paediatric patients, 1 cardiothoracic patients, and 3 of other medical disciplines (eTab.9). Administration of iv-TXA was not associated with an increased risk for total TE, however, the subgroup analysis showed significantly increased risk for TE events in the TXA-group of neurological patients (RD=0.007, 95% CI: 0.000 to 0.014, P=.04). Sensitivity analysis using random-effects-model showed robust effect estimates for total TE (RD=-0.000, 95% CI: -0.002 to 0.001, P=.43) but no significantly increased risk for TE in the subgroup of neurological patients was shown (RD=0.003, 95% CI: -0.012 to 0.017, P=.74) (eTab.10; eFig.38). In addition, a SA using the RR as effect measure with and without studies with double zero events revealed robust effect estimates for all subgroups (RR=1.02, 95% CI: 0.94 to 1.11, P=.56 and RR=1.03, 95% CI: 0.95 to 1.12, P=.52) (eFig.47; 48).

The addition of 4 studies within the subgroup of other surgical discipline showed an increased risk for VTE in the TXA-group (RD=0.003, 95% CI: 0.000 to 0.006, P=.03) which remained robust using random-effects-model (RD=0.004, 95% CI: 0.001 to 0.006, P=.01) (eTab.13; eFig.43; 44). In total, 7 trials provided data for VTE of which one trial[207] included >10,000 patients whereas the number of included patients in the remaining trials varied between 40 and 200 (eTab.13; eFig.43; 44). Almost half of the patients included in the HALI-IT trial[207] suffered from variceal bleeding due to liver disease and showed increased risk for VTE which might be associated with reduced fibrinolysis in these patients.

eTable 1: Study Characteristics

Year	Author	Medical Discipline	Control (n=)	TXA (n=)	TXA Application		Patients with risk for TE included[b]	Ref
1976	Biggs et al	Gastrointestinal	97	103	iv + oral	ad, nw[a]		190
1978	Chandra et al	Neurological	19	20	iv	ad, w[a]	√	173
1978	Fodstad et al	Neurological	23	23	iv	ad, nw[a]	√	174
1978	Maurice-Williams et al	Neurological	25	25	iv + oral	ad, nw[a]	√	175
1979	Engqvist et al	Gastrointestinal	73	76	iv + oral	ad, nw[a]		191
1979	Kaste et al	Neurological	32	32		ad, nw[a]		176
1981	Fodstad et al	Neurological	29	30	iv + oral	ad, nw[a]		177
1983	Barer et al	Gastrointestinal	260	256	iv + oral	ad, nw[a]	√	192
1984	Vermeulen et al	Neurological	238	241	iv / (iv + oral)[c]	ad, nw[a]		178
1987	Auvinen et al	Surgery of the thyroid gland	37	39	iv	ad, nw	√	193
1987	von Holstein et al	Gastrointestinal	82	72	iv + oral	ad, nw[a]		194
1990	Tsementzis et al	Neurological	50	50	iv + oral	ad, nw[a]		179
1993	Yassen et al	Liver surgery	10	10	iv	ad, w[a]	√	195
1995	Coffey et al	Cardiothoracic	14	16	iv	ad, w[a]	√	151
1995	Hiippala et al	Orthopaedic	13	15	iv	sd, w	√	48
1995	Horrow et al	Cardiothoracic	27	121	iv	ad, w	√	152
1995	Karski et al	Cardiothoracic	50	100	iv	sd, nw[a] / ad, nw[a]	√	153
1995	Speekenbrink et al	Cardiothoracic	15	15	iv	ad, w[a]	√	154
1996	Benoni et al	Orthopaedic	43	43	iv	ad, w	√	49
1996	Boylan et al	Liver surgery	20	25	iv	ad, w[a]		196
1996	Katsaros et al	Cardiothoracic	106	104	iv	sd, nw		155
1996	Shore-Lesserson et al	Cardiothoracic	13	17	iv	ad, w	√	156
1996	Zonis et al	Paediatric	42	40	iv	sd, w[a]		187
1997	Brown et al	Cardiothoracic	30	60	iv	ad, w[a]	√	157

1997	Dryden et al	Cardiothoracic	19	22	iv	sd, nw[a]		158
1997	Hiippala et al	Orthopaedic	38	39	iv	ad, w	√	50
1997	Kaspar et al	Liver surgery	16	16	iv	sd, w[a]	√	197
1998	Hardy et al	Cardiothoracic	45	43	iv	sd, nw[a]	√	159
1999	Dalmau et al	Liver surgery	40	42	iv	sd, nw	√	198
1999	Jansen et al	Orthopaedic	21	21	iv	ad, w		51
2000	Benoni et al	Orthopaedic	19	20	iv	ad, w	√	52
2000	Ekbäck et al	Orthopaedic	20	20	iv	ad, w	√	53
2000	Nuttall et al	Cardiothoracic	43	77	iv	ad, w[a]	√	160
2000	Roos et al	Neurological	233	229	iv + oral	ad, nw[a]		180
2001	Benoni et al	Orthopaedic	20	18	iv	sd, w	√	54
2001	Casati et al	Cardiothoracic	40	40	iv	ad, nw	√	161
2001	Engel et al	Orthopaedic	12	12	iv	ad, w	√	55
2001	Neilipovitz et al	Orthopaedic	18	22	iv	ad, w		56
2001	Tanaka et al	Orthopaedic	26	73	iv	sd, w / ad, w		57
2002	Hillman et al	Neurological	251	254	iv	ad, nw[a]		181
2002	Veien et al	Orthopaedic	15	15	iv	ad, w		58
2002	Zabeeda et al	Cardiothoracic	25	25	iv	ad, w[a]	√	162
2003	Good et al	Orthopaedic	24	27	iv	ad, w		59
2003	Husted et al	Orthopaedic	20	20	iv	ad, w		60
2003	Pleym et al	Cardiothoracic	39	40	iv	sd, w	√	163
2004	Andreasen et al	Cardiothoracic	23	21	iv	ad, nw	√	164
2004	Garneti et al	Orthopaedic	25	25	iv	sd, w	√	61
2004	Lemay et al	Orthopaedic	19	20	iv	ad, w		62
2004	Yamasaki et al	Orthopaedic	20	20	iv	sd, nw	√	63
2004	Zohar et al	Orthopaedic	20	40	iv / iv + oral[d]	ad, w		64
2005	Diprose et al	Cardiothoracic	60	60	iv	sd, nw[a]	√	165
2005	Johansson et al	Orthopaedic	53	47	iv	sd, w		65
2005	Karski et al	Cardiothoracic	165	147	iv	sd, w[a]	√	166
2005	Niskanen et al	Orthopaedic	20	19	iv	ad, w		66

2005	Orpen et al	Orthopaedic	14	15	iv	sd, w		68
2005	Ramezani et al	Diabetic haemorrhage	30	32	iv + oral	ad, w[a]		199
2005	Vanek et al	Cardiothoracic	30	32	iv	ad, nw		167
2006	Camarasa et al	Orthopaedic	60	35	iv	ad, w		67
2006	Celebi et al	Gynaecology	26	27	iv	sd, w	√	15
2006	Murphy et al	Cardiothoracic	50	50	iv	sd, nw	√	168
2006	Santos et al	Cardiothoracic	31	29	iv	ad, w[a]	√	169
2006	Wu et al	Liver surgery	106	108	iv	ad, nw		200
2007	Claeys et al	Orthopaedic	20	20	iv	sd, w	√	69
2007	Gohel et al	Gynaecology	50	50	iv	sd, nw		16
2007	Jimenez et al	Cardiothoracic	26	24	iv	ad, nw[a]	√	170
2007	Molloy et al	Orthopaedic	50	50	iv	ad, nw		70
2007	Sadeghi et al	Orthopaedic	35	32	iv	sd, w[a]		71
2008	Alvarez et al	Orthopaedic	49	46	iv	ad, w		72
2008	Caglar et al	Gynaecology		50	iv	ad, w		17
2008	Elwatidy et al	Orthopaedic	32	32	iv	ad, nw[a] / ad, w[a]		73
2008	Wong et al	Orthopaedic	74	73	iv	ad, w		74
2009	Choi et al	Maxillo-facial	29	32	iv	sd, w	√	42
2009	Jalaeilan et al	Orthopaedic	40	40	iv	ad, w	√	76
2009	Kakar et al	Orthopaedic	25	25	iv	ad, w		75
2009	Sekhavat et al	Gynaecology	45	45	iv	sd, nw		18
2010	CRASH-2 Collaborators	Trauma	10 067	10 060	iv	ad, nw		41
2010	Kazemi et al	Orthopaedic	32	32	iv	sd, w		77
2010	Rashmi et al	Gynaecology	50	50	iv	sd, nw	√	19
2010	Zufferey et al	Orthopaedic	53	57	iv	ad, w		78
2011	Alimian et al	Maxillo-facial	42	42	iv	sd, w	√	43
2011	Charoencholvanich et al	Orthopaedic	50	50	iv + oral	ad, w and nw[a]		79
2011	Crescenti et al	urological	100	100	iv	ad, nw		201
2011	Dadure et al	Paediatric	20	19	iv	ad, w	√	188
2011	Ducloy-Bouthors et al	Gynaecology	72	72	iv	ad, nw		20

2011	Farrokhi et al	Orthopaedic	38	38	iv	ad, w		80
2011	Goobie et al	Paediatric	20	23	iv	ad, w[a]		189
2011	Gungorduk et al	Gynaecology	330	330	iv	sd, nw	√	21
2011	Kumsar et al	urological	20	20	iv	sd, w	√	202
2011	Lin et al	Orthopaedic	50	50	iv	sd, w		81
2011	MacGillivray et al	Orthopaedic	20	40	iv	ad, w		82
2011	Malhotra et al	Orthopaedic	25	25	iv	sd, w		83
2011	Movafegh et al	Gynaecology	50	50	iv	sd, w		22
2011	Suksamosorn et al	Orthopaedic	21	22	iv	excluded		84
2011	Tsutsumimoto et al	Orthopaedic	20	20	iv	sd, w		85
2012	Chakravarthy et al	Cardiothoracic	48	50	iv	ad, w[a]	√	171
2012	Chareancholvanich et al	Orthopaedic	120	120	iv	ad w and nw[a]		86
2012	Gupta et al	Gynaecology	30	30	iv	sd, nw		23
2012	Imai et al	Orthopaedic	22	95	iv	sd, nw / ad, nw		87
2012	Lin et al	Orthopaedic	50	101	iv	sd, w / ad, w		88
2012	Raviraj et al	Orthopaedic	87	88	iv	ad, w	√	89
2012	Sankar et al	Maxillo-facial	25	25	iv	ad, w	√	44
2012	Xu et al	Orthopaedic	20	20	iv	ad, w		90
2013	Abdel-Aleem et al	Gynaecology	367	373	iv	sd, nw		24
2013	Aguilera et al	Orthopaedic	42	41	iv	ad, nw		91
2013	Gautam et al	Orthopaedic	13	14	iv	ad, w		92
2013	Goswami et al	Gynaecology	30	60	iv	sd, w		25
2013	Gungorduk et al	Gynaecology	219	220	iv	sd, nw		26
2013	Lee, S. H. et al	Orthopaedic	36	36	iv	ad, w		93
2013a	Lee, Y. C. et al	Orthopaedic	34	34	iv	ad, w		94
2013	Senturk et al	Gynaecology	122	101	iv	sd, nw		27
2013	Seo et al	Orthopaedic	50	50	iv	sd, nw		95
2013	Shahid et al	Gynaecology	36	38	iv	sd, nw		28
2013	Vijay et al	Orthopaedic	45	45	iv	ad, nw and w[a]		96
2013	Wang et al	Orthopaedic	30	30	iv	sd, w		97

2013	Xu et al	Gynaecology	86	88	iv	sd, w	√	29
2013	Yutthakasemsunt et al	Neurological	118	120	iv	ad, nw	√	182
2014	Bidolegui et al	Orthopaedic	25	25	iv	ad, w		98
2014	Dakir et al	Maxillo-facial	6	6	iv	sd, w		45
2014	Emara et al	Orthopaedic	20	20	iv	ad, w		99
2014	Ghosh et al	Gynaecology	70	70	iv	sd, nw		30
2014	Gobbur et al	Gynaecology	50	50	iv	sd, nw		32
2014	Kim et al	Orthopaedic	163	163	iv	ad, w		100
2014	Lundin et al	Gynaecology	50	50	iv	sd, w		31
2014	Oremus et al	Orthopaedic	49	49	iv	ad, nw		101
2014	Sarzaeem et al	Orthopaedic	50	50	iv	sd, nw		102
2014	Sprigg et al	Neurological	8	16	iv	ad, nw		183
2014	Verma et al	Orthopaedic	47	36	iv	ad, w[a]	√	103
2014	Wei et al	Orthopaedic	100	101	iv	sd, nw		104
2014	Yehia et al	Gynaecology	106	106	iv	sd, nw		33
2015	Ahmed et al	Gynaecology	62	62	iv	sd, w		34
2015	Arumugam et al	Neurological	15	15	iv	ad, nw[a]		184
2015	Digas et al	Orthopaedic	29	30	iv	sd, w		105
2015	Hsu et al	Orthopaedic	30	30	iv	ad, nw		106
2015	Jaszczyk et al	Orthopaedic	63	61	iv	sd, w		107
2015	Karaaslan et al	Orthopaedic	52	53	iv	ad, w	√	108
2015	Kundu et al	Orthopaedic	30	30	iv	sd, w		109
2015	Lin et al	Orthopaedic	40	40	iv + topical	ad, nw[a]		110
2015	Maged et al	Gynaecology	100	100	iv	sd, nw	√	35
2015	Motififard et al	Orthopaedic	45	45	iv	ad, nw		111
2015	Ngichabe et al	Gynaecology	17	17	iv	sd, nw		36
2015	Nuhi et al	Maxillo-facial	70	100	iv	sd, w		46
2015	Öztas et al	Orthopaedic	30	30	iv	ad, w		112
2015	Peters et al	Orthopaedic	13	19	iv	ad, w		113
2015	Raksakietisak et al	Orthopaedic	39	39	iv	ad, w		114

2015	Shen et al	Orthopaedic	40	41	iv	sd, w		115
2015	Shinde et al	Orthopaedic	28	28	iv	ad, w		116
2015	Vel et al	Neurological	50	50	iv	ad, nw	√	185
2015	Xie et al	Orthopaedic	42	41	iv	sd, w	√	117
2016	Barrachina et al	Orthopaedic	37	71	iv	sd, w / ad, w		118
2016	Baruah et al	Orthopaedic	30	30	iv	sd, w		119
2016	Chen et al	Orthopaedic	60	60	iv	sd, nw		120
2016	Drosos et al	Orthopaedic	30	30	iv	sd, nw		121
2016	Fraval et al	Orthopaedic	51	50	iv	ad, w		130
2016	Keyhani et al	Orthopaedic	40	40	iv	sd, nw		122
2016	Myles et al	Cardiothoracic	2 320	2 311	iv	sd, w[a]		172
2016	Ray et al	Gynaecology	50	50	iv	sd, nw		37
2016	Seviciu et al	Orthopaedic	63	58	iv	sd, w		123
2016	Shaaban et al	Gynaecology	66	66	iv	ad, w		38
2016	Topsoee et al	Gynaecology	167	165	iv	sd, nw		39
2016	Tzatzairis et al	Orthopaedic	40	40	iv	sd, nw		124
2016	Volquind et al	Orthopaedic	30	32	iv	sd, nw		125
2016	Wang et al	Orthopaedic	38	81	iv	sd, w		126
2016	Yi et al	Orthopaedic	50	100	iv / iv + topical*	sd, w		127
2016	Zekcer et al	Orthopaedic	30	30	iv	sd, w		128
2016	Zhang et al	Orthopaedic	25	25	iv	sd, nw		129
2017	Hooda et al	Neurological	30	30	iv	sd, nw		186
2017	Huang et al	Orthopaedic	50	100	iv + topical	ad, w and nw[a]		131
2017	Jendoubi et al	urological	67	64	iv	ad, w		203
2017	Lacko et al	Orthopaedic	30	30	iv	ad, w		132
2017	Melo et al	Orthopaedic	14	28	iv	sd, w / ad, w	√	133
2017	Prakash et al	Orthopaedic	50	50	iv	ad, w		134
2017	Song et al	Orthopaedic	50	50	iv	ad, w		135
2017	Sun et al	Orthopaedic	45	135	iv	sd, w		136
2017a	Sun et al	Orthopaedic	45	135	iv	sd, w		137

2017	Ugurlu et al	Orthopaedic	41	40	iv	sd, w		138
2017	Vara et al	Orthopaedic	49	53	iv	ad, w		139
2017	Wang, J. et al	Orthopaedic	50	50	iv	sd, nw		140
2017a	Wang, J. W. et al	Orthopaedic	98	100	iv	sd, nw		141
2017	Watts et al	Orthopaedic	69	69	iv	ad, w		142
2017	Woman Trial Collaborators	Gynaecology	9 985	10 036	iv	sd or ad, nw[e]		40
2017	Yen et al	Orthopaedic	30	31	iv	sd, nw		143
2017	Yuan et al	Orthopaedic	140	140	iv	ad, w	√	144
2017	Zekcer et al	Orthopaedic	30	30	iv	sd, w[e]		145
2017	Zeng et al	Orthopaedic	50	50	iv + topical	ad, w and nw[a]		146
2018	Apipan et al	Maxillo-facial	20	60	iv	sd, w		47
2018	Liu et al	Orthopaedic	72	147	iv	sd, w		147
2018	Lopez-Hualda et al	Orthopaedic	30	30	iv	sd, nw	√	148
2018	Mohammadi et al	Nephrological	66	64	iv	ad, nw		204
2018	Painter et al	Orthopaedic	69	71	iv	ad, w[a]		149
2018	Sprigg et al	Neurological	1 164	1 161	iv	ad, nw		6
2018	Tavakoli et al	Gastrointestinal	139	271	iv / iv + topical*	sd, nw[e] / ad, nw[a]		205
2018	Zhao et al	Orthopaedic	40	40	iv	ad, w		150

(+) = same group, but different regimens in the participating countries. (*) = more than one study group receiving iv TXA, "/" = divides different study groups. sd = single dose, ad = additional dose, w = weight adapted in mg/kg, nw = not weight adapted in g, TE = any thromboembolic event, ([e]) = not included in meta-regression, because VTE was not reported or iv TXA dose was not defined in detail. Studies with additional oral or topical administration were excluded from meta-regression. ([a]) = Patients with risk for TE comprise of patients with history of any TE, coronary artery disease, thrombophilia or contraindication for TXA.

eTable 2: Venous Thrombosis

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	7	0	358	1	263	Fixed-effect	-0.004 [-0.024, 0.017]	0.73	0%
						Random-effects	-0.005 [-0.023, 0.014]	0.62	
Neurological	11	38	1 778	31	1 767	Fixed-effect	0.004 [-0.006, 0.013]	0.44	0%
						Random-effects	0.003 [-0.005, 0.011]	0.46	
Gynaecological	26	9	12 356	14	12 286	Fixed-effect	-0.000 [-0.002, 0.001]	0.45	0%
						Random-effects	-0.000 [-0.001, 0.000]	0.21	
Orthopaedic	100	178	4 768	116	4 136	Fixed-effect	0.001 [-0.007, 0.009]	0.75	0%
						Random-effects	0.001 [-0.004, 0.007]	0.57	
Major trauma	1	40	10 060	41	10 067	Fixed-effect	-0.000 [-0.002, 0.002]	0.91	n. a.
						Random-effects	-0.000 [-0.002, 0.002]	0.91	
Maxillo-facial	6	0	265	0	192	Fixed-effect	0.000 [-0.023, 0.023]	1.00	0%
						Random-effects	0.000 [-0.019, 0.019]	1.00	
Paediatric	2	0	42	0	40	Fixed-effect	0.000 [-0.067, 0.067	1.00	0%
						Random-effects	0.000 [-0.064, 0.064]	1.00	
Other	10	7	707	10	581	Fixed-effect	-0.008 [-0.024, 0.008]	0.34	0%
						Random-effects	-0.007 [-0.02, 0.008]	0.38	
TOTAL	163	272	30 334	213	29 332	Fixed-effect	-0.000 [-0.002, 0.002]	0.99	0%

						Random-effects	-0.000 [-0.001, 0.000]	0.26	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of venous thrombosis. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence interval; n. a. = not applicable

eTable 3: Pulmonary Embolism

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	8	15	2 613	17	2 623	Fixed-effect	-0.001 [-0.005, 0.004]	0.75	0%
						Random-effects	-0.000 [-0.005, 0.004]	0.87	
Neurological	10	38	1 959	34	1 952	Fixed-effect	0.002 [-0.007, 0.011]	0.65	0%
						Random-effects	0.000 [-0.006, 0.01]	0.62	
Gynaecological	17	17	11 756	20	11 697	Fixed-effect	-0.000 [-0.002, 0.001]	0.67	0%
						Random-effects	-0.000 [-0.001, 0.001]	0.63	
Orthopaedic	80	8	4 136	10	3 510	Fixed-effect	-0.001 [-0.006, 0.004]	0.71	0%
						Random-effects	-0.001 [-0.005, 0.004]	0.73	
Major trauma	1	72	10 060	71	10 067	Fixed-effect	0.000 [-0.002, 0.002]	0.93	n. a.
						Random-effects	0.000 [-0.002, 0.002]	0.93	
Maxillo-facial	6	0	265	0	192	Fixed-effect	0.000 [-0.023, 0.023]	1.00	0%
						Random-effects	0.000 [-0.019, 0.019]	1.00	
Paediatric	2	0	42	0	40	Fixed-effect	0.000 [-0.067, 0.067]	1.00	0%
						Random-effects	0.000 [-0.064, 0.064]	1.00	
Other	5	2	324	1	326	Fixed-effect	0.003 [-0.015, 0.021]	0.75	0%
						Random-effects	0.000 [-0.016, 0.017]	0.99	
TOTAL	129	152	31 155	153	30 407	Fixed-effect	-0.000 [-0.001, 0.001]	0.89	0%
						Random-effects	-0.000 [-0.001, 0.001]	0.68	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of pulmonary embolism. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 4: Venous Thromboembolic and Pulmonary Embolism Event Rate

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	5	0	220	3	223	Fixed-effect	-0.014 [-0.038, 0.011]	0.28	0%
						Random-effects	-0.013 [-0.036, 0.01]	0.27	
Neurological	9	68	1 730	62	1 719	Fixed-effect	0.003 [-0.01, 0.016]	0.63	0%
						Random-effects	0.001 [-0.009, 0.011]	0.82	
Gynaecological	17	24	11 756	32	11 697	Fixed-effect	-0.001 [-0.002, 0.001]	0.33	0%
						Random-effects	-0.001 [-0.002, 0.001]	0.34	
Orthopaedic	79	143	4 117	91	3 497	Fixed-effect	-0.000 [-0.009, 0.008]	0.94	0%
						Random-effects	-0.001 [-0.005, 0.007]	0.79	
Major trauma	1	112	10 060	112	10 067	Fixed-effect	0.000 [-0.003, 0.003]	1.00	n. a.
						Random-effects	0.000 [-0.003, 0.003]	1.00	
Maxillo-facial	6	0	265	0	192	Fixed-effect	0.000 [-0.023, 0.023]	1.00	0%
						Random-effects	0.000 [-0.019, 0.019]	1.00	
Paediatric	2	0	42	0	40	Fixed-effect	0.000 [-0.067, 0.067]	1.00	0%
						Random-effects	0.000 [-0.064, 0.064]	1.00	
Other	4	1	248	4	253	Fixed-effect	-0.012 [-0.035, 0.011]	0.31	0%
						Random-effects	0.007 [-0.027, 0.014]	0.52	
TOTAL	123	348	24 438	304	27 688	Fixed-effect	-0.000 [-0.002, 0.002]	0.71	0%

						Random-effects	-0.001 [-0.002, 0.001]	0.39	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of venous thrombosis and pulmonary embolism. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 5: Myocardial Infarction or Ischaemia

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Neurological	4	14	1 341	7	1 314	Fixed-effect	0.005 [-0.002, 0.012]	0.14	0%
						Random-effects	0.004 [-0.003, 0.01]	0.24	
Gynaecological	2	2	10 366	3	10 315	Fixed-effect	-0.000 [-0.001, 0.000]	0.68	0%
						Random-effects	-0.000 [-0.001, 0.000]	0.65	
Orthopaedic	18	16	693	11	716	Fixed-effect	-0.007 [-0.011, 0.024]	0.47	0%
						Random-effects	-0.005 [-0.009, 0.02]	0.48	
Major trauma	1	35	10 060	55	10 067	Fixed-effect	-0.002 [-0.004, -0.000]	0.03	n. a.
						Random-effects	-0.002 [-0.004, -0.000]	0.03	
Other	4	3	240	1	240	Fixed-effect	0.008 [-0.013, 0.03]	0.45	0%
						Random-effects	0.006 [-0.015, 0.026]	0.59	
TOTAL	27	70	22 700	77	22 679	Fixed-effect	-0.000 [-0.001, 0.001]	0.56	0%
						Random-effects	-0.000 [-0.001, 0.000]	0.42	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of myocardial infarction and ischaemia. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 6: Cerebral Infarction or Ischaemia

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	14	43	3 100	39	2 955	Fixed-effect	0.001 [-0.005, 0.008]	0.74	0%
						Random-effects	-0.013 [-0.036, 0.01]	0.92	
Gynaecological	2	8	10 366	6	10 315	Fixed-effect	0.000 [-0.001, 0.001]	0.61	0%
						Random-effects	-0.001 [-0.002, 0.001]	0.60	
Orthopaedic	13	4	576	1	602	Fixed-effect	0.005 [-0.009, 0.02]	0.49	0%
						Random-effects	-0.001 [-0.005, 0.007]	0.67	
Major trauma	1	57	10 060	66	10 067	Fixed-effect	-0.001 [-0.003, 0.001]	0.42	n. a.
						Random-effects	0.000 [-0.003, 0.003]	0.42	
Paediatric	1	0	23	0	20	Fixed-effect	0.000 [-0.087, 0.087]	1.00	n. a.
						Random-effects	0.000 [-0.064, 0.064]	1.00	
Other	2	2	176	3	173	Fixed-effect	-0.006 [-0.033, 0.021]	0.67	42%
						Random-effects	0.007 [-0.027, 0.014]	0.76	
TOTAL	33	114	24 301	115	24 132	Fixed-effect	-0.000 [-0.001, 0.001]	0.9	0%
						Random-effects	0.001 [-0.001, 0.001]	0.79	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of stroke or cerebral ischaemia. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 7: Non-Bleeding Mortality

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	11	1	511	11	448	Fixed-effect	-0.025 [-0.045, -0.005]	0.02	0%
						Random-effects	-0.015 [-0.031, 0.002]	0.10	
Neurological	8	116	685	85	678	Fixed-effect	0.044 [0.007, 0.081]	0.02	28%
						Random-effects	0.021 [-0.014, 0.057]	0.24	
Gynaecological	8	72	10 871	65	10 814	Fixed-effect	0.001 [-0.002, 0.003]	0.58	0%
						Random-effects	0.001 [-0.002, 0.003]	0.61	
Orthopaedic	13	1	636	2	451	Fixed-effect	-0.002 [-0.018, 0.013]	0.77	0%
						Random-effects	-0.002 [-0.015, 0.012]	0.83	
Major trauma	1	974	10 060	1 039	10 067	Fixed-effect	-0.006 [-0.015, 0.002]	0.13	n. a.
						Random-effects	-0.006 [-0.015, 0.002]	0.13	
Paediatric	1	0	40	0	42	Fixed-effect	0.000 [-0.046, 0.046]	1.00	n. a.
						Random-effects	0.000 [-0.046, 0.046]	1.00	
Other	6	16	655	26	661	Fixed-effect	-0.014 [-0.034, 0.005]	0.15	41%
						Random-effects	-0.005 [-0.02, 0.011]	0.57	
TOTAL	48	1 180	23 458	1 228	23 161	Fixed-effect	-0.002 [-0.006, 0.002]	0.29	0%
						Random-effects	-0.000 [-0.002, 0.001]	0.92	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of any non-bleeding mortality. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable8: Summary of Sensitivity Analysis including Patients with increased Risk for total Thromboembolic Events

Subgroup	Studies	TXA		Control		Risk Difference [95% CI]	P	I^2
	(n=)	Events	(n=)	Events	(n=)			
Total Thromboembolic Events								
Cardiothoracic	13	14	724	16	553	-0.005 [-0.025, 0.015]	0.64	0%
Neurological	4	4	218	6	216	-0.009 [-0.04, 0.021]	0.55	0%
Gynaecological	5	2	595	2	592	-0.000 [-0.009, 0.009]	0.99	0%
Orthopaedic	17	21	660	17	668	0.005 [-0.014, 0.025]	0.58	0%
Major trauma	0							
Maxillo-facial	3	0	99	0	96	0.000 [-0.035, 0.035]	1.00	0%
Paediatric	2	0	42	0	40	0.000 [-0.067, 0.067]	1.00	0%
Other	5	4	127	2	123	0.015 [-0.033, 0.063]	0.54	0%
TOTAL fixed-effect	49	45	2 465	43	2 288	0.000 [-0.008, 0.009]	0.95	0%
TOTAL random-effects						-0.000 [-0.005, 0.005]	0.95	
Venous Thrombosis								
Cardiothoracic	6	0	254	0	157	0.000 [-0.028, 0.028]	1.00	0%
Neurological	4	4	218	3	216	0.005 [-0.021, 0.030]	0.73	0%
Gynaecological	5	2	595	2	592	-0.000 [-0.009, 0.009]	0.99	0%
Orthopaedic	17	25	660	22	668	0.004 [-0.018, 0.026]	0.72	0%
Major trauma	0							
Maxillo-facial	3	0	99	0	96	0.000 [-0.035, 0.035]	1.00	0%
Paediatric	2	0	42	0	40	0.000 [-0.067, 0.067]	1.00	0%
Other	5	4	127	2	123	0.015 [-0.033, 0.063]	0.54	0%
TOTAL fixed-effect	42	35	1 995	29	1 892	0.003 [-0.007, 0.013]	0.57	0%
TOTAL random-effects						0.000 [-0.005, 0.005]	0.99	
Pulmonary Embolism								

Cardiothoracic	5	0	166	1	167	-0.006 [-0.035, 0.023]	0.68	0%
Neurological	2	0	170	0	168	0.000 [-0.016, 0.016]	1.00	0%
Gynaecological	3	0	457	0	456	0.000 [-0.007, 0.007]	1.00	0%
Orthopaedic	10	2	432	3	445	-0.002 [-0.019, 0.019]	0.81	0%
Major trauma	0							
Maxillo-facial	3	0	99	0	96	0.000 [-0.034, 0.034]	1.00	0%
Paediatric	2	0	42	0	40	0.000 [-0.067, 0.067]	1.00	0%
Other	1	0	20	0	20	0.000 [-0.092, 0.092]	1.00	n. a.
TOTAL fixed-effect	26	2	1 386	4	1 392	-0.001 [-0.009, 0.007]	0.73	0%
TOTAL random-effects						-0.000 [-0.005, 0.004]	0.9	
Pulmonary Embolism and Venous Thrombosis								
Cardiothoracic	4	0	116	1	117	-0.009 [-0.046, 0.029]	0.65	0%
Neurological	2	0	170	0	168	0.000 [-0.016, 0.016]	1.00	0%
Gynaecological	3	0	457	0	456	-0.000 [-0.007, 0.007]	1.00	0%
Orthopaedic	10	17	432	17	445	0.000 [-0.028, 0.028]	0.99	0%
Major trauma	0							
Maxillo-facial	3	0	99	0	96	0.000 [-0.035, 0.035]	1.00	0%
Paediatric	2	0	42	0	40	0.000 [-0.067, 0.067]	1.00	0%
Other	1	0	20	0	20	0.000 [-0.092, 0.092]	1.00	n. a.
TOTAL fixed-effect	25	17	1 336	18	1 342	-0.000 [-0.012, 0.010]	0.89	0%
TOTAL random-effects						-0.000 [-0.005, 0.005]	0.97	
Overall Mortality								
Cardiothoracic	12	5	569	7	525	-0.005 [-0.023, 0.013]	0.74	0%
Neurological	4	22	188	43	185	-0.115 [-0.188, -0.041]	0.002	55%
Gynaecological	1	0	88	0	86	0.000 [-0.022, 0.022]	1.00	n. a.
Orthopaedic	1	0	39	1	38	-0.026 [-0.96, 0.043]	0.46	n. a.
Major trauma	0							
Maxillo-facial	0							
Paediatric	0							

Other	2	17	272	35	276	-0.064 [-0.113, -0.015]	0.01	61%
TOTAL fixed-effect	20	44	1 156	86	1 110	-0.038 [-0.057, -0.018]	<0.001	67%
TOTAL random-effects						-0.018 [-0.043, -0.007]	0.15	

Summary of forest plot of intravenous tranexamic acid compared with control in patients with increased risk for thromboembolism (TE), including patients with history of any TE, coronary artery disease, thrombophilia or contraindication for TXA.
TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 9: Study Characteristics of Updated Meta-Analysis

Year	Author	Medical Discipline	Control (n=)	TXA (n=)	TXA Application		Ref
2018	Batibay et al	Orthopaedic	35	35	iv	sd, w	209
2018	Zhou et al	Orthopaedic	57	57	iv	ad, w	228
2018	Zhou et al	Orthopaedic	50	50	iv	sd, nw	229
2018	Sentilhes et al	Gynaecology	1 849	1 844	iv	sd, nw	224
2019	Chen et al	Orthopaedic	86	85	iv	ad, w	210
2019	Clave et al	Orthopaedic	69	142	iv*	ad, nw	211
2019	Felli et al	Orthopaedic	40	40	iv	sd, w	213
2019	Karampinas et al	Orthopaedic	54	46	iv + topical	ad, w and nw	215
2019	Mu et al	Orthopaedic	42	45	iv	ad, w	221
2019	Xu et al	Orthopaedic	67	68	iv	sd, w	226
2019	Abdul et al	Gynaecology	40	40	iv	sd, w	208
2019	Fenger-Eriksen et al	Paediatric	15	15	iv	ad, w	214
2019	The CRASH-3 trial collaborators	Neurological	4 514	4 613	iv	ad, nw	206
2019	Zaman et al	Otorhinolaryngology	88	88	iv	sd, w	226
2020	Cuff et al	Orthopaedic	48	53	iv	sd, nw	212
2020	Lei et al	Orthopaedic	50	150	iv*	ad, w and nw	216
2020	Levack et al	Orthopaedic	41	40	iv	sd, w	217
2020	Liu et al	Orthopaedic	35	37	iv	sd, nw	218
2020	The HALT-IT Trial Collaborators	Gastrointestinal	5 981	5 956	iv	ad, nw	207
2020	Monaco et al	Cardiothoracic	50	50	iv	ad, nw	220
2020	Opoku-Anane et al	Gynaecology	30	30	iv	sd, w	222
2020	Rowell et al	Neurological	309	657	iv*	sd, nw / ad, nw	223
2020	Meretoja et al	Neurological	50	50	iv	ad, nw	219
2020	Sidelmann et al	Maxillo-facial	46	51	iv	sd, nw	225

(*) = more than one study group receiving iv TXA, "/" = divides different study groups. sd = single dose, ad = additional dose, w = weight adapted in mg/kg, nw = not weight adapted in g

eTable 10: Total Thromboembolic Events of Updated Meta-Analysis

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	17	74	3 221	76	3 059	Fixed-effect	-0.001 [-0.009, 0.007]	0.84	0%
						Random-effects	0.001 [-0.007, 0.008]	0.91	
Neurological	16	409	7 367	326	6 913	Fixed-effect	0.007 [0.000, 0.014]	0.04	36%
						Random-effects	0.003 [-0.012, 0.017]	0.74	
Gynaecological	29	36	14 270	45	14 205	Fixed-effect	-0.001 [-0.002, 0.001]	0.37	0%
						Random-effects	-0.001 [-0.002, 0.001]	0.21	
Orthopaedic	111	189	5 519	131	4 695	Fixed-effect	0.001 [-0.007, 0.008]	0.84	0%
						Random-effects	0.001 [-0.004, 0.006]	0.63	
Major trauma	1	204	10 060	233	10 067	Fixed-effect	-0.003 [-0.007, 0.001]	0.16	n. a.
						Random-effects	-0.003 [-0.007, 0.001]	0.16	
Maxillo-facial	6	0	265	0	192	Fixed-effect	0.000 [-0.023, 0.023]	1.00	0%
						Random-effects	0.000 [-0.019, 0.019]	1.00	
Paediatric	3	0	57	0	55	Fixed-effect	0.000 [-0.060, 0.060]	1.00	0%
						Random-effects	0.000 [-0.057, 0.057]	1.00	
Other	15	108	6894	89	6785	Fixed-effect	0.003 [-0.002, 0.007]	0.23	0%
						Random-effects	0.003 [-0.001, 0.007]	0.18	
TOTAL	198	1 020	47 653	900	45 971	Fixed-effect	0.001 [-0.001, 0.002]	0.49	0%

						Random-effects	-0.000 [-0.002, 0.001]	0.43	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk for total thromboembolic events. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 11: Venous Thrombosis of Updated Meta-Analysis

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	8	0	408	1	313	Fixed-effect	-0.003 [-0.021, 0.015]	0.74	0%
						Random-effects	-0.004 [-0.020, 0.013]	0.65	
Neurological	14	66	7 088	52	6 6630	Fixed-effect	0.001 [-0.002, 0.004]	0.63	0%
						Random-effects	0.001 [-0.002, 0.003]	0.54	
Gynaecological	29	10	14 270	18	14 205	Fixed-effect	-0.001 [-0.002, 0.000]	0.26	0%
						Random-effects	-0.001 [-0.001, 0.000]	0.12	
Orthopaedic	113	189	5 581	129	4 760	Fixed-effect	0.001 [-0.007, 0.008]	0.85	0%
						Random-effects	0.001 [-0.004, 0.006]	0.64	
Major trauma	1	40	10 060	41	10 067	Fixed-effect	-0.000 [-0.002, 0.002]	0.91	n. a.
						Random-effects	-0.000 [-0.002, 0.002]	0.91	
Maxillo-facial	6	0	265	0	192	Fixed-effect	0.000 [-0.023, 0.023]	1.00	0%
						Random-effects	0.000 [-0.019, 0.019]	1.00	
Paediatric	3	0	57	0	55	Fixed-effect	0.000 [-0.060, 0.060]	1.00	0%
						Random-effects	0.000 [-0.057, 0.057]	1.00	
Other	13	30	6 802	22	6696	Fixed-effect	0.001 [-0.001, 0.003]	0.45	0%
						Random-effects	0.002 [-0.000, 0.004]	0.08	
TOTAL	187	335	44 531	263	42 918	Fixed-effect	0.000 [-0.001, 0.001]	0.85	0%

						Random-effects	-0.000 [-0.001, 0.000]	0.47	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of venous thrombosis. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 12: Pulmonary Embolism of Updated Meta-Analysis

Subgroup	Studies (n=)	Events	(n=)	Events	(n=)	Model	Risk Difference [95% CI]	P	I^2
Cardiothoracic	9	15	2 663	17	2 673	Fixed-effect	-0.001 [-0.005, 0.004]	0.76	0%
						Random-effects	-0.000 [-0.005, 0.004]	0.65	
Neurological	14	65	7 319	58	6 865	Fixed-effect	0.000 [-0.003, 0.003]	0.90	0%
						Random-effects	0.000 [-0.002, 0.002]	0.98	
Gynaecological	19	17	13 640	20	13 586	Fixed-effect	-0.000 [-0.001, 0.001]	0.68	0%
						Random-effects	-0.000 [-0.001, 0.001]	0.12	
Orthopaedic	85	11	4 641	12	3 840	Fixed-effect	-0.001 [-0.006, 0.004]	0.72	0%
						Random-effects	-0.001 [-0.005, 0.004]	0.64	
Major trauma	1	72	10 060	71	10 067	Fixed-effect	0.000 [-0.002, 0.002]	0.93	n. a.
						Random-effects	0.000 [-0.002, 0.002]	0.91	
Maxillo-facial	6	0	265	0	192	Fixed-effect	0.000 [-0.023, 0.023]	1.00	0%
						Random-effects	0.000 [-0.019, 0.019]	1.00	
Paediatric	2	0	42	0	40	Fixed-effect	0.000 [-0.067, 0.067]	1.00	0%
						Random-effects	0.000 [-0.064, 0.064]	1.00	
Other	8	30	6 419	17	6 441	Fixed-effect	0.002 [-0.000, 0.004]	0.08	0%
						Random-effects	0.000 [-0.000, 0.004]	0.08	
TOTAL	144	210	45 049	195	43 704	Fixed-effect	0.000 [-0.001, 0.001]	0.74	0%

						Random-effects	0.000 [-0.001, 0.001]	0.81	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of pulmonary embolism. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 13: Venous Thromboembolic and Pulmonary Embolism Event Rate of Updated Meta-Analysis

Subgroup	Studies (n=)	Events	(n=)	Events	(n=)	Model	Risk Difference [95% CI]	P	I^2
Cardiothoracic	6	0	270	3	273	Fixed-effect	-0.011 [-0.032, 0.010]	0.31	0%
						Random-effects	-0.001 [-0.023, 0.01]	0.34	
Neurological	16	124	9 004	111	8 551	Fixed-effect	-0.000 [-0.004, 0.003]	0.93	0%
						Random-effects	-0.001 [-0.003, 0.001]	0.34	
Gynaecological	17	24	11 756	32	11 697	Fixed-effect	-0.001 [-0.002, 0.001]	0.33	0%
						Random-effects	-0.001 [-0.002, 0.001]	0.34	
Orthopaedic	90	158	4 889	107	4 084	Fixed-effect	-0.001 [-0.008, 0.007]	0.90	0%
						Random-effects	0.001 [-0.005, 0.006]	0.77	
Major trauma	1	112	10 060	112	10 067	Fixed-effect	0.000 [-0.003, 0.003]	1.00	n. a.
						Random-effects	0.000 [-0.003, 0.003]	1.00	
Maxillo-facial	6	0	265	0	192	Fixed-effect	0.000 [-0.023, 0.023]	1.00	0%
						Random-effects	0.000 [-0.019, 0.019]	1.00	
Paediatric	3	0	57	0	55	Fixed-effect	0.000 [-0.06, 0.06]	1.00	0%
						Random-effects	0.000 [-0.057, 0.057]	1.00	
Other	7	52	6 343	32	6 368	Fixed-effect	0.003 [0.000, 0.006]	0.03	0%
						Random-effects	0.004 [0.001, 0.006]	0.01	
TOTAL	146	470	42 644	397	41 287	Fixed-effect	0.000 [-0.001, 0.002]	0.85	0%

						Random-effects	-0.000 [-0.001, 0.001]	0.72	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of venous thrombosis and pulmonary embolism. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eTable 14: Overall Mortality of Updated Meta-Analysis

Subgroup	Studies (n=)	TXA		Control		Model	Risk Difference [95% CI]	P	I^2
		Events	(n=)	Events	(n=)				
Cardiothoracic	15	32	3 040	48	3 006	Fixed-effect	-0.006 [-0.012, 0.001]	0.08	0%
						Random-effects	-0.003 [-0.009, 0.003]	0.26	
Neurological	16	1 395	7 337	1 403	6 875	Fixed-effect	-0.012 [-0.025, 0.001]	0.07	19%
						Random-effects	-0.013 [-0.034, 0.007]	0.21	
Gynaecological	227	227	10 871	256	10 814	Fixed-effect	-0.003 [-0.007, 0.001]	0.17	0%
						Random-effects	-0.002 [-0.005, 0.002]	0.31	
Orthopaedic	18	23	979	21	788	Fixed-effect	0.002 [-0.015, 0.019]	0.84	0%
						Random-effects	-0.002 [-0.014, 0.01]	0.75	
Major trauma	1	1 463	10 060	1 613	10 067	Fixed-effect	-0.015 [-0.023, -0.005]	0.004	n. a.
						Random-effects	-0.015 [-0.023, -0.005]	0.004	
Paediatric	1	0	40	0	42	Fixed-effect	0.000 [-0.046, 0.046]	1.00	n. a.
						Random-effects	0.000 [-0.047, 0.047]	1.00	
Other	11	616	7 031	623	6 923	Fixed-effect	-0.003 [-0.012, 0.007]	0.61	31%
						Random-effects	-0.007 [-0.02, 0.005]	0.25	
TOTAL	70	3 756	39 358	3 964	38 515	Fixed-effect	-0.007 [-0.012, -0.004]	<0.001	5%
						Random-effects	-0.004 [-0.007, -0.000]	0.02	

Summary of forest plot of intravenous tranexamic acid compared with control showing risk of overall mortality and pulmonary embolism. TXA = Tranexamic Acid; n = number of included patients; CI = Confidence Interval; n. a. = not applicable

eAppendix 11. References on Total Thromboembolic Events

In total, 176 studies [6, 15-70, 72-144, 146-150, 152-157, 159, 161-164, 166-169, 172, 174-180, 182, 183, 185, 186, 188, 189, 191, 193-198, 201-205] provided data on total TE in 65,900 patients (n=33,487 TXA group vs. n=32,413 control group).

eAppendix 12. References on Venous Thrombosis Events

In total, 163 studies[6, 15-70, 72-112, 114-144, 146-150, 152, 154-156, 161, 163, 164, 174-179, 182, 183, 185, 186, 188, 189, 193-196, 198, 201-205] provided data on VT events in 59,666 patients (n=30,334 TXA group vs. n=29,332 control group).

eAppendix 13. References on Pulmonary Embolism Events

In total, 129 studies[6, 15, 17, 20-24, 26, 28, 30, 31, 34-36, 38-47, 49, 50, 54, 57, 58, 60-68, 70, 72-74, 77-82, 84-88, 92, 93, 95-104, 106, 107, 110, 111, 113, 114, 116-127, 129-131, 133-137, 139-144, 146-150, 154, 155, 161, 163, 164, 167, 168, 172, 176-180, 182, 183, 185, 186, 188, 189, 191, 201-204, 206, 207] provided data on PE events in 61,562 patients (n=31,155 TXA group vs. n=30,407 control group).

eAppendix 14. References on Venous Thromboembolic Events

To assess the total number of VTE, PE and VT were combined and analysed. In total, 123 studies [6, 15, 17, 20-24, 26, 28, 30, 31, 34-36, 38-47, 49, 50, 54, 57, 58, 60-68, 70, 72-74, 77-82, 84-88, 92, 93, 95-104, 106, 107, 110, 111, 114, 116-127, 129-131, 133-137, 139-144, 146-150, 154, 155, 161, 163, 164, 176-179, 182, 183, 185, 186, 188, 189, 201-204, 206, 207] provided data on VTE in 56,126 patients (n=28,438 TXA group vs. n=27,688 control group).

eAppendix 15. References on Overall Mortality

In total, 63[6,20,24,29-31,36,39-41,50,70,71,78,91,93,105,113,115,128,136,137,142,143,145,149,151,155-160,162,164-166,168-170,172-179,181-184,186,187,190-192,194,196,197,200,201,205] studies assessed the overall mortality in 55,305 patients (n=27,865 TXA group vs. n=27,440 control group).

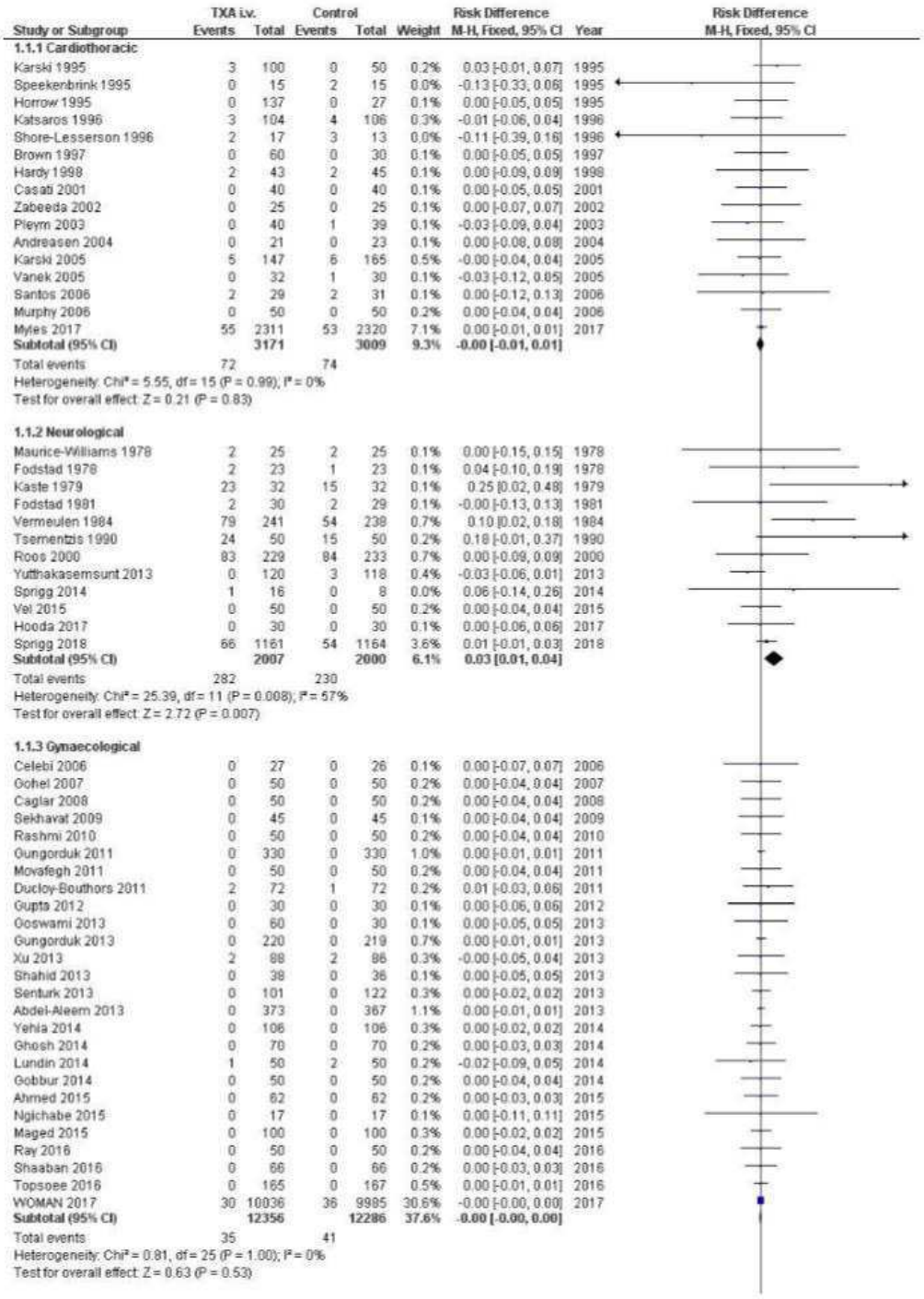
eAppendix 16. References on Non-bleeding Mortality

In total, 48[20,24,29-31,36,39-41,50,70,71,91,93,105,113,115,128,136,137,143,145,155-160,162,165,168-170,174-179,181,186,187,190,192,194,197,200,201] studies assessed non-bleeding mortality in 46,619 patients (n=23,458 TXA group vs. n=23,161 control group).

eAppendix 17. References on Bleeding Mortality

In total, 49 studies[20,24,29-31,36,39-41,50,70,71,91,93,105,113,115,128,136,137,143,145,155-160,162,165,167-170,174-179,181,186,187,190,192,194,197,200,201] assessed the bleeding mortality in 46,702 patients (n=23,501 TXA group vs. n=23,201 control group).

eFigure 1: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



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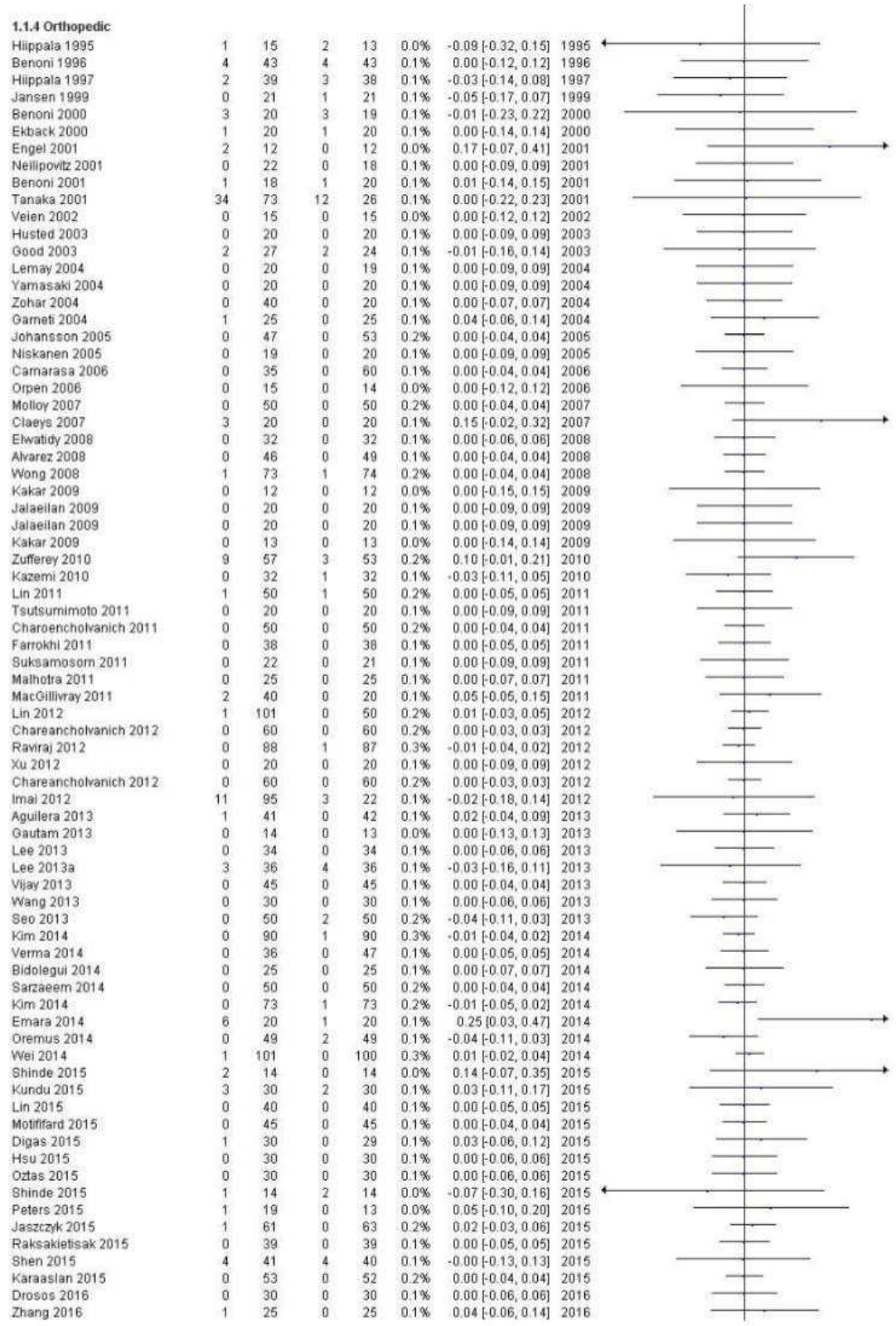

1.1.4 Orthopedic							
Hiippala 1995	1	15	2	13	0.0%	-0.09 [-0.32, 0.15]	1995
Benoni 1996	4	43	4	43	0.1%	0.00 [-0.12, 0.12]	1996
Hiippala 1997	2	39	3	38	0.1%	-0.03 [-0.14, 0.09]	1997
Jansen 1999	0	21	1	21	0.1%	-0.05 [-0.17, 0.07]	1999
Benoni 2000	3	20	3	19	0.1%	-0.01 [-0.23, 0.22]	2000
Ekback 2000	1	20	1	20	0.1%	0.00 [-0.14, 0.14]	2000
Engel 2001	2	12	0	12	0.0%	0.17 [-0.07, 0.41]	2001
Neilipovitz 2001	0	22	0	18	0.1%	0.00 [-0.09, 0.09]	2001
Benoni 2001	1	18	1	20	0.1%	0.01 [-0.14, 0.15]	2001
Tanaka 2001	34	73	12	26	0.1%	0.00 [-0.22, 0.23]	2001
Veien 2002	0	15	0	15	0.0%	0.00 [-0.12, 0.12]	2002
Husted 2003	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2003
Good 2003	2	27	2	24	0.1%	-0.01 [-0.16, 0.14]	2003
Lemay 2004	0	20	0	19	0.1%	0.00 [-0.09, 0.09]	2004
Yamasaki 2004	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2004
Zohar 2004	0	40	0	20	0.1%	0.00 [-0.07, 0.07]	2004
Garneti 2004	1	25	0	25	0.1%	0.04 [-0.06, 0.14]	2004
Johansson 2005	0	47	0	53	0.2%	0.00 [-0.04, 0.04]	2005
Niskanen 2005	0	19	0	20	0.1%	0.00 [-0.09, 0.09]	2005
Camarasa 2006	0	35	0	60	0.1%	0.00 [-0.04, 0.04]	2006
Orpen 2006	0	15	0	14	0.0%	0.00 [-0.12, 0.12]	2006
Molloy 2007	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2007
Claeys 2007	3	20	0	20	0.1%	0.15 [-0.02, 0.32]	2007
Elwatidy 2008	0	32	0	32	0.1%	0.00 [-0.06, 0.06]	2008
Alvarez 2008	0	46	0	49	0.1%	0.00 [-0.04, 0.04]	2008
Wong 2008	1	73	1	74	0.2%	0.00 [-0.04, 0.04]	2008
Kakar 2009	0	12	0	12	0.0%	0.00 [-0.15, 0.15]	2009
Jalaeilan 2009	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2009
Jalaeilan 2009	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2009
Kakar 2009	0	13	0	13	0.0%	0.00 [-0.14, 0.14]	2009
Zufferey 2010	9	57	3	53	0.2%	0.10 [-0.01, 0.21]	2010
Kazemi 2010	0	32	1	32	0.1%	-0.03 [-0.11, 0.05]	2010
Lin 2011	1	50	1	50	0.2%	0.00 [-0.05, 0.05]	2011
Tsutsumimoto 2011	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2011
Charoencholvanich 2011	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2011
Farrokhi 2011	0	38	0	38	0.1%	0.00 [-0.05, 0.05]	2011
Suksamosorn 2011	0	22	0	21	0.1%	0.00 [-0.09, 0.09]	2011
Malhotra 2011	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2011
MacGillivray 2011	2	40	0	20	0.1%	0.05 [-0.05, 0.15]	2011
Lin 2012	1	101	0	50	0.2%	0.01 [-0.03, 0.05]	2012
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Raviraj 2012	0	88	1	87	0.3%	-0.01 [-0.04, 0.02]	2012
Xu 2012	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2012
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Imai 2012	11	95	3	22	0.1%	-0.02 [-0.18, 0.14]	2012
Aguilera 2013	1	41	0	42	0.1%	0.02 [-0.04, 0.09]	2013
Gautam 2013	0	14	0	13	0.0%	0.00 [-0.13, 0.13]	2013
Lee 2013	0	34	0	34	0.1%	0.00 [-0.06, 0.06]	2013
Lee 2013a	3	36	4	36	0.1%	-0.03 [-0.16, 0.11]	2013
Vijay 2013	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2013
Wang 2013	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2013
Seo 2013	0	50	2	50	0.2%	-0.04 [-0.11, 0.03]	2013
Kim 2014	0	90	1	90	0.3%	-0.01 [-0.04, 0.02]	2014
Verma 2014	0	36	0	47	0.1%	0.00 [-0.05, 0.05]	2014
Bidolegui 2014	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2014
Sarzaeem 2014	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2014
Kim 2014	0	73	1	73	0.2%	-0.01 [-0.05, 0.02]	2014
Emara 2014	6	20	1	20	0.1%	0.25 [0.03, 0.47]	2014
Oremus 2014	0	49	2	49	0.1%	-0.04 [-0.11, 0.03]	2014
Wei 2014	1	101	0	100	0.3%	0.01 [-0.02, 0.04]	2014
Shinde 2015	2	14	0	14	0.0%	0.14 [-0.07, 0.35]	2015
Kundu 2015	3	30	2	30	0.1%	0.03 [-0.11, 0.17]	2015
Lin 2015	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2015
Motiflfard 2015	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2015
Digas 2015	1	30	0	29	0.1%	0.03 [-0.06, 0.12]	2015
Hsu 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Oztas 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Shinde 2015	1	14	2	14	0.0%	-0.07 [-0.30, 0.16]	2015
Peters 2015	1	19	0	13	0.0%	0.05 [-0.10, 0.20]	2015
Jaszczyk 2015	1	61	0	63	0.2%	0.02 [-0.03, 0.06]	2015
Raksakietisak 2015	0	39	0	39	0.1%	0.00 [-0.05, 0.05]	2015
Shen 2015	4	41	4	40	0.1%	-0.00 [-0.13, 0.13]	2015
Karaaslan 2015	0	53	0	52	0.2%	0.00 [-0.04, 0.04]	2015
Drosos 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Zhang 2016	1	25	0	25	0.1%	0.04 [-0.06, 0.14]	2016

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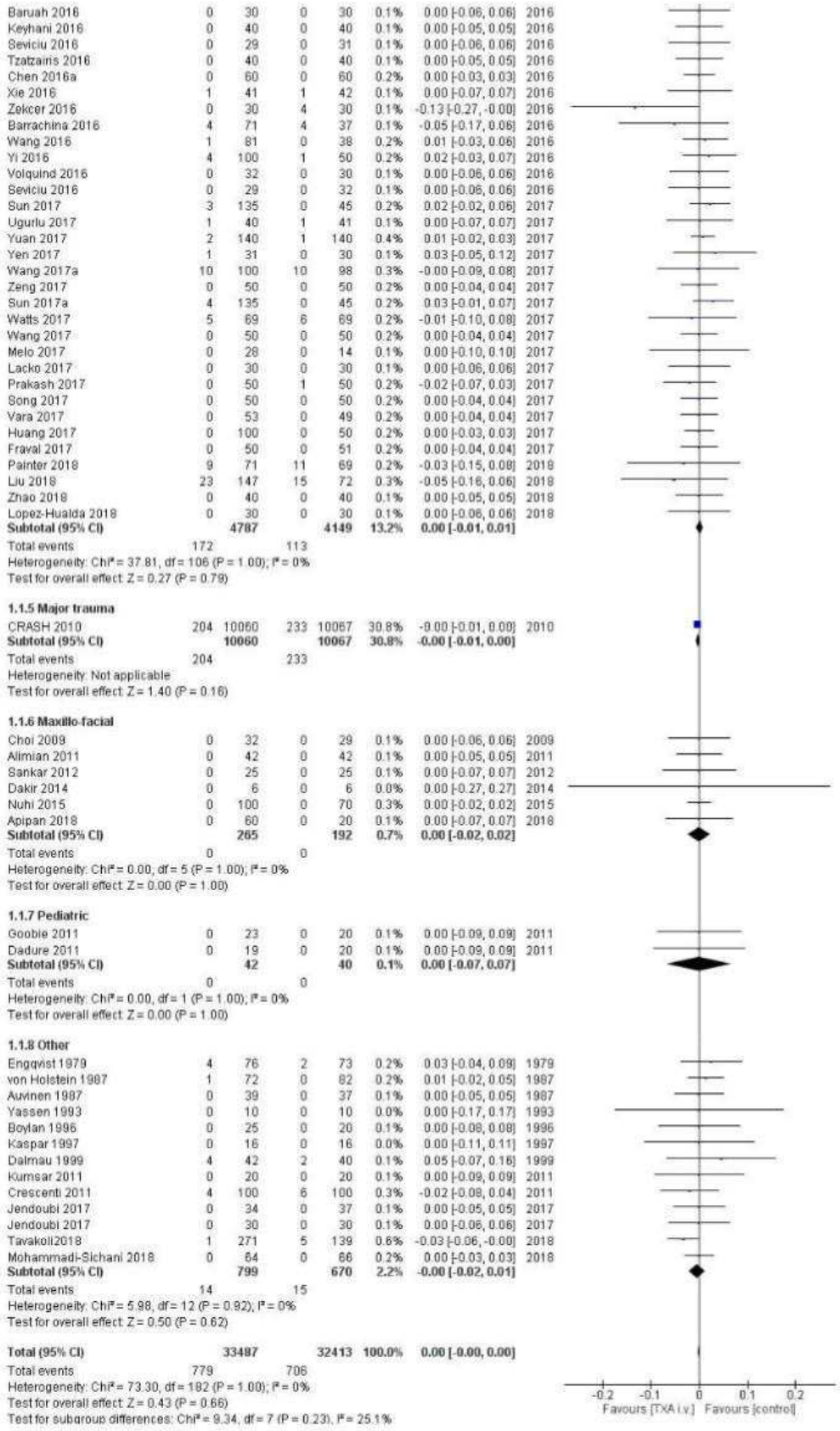
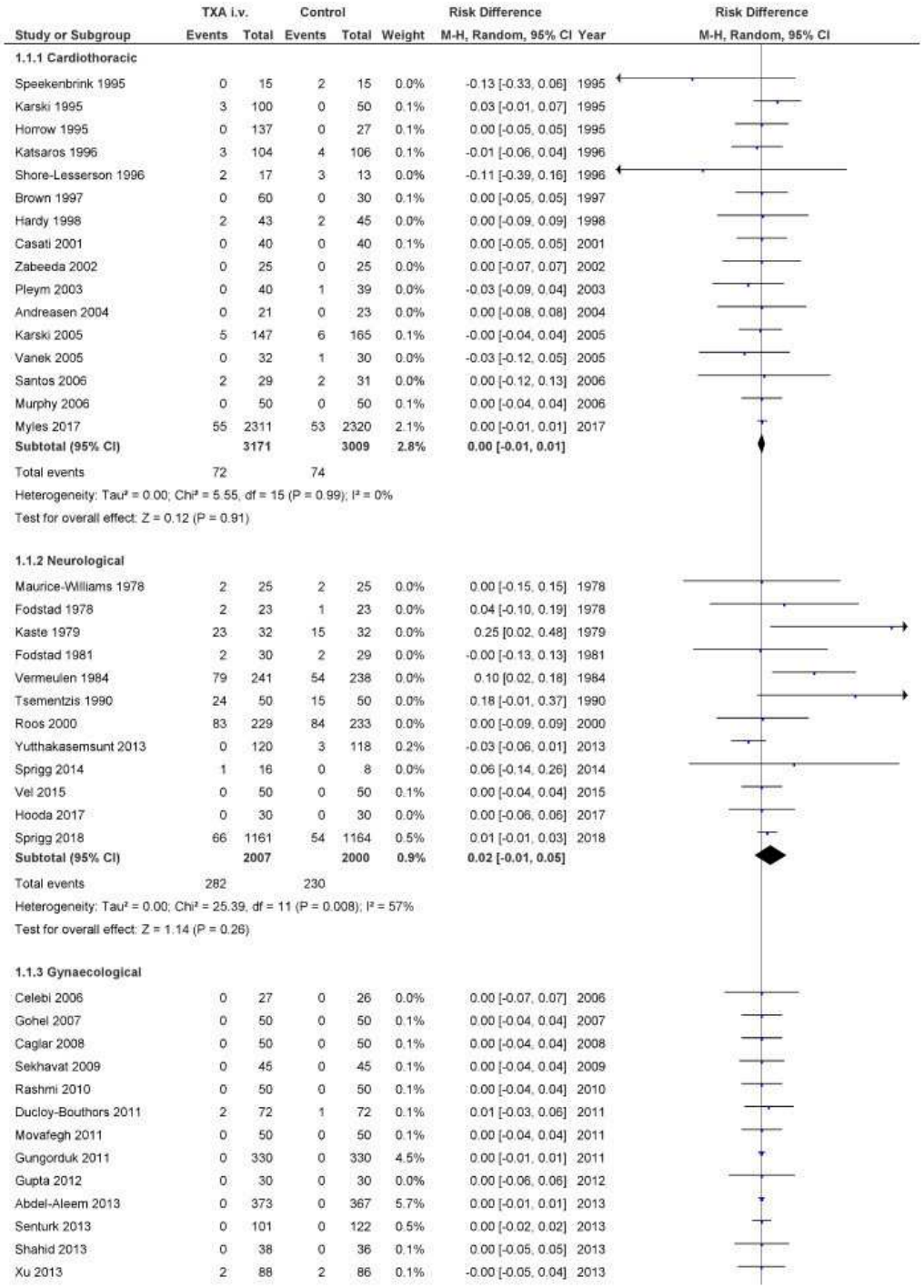


eFigure 2: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model



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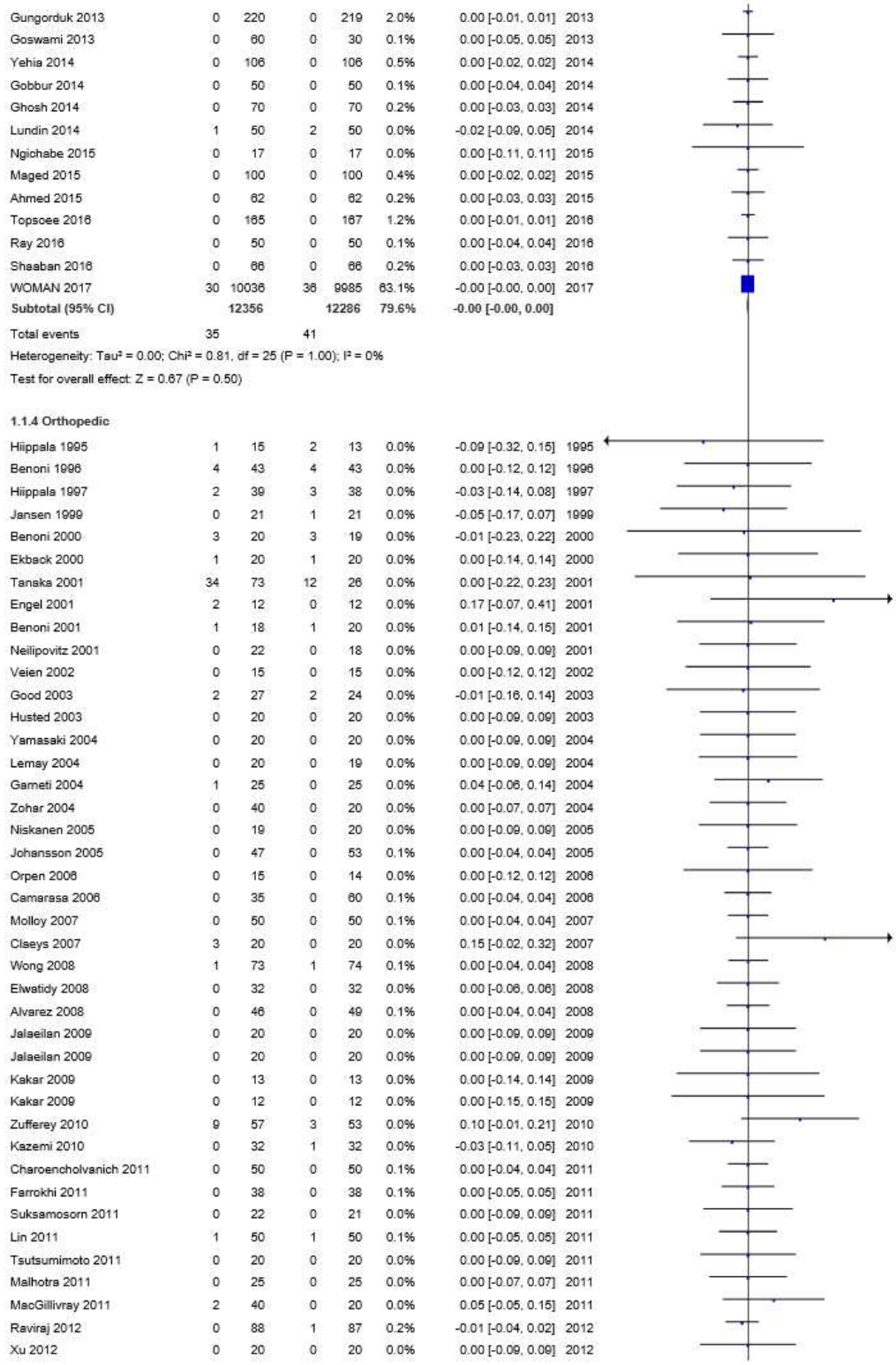

Gungorduk 2013	0	220	0	219	2.0%	0.00 [-0.01, 0.01]	2013
Goswami 2013	0	60	0	30	0.1%	0.00 [-0.05, 0.05]	2013
Yehia 2014	0	106	0	106	0.5%	0.00 [-0.02, 0.02]	2014
Gobbur 2014	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2014
Ghosh 2014	0	70	0	70	0.2%	0.00 [-0.03, 0.03]	2014
Lundin 2014	1	50	2	50	0.0%	-0.02 [-0.09, 0.05]	2014
Ngichabe 2015	0	17	0	17	0.0%	0.00 [-0.11, 0.11]	2015
Maged 2015	0	100	0	100	0.4%	0.00 [-0.02, 0.02]	2015
Ahmed 2015	0	62	0	62	0.2%	0.00 [-0.03, 0.03]	2015
Topsoee 2016	0	165	0	167	1.2%	0.00 [-0.01, 0.01]	2016
Ray 2016	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2016
Shaaban 2016	0	66	0	66	0.2%	0.00 [-0.03, 0.03]	2016
WOMAN 2017	30	10036	36	9985	63.1%	-0.00 [-0.00, 0.00]	2017
Subtotal (95% CI)		**12356**		**12286**	**79.6%**	**-0.00 [-0.00, 0.00]**	
Total events	35		41				

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 25 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.67 (P = 0.50)

1.1.4 Orthopedic

Hiippala 1995	1	15	2	13	0.0%	-0.09 [-0.32, 0.15]	1995
Benoni 1996	4	43	4	43	0.0%	0.00 [-0.12, 0.12]	1996
Hiippala 1997	2	39	3	38	0.0%	-0.03 [-0.14, 0.08]	1997
Jansen 1999	0	21	1	21	0.0%	-0.05 [-0.17, 0.07]	1999
Benoni 2000	3	20	3	19	0.0%	-0.01 [-0.23, 0.22]	2000
Ekback 2000	1	20	1	20	0.0%	0.00 [-0.14, 0.14]	2000
Tanaka 2001	34	73	12	26	0.0%	0.00 [-0.22, 0.23]	2001
Engel 2001	2	12	0	12	0.0%	0.17 [-0.07, 0.41]	2001
Benoni 2001	1	18	1	20	0.0%	0.01 [-0.14, 0.15]	2001
Neilipovitz 2001	0	22	0	18	0.0%	0.00 [-0.09, 0.09]	2001
Veien 2002	0	15	0	15	0.0%	0.00 [-0.12, 0.12]	2002
Good 2003	2	27	2	24	0.0%	-0.01 [-0.16, 0.14]	2003
Husted 2003	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2003
Yamasaki 2004	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2004
Lemay 2004	0	20	0	19	0.0%	0.00 [-0.09, 0.09]	2004
Gameti 2004	1	25	0	25	0.0%	0.04 [-0.06, 0.14]	2004
Zohar 2004	0	40	0	20	0.0%	0.00 [-0.07, 0.07]	2004
Niskanen 2005	0	19	0	20	0.0%	0.00 [-0.09, 0.09]	2005
Johansson 2005	0	47	0	53	0.1%	0.00 [-0.04, 0.04]	2005
Orpen 2006	0	15	0	14	0.0%	0.00 [-0.12, 0.12]	2006
Camarasa 2006	0	35	0	60	0.1%	0.00 [-0.04, 0.04]	2006
Molloy 2007	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2007
Claeys 2007	3	20	0	20	0.0%	0.15 [-0.02, 0.32]	2007
Wong 2008	1	73	1	74	0.1%	0.00 [-0.04, 0.04]	2008
Elwatidy 2008	0	32	0	32	0.0%	0.00 [-0.06, 0.06]	2008
Alvarez 2008	0	46	0	49	0.1%	0.00 [-0.04, 0.04]	2008
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Kakar 2009	0	13	0	13	0.0%	0.00 [-0.14, 0.14]	2009
Kakar 2009	0	12	0	12	0.0%	0.00 [-0.15, 0.15]	2009
Zufferey 2010	9	57	3	53	0.0%	0.10 [-0.01, 0.21]	2010
Kazemi 2010	0	32	1	32	0.0%	-0.03 [-0.11, 0.05]	2010
Charoencholvanich 2011	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2011
Farrokhi 2011	0	38	0	38	0.1%	0.00 [-0.05, 0.05]	2011
Suksamosorn 2011	0	22	0	21	0.0%	0.00 [-0.09, 0.09]	2011
Lin 2011	1	50	1	50	0.1%	0.00 [-0.05, 0.05]	2011
Tsutsumimoto 2011	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2011
Malhotra 2011	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2011
MacGillivray 2011	2	40	0	20	0.0%	0.05 [-0.05, 0.15]	2011
Raviraj 2012	0	88	1	87	0.2%	-0.01 [-0.04, 0.02]	2012
Xu 2012	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2012

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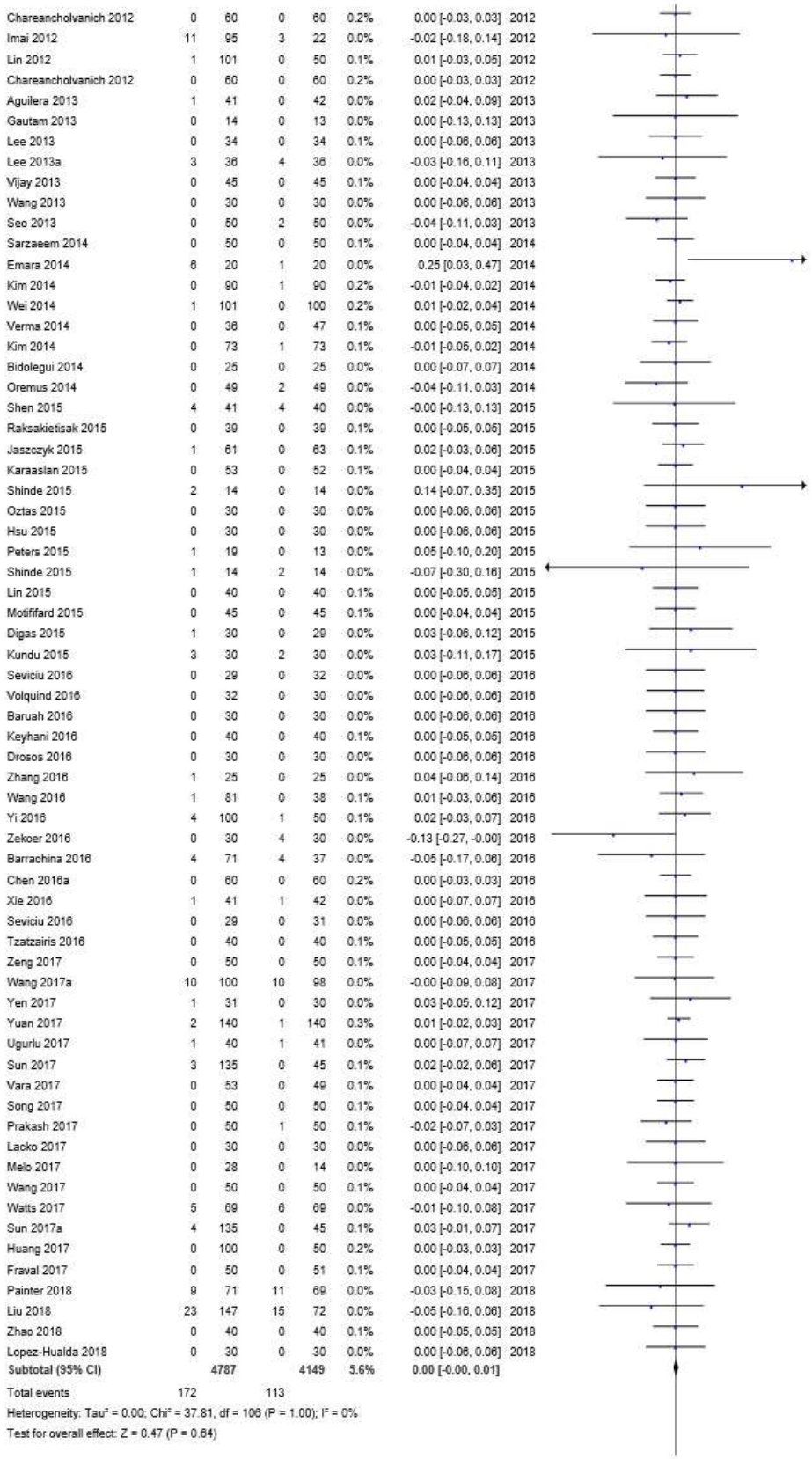

Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Imai 2012	11	95	3	22	0.0%	-0.02 [-0.18, 0.14]	2012
Lin 2012	1	101	0	50	0.1%	0.01 [-0.03, 0.05]	2012
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Aguilera 2013	1	41	0	42	0.0%	0.02 [-0.04, 0.09]	2013
Gautam 2013	0	14	0	13	0.0%	0.00 [-0.13, 0.13]	2013
Lee 2013	0	34	0	34	0.1%	0.00 [-0.06, 0.06]	2013
Lee 2013a	3	36	4	36	0.0%	-0.03 [-0.16, 0.11]	2013
Vijay 2013	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2013
Wang 2013	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2013
Seo 2013	0	50	2	50	0.0%	-0.04 [-0.11, 0.03]	2013
Sarzaeem 2014	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2014
Emara 2014	6	20	1	20	0.0%	0.25 [0.03, 0.47]	2014
Kim 2014	0	90	1	90	0.2%	-0.01 [-0.04, 0.02]	2014
Wei 2014	1	101	0	100	0.2%	0.01 [-0.02, 0.04]	2014
Verma 2014	0	36	0	47	0.1%	0.00 [-0.05, 0.05]	2014
Kim 2014	0	73	1	73	0.1%	-0.01 [-0.05, 0.02]	2014
Bidolegui 2014	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2014
Oremus 2014	0	49	2	49	0.0%	-0.04 [-0.11, 0.03]	2014
Shen 2015	4	41	4	40	0.0%	-0.00 [-0.13, 0.13]	2015
Raksakietisak 2015	0	39	0	39	0.1%	0.00 [-0.05, 0.05]	2015
Jaszczyk 2015	1	61	0	63	0.1%	0.02 [-0.03, 0.06]	2015
Karaaslan 2015	0	53	0	52	0.1%	0.00 [-0.04, 0.04]	2015
Shinde 2015	2	14	0	14	0.0%	0.14 [-0.07, 0.35]	2015
Oztas 2015	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2015
Hsu 2015	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2015
Peters 2015	1	19	0	13	0.0%	0.05 [-0.10, 0.20]	2015
Shinde 2015	1	14	2	14	0.0%	-0.07 [-0.30, 0.16]	2015
Lin 2015	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2015
Motififard 2015	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2015
Digas 2015	1	30	0	29	0.0%	0.03 [-0.06, 0.12]	2015
Kundu 2015	3	30	2	30	0.0%	0.03 [-0.11, 0.17]	2015
Seviciu 2016	0	29	0	32	0.0%	0.00 [-0.06, 0.06]	2016
Volquind 2016	0	32	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Baruah 2016	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Keyhani 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Drosos 2016	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Zhang 2016	1	25	0	25	0.0%	0.04 [-0.06, 0.14]	2016
Wang 2016	1	81	0	38	0.1%	0.01 [-0.03, 0.06]	2016
Yi 2016	4	100	1	50	0.1%	0.02 [-0.03, 0.07]	2016
Zekoer 2016	0	30	4	30	0.0%	-0.13 [-0.27, -0.00]	2016
Barrachina 2016	4	71	4	37	0.0%	-0.05 [-0.17, 0.06]	2016
Chen 2016a	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2016
Xie 2016	1	41	1	42	0.0%	0.00 [-0.07, 0.07]	2016
Seviciu 2016	0	29	0	31	0.0%	0.00 [-0.06, 0.06]	2016
Tzatzairis 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Zeng 2017	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2017
Wang 2017a	10	100	10	98	0.0%	-0.00 [-0.09, 0.08]	2017
Yen 2017	1	31	0	30	0.0%	0.03 [-0.05, 0.12]	2017
Yuan 2017	2	140	1	140	0.3%	0.01 [-0.02, 0.03]	2017
Ugurlu 2017	1	40	1	41	0.0%	0.00 [-0.07, 0.07]	2017
Sun 2017	3	135	0	45	0.1%	0.02 [-0.02, 0.06]	2017
Vara 2017	0	53	0	49	0.1%	0.00 [-0.04, 0.04]	2017
Song 2017	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2017
Prakash 2017	0	50	1	50	0.1%	-0.02 [-0.07, 0.03]	2017
Lacko 2017	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2017
Melo 2017	0	28	0	14	0.0%	0.00 [-0.10, 0.10]	2017
Wang 2017	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2017
Watts 2017	5	69	6	69	0.0%	-0.01 [-0.10, 0.08]	2017
Sun 2017a	4	135	0	45	0.1%	0.03 [-0.01, 0.07]	2017
Huang 2017	0	100	0	50	0.2%	0.00 [-0.03, 0.03]	2017
Fraval 2017	0	50	0	51	0.1%	0.00 [-0.04, 0.04]	2017
Painter 2018	9	71	11	69	0.0%	-0.03 [-0.15, 0.08]	2018
Liu 2018	23	147	15	72	0.0%	-0.05 [-0.16, 0.06]	2018
Zhao 2018	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2018
Lopez-Hualda 2018	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2018
Subtotal (95% CI)		**4787**		**4149**	**5.6%**	**0.00 [-0.00, 0.01]**	
Total events	172		113				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 37.81$, df = 106 (P = 1.00); $I^2 = 0\%$

Test for overall effect: Z = 0.47 (P = 0.64)

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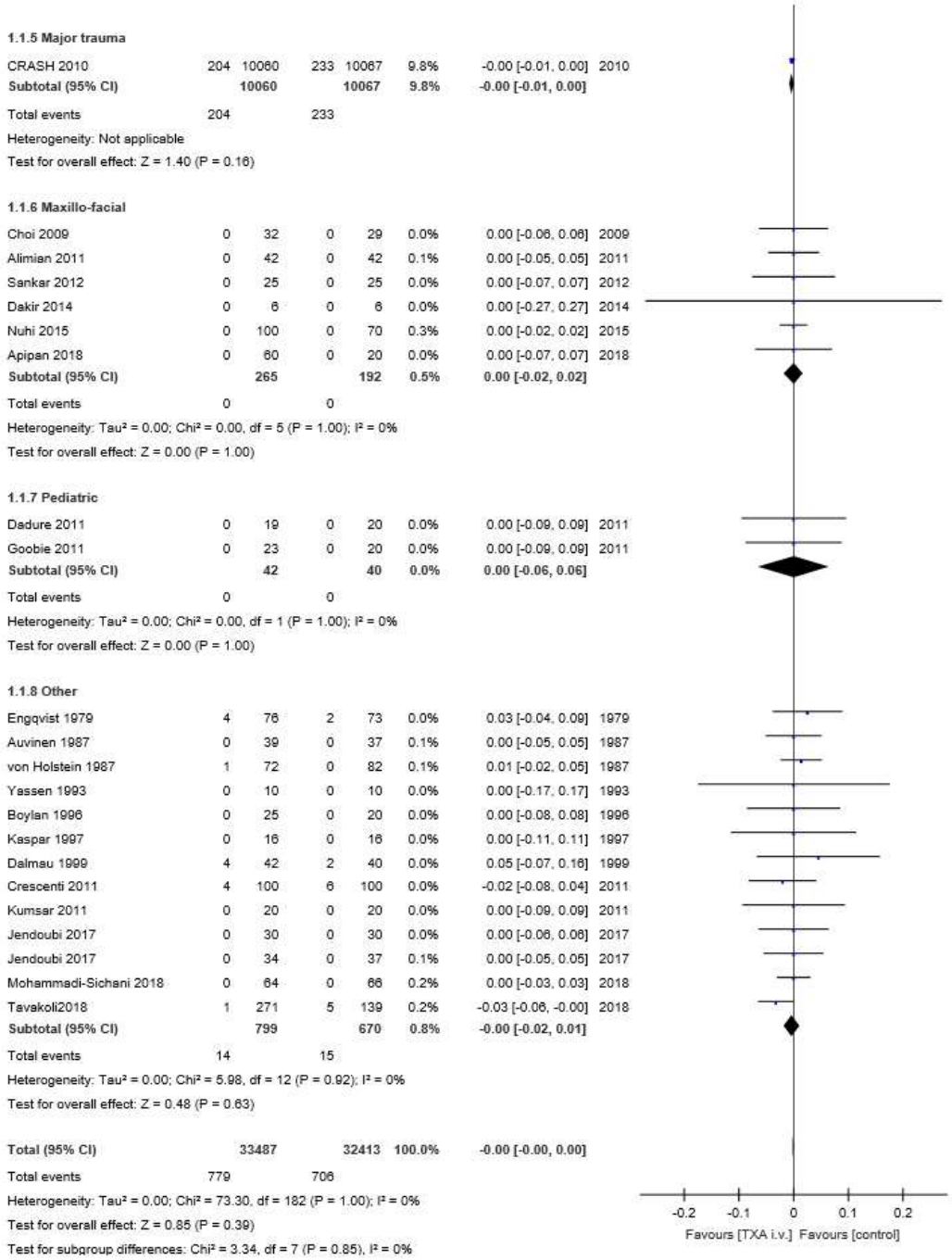
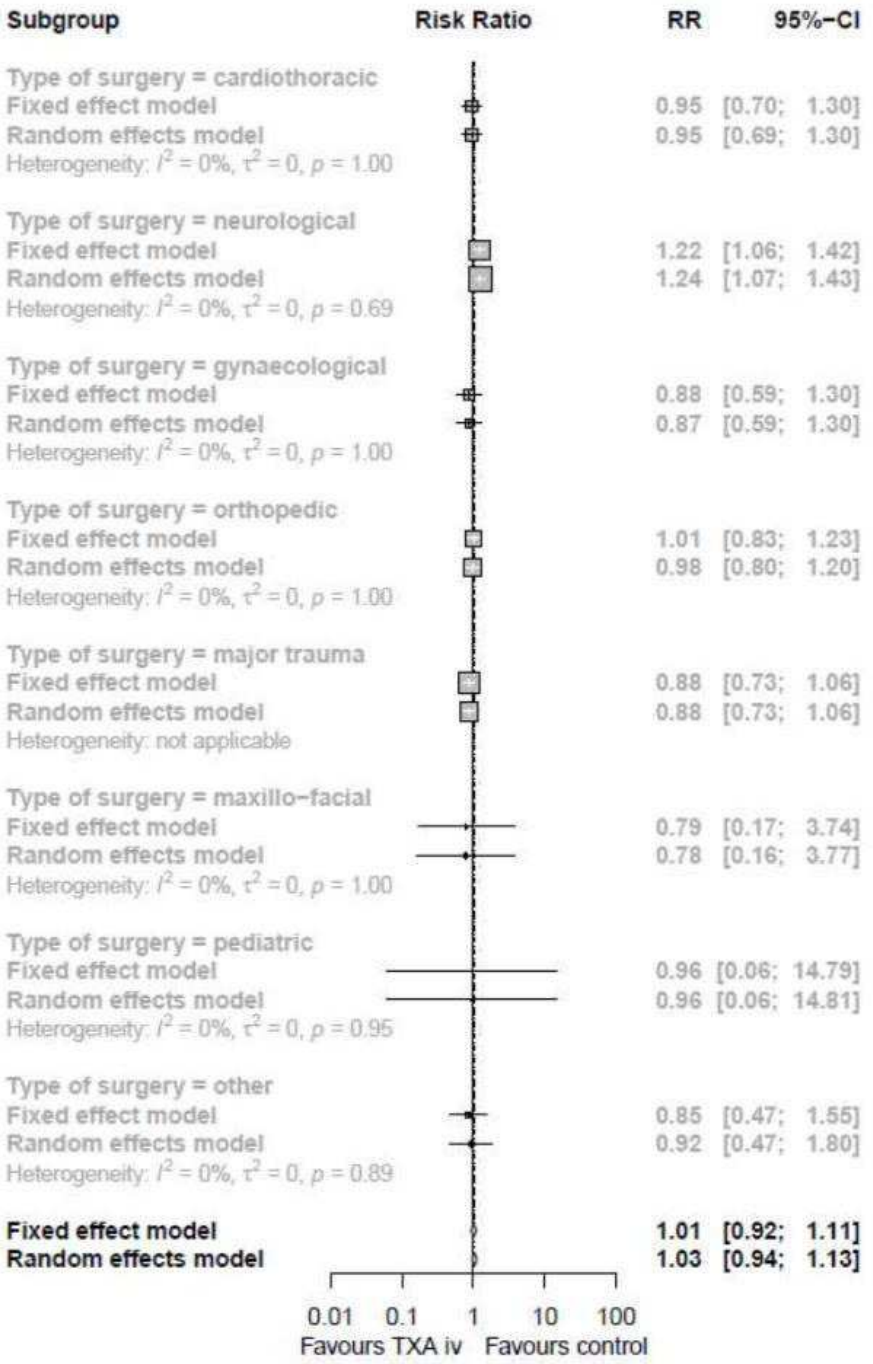
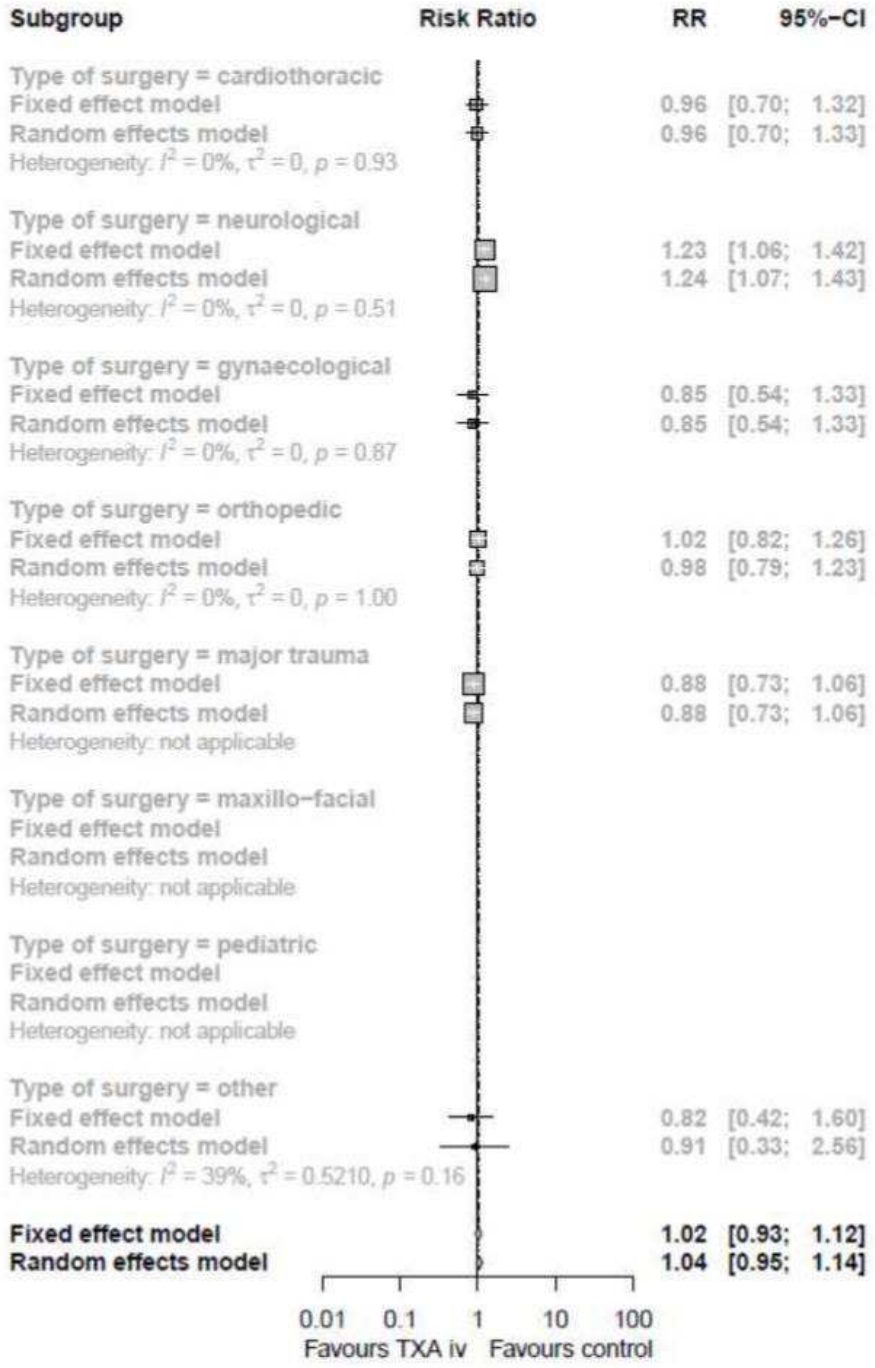


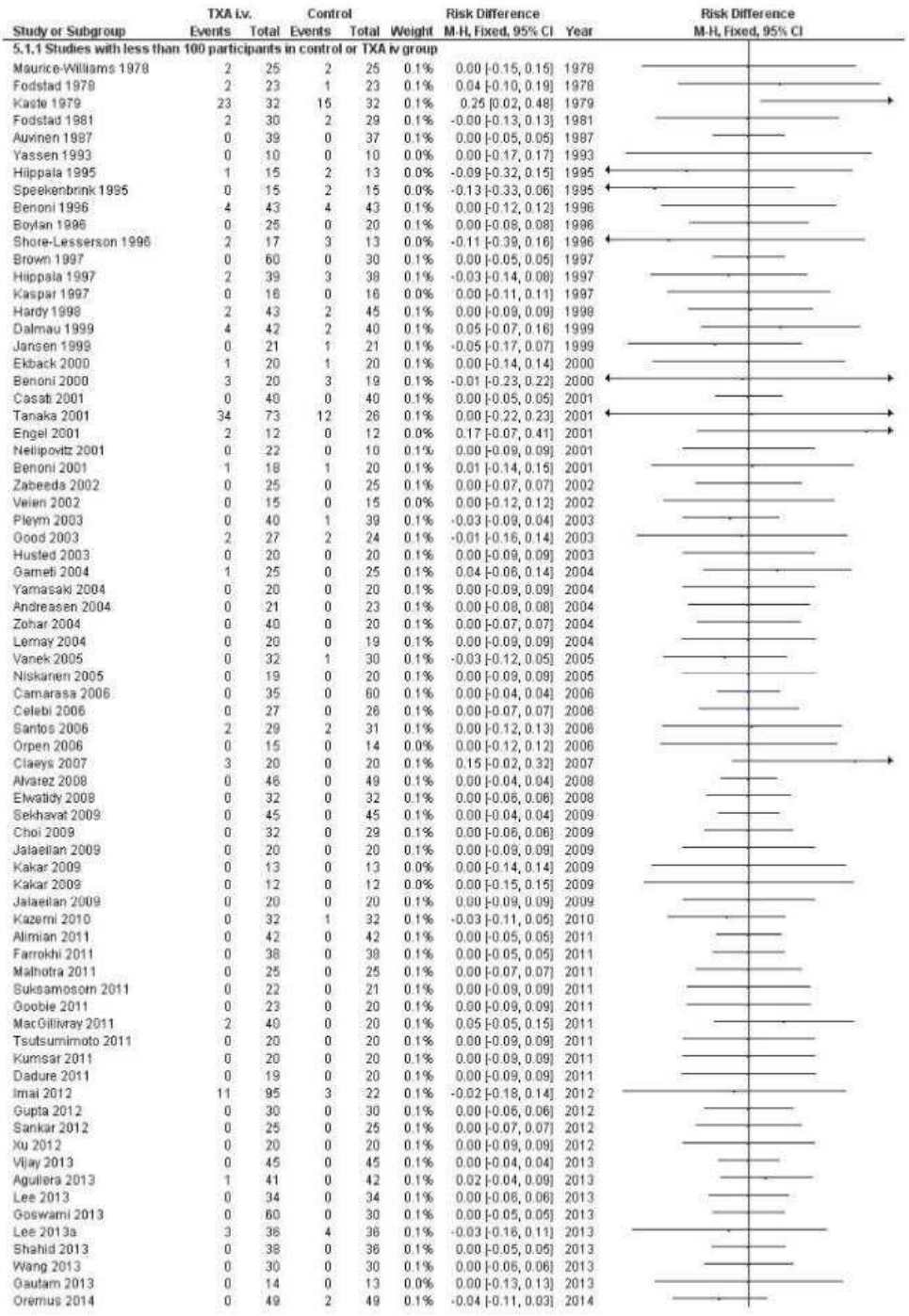
eFigure 3: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control analysed with Risk Ratio in Studies with Zero Events



eFigure 4: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control analysed with Risk Ratio in Studies without Zero Events



eFigure 5: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control according to Sample Size using the Fixed-Effect Model



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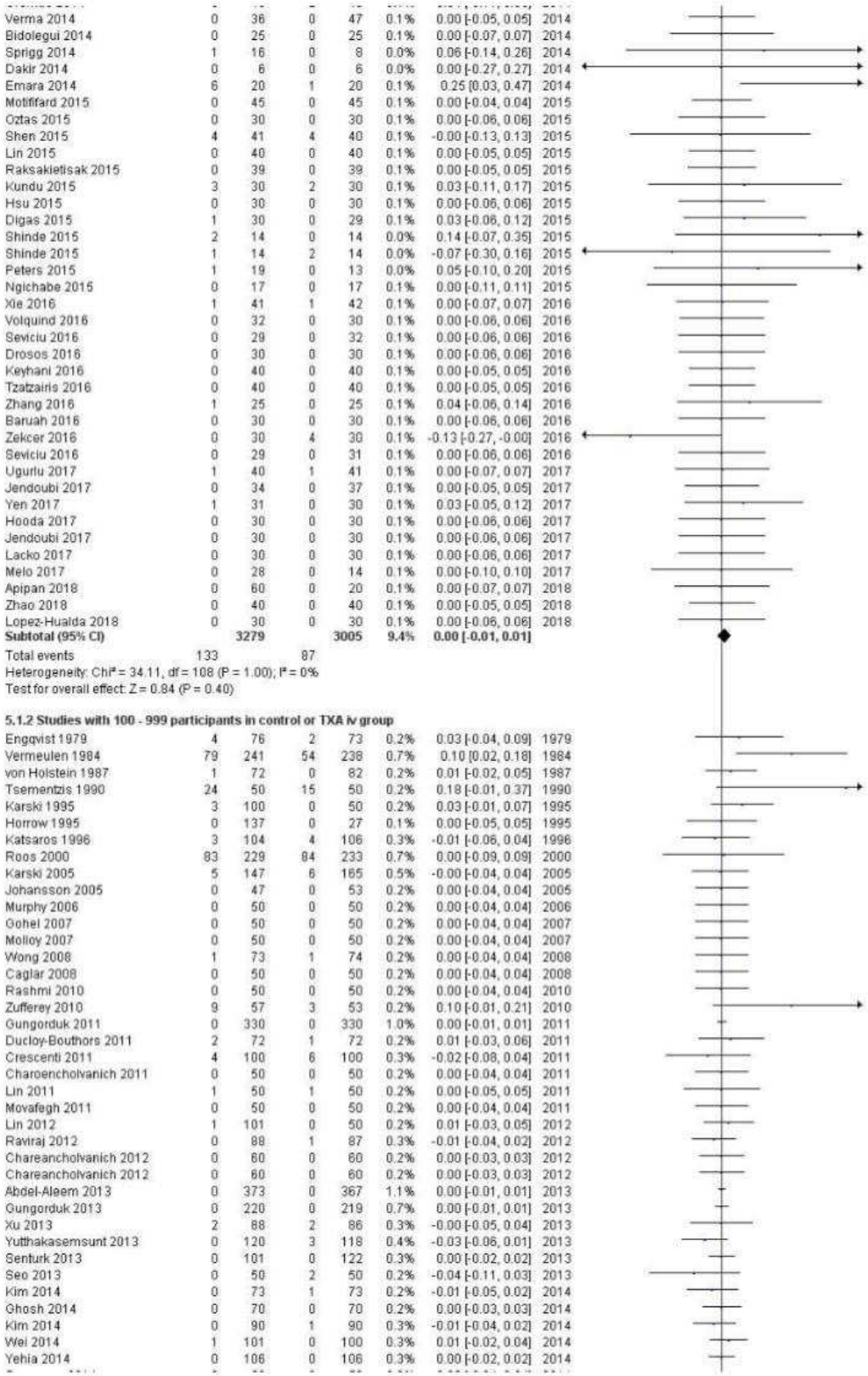

Verma 2014	0	36	0	47	0.1%	0.00 [-0.05, 0.05]	2014
Bidolegui 2014	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2014
Sprigg 2014	1	16	0	8	0.0%	0.06 [-0.14, 0.26]	2014
Dakir 2014	0	6	0	6	0.0%	0.00 [-0.27, 0.27]	2014
Emara 2014	6	20	1	20	0.1%	0.25 [0.03, 0.47]	2014
Motiffard 2015	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2015
Oztas 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Shen 2015	4	41	4	40	0.1%	-0.00 [-0.13, 0.13]	2015
Lin 2015	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2015
Raksakietisak 2015	0	39	0	39	0.1%	0.00 [-0.05, 0.05]	2015
Kundu 2015	3	30	2	30	0.1%	0.03 [-0.11, 0.17]	2015
Hsu 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Digas 2015	1	30	0	29	0.1%	0.03 [-0.06, 0.12]	2015
Shinde 2015	2	14	0	14	0.0%	0.14 [-0.07, 0.35]	2015
Shinde 2015	1	14	2	14	0.0%	-0.07 [-0.30, 0.16]	2015
Peters 2015	1	19	0	13	0.0%	0.05 [-0.10, 0.20]	2015
Ngichabe 2015	0	17	0	17	0.1%	0.00 [-0.11, 0.11]	2015
Xie 2016	1	41	1	42	0.1%	0.00 [-0.07, 0.07]	2016
Volquind 2016	0	32	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Seviciu 2016	0	29	0	32	0.1%	0.00 [-0.06, 0.06]	2016
Drosos 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Keyhani 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Tzatzairis 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Zhang 2016	1	25	0	25	0.1%	0.04 [-0.06, 0.14]	2016
Baruah 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Zekcer 2016	0	30	4	30	0.1%	-0.13 [-0.27, -0.00]	2016
Seviciu 2016	0	29	0	31	0.1%	0.00 [-0.06, 0.06]	2016
Ugurlu 2017	1	40	1	41	0.1%	0.00 [-0.07, 0.07]	2017
Jendoubi 2017	0	34	0	37	0.1%	0.00 [-0.05, 0.05]	2017
Yen 2017	1	31	0	30	0.1%	0.03 [-0.05, 0.12]	2017
Hooda 2017	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2017
Jendoubi 2017	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2017
Lacko 2017	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2017
Melo 2017	0	28	0	14	0.1%	0.00 [-0.10, 0.10]	2017
Apipan 2018	0	60	0	20	0.1%	0.00 [-0.07, 0.07]	2018
Zhao 2018	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2018
Lopez-Hualda 2018	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2018
Subtotal (95% CI)		**3279**		**3005**	**9.4%**	**0.00 [-0.01, 0.01]**	
Total events	133		87				
Heterogeneity: Chi² = 34.11, df = 108 (P = 1.00); I² = 0%							
Test for overall effect: Z = 0.84 (P = 0.40)							
5.1.2 Studies with 100 - 999 participants in control or TXA iv group							
Engqvist 1979	4	76	2	73	0.2%	0.03 [-0.04, 0.09]	1979
Vermeulen 1984	79	241	54	238	0.7%	0.10 [0.02, 0.18]	1984
von Holstein 1987	1	72	0	82	0.2%	0.01 [-0.02, 0.05]	1987
Tsementzis 1990	24	50	15	50	0.2%	0.18 [-0.01, 0.37]	1990
Karski 1995	3	100	0	50	0.2%	0.03 [-0.01, 0.07]	1995
Horrow 1995	0	137	0	27	0.1%	0.00 [-0.05, 0.05]	1995
Katsaros 1996	3	104	4	106	0.3%	-0.01 [-0.06, 0.04]	1996
Roos 2000	83	229	84	233	0.7%	0.00 [-0.09, 0.09]	2000
Karski 2005	5	147	6	165	0.5%	-0.00 [-0.04, 0.04]	2005
Johansson 2005	0	47	0	53	0.2%	0.00 [-0.04, 0.04]	2005
Murphy 2006	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2006
Gohel 2007	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2007
Molloy 2007	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2007
Wong 2008	1	73	1	74	0.2%	0.00 [-0.04, 0.04]	2008
Caglar 2008	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2008
Rashmi 2010	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2010
Zufferey 2010	9	57	3	53	0.2%	0.10 [-0.01, 0.21]	2010
Gungorduk 2011	0	330	0	330	1.0%	0.00 [-0.01, 0.01]	2011
Ducloy-Bouthors 2011	2	72	1	72	0.2%	0.01 [-0.03, 0.06]	2011
Crescenti 2011	4	100	6	100	0.3%	-0.02 [-0.08, 0.04]	2011
Charoencholvanich 2011	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2011
Lin 2011	1	50	1	50	0.2%	0.00 [-0.05, 0.05]	2011
Movafegh 2011	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2011
Lin 2012	1	101	0	50	0.2%	0.01 [-0.03, 0.05]	2012
Raviraj 2012	0	88	1	87	0.3%	-0.01 [-0.04, 0.02]	2012
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Abdel-Aleem 2013	0	373	0	367	1.1%	0.00 [-0.01, 0.01]	2013
Gungorduk 2013	0	220	0	219	0.7%	0.00 [-0.01, 0.01]	2013
Xu 2013	2	88	2	86	0.3%	-0.00 [-0.05, 0.04]	2013
Yutthakasemsunt 2013	0	120	3	118	0.4%	-0.03 [-0.06, 0.01]	2013
Senturk 2013	0	101	0	122	0.3%	0.00 [-0.02, 0.02]	2013
Seo 2013	0	50	2	50	0.2%	-0.04 [-0.11, 0.03]	2013
Kim 2014	0	73	1	73	0.2%	-0.01 [-0.05, 0.02]	2014
Ghosh 2014	0	70	0	70	0.2%	0.00 [-0.03, 0.03]	2014
Kim 2014	0	90	1	90	0.3%	-0.01 [-0.04, 0.02]	2014
Wei 2014	1	101	0	100	0.3%	0.01 [-0.02, 0.04]	2014
Yehia 2014	0	106	0	106	0.3%	0.00 [-0.02, 0.02]	2014

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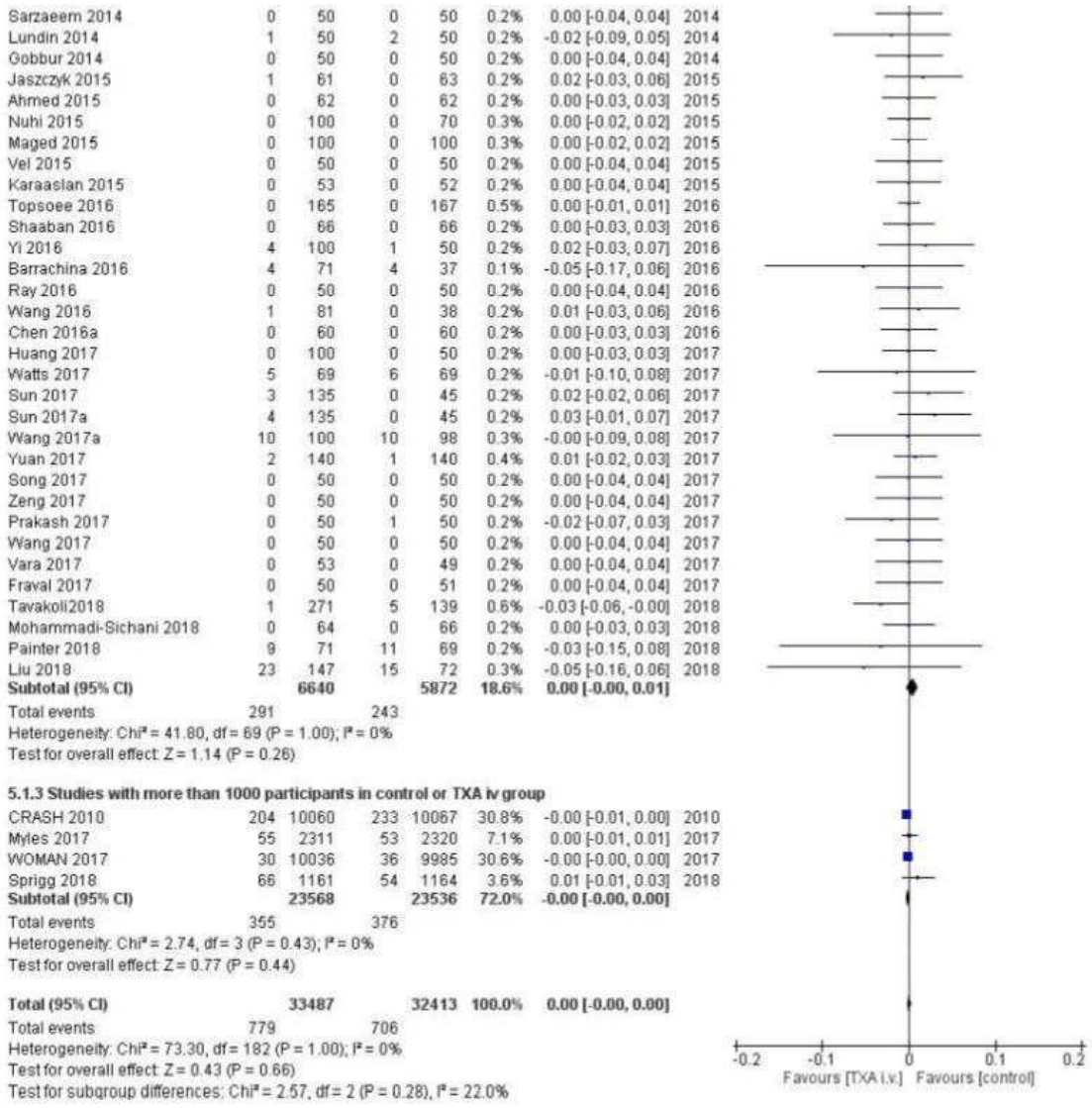
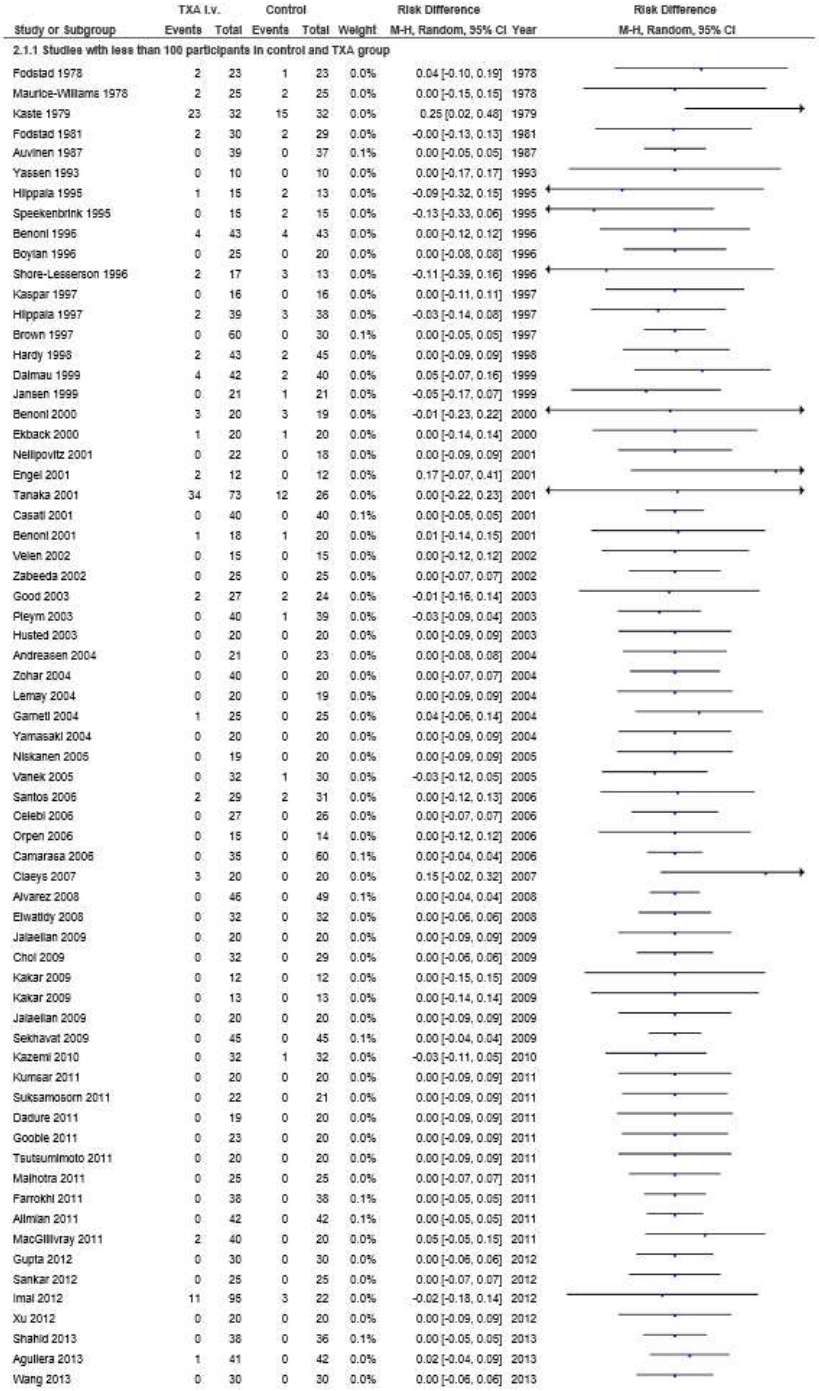


eFigure 6: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control according to Sample Size using the Random-Effects Model



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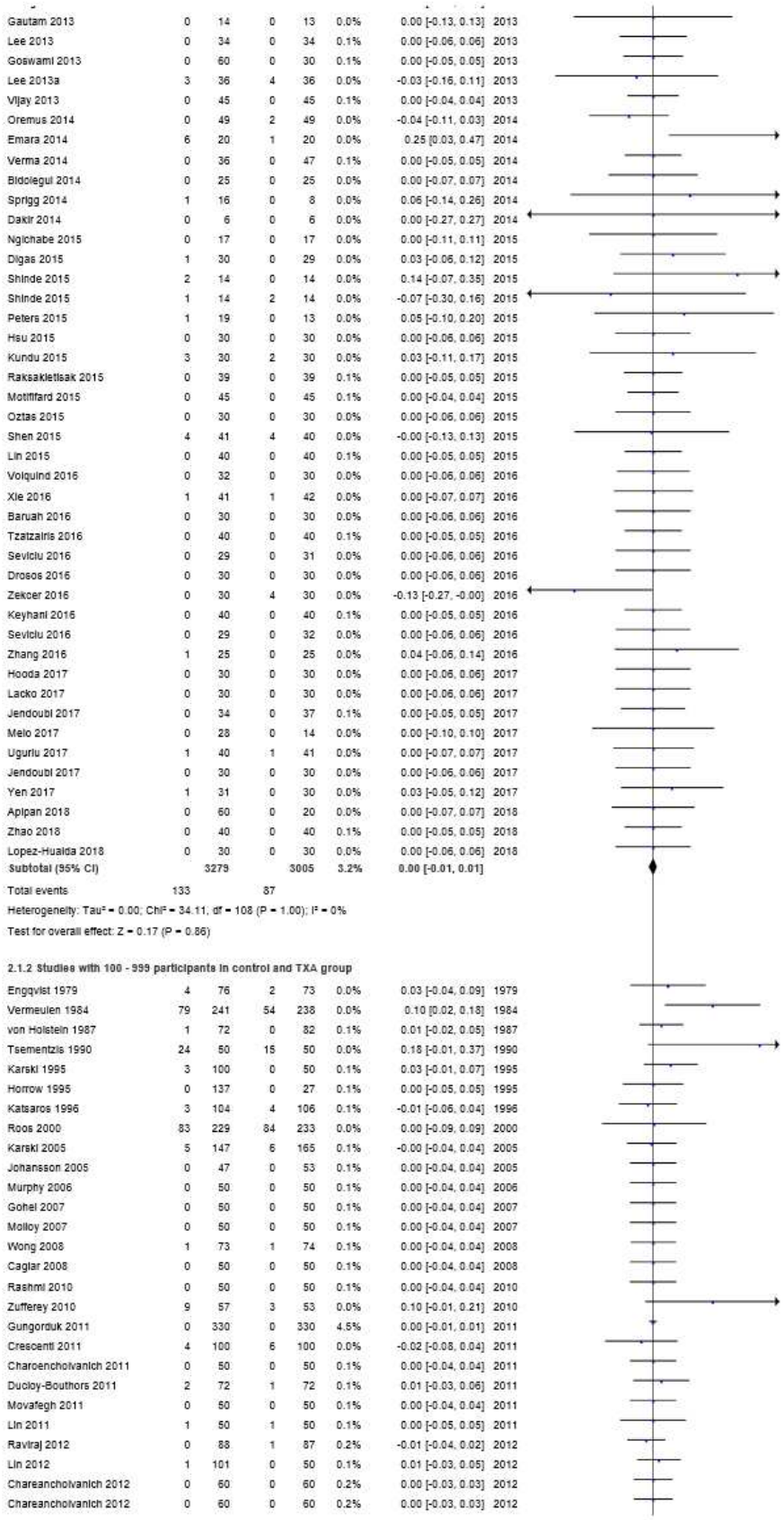

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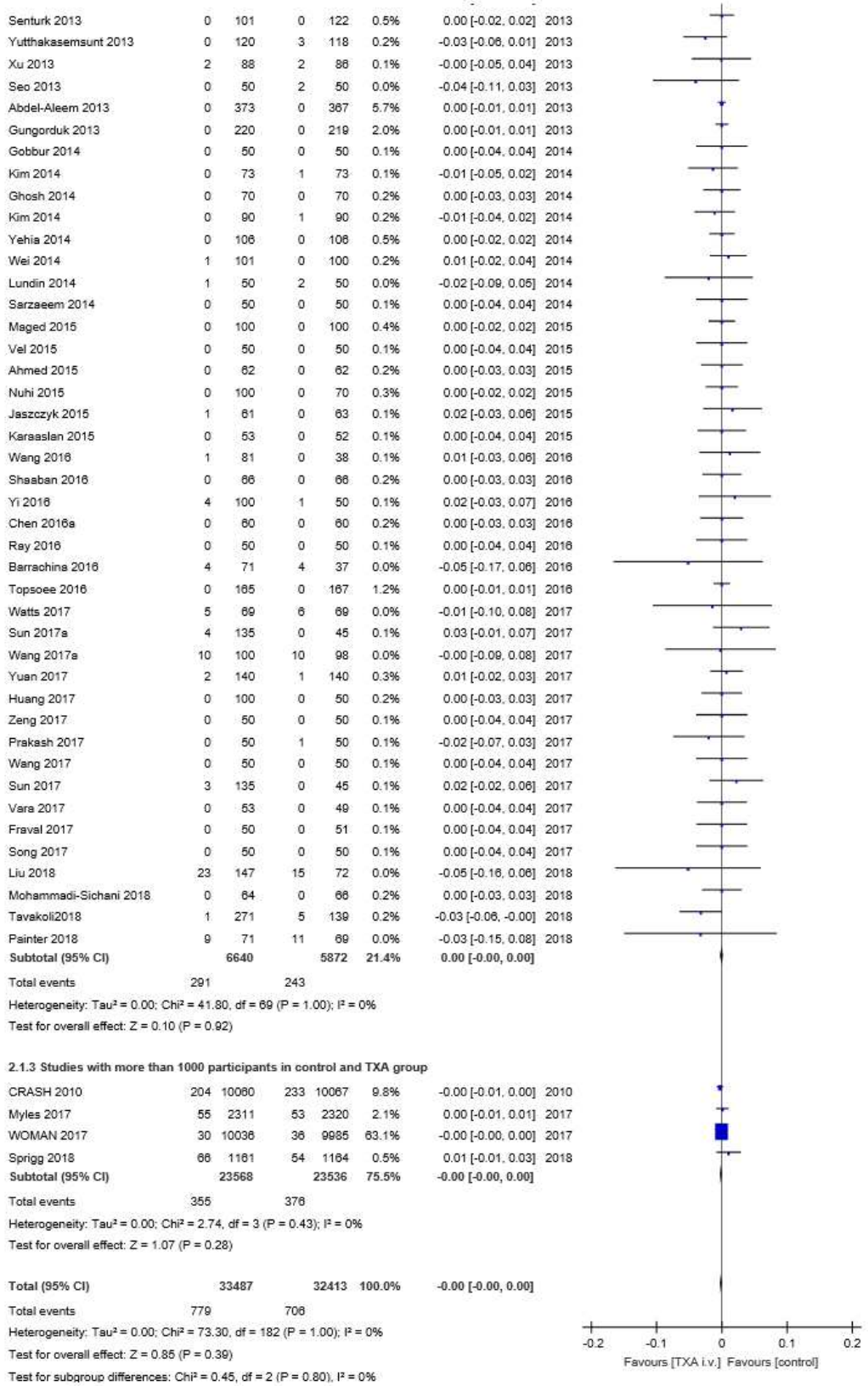

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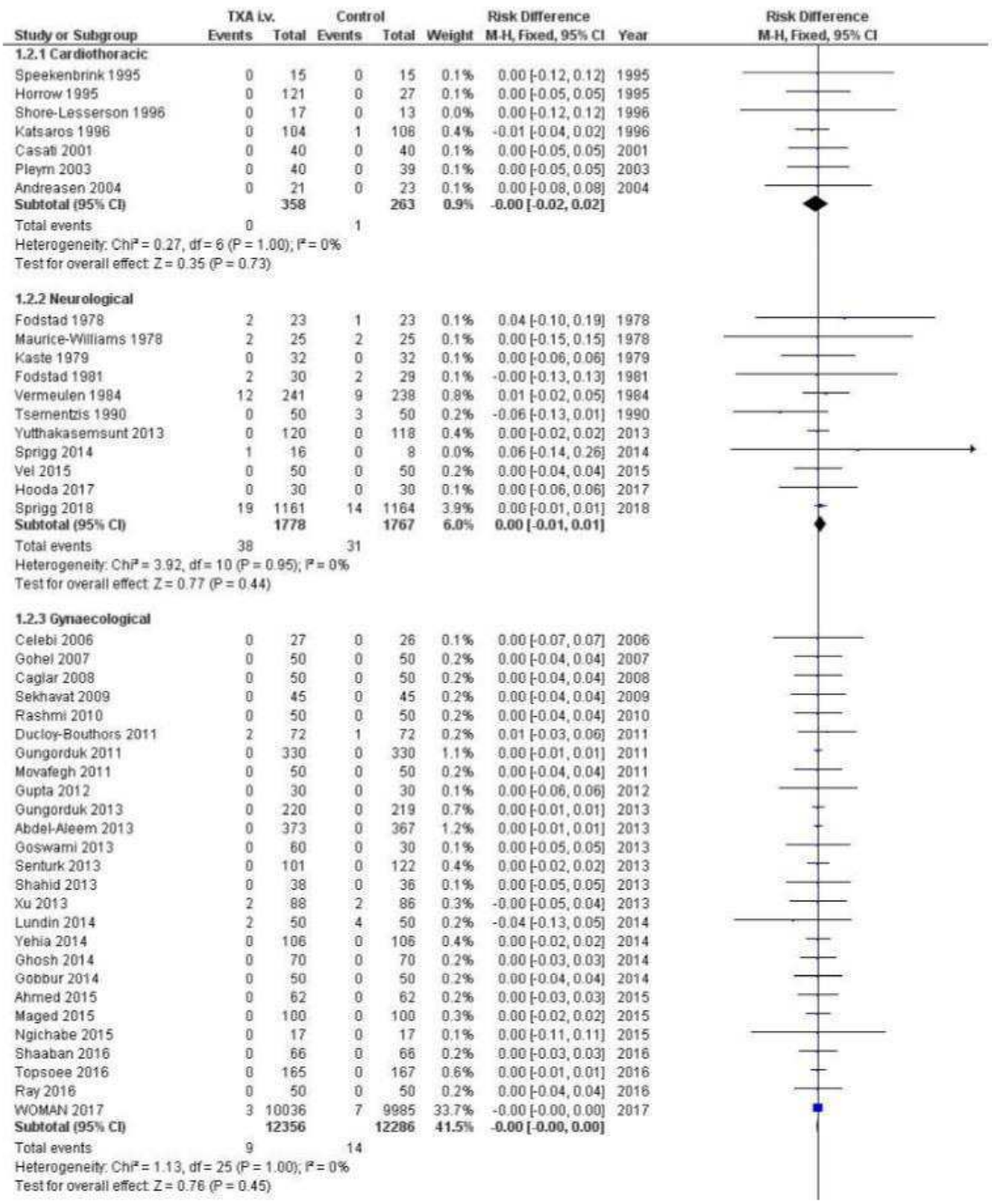
eFigure 7: Venous Thrombosis Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



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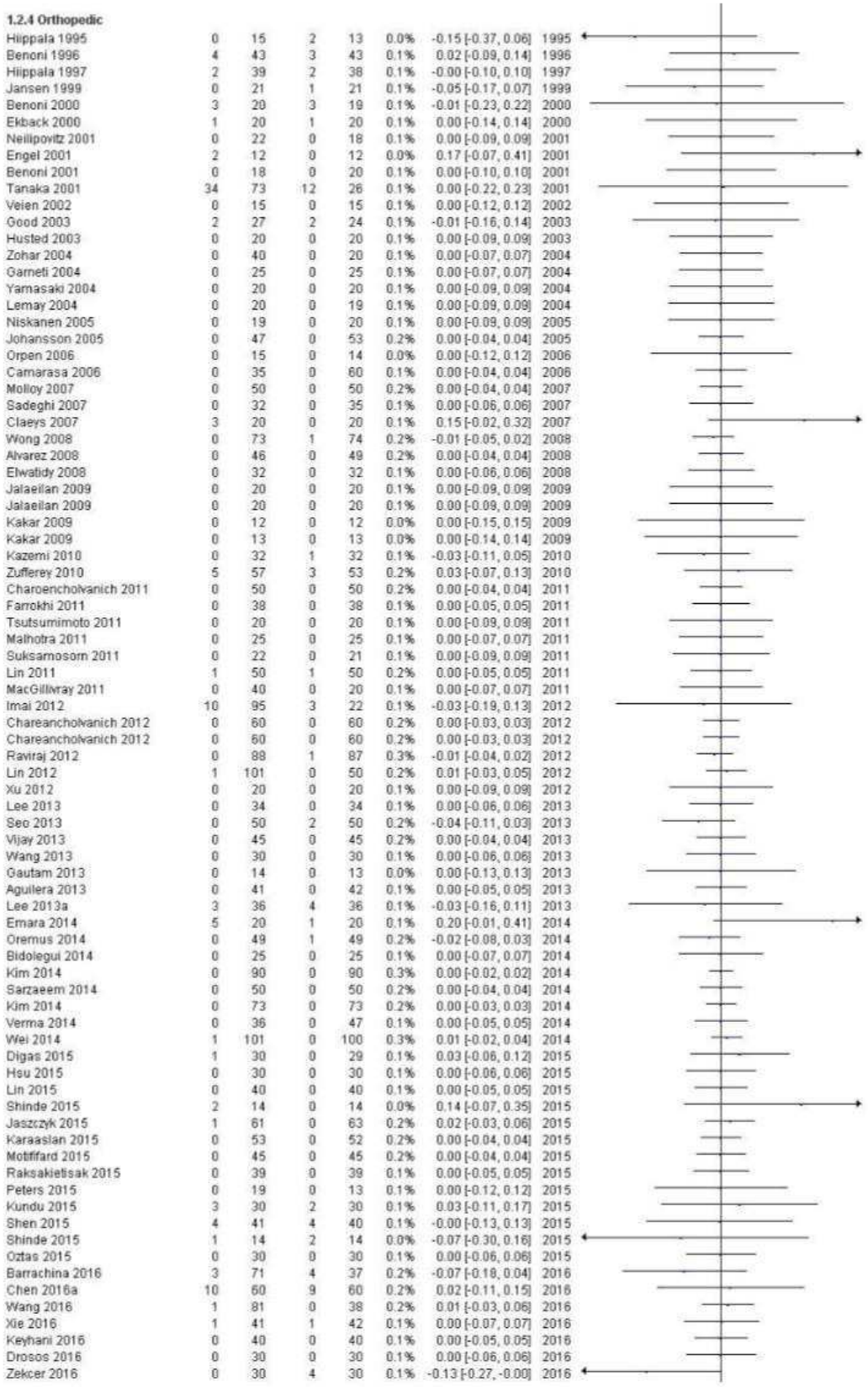

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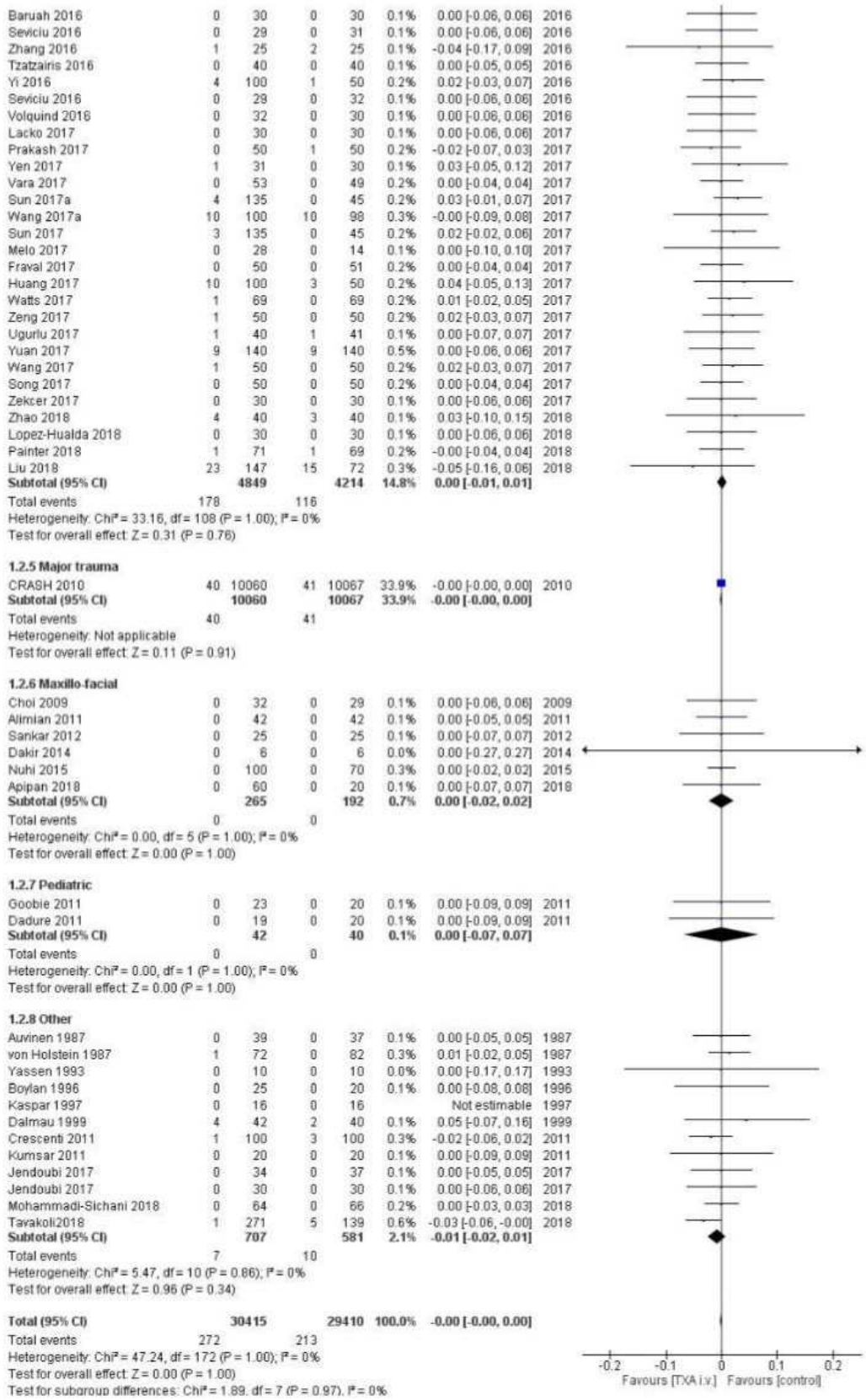
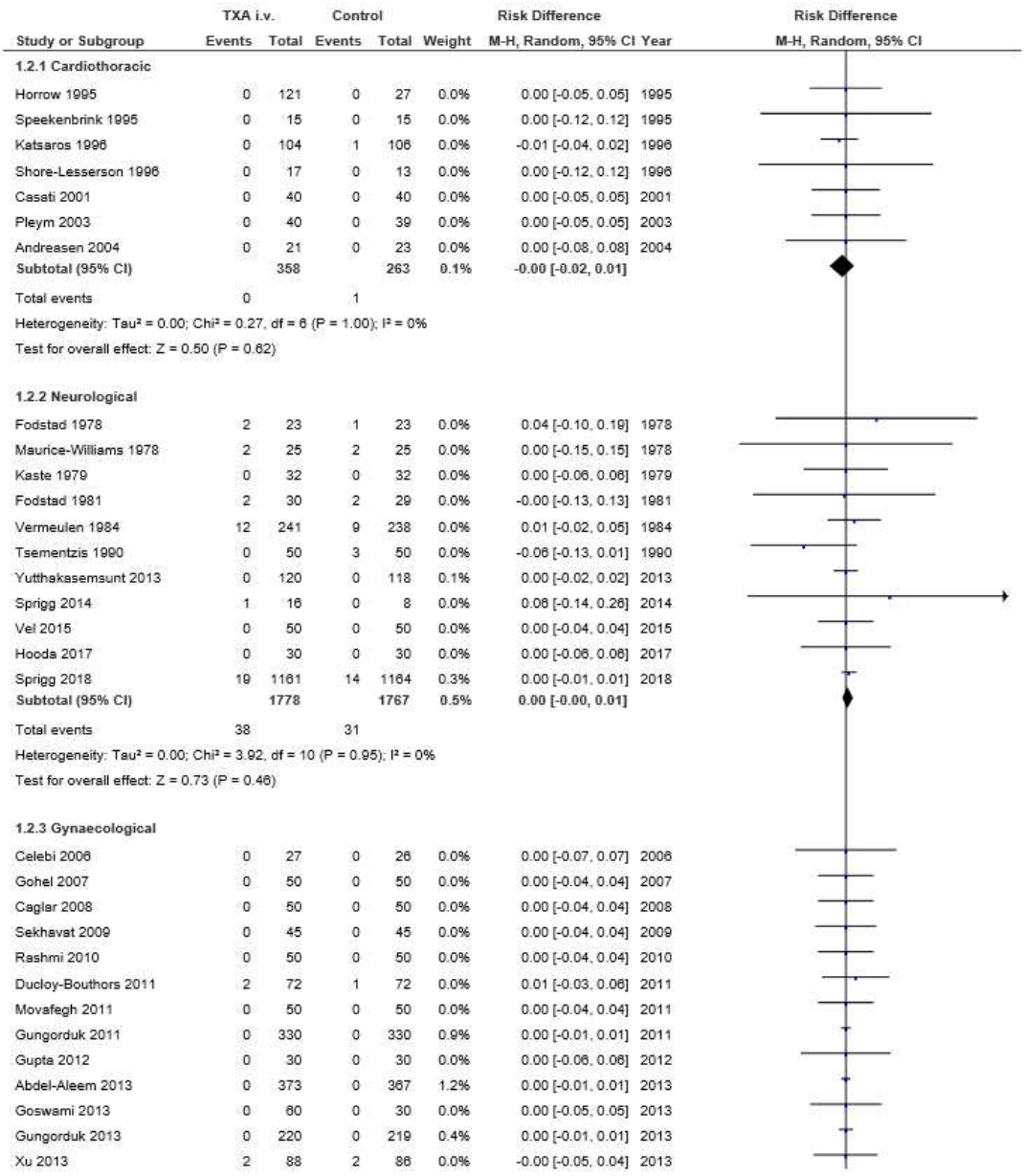


eFigure 8: Venous Thrombosis Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model



Study or Subgroup	TXA i.v. Events	TXA i.v. Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI	Year
1.2.1 Cardiothoracic							
Horrow 1995	0	121	0	27	0.0%	0.00 [-0.05, 0.05]	1995
Speekenbrink 1995	0	15	0	15	0.0%	0.00 [-0.12, 0.12]	1995
Katsaros 1996	0	104	1	106	0.0%	-0.01 [-0.04, 0.02]	1996
Shore-Lesserson 1996	0	17	0	13	0.0%	0.00 [-0.12, 0.12]	1996
Casati 2001	0	40	0	40	0.0%	0.00 [-0.05, 0.05]	2001
Pleym 2003	0	40	0	39	0.0%	0.00 [-0.05, 0.05]	2003
Andreasen 2004	0	21	0	23	0.0%	0.00 [-0.08, 0.08]	2004
Subtotal (95% CI)		358		263	0.1%	**-0.00 [-0.02, 0.01]**	
Total events	0		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 6 (P = 1.00); I² = 0%							
Test for overall effect: Z = 0.50 (P = 0.62)							
1.2.2 Neurological							
Fodstad 1978	2	23	1	23	0.0%	0.04 [-0.10, 0.19]	1978
Maurice-Williams 1978	2	25	2	25	0.0%	0.00 [-0.15, 0.15]	1978
Kaste 1979	0	32	0	32	0.0%	0.00 [-0.06, 0.06]	1979
Fodstad 1981	2	30	2	29	0.0%	-0.00 [-0.13, 0.13]	1981
Vermeulen 1984	12	241	9	238	0.0%	0.01 [-0.02, 0.05]	1984
Tsementzis 1990	0	50	3	50	0.0%	-0.06 [-0.13, 0.01]	1990
Yutthakasemsunt 2013	0	120	0	118	0.1%	0.00 [-0.02, 0.02]	2013
Sprigg 2014	1	16	0	8	0.0%	0.06 [-0.14, 0.26]	2014
Vel 2015	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2015
Hooda 2017	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2017
Sprigg 2018	19	1161	14	1164	0.3%	0.00 [-0.01, 0.01]	2018
Subtotal (95% CI)		1778		1767	0.5%	**0.00 [-0.00, 0.01]**	
Total events	38		31				
Heterogeneity: Tau² = 0.00; Chi² = 3.92, df = 10 (P = 0.95); I² = 0%							
Test for overall effect: Z = 0.73 (P = 0.46)							
1.2.3 Gynaecological							
Celebi 2006	0	27	0	26	0.0%	0.00 [-0.07, 0.07]	2006
Gohel 2007	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2007
Caglar 2008	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2008
Sekhavat 2009	0	45	0	45	0.0%	0.00 [-0.04, 0.04]	2009
Rashmi 2010	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2010
Ducloy-Bouthors 2011	2	72	1	72	0.0%	0.01 [-0.03, 0.06]	2011
Movafegh 2011	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2011
Gungorduk 2011	0	330	0	330	0.9%	0.00 [-0.01, 0.01]	2011
Gupta 2012	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2012
Abdel-Aleem 2013	0	373	0	367	1.2%	0.00 [-0.01, 0.01]	2013
Goswami 2013	0	60	0	30	0.0%	0.00 [-0.05, 0.05]	2013
Gungorduk 2013	0	220	0	219	0.4%	0.00 [-0.01, 0.01]	2013
Xu 2013	2	88	2	86	0.0%	-0.00 [-0.05, 0.04]	2013

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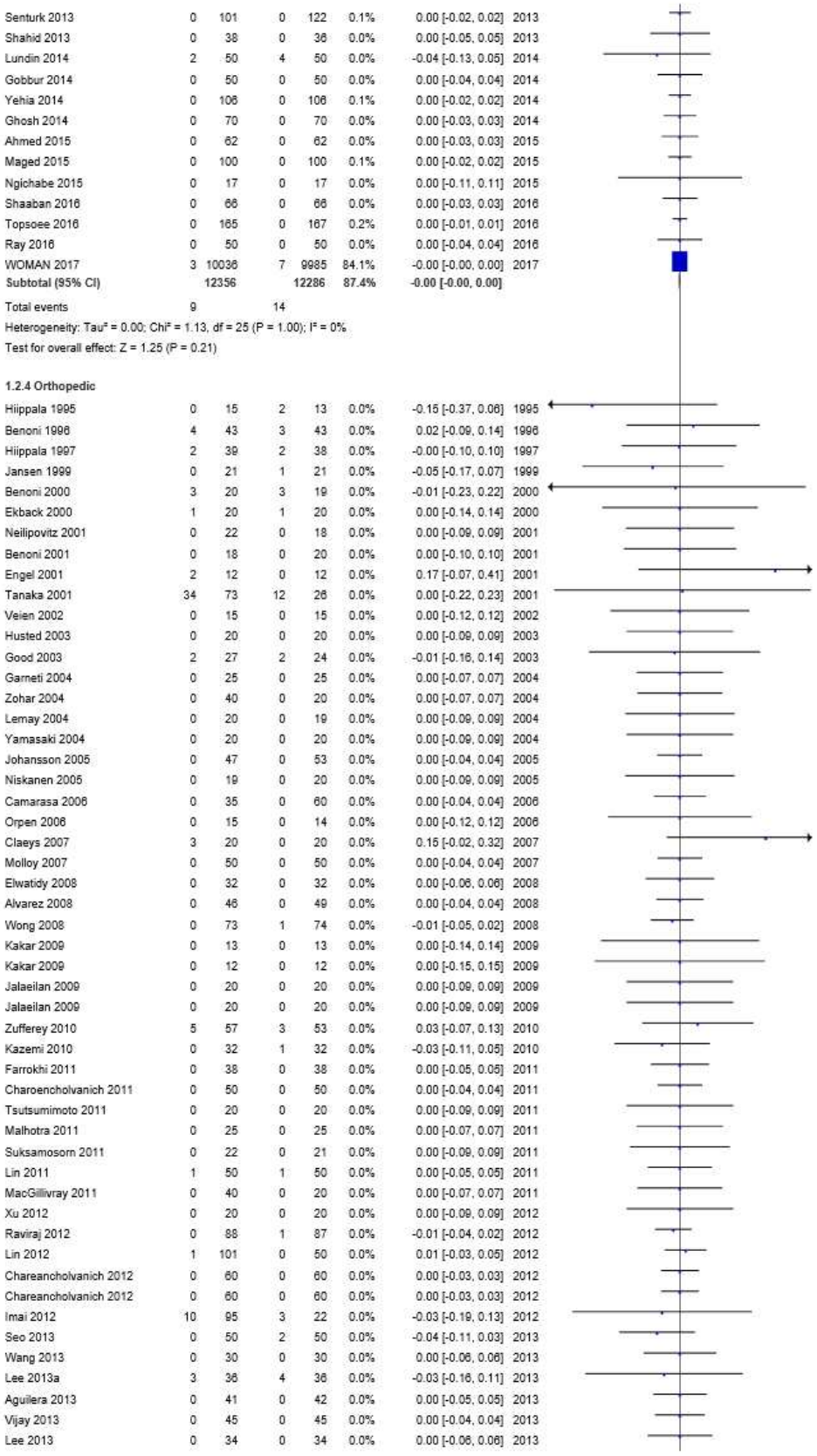


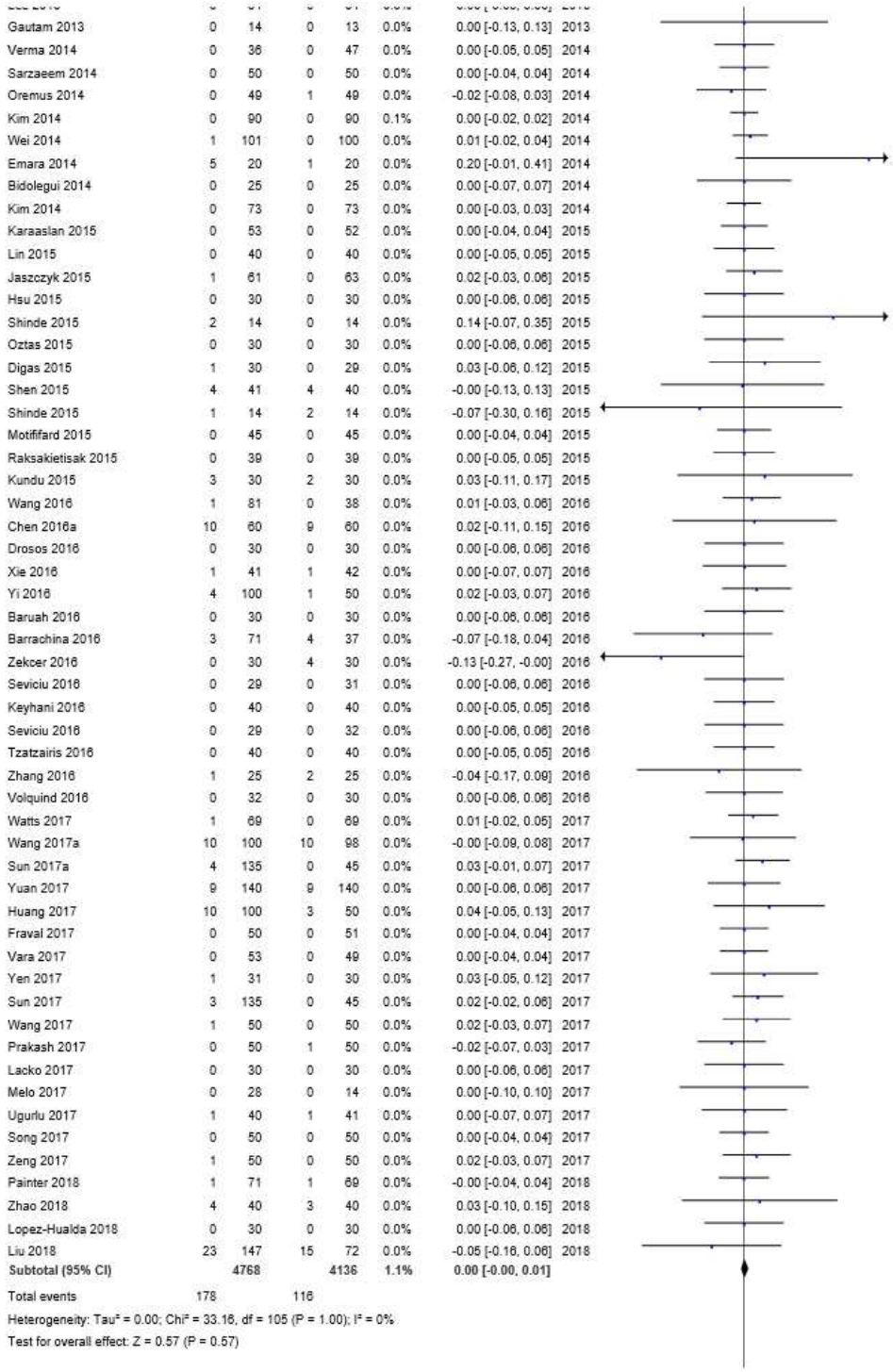
Senturk 2013	0	101	0	122	0.1%	0.00 [-0.02, 0.02]	2013
Shahid 2013	0	38	0	36	0.0%	0.00 [-0.05, 0.05]	2013
Lundin 2014	2	50	4	50	0.0%	-0.04 [-0.13, 0.05]	2014
Gobbur 2014	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2014
Yehia 2014	0	106	0	106	0.1%	0.00 [-0.02, 0.02]	2014
Ghosh 2014	0	70	0	70	0.0%	0.00 [-0.03, 0.03]	2014
Ahmed 2015	0	62	0	62	0.0%	0.00 [-0.03, 0.03]	2015
Maged 2015	0	100	0	100	0.1%	0.00 [-0.02, 0.02]	2015
Ngichabe 2015	0	17	0	17	0.0%	0.00 [-0.11, 0.11]	2015
Shaaban 2016	0	66	0	66	0.0%	0.00 [-0.03, 0.03]	2016
Topsoee 2016	0	165	0	167	0.2%	0.00 [-0.01, 0.01]	2016
Ray 2016	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2016
WOMAN 2017	3	10036	7	9985	84.1%	-0.00 [-0.00, 0.00]	2017
Subtotal (95% CI)		**12356**		**12286**	**87.4%**	**-0.00 [-0.00, 0.00]**	
Total events	9		14				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.13$, df = 25 (P = 1.00); $I^2 = 0\%$

Test for overall effect: Z = 1.25 (P = 0.21)

1.2.4 Orthopedic

Hiippala 1995	0	15	2	13	0.0%	-0.15 [-0.37, 0.06]	1995
Benoni 1996	4	43	3	43	0.0%	0.02 [-0.09, 0.14]	1996
Hiippala 1997	2	39	2	38	0.0%	-0.00 [-0.10, 0.10]	1997
Jansen 1999	0	21	1	21	0.0%	-0.05 [-0.17, 0.07]	1999
Benoni 2000	3	20	3	19	0.0%	-0.01 [-0.23, 0.22]	2000
Ekback 2000	1	20	1	20	0.0%	0.00 [-0.14, 0.14]	2000
Neilipovitz 2001	0	22	0	18	0.0%	0.00 [-0.09, 0.09]	2001
Benoni 2001	0	18	0	20	0.0%	0.00 [-0.10, 0.10]	2001
Engel 2001	2	12	0	12	0.0%	0.17 [-0.07, 0.41]	2001
Tanaka 2001	34	73	12	26	0.0%	0.00 [-0.22, 0.23]	2001
Veien 2002	0	15	0	15	0.0%	0.00 [-0.12, 0.12]	2002
Husted 2003	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2003
Good 2003	2	27	2	24	0.0%	-0.01 [-0.16, 0.14]	2003
Garneti 2004	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2004
Zohar 2004	0	40	0	20	0.0%	0.00 [-0.07, 0.07]	2004
Lemay 2004	0	20	0	19	0.0%	0.00 [-0.09, 0.09]	2004
Yamasaki 2004	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2004
Johansson 2005	0	47	0	53	0.0%	0.00 [-0.04, 0.04]	2005
Niskanen 2005	0	19	0	20	0.0%	0.00 [-0.09, 0.09]	2005
Camarasa 2006	0	35	0	60	0.0%	0.00 [-0.04, 0.04]	2006
Orpen 2006	0	15	0	14	0.0%	0.00 [-0.12, 0.12]	2006
Claeys 2007	3	20	0	20	0.0%	0.15 [-0.02, 0.32]	2007
Molloy 2007	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2007
Elwatidy 2008	0	32	0	32	0.0%	0.00 [-0.06, 0.06]	2008
Alvarez 2008	0	46	0	49	0.0%	0.00 [-0.04, 0.04]	2008
Wong 2008	0	73	1	74	0.0%	-0.01 [-0.05, 0.02]	2008
Kakar 2009	0	13	0	13	0.0%	0.00 [-0.14, 0.14]	2009
Kakar 2009	0	12	0	12	0.0%	0.00 [-0.15, 0.15]	2009
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Zufferey 2010	5	57	3	53	0.0%	0.03 [-0.07, 0.13]	2010
Kazemi 2010	0	32	1	32	0.0%	-0.03 [-0.11, 0.05]	2010
Farrokhi 2011	0	38	0	38	0.0%	0.00 [-0.05, 0.05]	2011
Charoencholvanich 2011	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2011
Tsutsumimoto 2011	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2011
Malhotra 2011	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2011
Suksamosorn 2011	0	22	0	21	0.0%	0.00 [-0.09, 0.09]	2011
Lin 2011	1	50	1	50	0.0%	0.00 [-0.05, 0.05]	2011
MacGillivray 2011	0	40	0	20	0.0%	0.00 [-0.07, 0.07]	2011
Xu 2012	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2012
Raviraj 2012	0	88	1	87	0.0%	-0.01 [-0.04, 0.02]	2012
Lin 2012	1	101	0	50	0.0%	0.01 [-0.03, 0.05]	2012
Chareancholvanich 2012	0	60	0	60	0.0%	0.00 [-0.03, 0.03]	2012
Chareancholvanich 2012	0	60	0	60	0.0%	0.00 [-0.03, 0.03]	2012
Imai 2012	10	95	3	22	0.0%	-0.03 [-0.19, 0.13]	2012
Seo 2013	0	50	2	50	0.0%	-0.04 [-0.11, 0.03]	2013
Wang 2013	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2013
Lee 2013a	3	36	4	36	0.0%	-0.03 [-0.16, 0.11]	2013
Aguilera 2013	0	41	0	42	0.0%	0.00 [-0.05, 0.05]	2013
Vijay 2013	0	45	0	45	0.0%	0.00 [-0.04, 0.04]	2013
Lee 2013	0	34	0	34	0.0%	0.00 [-0.06, 0.06]	2013



Gautam 2013	0	14	0	13	0.0%	0.00 [-0.13, 0.13]	2013
Verma 2014	0	36	0	47	0.0%	0.00 [-0.05, 0.05]	2014
Sarzaeem 2014	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2014
Oremus 2014	0	49	1	49	0.0%	-0.02 [-0.08, 0.03]	2014
Kim 2014	0	90	0	90	0.1%	0.00 [-0.02, 0.02]	2014
Wei 2014	1	101	0	100	0.0%	0.01 [-0.02, 0.04]	2014
Emara 2014	5	20	1	20	0.0%	0.20 [-0.01, 0.41]	2014
Bidolegui 2014	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2014
Kim 2014	0	73	0	73	0.0%	0.00 [-0.03, 0.03]	2014
Karaaslan 2015	0	53	0	52	0.0%	0.00 [-0.04, 0.04]	2015
Lin 2015	0	40	0	40	0.0%	0.00 [-0.05, 0.05]	2015
Jaszczyk 2015	1	61	0	63	0.0%	0.02 [-0.03, 0.06]	2015
Hsu 2015	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2015
Shinde 2015	2	14	0	14	0.0%	0.14 [-0.07, 0.35]	2015
Oztas 2015	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2015
Digas 2015	1	30	0	29	0.0%	0.03 [-0.06, 0.12]	2015
Shen 2015	4	41	4	40	0.0%	-0.00 [-0.13, 0.13]	2015
Shinde 2015	1	14	2	14	0.0%	-0.07 [-0.30, 0.16]	2015
Motififard 2015	0	45	0	45	0.0%	0.00 [-0.04, 0.04]	2015
Raksakietisak 2015	0	39	0	39	0.0%	0.00 [-0.05, 0.05]	2015
Kundu 2015	3	30	2	30	0.0%	0.03 [-0.11, 0.17]	2015
Wang 2016	1	81	0	38	0.0%	0.01 [-0.03, 0.06]	2016
Chen 2016a	10	60	9	60	0.0%	0.02 [-0.11, 0.15]	2016
Drosos 2016	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Xie 2016	1	41	1	42	0.0%	0.00 [-0.07, 0.07]	2016
Yi 2016	4	100	1	50	0.0%	0.02 [-0.03, 0.07]	2016
Baruah 2016	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Barrachina 2016	3	71	4	37	0.0%	-0.07 [-0.18, 0.04]	2016
Zekcer 2016	0	30	4	30	0.0%	-0.13 [-0.27, -0.00]	2016
Seviciu 2016	0	29	0	31	0.0%	0.00 [-0.06, 0.06]	2016
Keyhani 2016	0	40	0	40	0.0%	0.00 [-0.05, 0.05]	2016
Seviciu 2016	0	29	0	32	0.0%	0.00 [-0.06, 0.06]	2016
Tzatzairis 2016	0	40	0	40	0.0%	0.00 [-0.05, 0.05]	2016
Zhang 2016	1	25	2	25	0.0%	-0.04 [-0.17, 0.09]	2016
Volquind 2016	0	32	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Watts 2017	1	69	0	69	0.0%	0.01 [-0.02, 0.05]	2017
Wang 2017a	10	100	10	98	0.0%	-0.00 [-0.09, 0.08]	2017
Sun 2017a	4	135	0	45	0.0%	0.03 [-0.01, 0.07]	2017
Yuan 2017	9	140	9	140	0.0%	0.00 [-0.06, 0.06]	2017
Huang 2017	10	100	3	50	0.0%	0.04 [-0.05, 0.13]	2017
Fraval 2017	0	50	0	51	0.0%	0.00 [-0.04, 0.04]	2017
Vara 2017	0	53	0	49	0.0%	0.00 [-0.04, 0.04]	2017
Yen 2017	1	31	0	30	0.0%	0.03 [-0.05, 0.12]	2017
Sun 2017	3	135	0	45	0.0%	0.02 [-0.02, 0.06]	2017
Wang 2017	1	50	0	50	0.0%	0.02 [-0.03, 0.07]	2017
Prakash 2017	0	50	1	50	0.0%	-0.02 [-0.07, 0.03]	2017
Lacko 2017	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2017
Melo 2017	0	28	0	14	0.0%	0.00 [-0.10, 0.10]	2017
Ugurlu 2017	1	40	1	41	0.0%	0.00 [-0.07, 0.07]	2017
Song 2017	0	50	0	50	0.0%	0.00 [-0.04, 0.04]	2017
Zeng 2017	1	50	0	50	0.0%	0.02 [-0.03, 0.07]	2017
Painter 2018	1	71	1	69	0.0%	-0.00 [-0.04, 0.04]	2018
Zhao 2018	4	40	3	40	0.0%	0.03 [-0.10, 0.15]	2018
Lopez-Hualda 2018	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2018
Liu 2018	23	147	15	72	0.0%	-0.05 [-0.16, 0.06]	2018
Subtotal (95% CI)		**4768**		**4136**	**1.1%**	**0.00 [-0.00, 0.01]**	
Total events	178		116				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 33.16$, df = 105 (P = 1.00); $I^2 = 0\%$

Test for overall effect: Z = 0.57 (P = 0.57)

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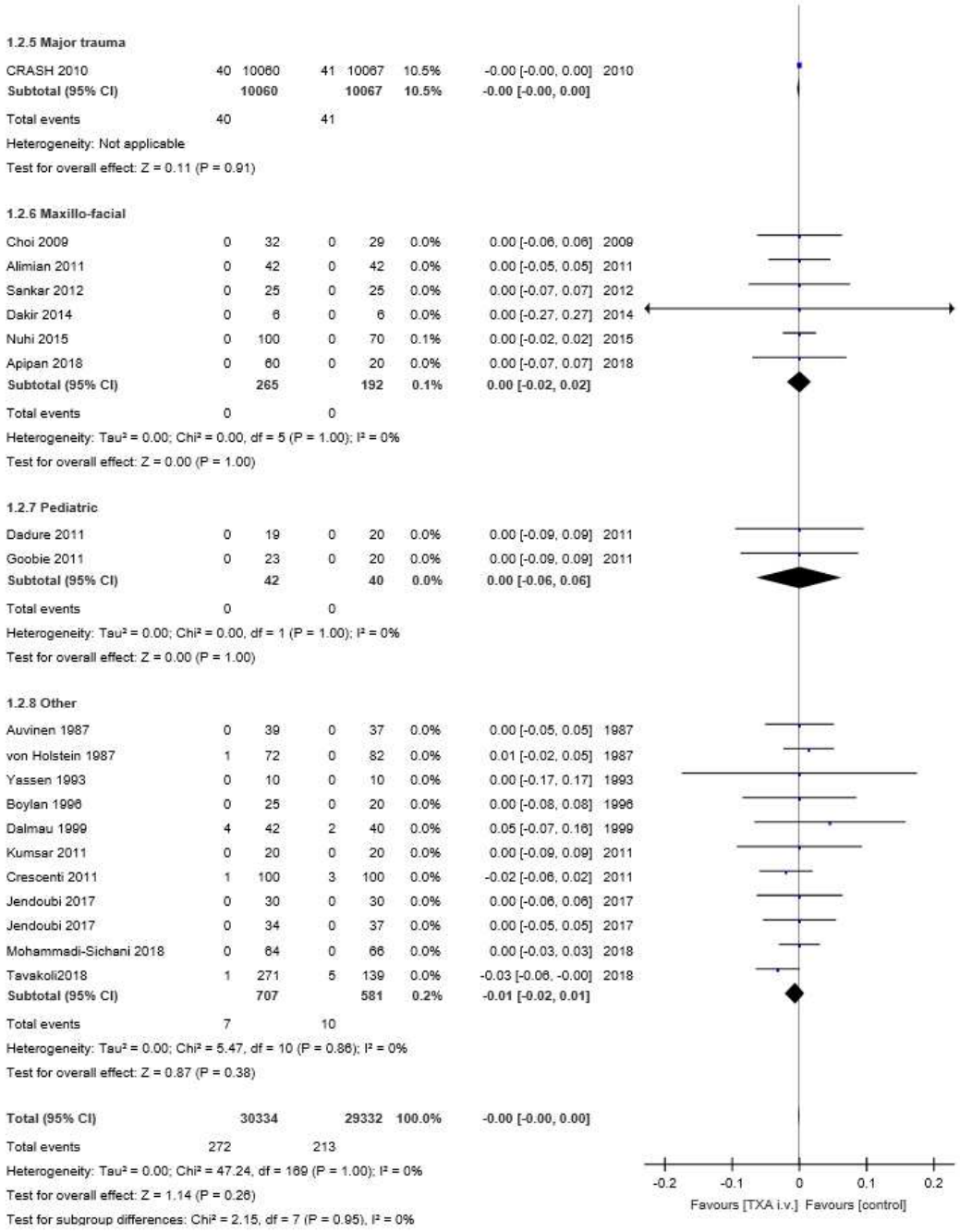
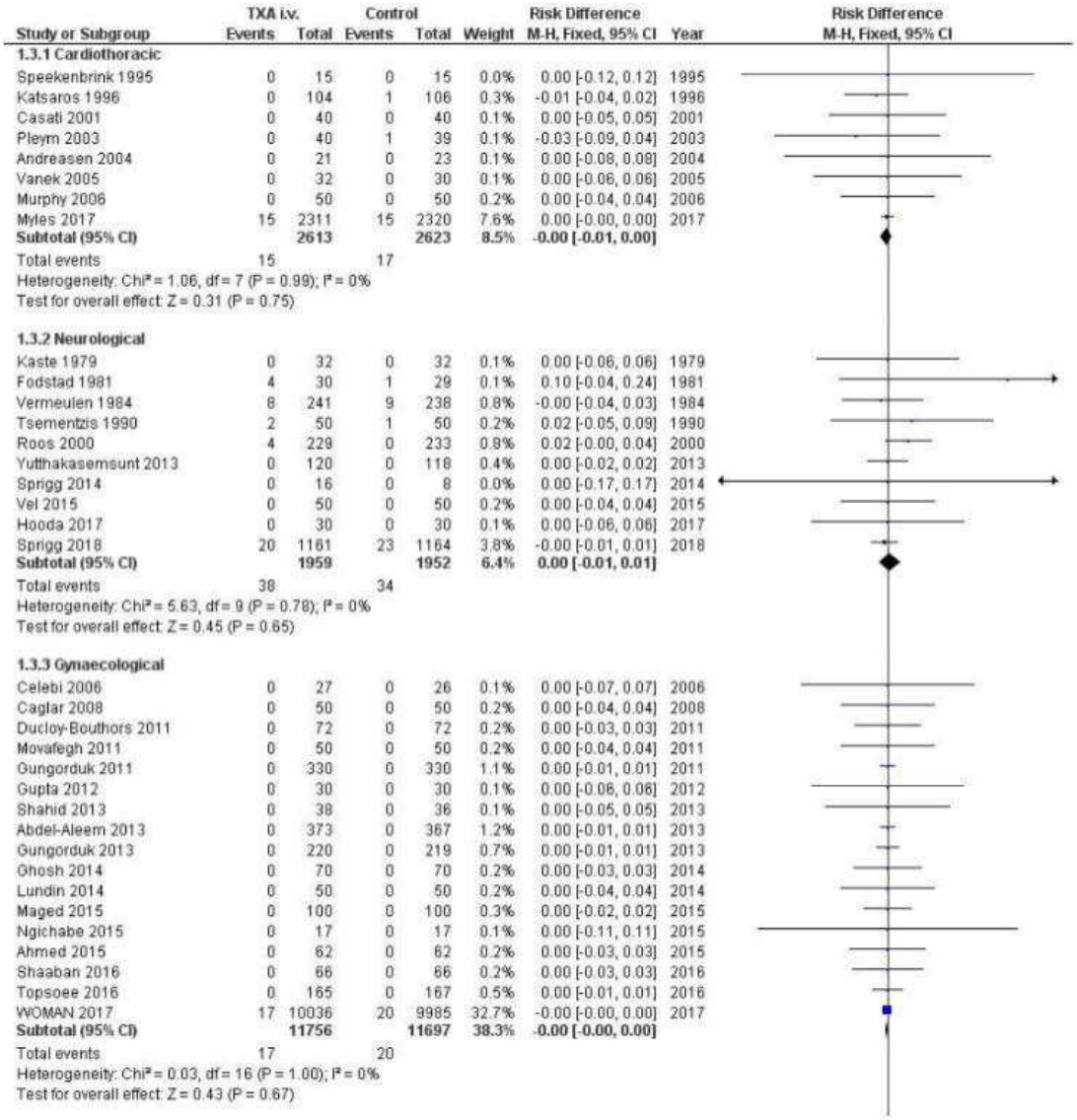


eFigure 9: Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect model.



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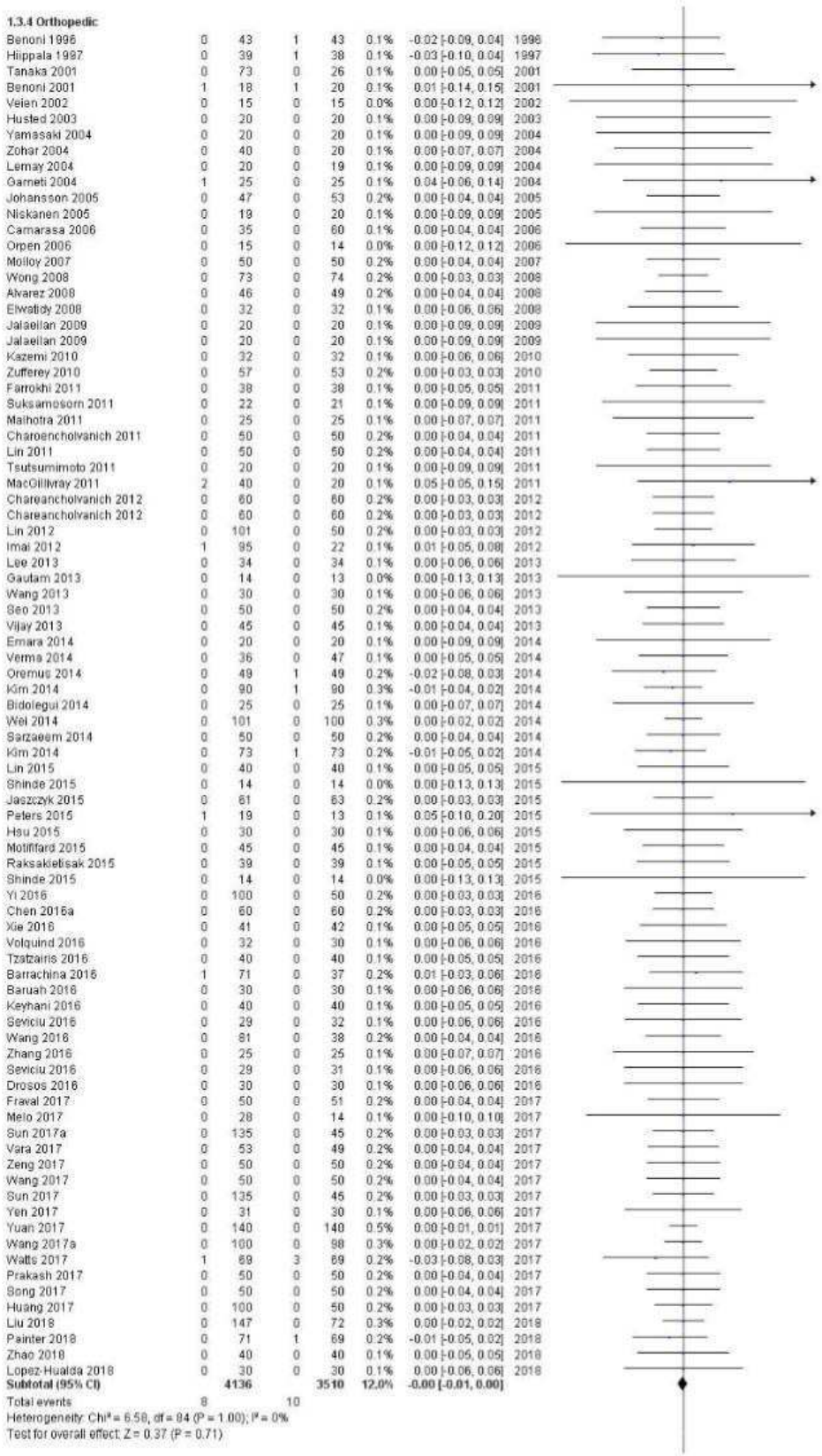

1.3.4 Orthopedic							
Benoni 1996	0	43	1	43	0.1%	-0.02 [-0.09, 0.04]	1996
Hiippala 1997	0	39	1	38	0.1%	-0.03 [-0.10, 0.04]	1997
Tanaka 2001	0	73	0	26	0.1%	0.00 [-0.05, 0.05]	2001
Benoni 2001	1	18	1	20	0.1%	0.01 [-0.14, 0.15]	2001
Veien 2002	0	15	0	15	0.0%	0.00 [-0.12, 0.12]	2002
Husted 2003	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2003
Yamasaki 2004	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2004
Zohar 2004	0	40	0	20	0.1%	0.00 [-0.07, 0.07]	2004
Lemay 2004	0	20	0	19	0.1%	0.00 [-0.09, 0.09]	2004
Garneti 2004	1	25	0	25	0.1%	0.04 [-0.06, 0.14]	2004
Johansson 2005	0	47	0	53	0.2%	0.00 [-0.04, 0.04]	2005
Niskanen 2005	0	19	0	20	0.1%	0.00 [-0.09, 0.09]	2005
Camarasa 2006	0	35	0	60	0.1%	0.00 [-0.04, 0.04]	2006
Orpen 2006	0	15	0	14	0.0%	0.00 [-0.12, 0.12]	2006
Molloy 2007	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2007
Wong 2008	0	73	0	74	0.2%	0.00 [-0.03, 0.03]	2008
Alvarez 2008	0	46	0	49	0.2%	0.00 [-0.04, 0.04]	2008
Elwatidy 2008	0	32	0	32	0.1%	0.00 [-0.06, 0.06]	2008
Jalaeilan 2009	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2009
Jalaeilan 2009	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2009
Kazemi 2010	0	32	0	32	0.1%	0.00 [-0.06, 0.06]	2010
Zufferey 2010	0	57	0	53	0.2%	0.00 [-0.03, 0.03]	2010
Farrokhi 2011	0	38	0	38	0.1%	0.00 [-0.05, 0.05]	2011
Suksamosorn 2011	0	22	0	21	0.1%	0.00 [-0.09, 0.09]	2011
Malhotra 2011	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2011
Charoencholvanich 2011	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2011
Lin 2011	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2011
Tsutsumimoto 2011	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2011
MacGillivray 2011	2	40	0	20	0.1%	0.05 [-0.05, 0.15]	2011
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Lin 2012	0	101	0	50	0.2%	0.00 [-0.03, 0.03]	2012
Imai 2012	1	95	0	22	0.1%	0.01 [-0.05, 0.08]	2012
Lee 2013	0	34	0	34	0.1%	0.00 [-0.06, 0.06]	2013
Gautam 2013	0	14	0	13	0.0%	0.00 [-0.13, 0.13]	2013
Wang 2013	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2013
Seo 2013	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2013
Vijay 2013	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2013
Emara 2014	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2014
Verma 2014	0	36	0	47	0.1%	0.00 [-0.05, 0.05]	2014
Oremus 2014	0	49	1	49	0.2%	-0.02 [-0.08, 0.03]	2014
Kim 2014	0	90	1	90	0.3%	-0.01 [-0.04, 0.02]	2014
Bidolegui 2014	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2014
Wei 2014	0	101	0	100	0.3%	0.00 [-0.02, 0.02]	2014
Sarzaeem 2014	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2014
Kim 2014	0	73	1	73	0.2%	-0.01 [-0.05, 0.02]	2014
Lin 2015	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2015
Shinde 2015	0	14	0	14	0.0%	0.00 [-0.13, 0.13]	2015
Jaszczyk 2015	0	61	0	63	0.2%	0.00 [-0.03, 0.03]	2015
Peters 2015	1	19	0	13	0.1%	0.05 [-0.10, 0.20]	2015
Hsu 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Motiffard 2015	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2015
Raksakietisak 2015	0	39	0	39	0.1%	0.00 [-0.05, 0.05]	2015
Shinde 2015	0	14	0	14	0.0%	0.00 [-0.13, 0.13]	2015
Yi 2016	0	100	0	50	0.2%	0.00 [-0.03, 0.03]	2016
Chen 2016a	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2016
Xie 2016	0	41	0	42	0.1%	0.00 [-0.05, 0.05]	2016
Volquind 2016	0	32	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Tzstzairis 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Barrachina 2016	1	71	0	37	0.2%	0.01 [-0.03, 0.06]	2016
Baruah 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Keyhani 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Seviciu 2016	0	29	0	32	0.1%	0.00 [-0.06, 0.06]	2016
Wang 2016	0	81	0	38	0.2%	0.00 [-0.04, 0.04]	2016
Zhang 2016	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2016
Seviciu 2016	0	29	0	31	0.1%	0.00 [-0.06, 0.06]	2016
Drosos 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Fraval 2017	0	50	0	51	0.2%	0.00 [-0.04, 0.04]	2017
Melo 2017	0	28	0	14	0.1%	0.00 [-0.10, 0.10]	2017
Sun 2017a	0	135	0	45	0.2%	0.00 [-0.03, 0.03]	2017
Vara 2017	0	53	0	49	0.2%	0.00 [-0.04, 0.04]	2017
Zeng 2017	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2017
Wang 2017	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2017
Sun 2017	0	135	0	45	0.2%	0.00 [-0.03, 0.03]	2017
Yen 2017	0	31	0	30	0.1%	0.00 [-0.06, 0.06]	2017
Yuan 2017	0	140	0	140	0.5%	0.00 [-0.01, 0.01]	2017
Wang 2017a	0	100	0	98	0.3%	0.00 [-0.02, 0.02]	2017
Watts 2017	1	69	3	69	0.2%	-0.03 [-0.08, 0.03]	2017
Prakash 2017	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2017
Song 2017	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2017
Huang 2017	0	100	0	50	0.2%	0.00 [-0.03, 0.03]	2017
Liu 2018	0	147	0	72	0.3%	0.00 [-0.02, 0.02]	2018
Painter 2018	0	71	1	69	0.2%	-0.01 [-0.05, 0.02]	2018
Zhao 2018	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2018
Lopez-Hualda 2018	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2018
Subtotal (95% CI)		**4136**		**3510**	**12.0%**	**-0.00 [-0.01, 0.00]**	
Total events	8		10				

Heterogeneity: Chi² = 6.58, df = 84 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

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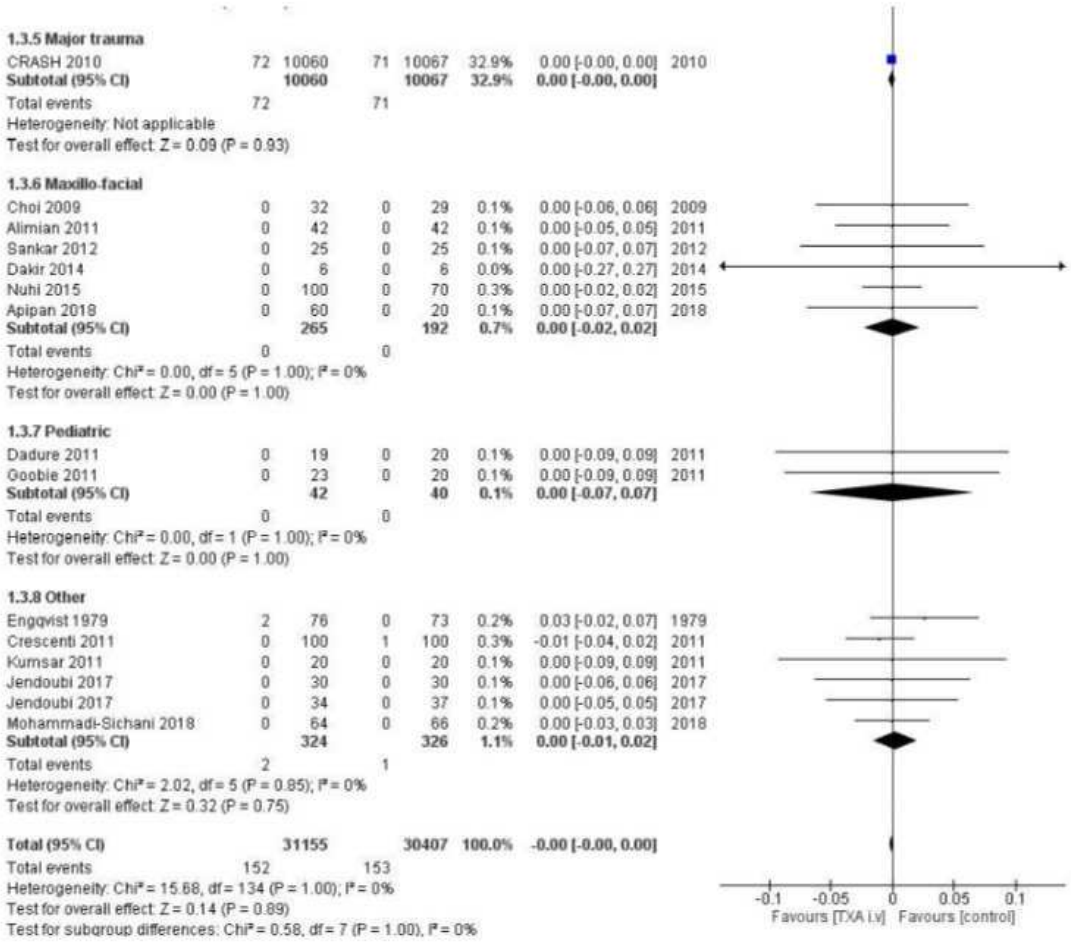
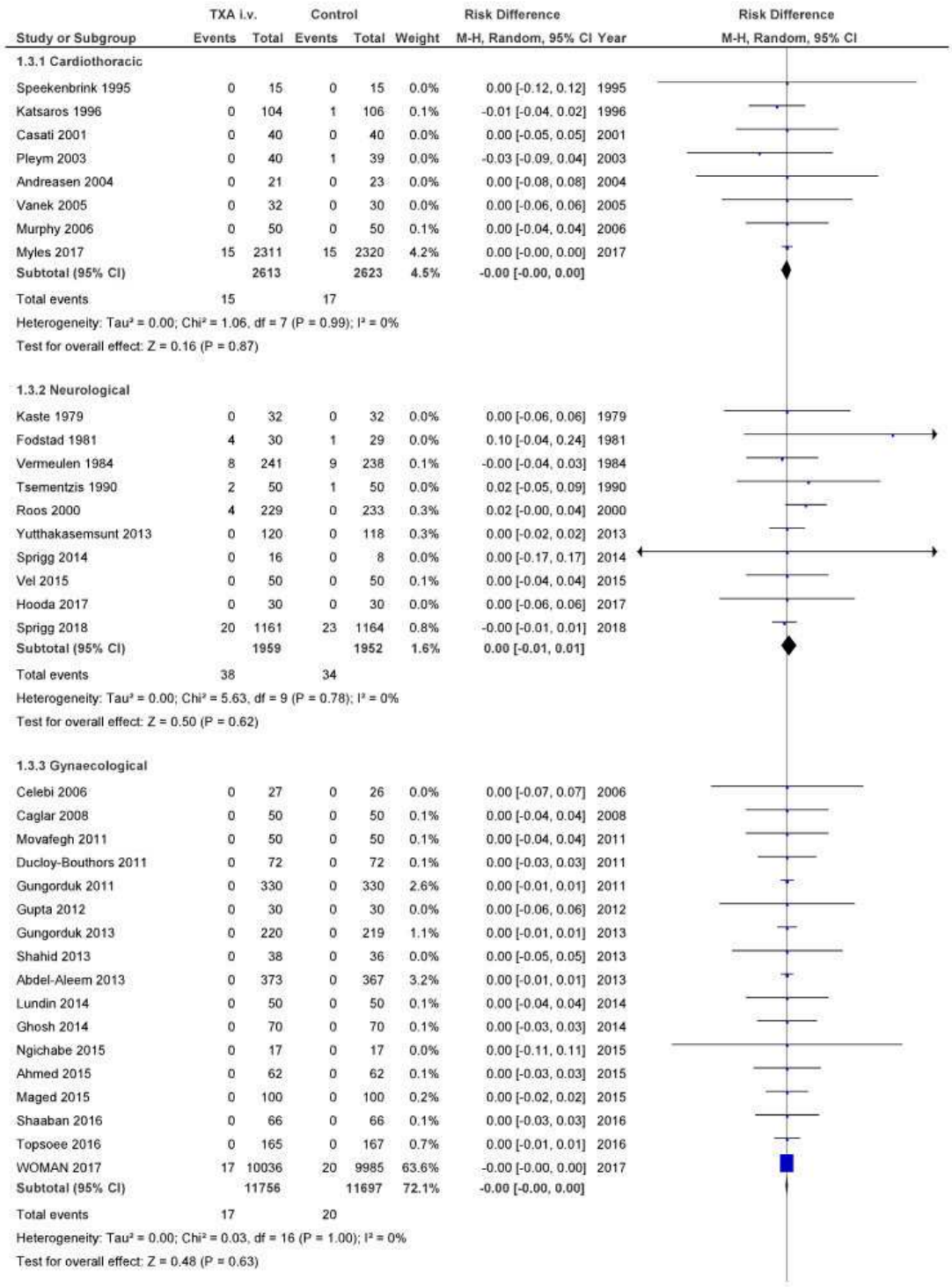


eFigure 10: Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model



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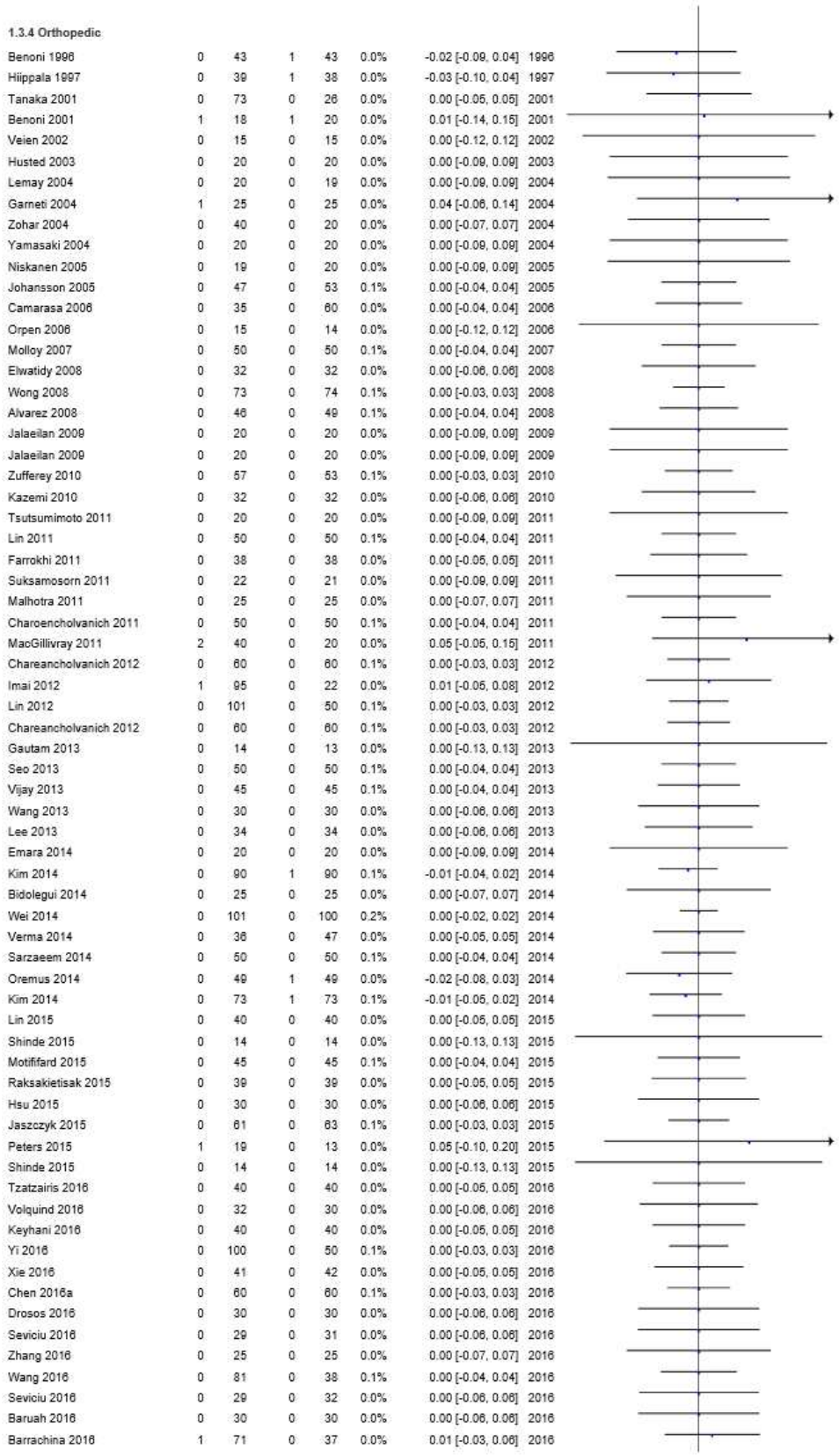

1.3.4 Orthopedic							
Benoni 1996	0	43	1	43	0.0%	-0.02 [-0.09, 0.04]	1996
Hiippala 1997	0	39	1	38	0.0%	-0.03 [-0.10, 0.04]	1997
Tanaka 2001	0	73	0	26	0.0%	0.00 [-0.05, 0.05]	2001
Benoni 2001	1	18	1	20	0.0%	0.01 [-0.14, 0.15]	2001
Veien 2002	0	15	0	15	0.0%	0.00 [-0.12, 0.12]	2002
Husted 2003	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2003
Lemay 2004	0	20	0	19	0.0%	0.00 [-0.09, 0.09]	2004
Garneti 2004	1	25	0	25	0.0%	0.04 [-0.06, 0.14]	2004
Zohar 2004	0	40	0	20	0.0%	0.00 [-0.07, 0.07]	2004
Yamasaki 2004	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2004
Niskanen 2005	0	19	0	20	0.0%	0.00 [-0.09, 0.09]	2005
Johansson 2005	0	47	0	53	0.1%	0.00 [-0.04, 0.04]	2005
Camarasa 2006	0	35	0	60	0.0%	0.00 [-0.04, 0.04]	2006
Orpen 2006	0	15	0	14	0.0%	0.00 [-0.12, 0.12]	2006
Molloy 2007	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2007
Elwatidy 2008	0	32	0	32	0.0%	0.00 [-0.06, 0.06]	2008
Wong 2008	0	73	0	74	0.1%	0.00 [-0.03, 0.03]	2008
Alvarez 2008	0	46	0	49	0.1%	0.00 [-0.04, 0.04]	2008
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Zufferey 2010	0	57	0	53	0.1%	0.00 [-0.03, 0.03]	2010
Kazemi 2010	0	32	0	32	0.0%	0.00 [-0.06, 0.06]	2010
Tsutsumimoto 2011	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2011
Lin 2011	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2011
Farrokhi 2011	0	38	0	38	0.0%	0.00 [-0.05, 0.05]	2011
Suksamosorn 2011	0	22	0	21	0.0%	0.00 [-0.09, 0.09]	2011
Malhotra 2011	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2011
Charoencholvanich 2011	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2011
MacGillivray 2011	2	40	0	20	0.0%	0.05 [-0.05, 0.15]	2011
Chareancholvanich 2012	0	60	0	60	0.1%	0.00 [-0.03, 0.03]	2012
Imai 2012	1	95	0	22	0.0%	0.01 [-0.05, 0.08]	2012
Lin 2012	0	101	0	50	0.1%	0.00 [-0.03, 0.03]	2012
Chareancholvanich 2012	0	60	0	60	0.1%	0.00 [-0.03, 0.03]	2012
Gautam 2013	0	14	0	13	0.0%	0.00 [-0.13, 0.13]	2013
Seo 2013	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2013
Vijay 2013	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2013
Wang 2013	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2013
Lee 2013	0	34	0	34	0.0%	0.00 [-0.06, 0.06]	2013
Emara 2014	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2014
Kim 2014	0	90	1	90	0.1%	-0.01 [-0.04, 0.02]	2014
Bidolegui 2014	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2014
Wei 2014	0	101	0	100	0.2%	0.00 [-0.02, 0.02]	2014
Verma 2014	0	36	0	47	0.0%	0.00 [-0.05, 0.05]	2014
Sarzaeem 2014	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2014
Oremus 2014	0	49	1	49	0.0%	-0.02 [-0.08, 0.03]	2014
Kim 2014	0	73	1	73	0.1%	-0.01 [-0.05, 0.02]	2014
Lin 2015	0	40	0	40	0.0%	0.00 [-0.05, 0.05]	2015
Shinde 2015	0	14	0	14	0.0%	0.00 [-0.13, 0.13]	2015
Motififard 2015	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2015
Raksakietisak 2015	0	39	0	39	0.0%	0.00 [-0.05, 0.05]	2015
Hsu 2015	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2015
Jaszczyk 2015	0	61	0	63	0.1%	0.00 [-0.03, 0.03]	2015
Peters 2015	1	19	0	13	0.0%	0.05 [-0.10, 0.20]	2015
Shinde 2015	0	14	0	14	0.0%	0.00 [-0.13, 0.13]	2015
Tzatzairis 2016	0	40	0	40	0.0%	0.00 [-0.05, 0.05]	2016
Volquind 2016	0	32	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Keyhani 2016	0	40	0	40	0.0%	0.00 [-0.05, 0.05]	2016
Yi 2016	0	100	0	50	0.1%	0.00 [-0.03, 0.03]	2016
Xie 2016	0	41	0	42	0.0%	0.00 [-0.05, 0.05]	2016
Chen 2016a	0	60	0	60	0.1%	0.00 [-0.03, 0.03]	2016
Drosos 2016	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Seviciu 2016	0	29	0	31	0.0%	0.00 [-0.06, 0.06]	2016
Zhang 2016	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2016
Wang 2016	0	81	0	38	0.1%	0.00 [-0.04, 0.04]	2016
Seviciu 2016	0	29	0	32	0.0%	0.00 [-0.06, 0.06]	2016
Baruah 2016	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2016
Barrachina 2016	1	71	0	37	0.0%	0.01 [-0.03, 0.06]	2016

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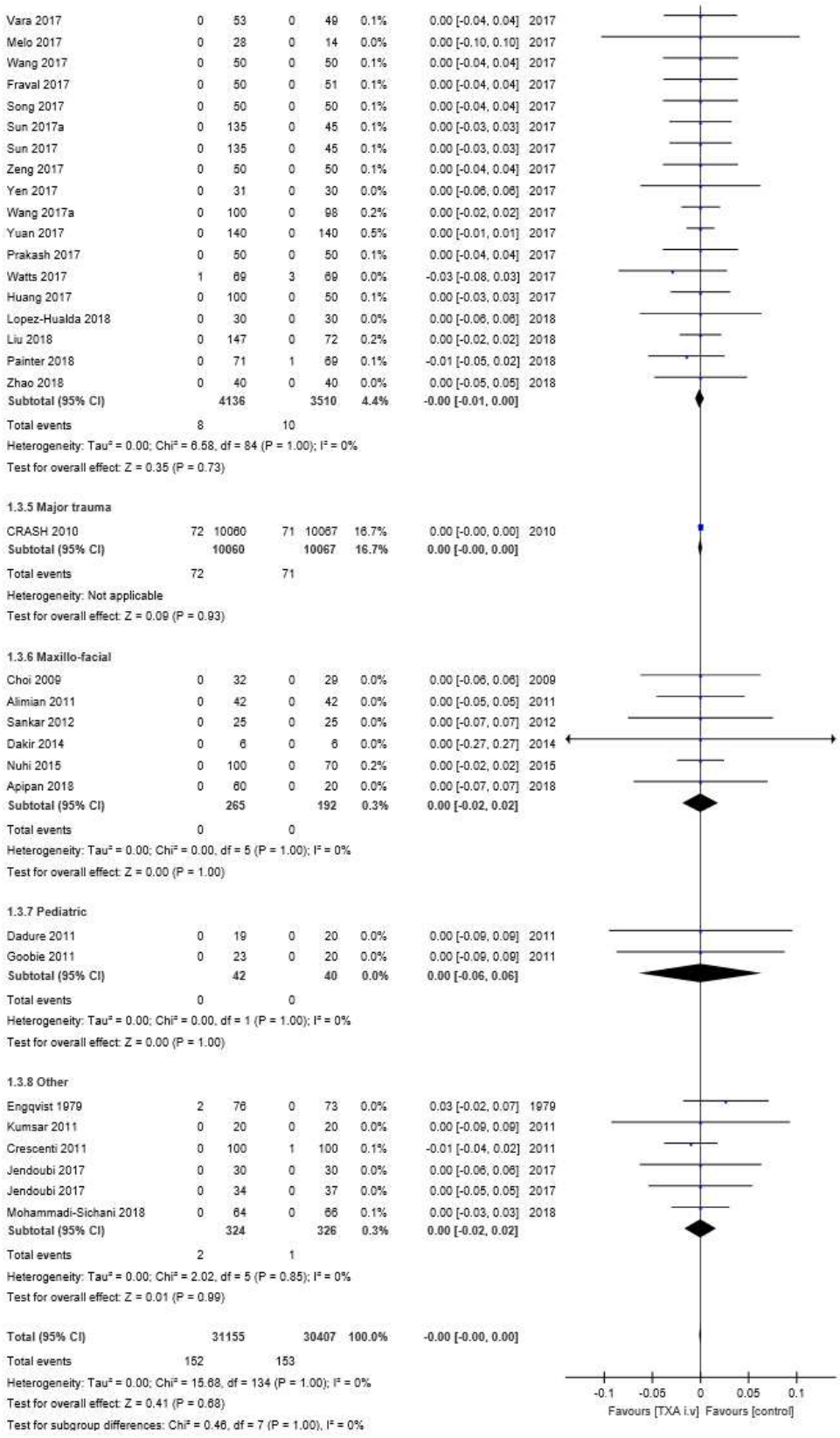
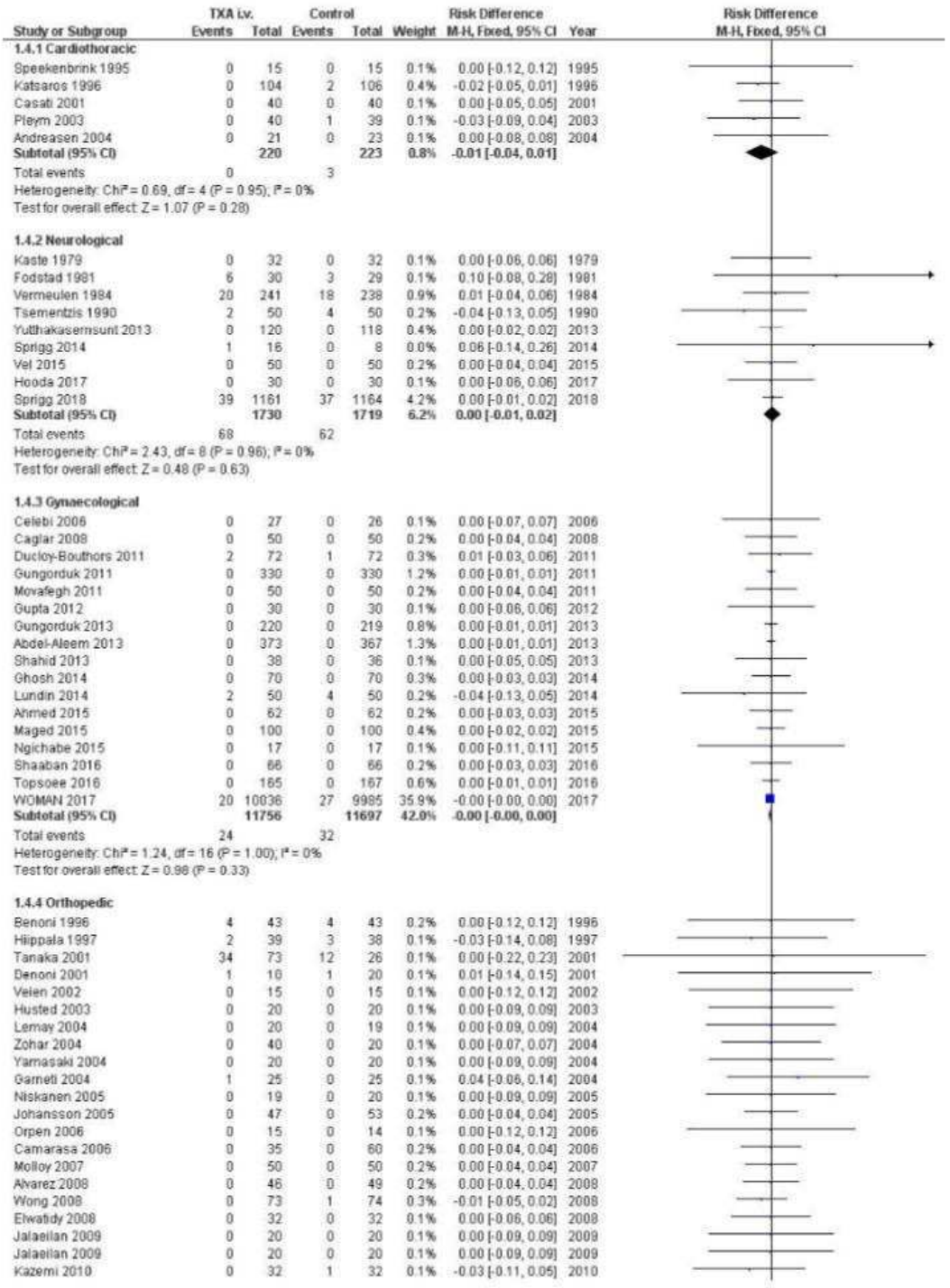


eFigure 11: Venous Thromboembolic and Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



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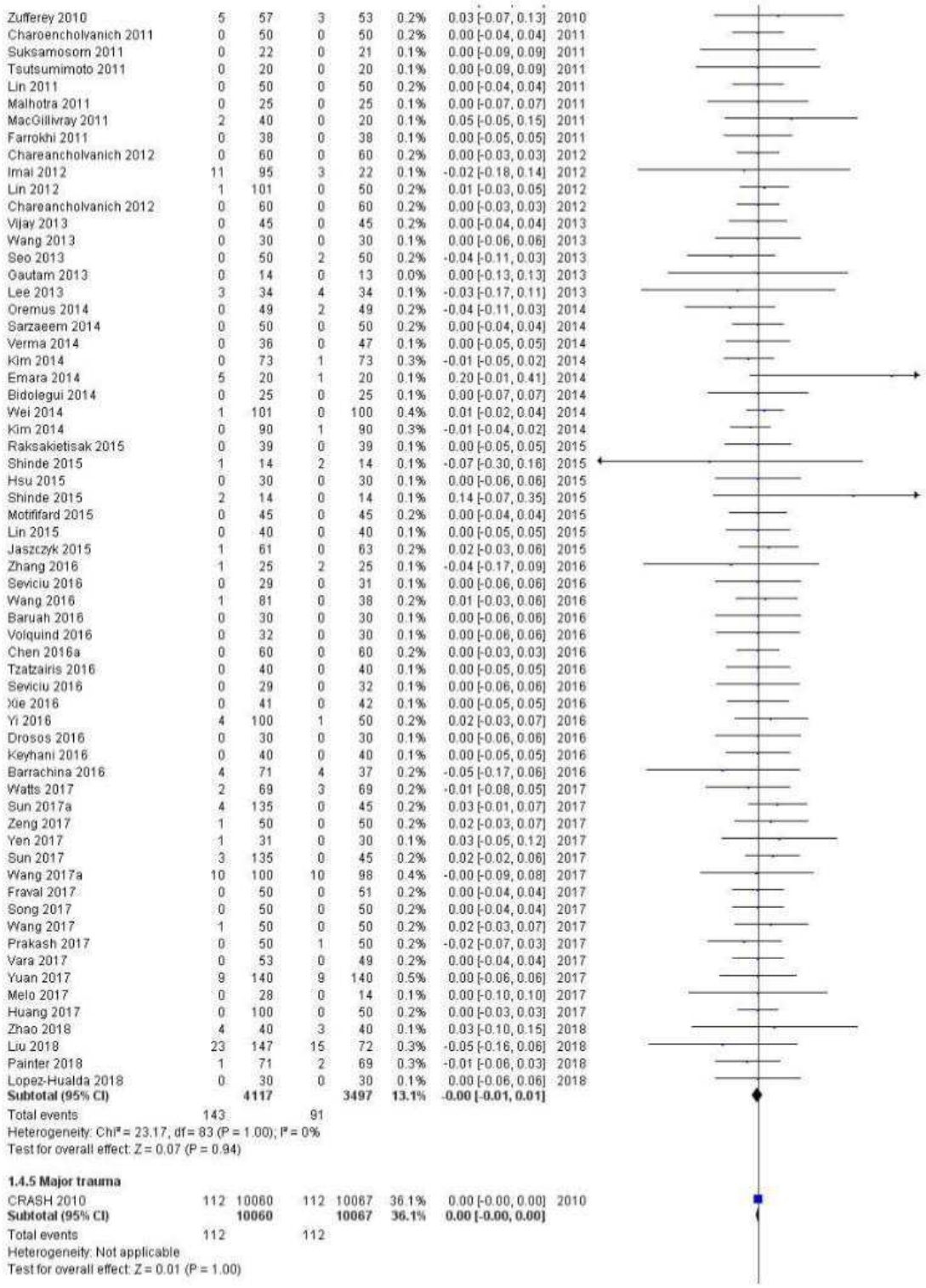

Zufferey 2010	5	57	3	53	0.2%	0.03 [-0.07, 0.13]	2010
Charoencholvanich 2011	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2011
Suksamosorn 2011	0	22	0	21	0.1%	0.00 [-0.09, 0.09]	2011
Tsutsumimoto 2011	0	20	0	20	0.1%	0.00 [-0.09, 0.09]	2011
Lin 2011	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2011
Malhotra 2011	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2011
MacGillivray 2011	2	40	0	20	0.1%	0.05 [-0.05, 0.15]	2011
Farrokhi 2011	0	38	0	38	0.1%	0.00 [-0.05, 0.05]	2011
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Imai 2012	11	95	3	22	0.1%	-0.02 [-0.18, 0.14]	2012
Lin 2012	1	101	0	50	0.2%	0.01 [-0.03, 0.05]	2012
Chareancholvanich 2012	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2012
Vijay 2013	0	45	0	45	0.2%	0.00 [-0.04, 0.04]	2013
Wang 2013	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2013
Seo 2013	0	50	2	50	0.2%	-0.04 [-0.11, 0.03]	2013
Gautam 2013	0	14	0	13	0.0%	0.00 [-0.13, 0.13]	2013
Lee 2013	3	34	4	34	0.1%	-0.03 [-0.17, 0.11]	2013
Oremus 2014	0	49	2	49	0.2%	-0.04 [-0.11, 0.03]	2014
Sarzaeem 2014	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2014
Verma 2014	0	36	0	47	0.1%	0.00 [-0.05, 0.05]	2014
Kim 2014	0	73	1	73	0.3%	-0.01 [-0.05, 0.02]	2014
Emara 2014	5	20	1	20	0.1%	0.20 [-0.01, 0.41]	2014
Bidolegui 2014	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2014
Wei 2014	1	101	0	100	0.4%	0.01 [-0.02, 0.04]	2014
Kim 2014	0	90	1	90	0.3%	-0.01 [-0.04, 0.02]	2014
Raksakietisak 2015	0	39	0	39	0.1%	0.00 [-0.05, 0.05]	2015
Shinde 2015	1	14	2	14	0.1%	-0.07 [-0.30, 0.16]	2015
Hsu 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Shinde 2015	2	14	0	14	0.1%	0.14 [-0.07, 0.35]	2015
Motififard 2015	0	45	0	45	0.2%	0.00 [-0.04, 0.04]	2015
Lin 2015	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2015
Jaszczyk 2015	1	61	0	63	0.2%	0.02 [-0.03, 0.06]	2015
Zhang 2016	1	25	2	25	0.1%	-0.04 [-0.17, 0.09]	2016
Seviciu 2016	0	29	0	31	0.1%	0.00 [-0.06, 0.06]	2016
Wang 2016	1	81	0	38	0.2%	0.01 [-0.03, 0.06]	2016
Baruah 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Volquind 2016	0	32	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Chen 2016a	0	60	0	60	0.2%	0.00 [-0.03, 0.03]	2016
Tzatzairis 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Seviciu 2016	0	29	0	32	0.1%	0.00 [-0.06, 0.06]	2016
Xie 2016	0	41	0	42	0.1%	0.00 [-0.05, 0.05]	2016
Yi 2016	4	100	1	50	0.2%	0.02 [-0.03, 0.07]	2016
Drosos 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Keyhani 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Barrachina 2016	4	71	4	37	0.2%	-0.05 [-0.17, 0.06]	2016
Watts 2017	2	69	3	69	0.2%	-0.01 [-0.08, 0.05]	2017
Sun 2017a	4	135	0	45	0.2%	0.03 [-0.01, 0.07]	2017
Zeng 2017	1	50	0	50	0.2%	0.02 [-0.03, 0.07]	2017
Yen 2017	1	31	0	30	0.1%	0.03 [-0.05, 0.12]	2017
Sun 2017	3	135	0	45	0.2%	0.02 [-0.02, 0.06]	2017
Wang 2017a	10	100	10	98	0.4%	-0.00 [-0.09, 0.08]	2017
Fraval 2017	0	50	0	51	0.2%	0.00 [-0.04, 0.04]	2017
Song 2017	0	50	0	50	0.2%	0.00 [-0.04, 0.04]	2017
Wang 2017	1	50	0	50	0.2%	0.02 [-0.03, 0.07]	2017
Prakash 2017	0	50	1	50	0.2%	-0.02 [-0.07, 0.03]	2017
Vara 2017	0	53	0	49	0.2%	0.00 [-0.04, 0.04]	2017
Yuan 2017	9	140	9	140	0.5%	0.00 [-0.06, 0.06]	2017
Melo 2017	0	28	0	14	0.1%	0.00 [-0.10, 0.10]	2017
Huang 2017	0	100	0	50	0.2%	0.00 [-0.03, 0.03]	2017
Zhao 2018	4	40	3	40	0.1%	0.03 [-0.10, 0.15]	2018
Liu 2018	23	147	15	72	0.3%	-0.05 [-0.16, 0.06]	2018
Painter 2018	1	71	2	69	0.3%	-0.01 [-0.06, 0.03]	2018
Lopez-Hualda 2018	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2018
Subtotal (95% CI)		**4117**		**3497**	**13.1%**	**-0.00 [-0.01, 0.01]**	
Total events	143		91				
Heterogeneity: Chi² = 23.17, df = 83 (P = 1.00); I² = 0%							
Test for overall effect: Z = 0.07 (P = 0.94)							
1.4.5 Major trauma							
CRASH 2010	112	10060	112	10067	36.1%	0.00 [-0.00, 0.00]	2010
Subtotal (95% CI)		**10060**		**10067**	**36.1%**	**0.00 [-0.00, 0.00]**	
Total events	112		112				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.01 (P = 1.00)							

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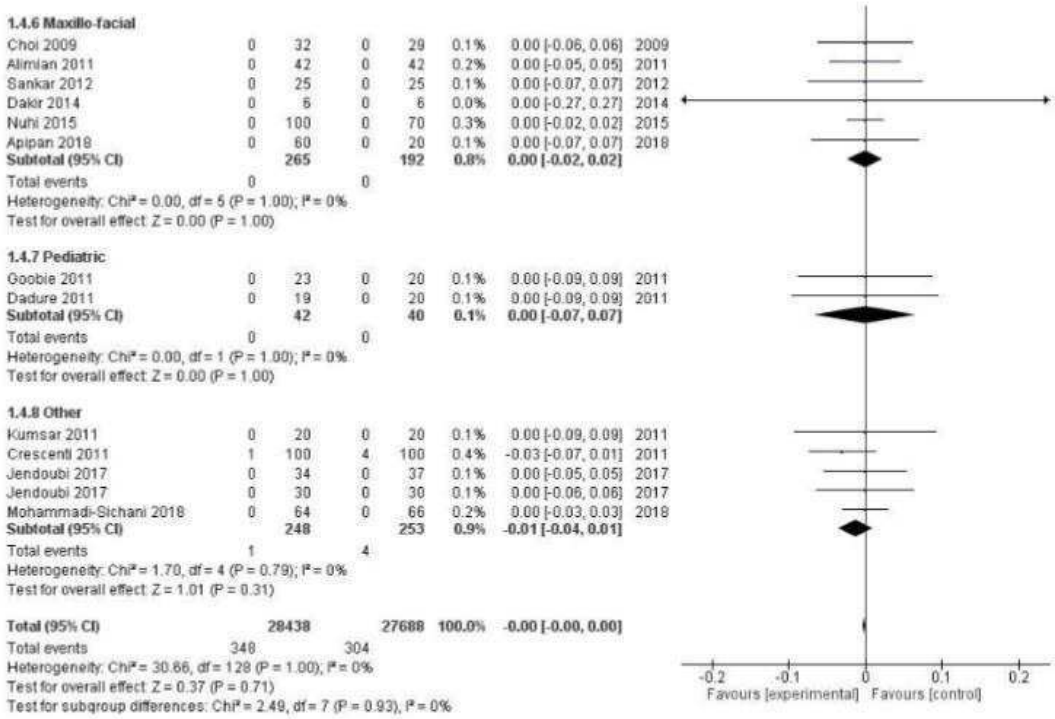
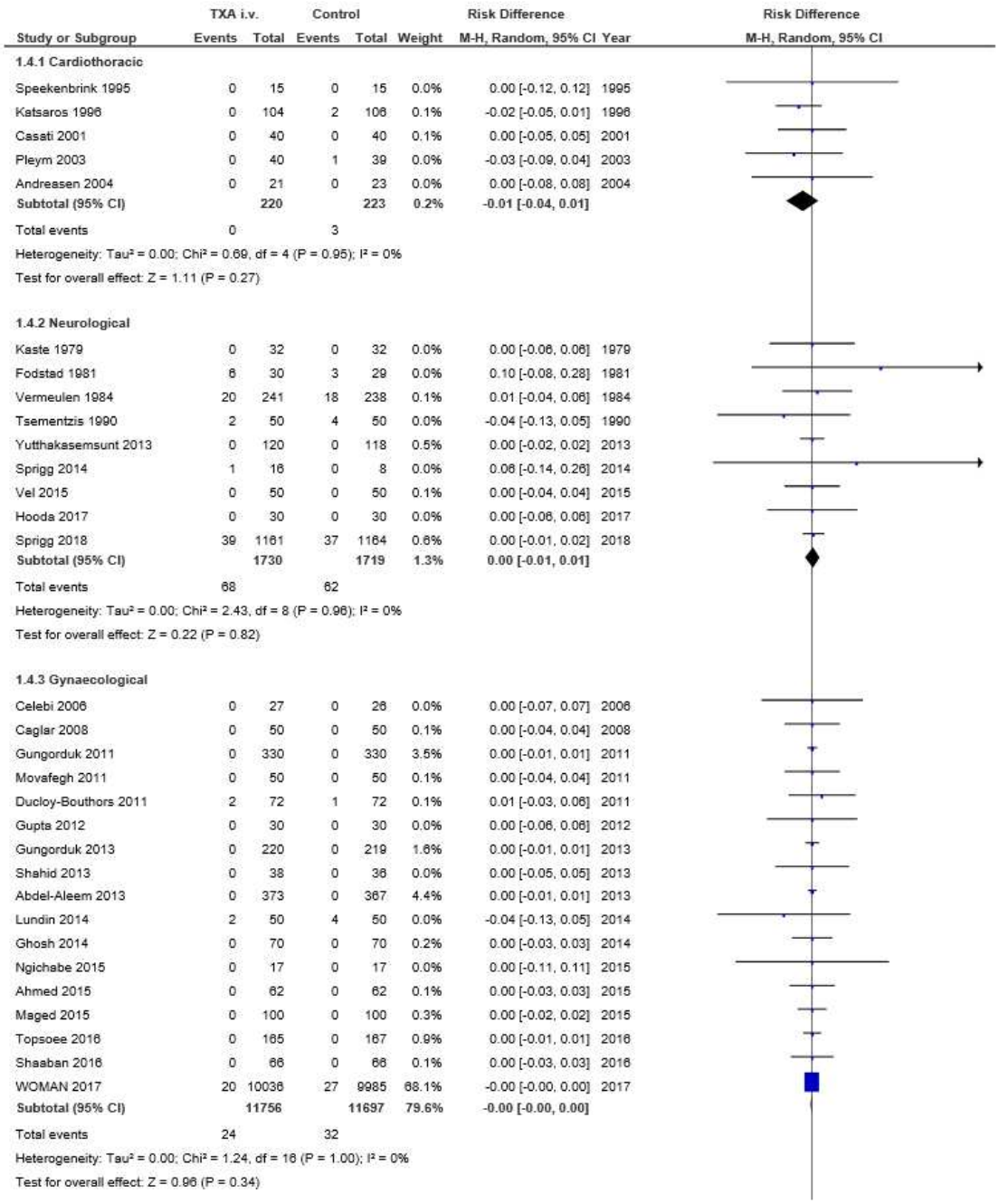


eFigure 12: Venous Thromboembolic and Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model



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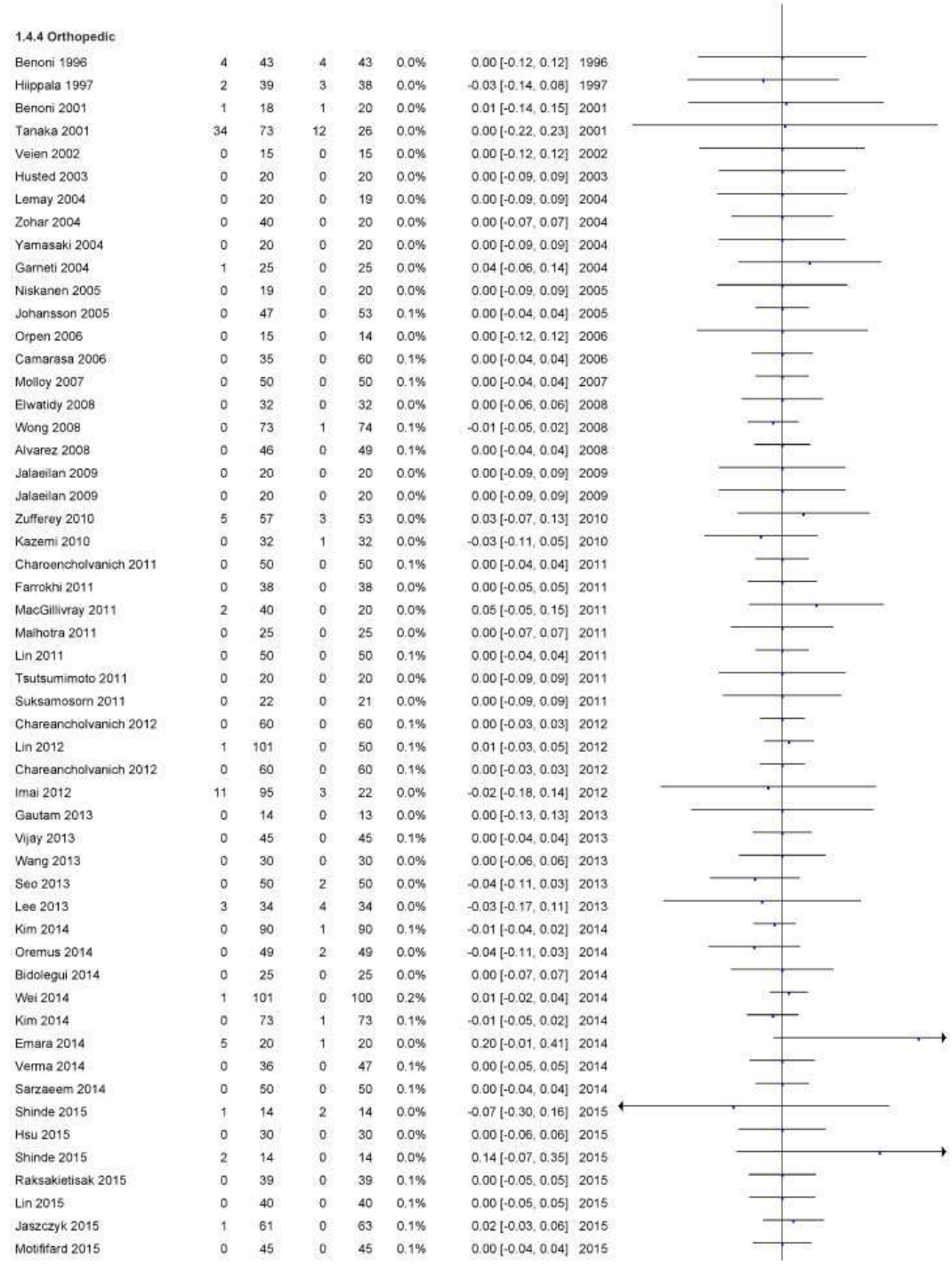

1.4.4 Orthopedic							
Benoni 1996	4	43	4	43	0.0%	0.00 [-0.12, 0.12]	1996
Hiippala 1997	2	39	3	38	0.0%	-0.03 [-0.14, 0.08]	1997
Benoni 2001	1	18	1	20	0.0%	0.01 [-0.14, 0.15]	2001
Tanaka 2001	34	73	12	26	0.0%	0.00 [-0.22, 0.23]	2001
Veien 2002	0	15	0	15	0.0%	0.00 [-0.12, 0.12]	2002
Husted 2003	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2003
Lemay 2004	0	20	0	19	0.0%	0.00 [-0.09, 0.09]	2004
Zohar 2004	0	40	0	20	0.0%	0.00 [-0.07, 0.07]	2004
Yamasaki 2004	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2004
Garneti 2004	1	25	0	25	0.0%	0.04 [-0.06, 0.14]	2004
Niskanen 2005	0	19	0	20	0.0%	0.00 [-0.09, 0.09]	2005
Johansson 2005	0	47	0	53	0.1%	0.00 [-0.04, 0.04]	2005
Orpen 2006	0	15	0	14	0.0%	0.00 [-0.12, 0.12]	2006
Camarasa 2006	0	35	0	60	0.1%	0.00 [-0.04, 0.04]	2006
Molloy 2007	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2007
Elwatidy 2008	0	32	0	32	0.0%	0.00 [-0.06, 0.06]	2008
Wong 2008	0	73	1	74	0.1%	-0.01 [-0.05, 0.02]	2008
Alvarez 2008	0	46	0	49	0.1%	0.00 [-0.04, 0.04]	2008
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Jalaeilan 2009	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2009
Zufferey 2010	5	57	3	53	0.0%	0.03 [-0.07, 0.13]	2010
Kazemi 2010	0	32	1	32	0.0%	-0.03 [-0.11, 0.05]	2010
Charoencholvanich 2011	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2011
Farrokhi 2011	0	38	0	38	0.0%	0.00 [-0.05, 0.05]	2011
MacGillivray 2011	2	40	0	20	0.0%	0.05 [-0.05, 0.15]	2011
Malhotra 2011	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2011
Lin 2011	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2011
Tsutsumimoto 2011	0	20	0	20	0.0%	0.00 [-0.09, 0.09]	2011
Suksamosorn 2011	0	22	0	21	0.0%	0.00 [-0.09, 0.09]	2011
Chareancholvanich 2012	0	60	0	60	0.1%	0.00 [-0.03, 0.03]	2012
Lin 2012	1	101	0	50	0.1%	0.01 [-0.03, 0.05]	2012
Chareancholvanich 2012	0	60	0	60	0.1%	0.00 [-0.03, 0.03]	2012
Imai 2012	11	95	3	22	0.0%	-0.02 [-0.18, 0.14]	2012
Gautam 2013	0	14	0	13	0.0%	0.00 [-0.13, 0.13]	2013
Vijay 2013	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2013
Wang 2013	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2013
Seo 2013	0	50	2	50	0.0%	-0.04 [-0.11, 0.03]	2013
Lee 2013	3	34	4	34	0.0%	-0.03 [-0.17, 0.11]	2013
Kim 2014	0	90	1	90	0.1%	-0.01 [-0.04, 0.02]	2014
Oremus 2014	0	49	2	49	0.0%	-0.04 [-0.11, 0.03]	2014
Bidolegui 2014	0	25	0	25	0.0%	0.00 [-0.07, 0.07]	2014
Wei 2014	1	101	0	100	0.2%	0.01 [-0.02, 0.04]	2014
Kim 2014	0	73	1	73	0.1%	-0.01 [-0.05, 0.02]	2014
Emara 2014	5	20	1	20	0.0%	0.20 [-0.01, 0.41]	2014
Verma 2014	0	36	0	47	0.1%	0.00 [-0.05, 0.05]	2014
Sarzaeem 2014	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2014
Shinde 2015	1	14	2	14	0.0%	-0.07 [-0.30, 0.16]	2015
Hsu 2015	0	30	0	30	0.0%	0.00 [-0.06, 0.06]	2015
Shinde 2015	2	14	0	14	0.0%	0.14 [-0.07, 0.35]	2015
Raksakietisak 2015	0	39	0	39	0.1%	0.00 [-0.05, 0.05]	2015
Lin 2015	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2015
Jaszczyk 2015	1	61	0	63	0.1%	0.02 [-0.03, 0.06]	2015
Motiffard 2015	0	45	0	45	0.1%	0.00 [-0.04, 0.04]	2015

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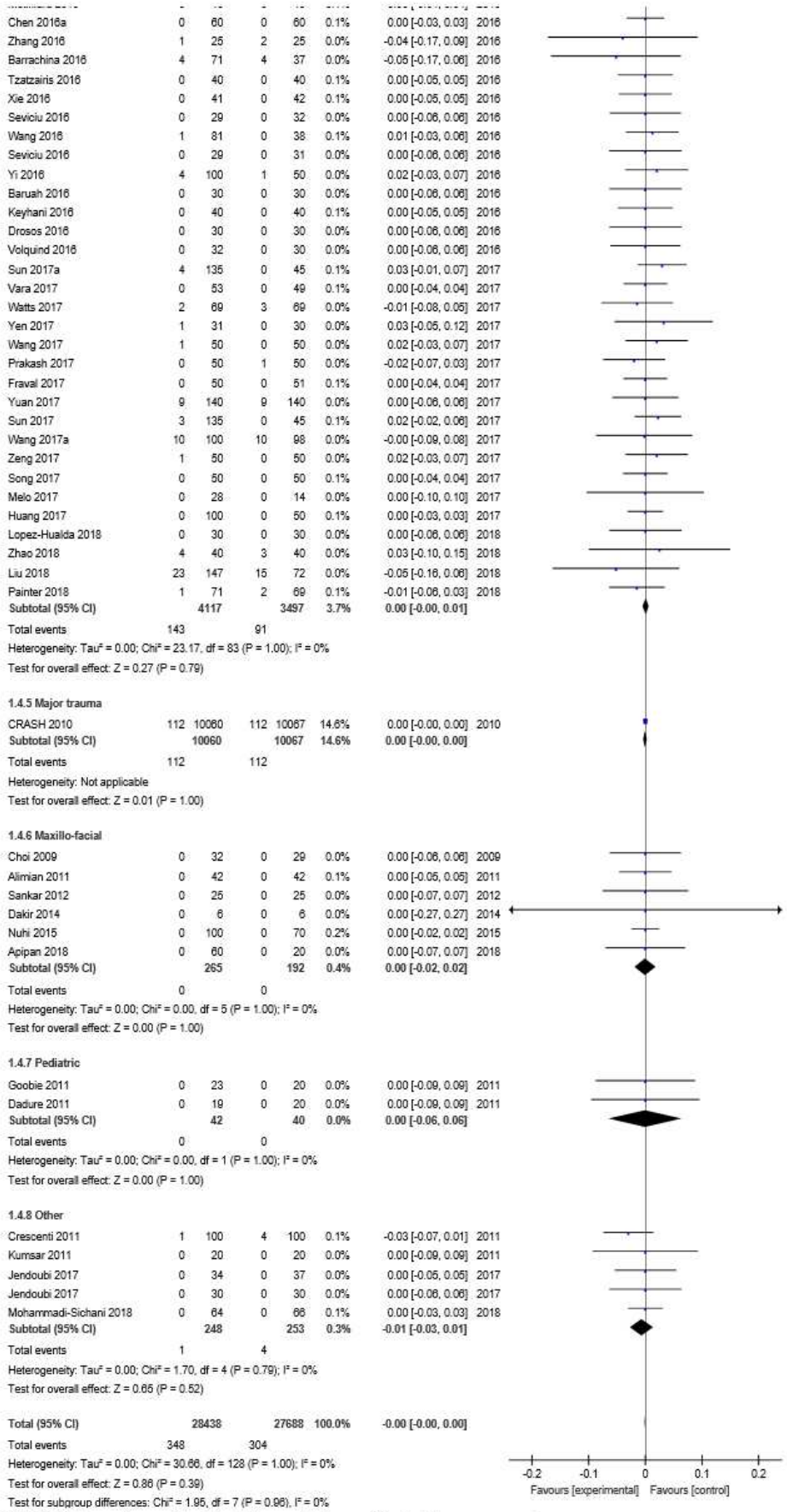
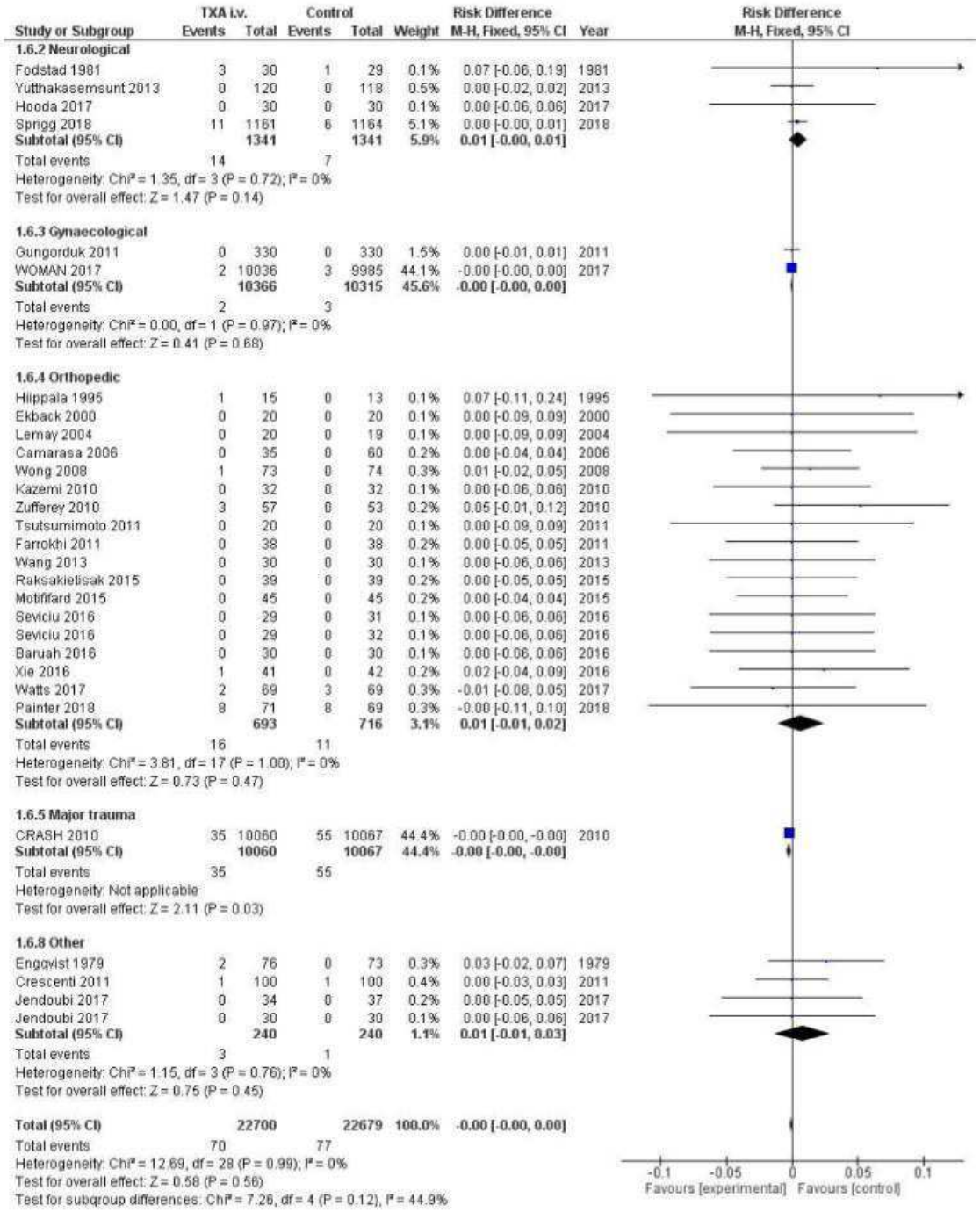
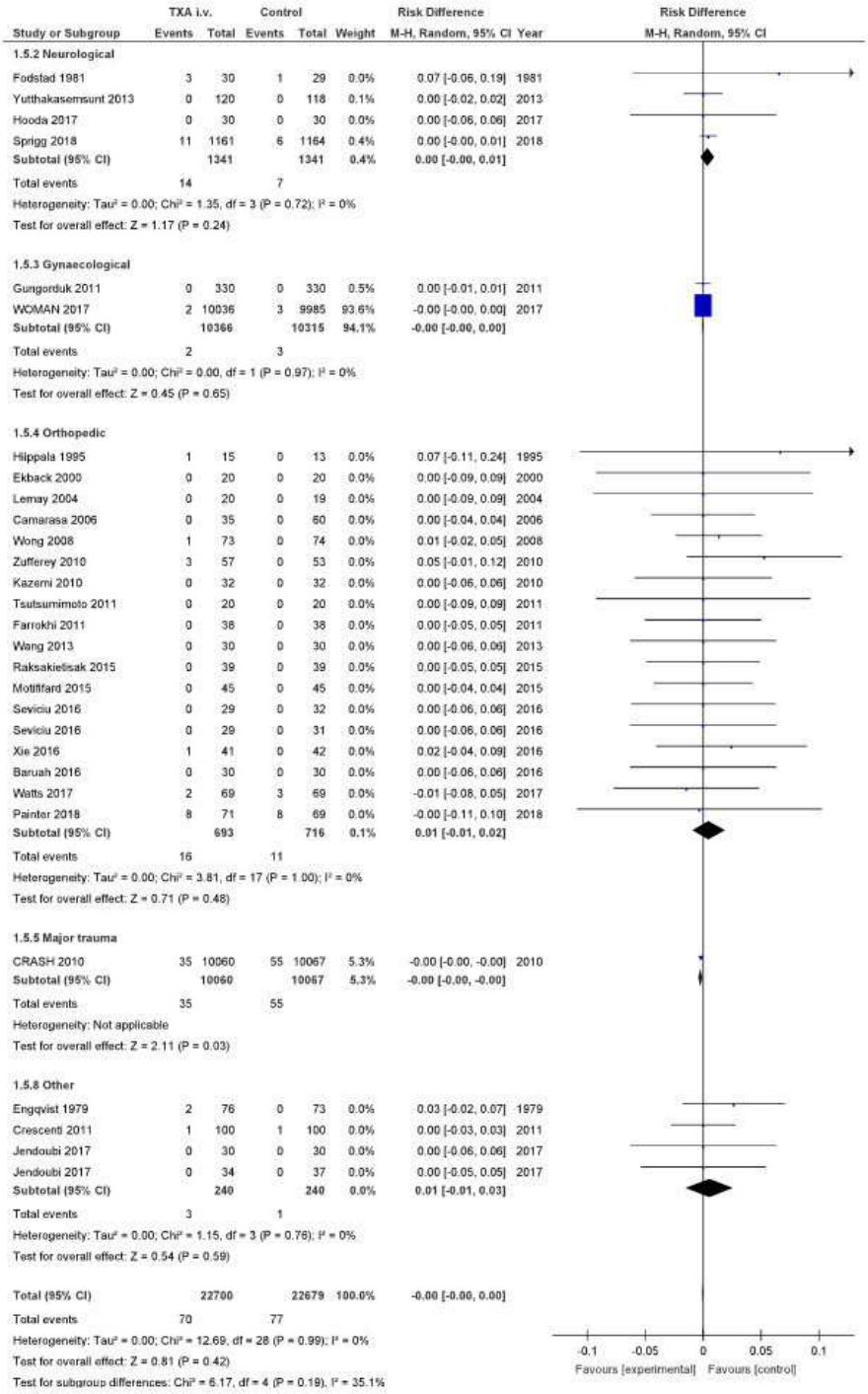


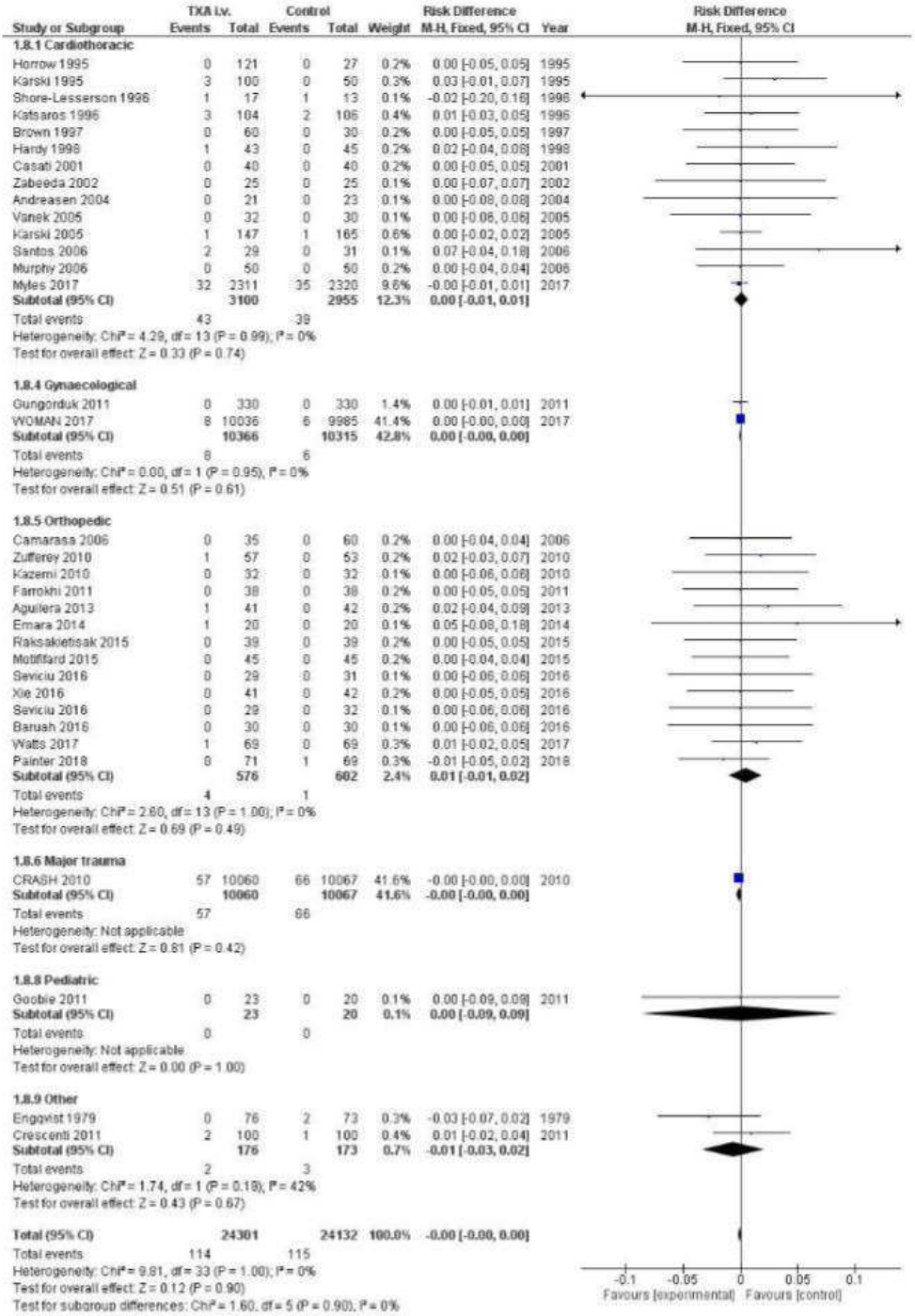
eFigure 13: Myocardial Infarction Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



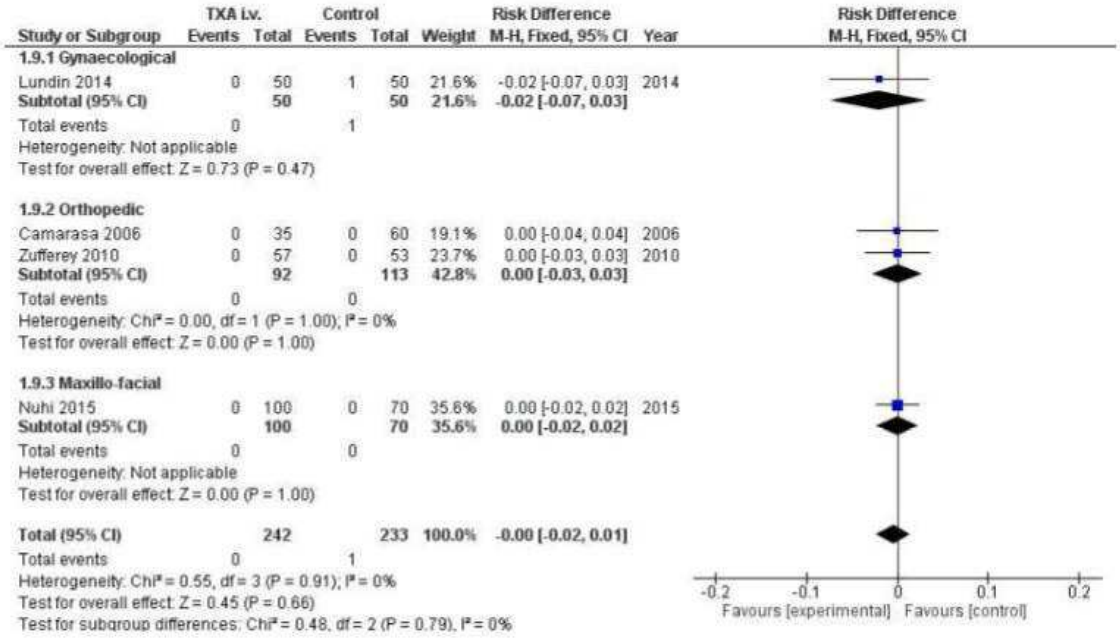
eFigure 14: Myocardial Infarction Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model



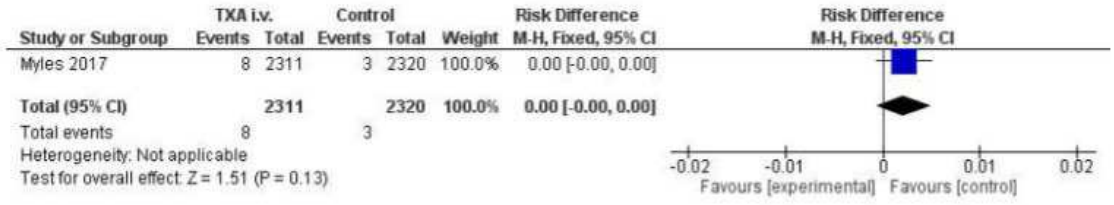
eFigure 15: Cerebral Ischaemia Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



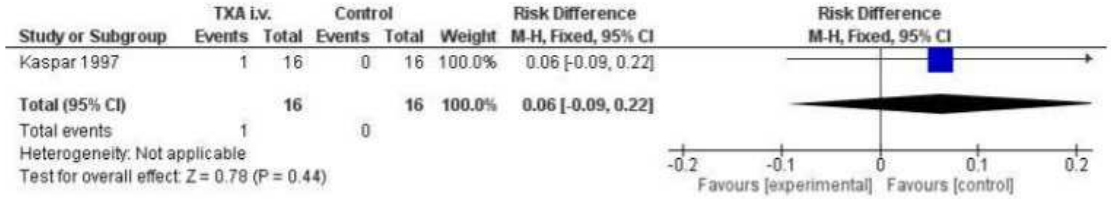
eFigure 16: Limb Ischaemia Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



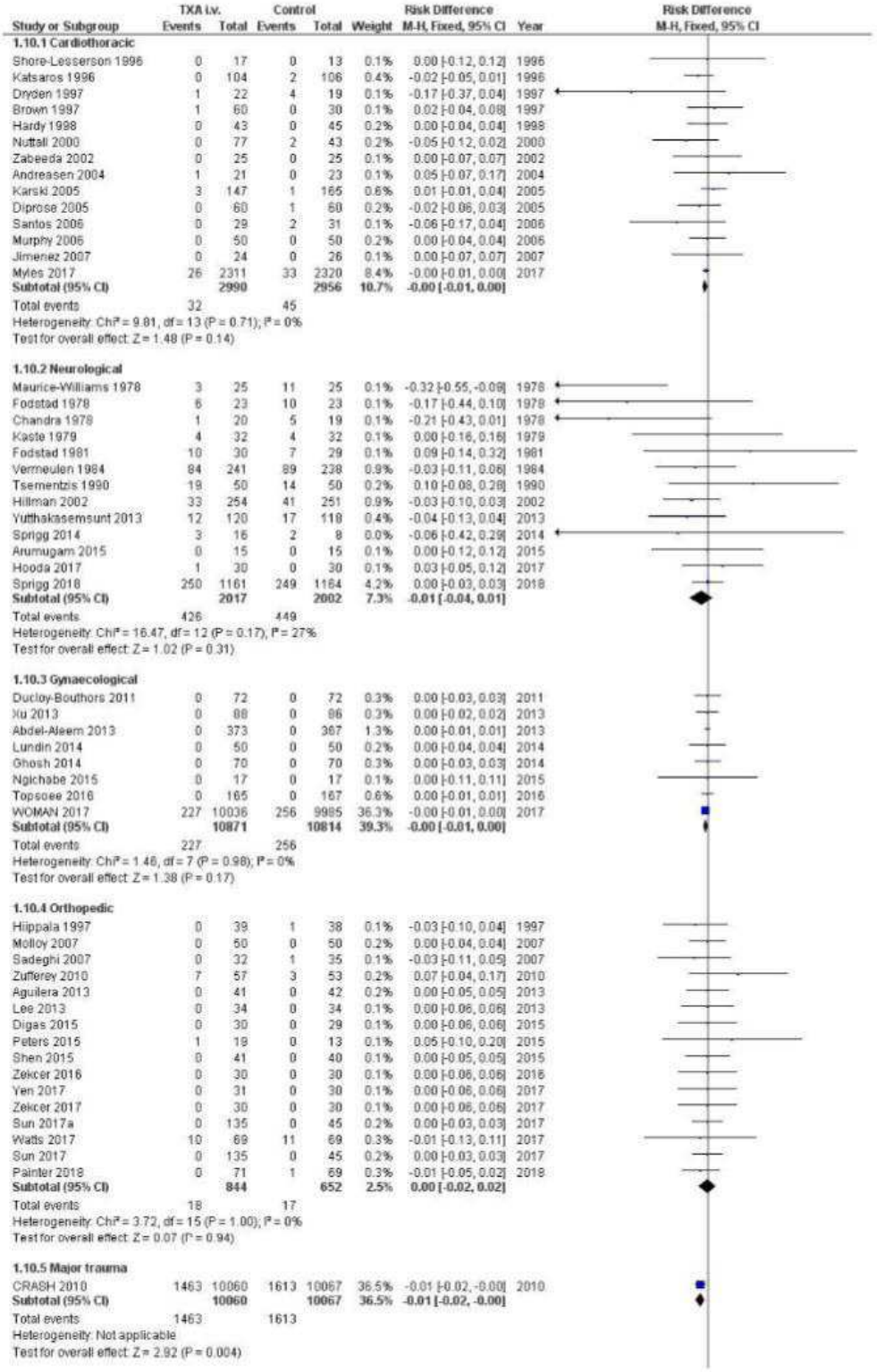
eFigure 17: Mesenteric Ischaemia Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model.



eFigure 18: Hepatic Artery Thrombosis Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



eFigure 19: Overall Mortality Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



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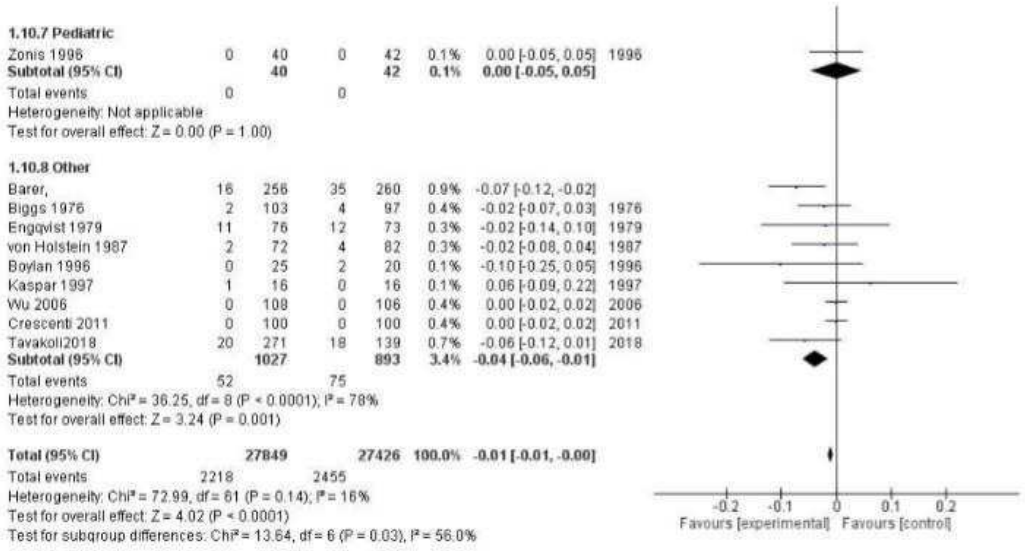
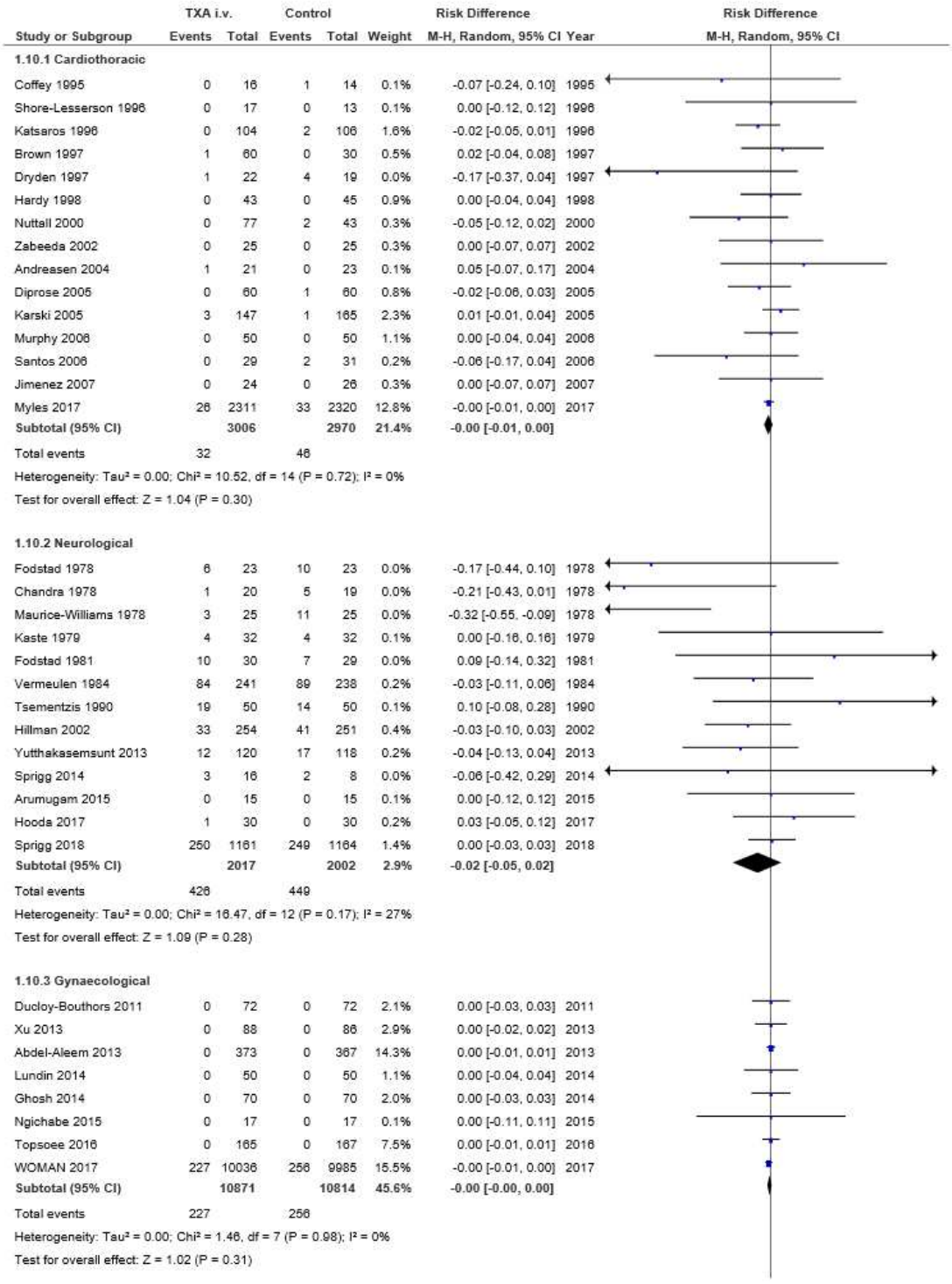


eFigure 20: Overall Mortality Rate in Patients receiving TXA compared to Control using the Random-Effects Model



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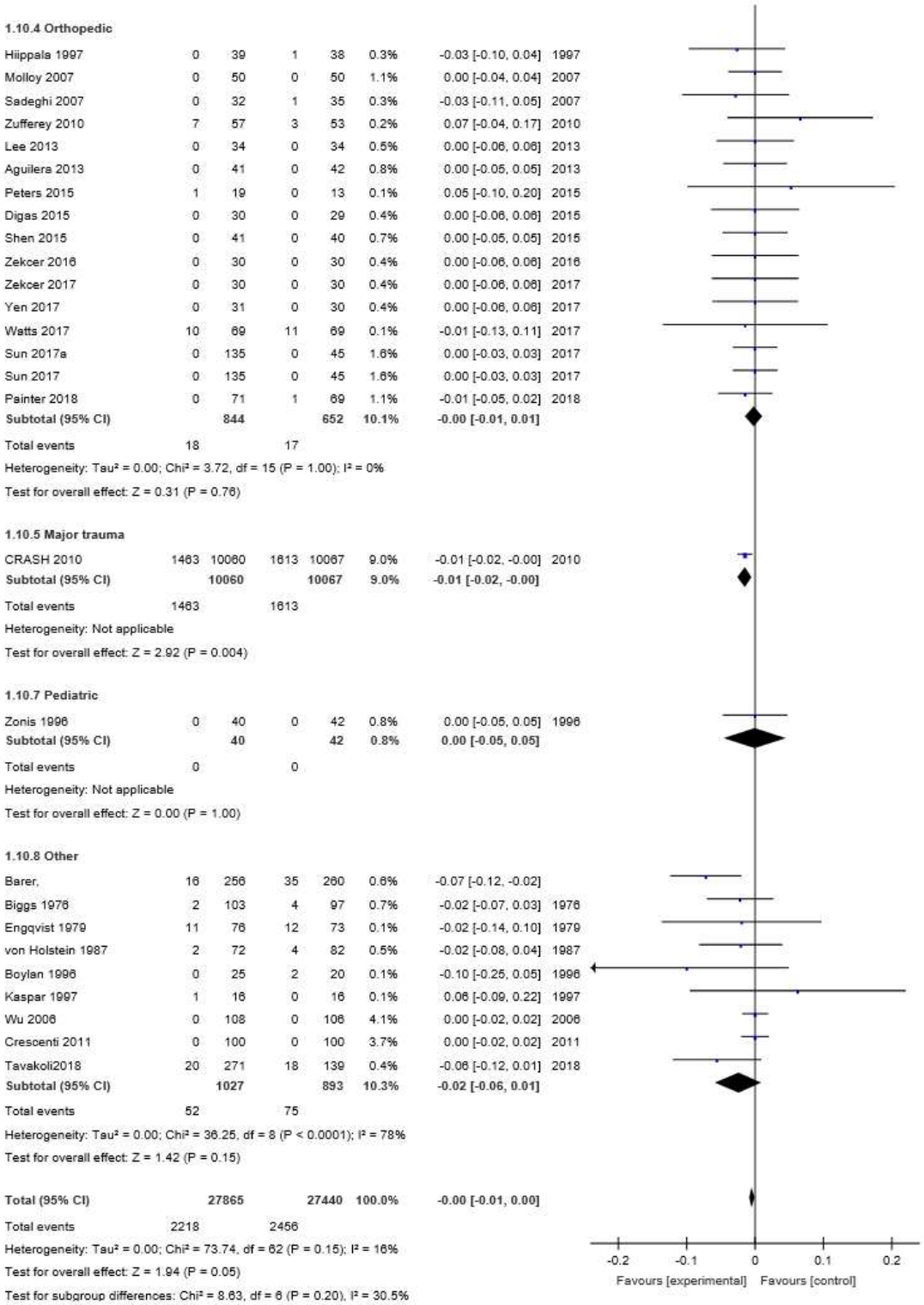
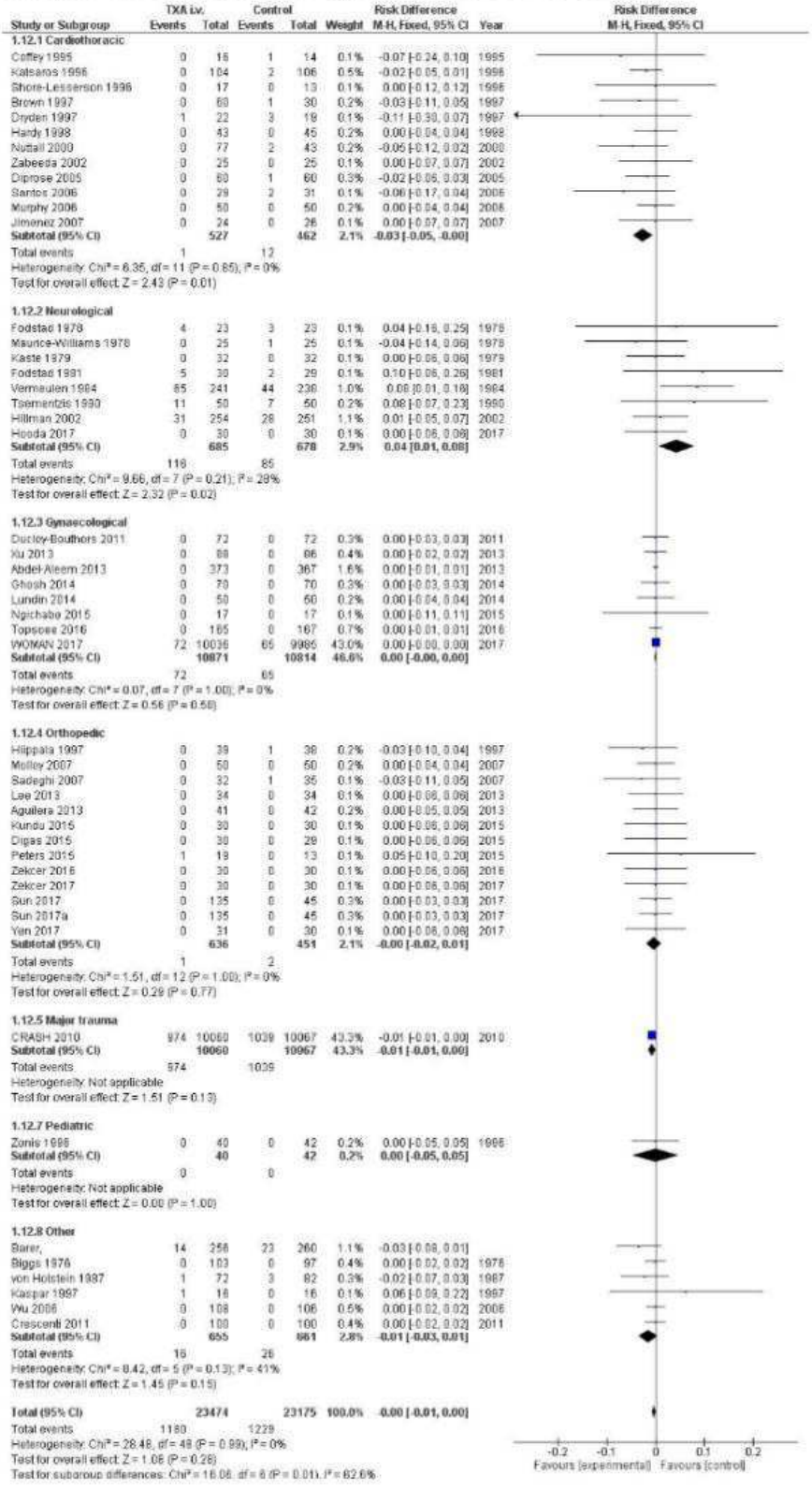
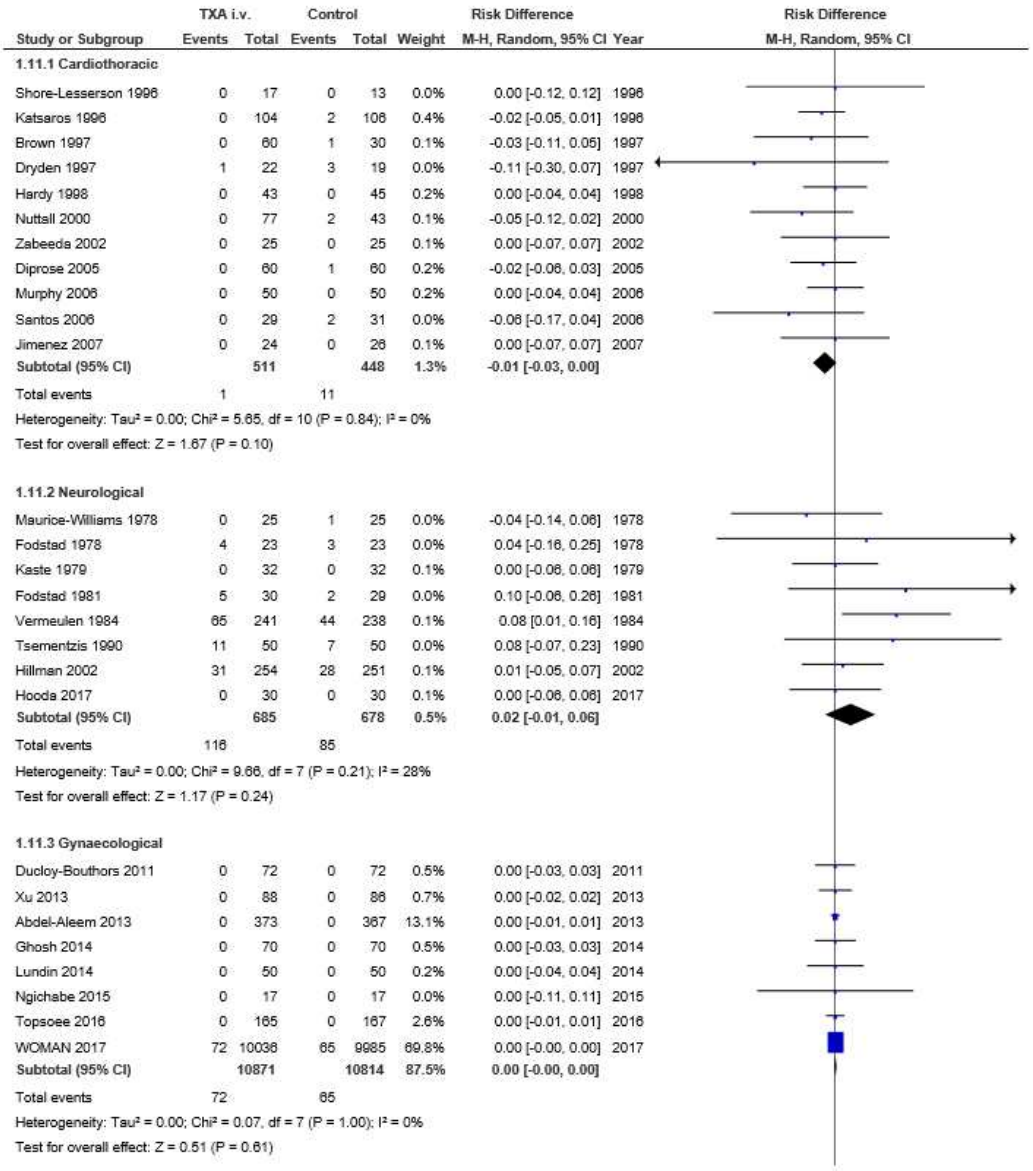


eFigure 21: Non-Bleeding associated Mortality Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model



eFigure 22: Non-Bleeding associated Mortality Rate in Patients receiving TXA compared to Control using the Random-Effects Model



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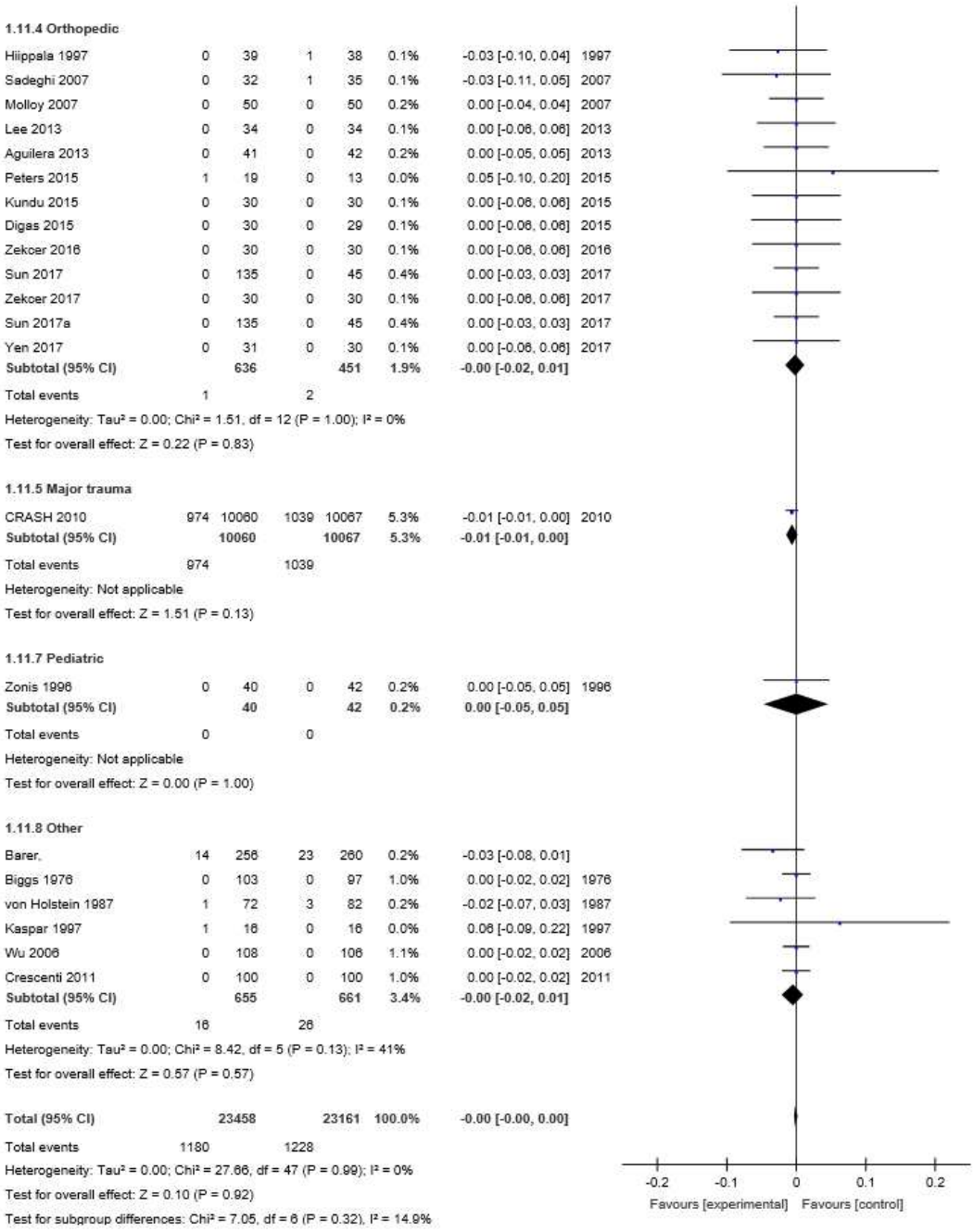
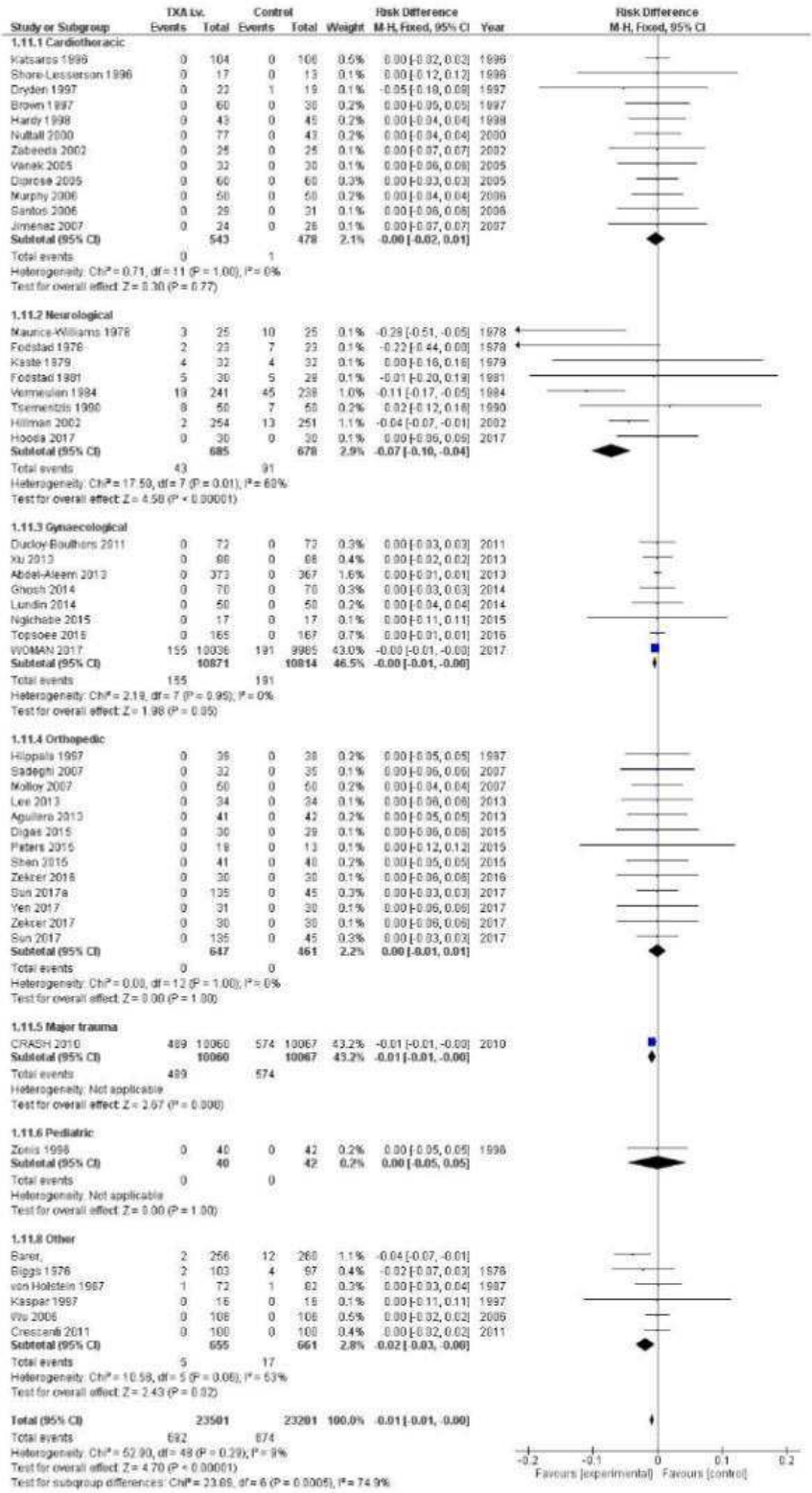
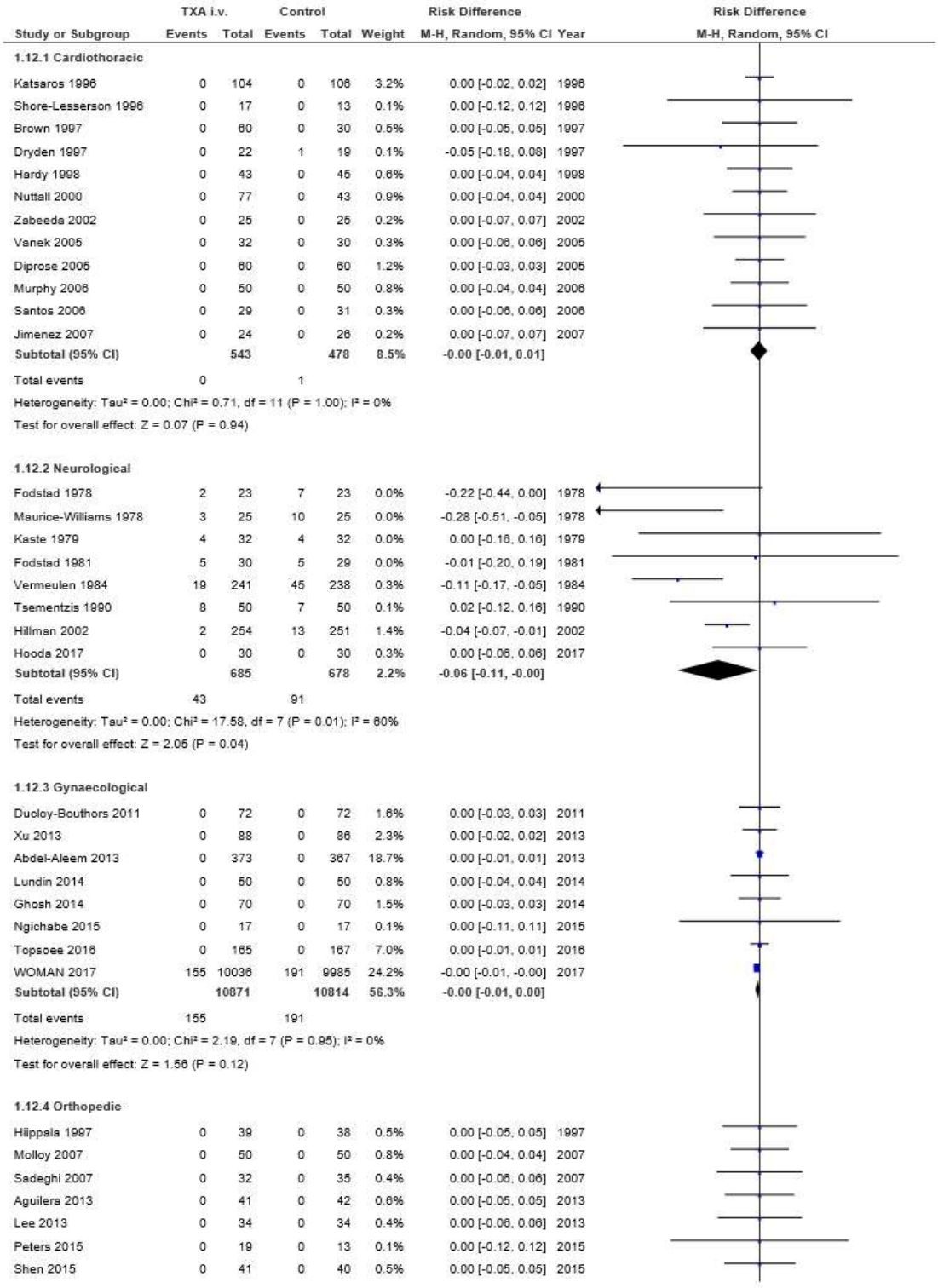


eFigure 23: Bleeding associated Mortality Rate in Patients receiving TXA compared to Control using the Fixed-Effect model



eFigure 24: Bleeding associated Mortality Rate in Patients receiving TXA compared to Control using the Random-Effects Model



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Digas 2015	0	30	0	29	0.3%	0.00 [-0.06, 0.06]	2015
Zekcer 2016	0	30	0	30	0.3%	0.00 [-0.06, 0.06]	2016
Yen 2017	0	31	0	30	0.3%	0.00 [-0.06, 0.06]	2017
Sun 2017	0	135	0	45	1.2%	0.00 [-0.03, 0.03]	2017
Sun 2017a	0	135	0	45	1.2%	0.00 [-0.03, 0.03]	2017
Zekcer 2017	0	30	0	30	0.3%	0.00 [-0.06, 0.06]	2017
Subtotal (95% CI)		647		461	6.9%	**0.00 [-0.01, 0.01]**	
Total events	0		0				

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 12 (P = 1.00); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)

1.12.5 Major trauma

CRASH 2010	489	10060	574	10067	16.2%	-0.01 [-0.01, -0.00]	2010
Subtotal (95% CI)		**10060**		**10067**	**16.2%**	**-0.01 [-0.01, -0.00]**	
Total events	489		574				

Heterogeneity: Not applicable

Test for overall effect: Z = 2.67 (P = 0.008)

1.12.6 Pediatric

Zonis 1996	0	40	0	42	0.6%	0.00 [-0.05, 0.05]	1996
Subtotal (95% CI)		**40**		**42**	**0.6%**	**0.00 [-0.05, 0.05]**	
Total events	0		0				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

1.12.8 Other

Barer,	2	256	12	260	1.5%	-0.04 [-0.07, -0.01]	
Biggs 1976	2	103	4	97	0.5%	-0.02 [-0.07, 0.03]	1976
von Holstein 1987	1	72	1	82	0.9%	0.00 [-0.03, 0.04]	1987
Kaspar 1997	0	16	0	16	0.1%	0.00 [-0.11, 0.11]	1997
Wu 2006	0	108	0	106	3.4%	0.00 [-0.02, 0.02]	2006
Crescenti 2011	0	100	0	100	3.0%	0.00 [-0.02, 0.02]	2011
Subtotal (95% CI)		655		661	9.4%	**-0.01 [-0.03, 0.01]**	
Total events	5		17				

Heterogeneity: Tau² = 0.00; Chi² = 10.58, df = 5 (P = 0.06); I² = 53%

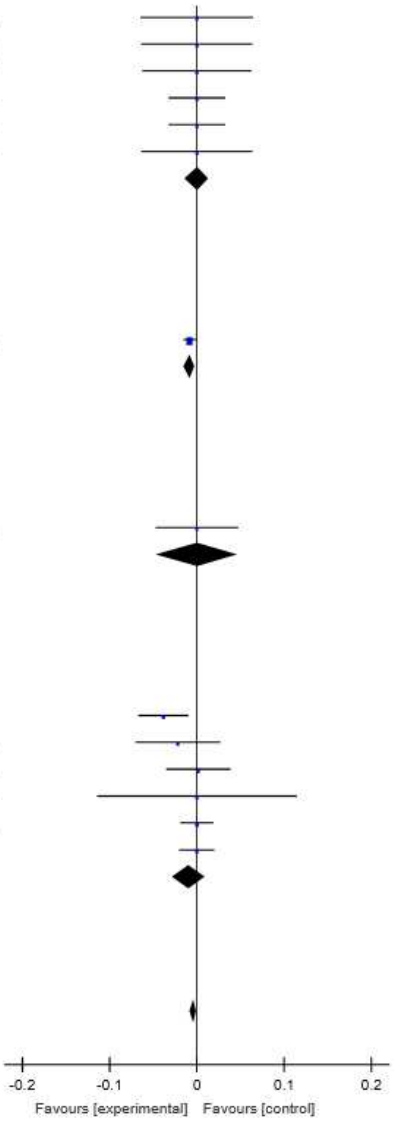
Test for overall effect: Z = 1.03 (P = 0.30)

Total (95% CI)		**23501**		**23201**	**100.0%**	**-0.00 [-0.01, -0.00]**	
Total events	692		874				

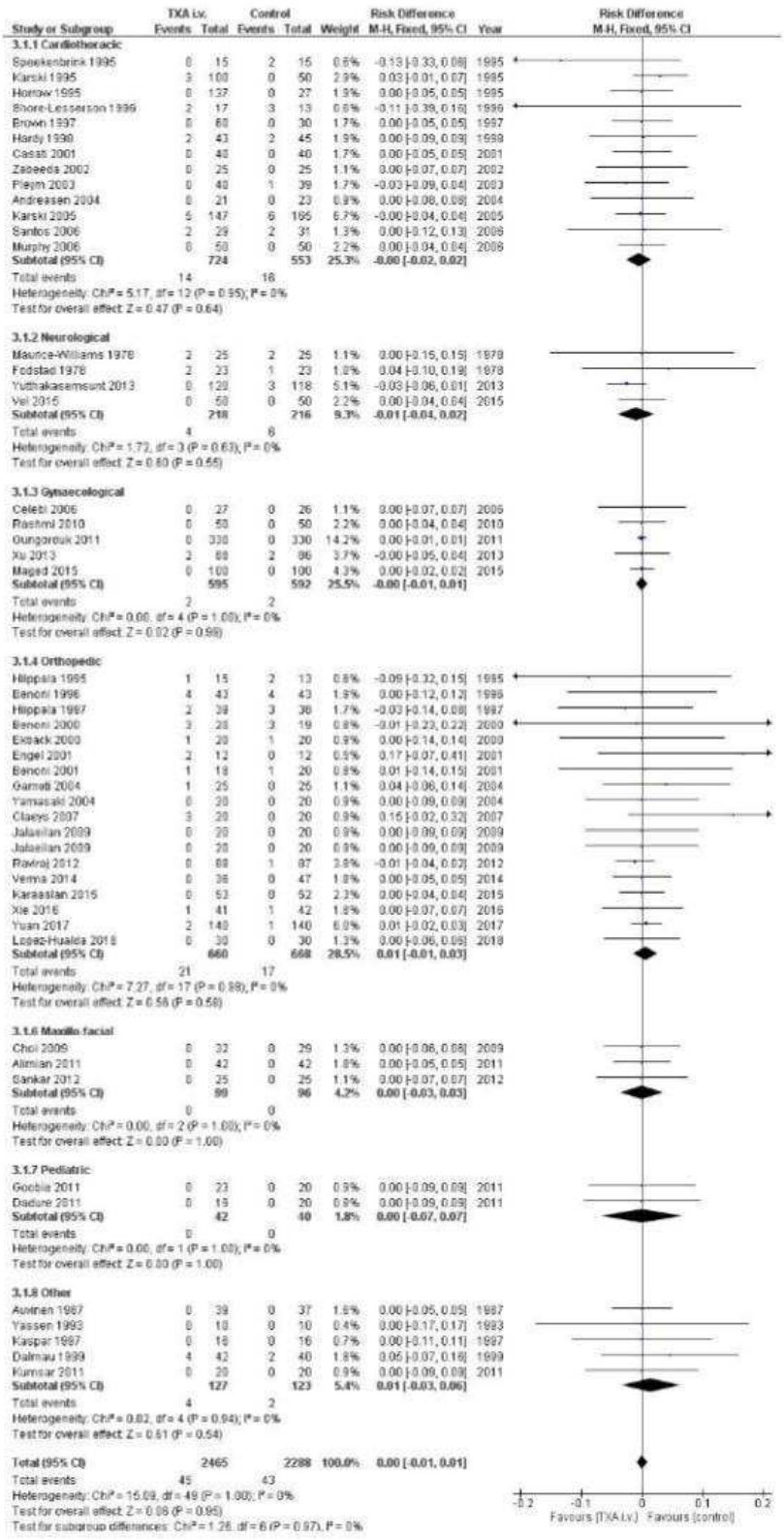
Heterogeneity: Tau² = 0.00; Chi² = 52.90, df = 48 (P = 0.29); I² = 9%

Test for overall effect: Z = 2.26 (P = 0.02)

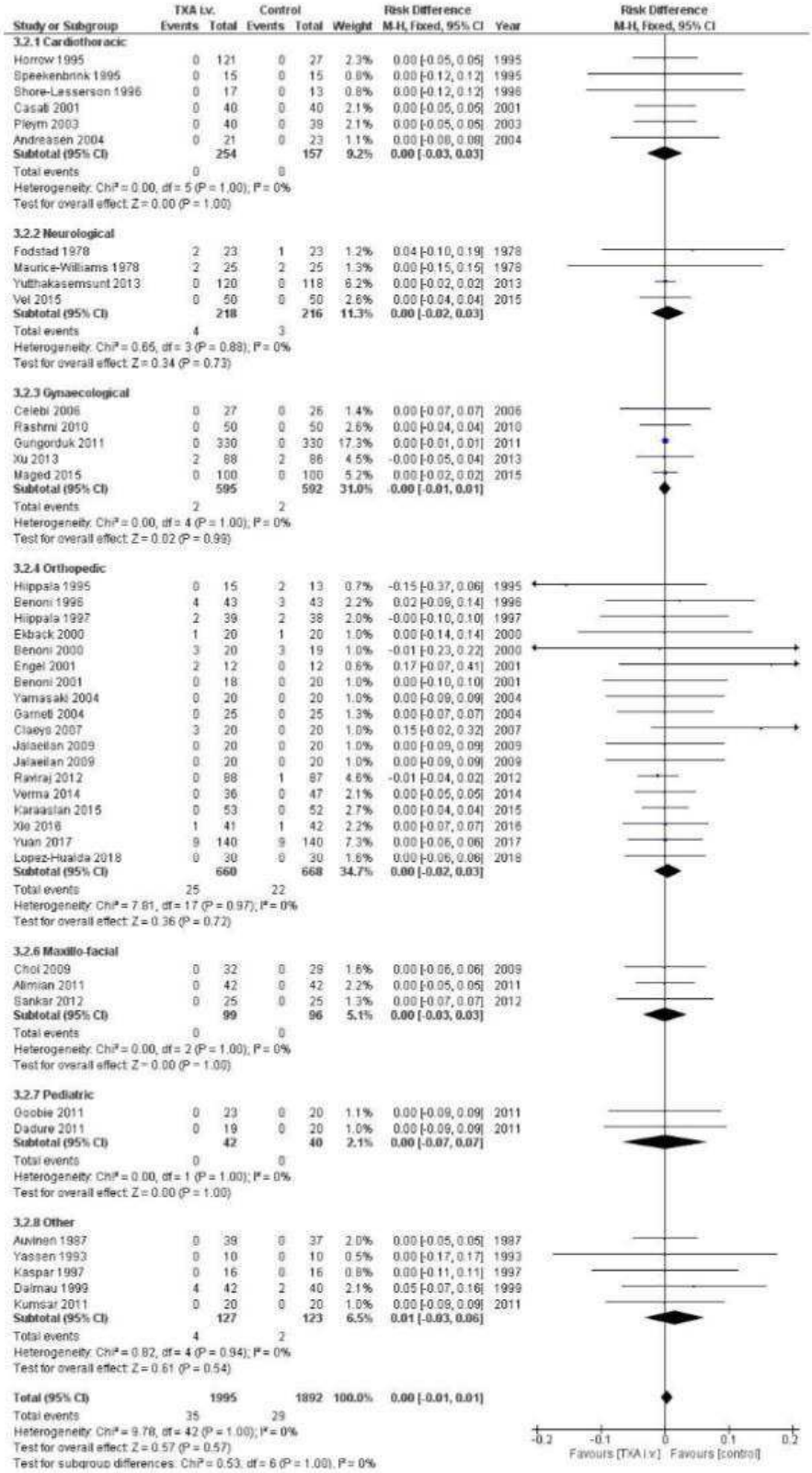
Test for subgroup differences: Chi² = 7.81, df = 6 (P = 0.25), I² = 23.2%



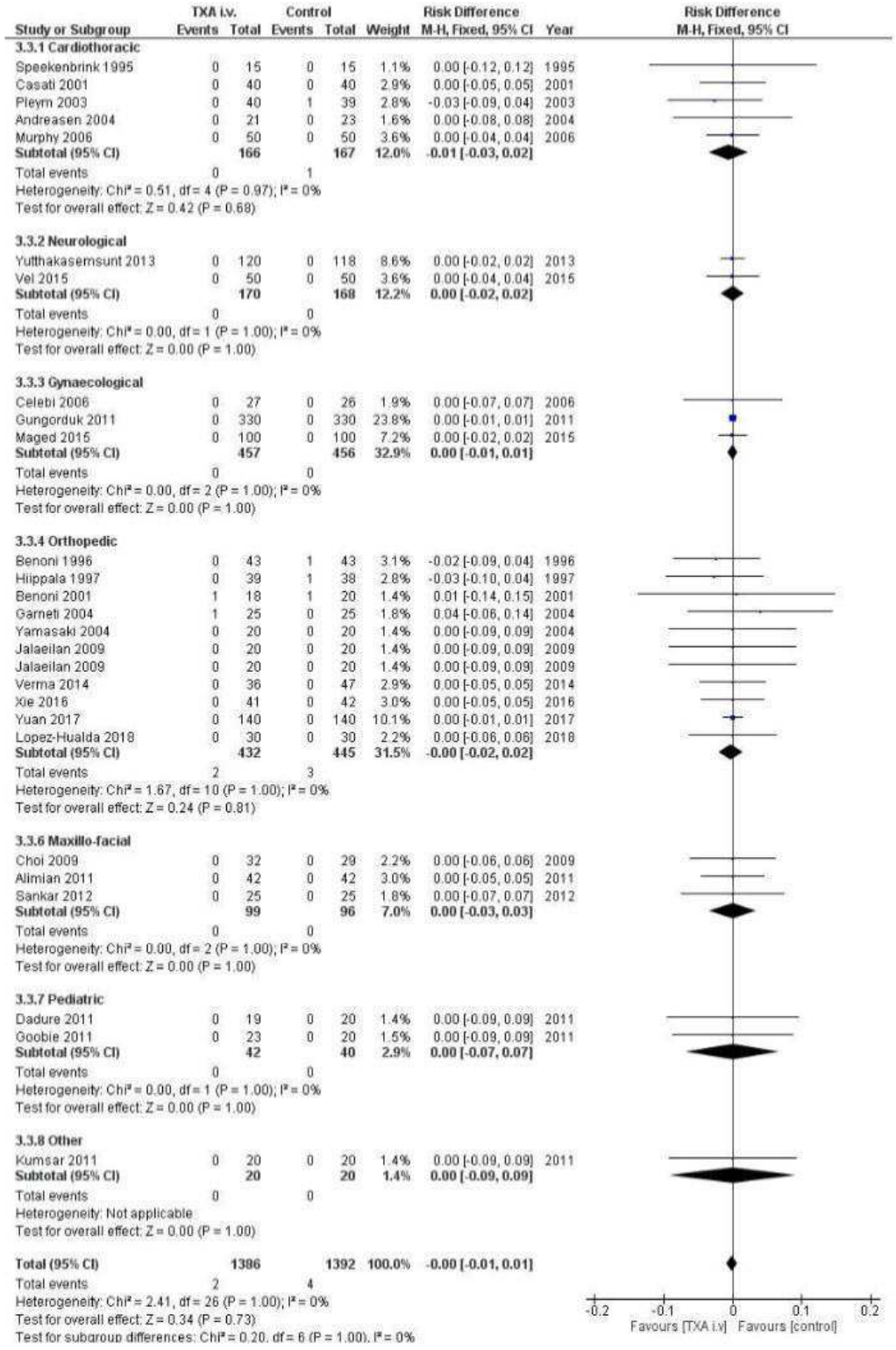
eFigure 25: Total Thromboembolic Event Rate in High Risk Patients receiving TXA compared to Control using the Fixed-Effect Model



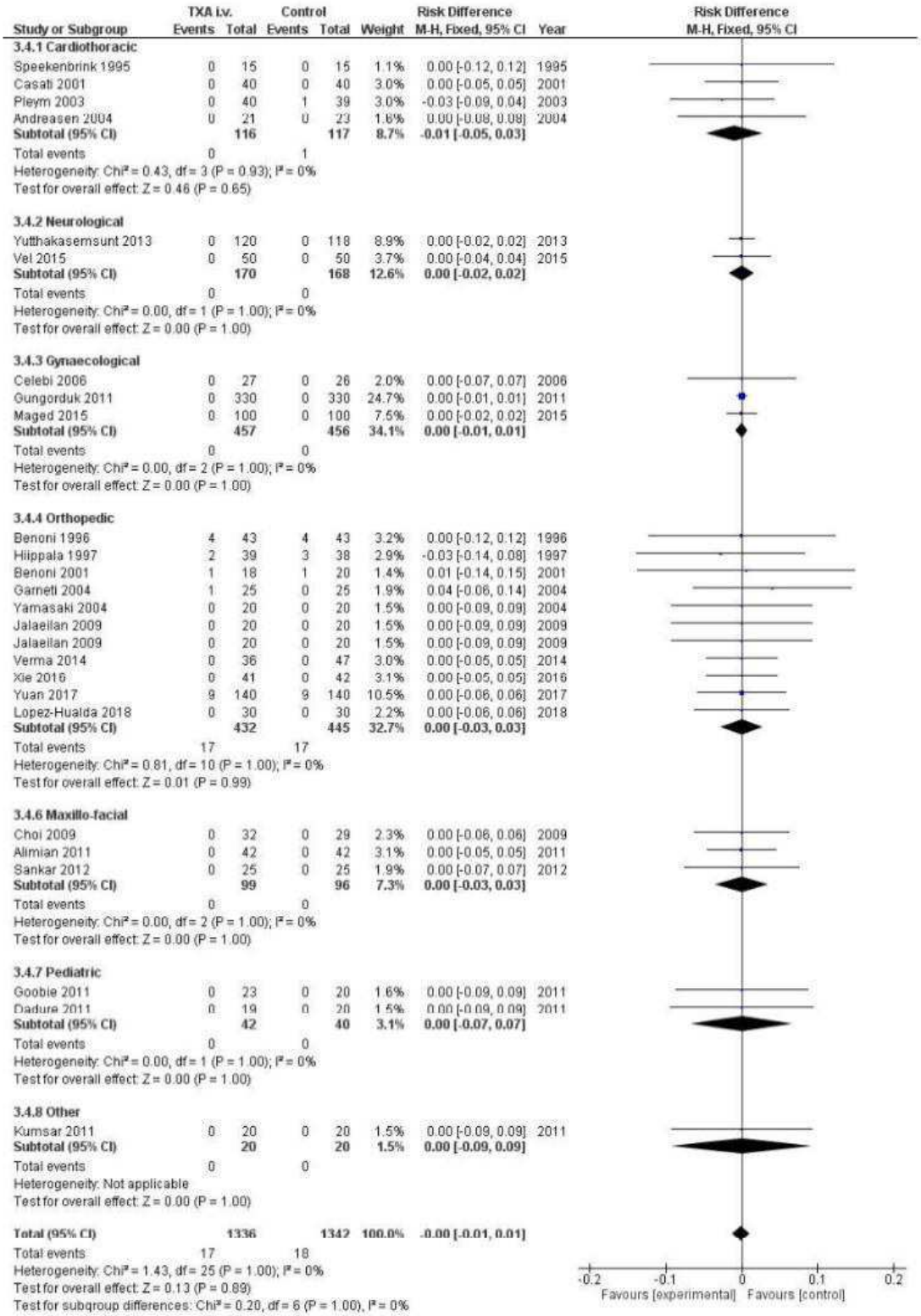
eFigure 26: Venous Thrombosis Event Rate in High Risk Patients receiving TXA compared to Control using the Fixed-Effect Model



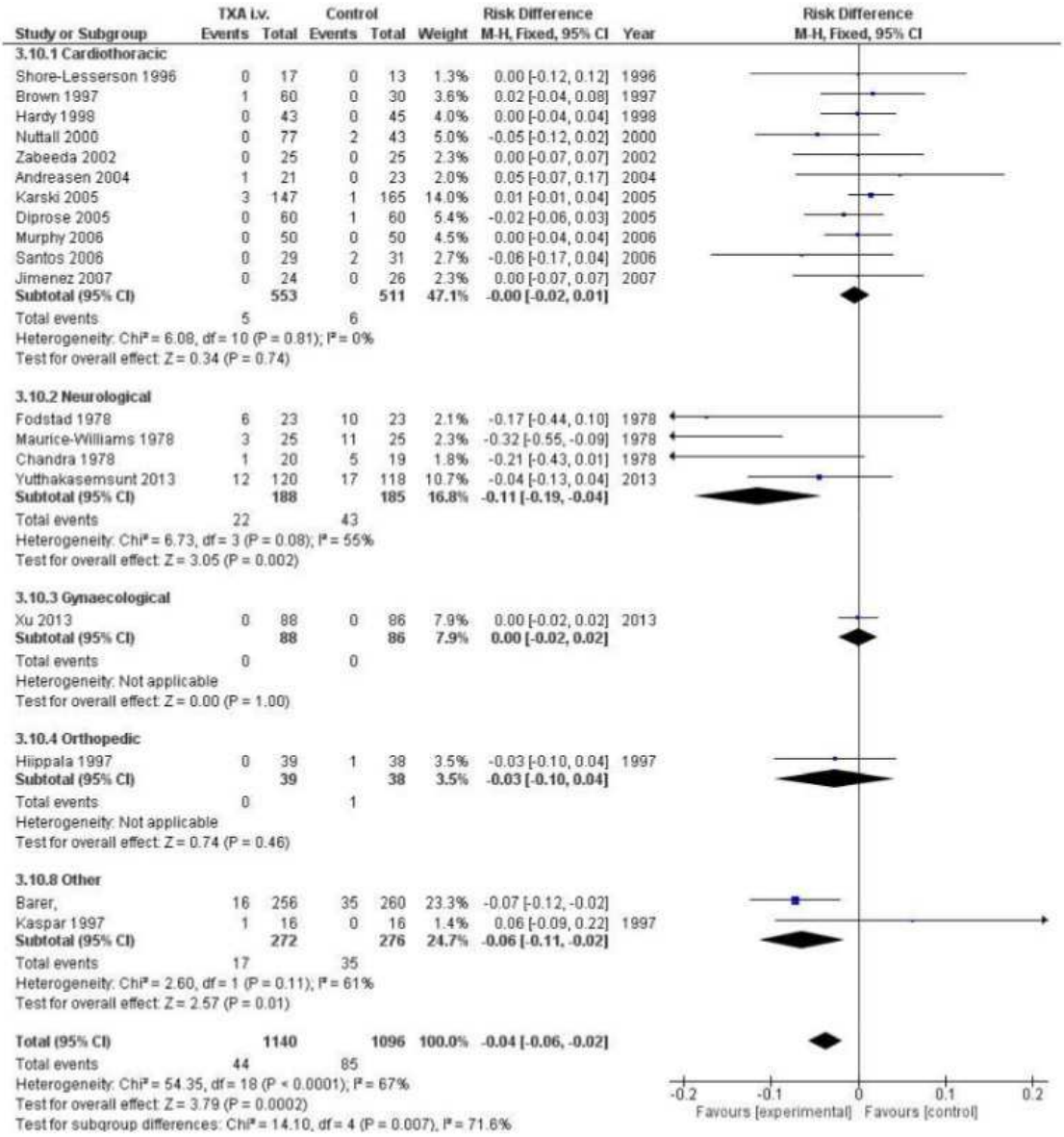
eFigure 27: Pulmonary Embolism Event Rate in High Risk Patients receiving TXA compared to Control using the Fixed-Effect Model



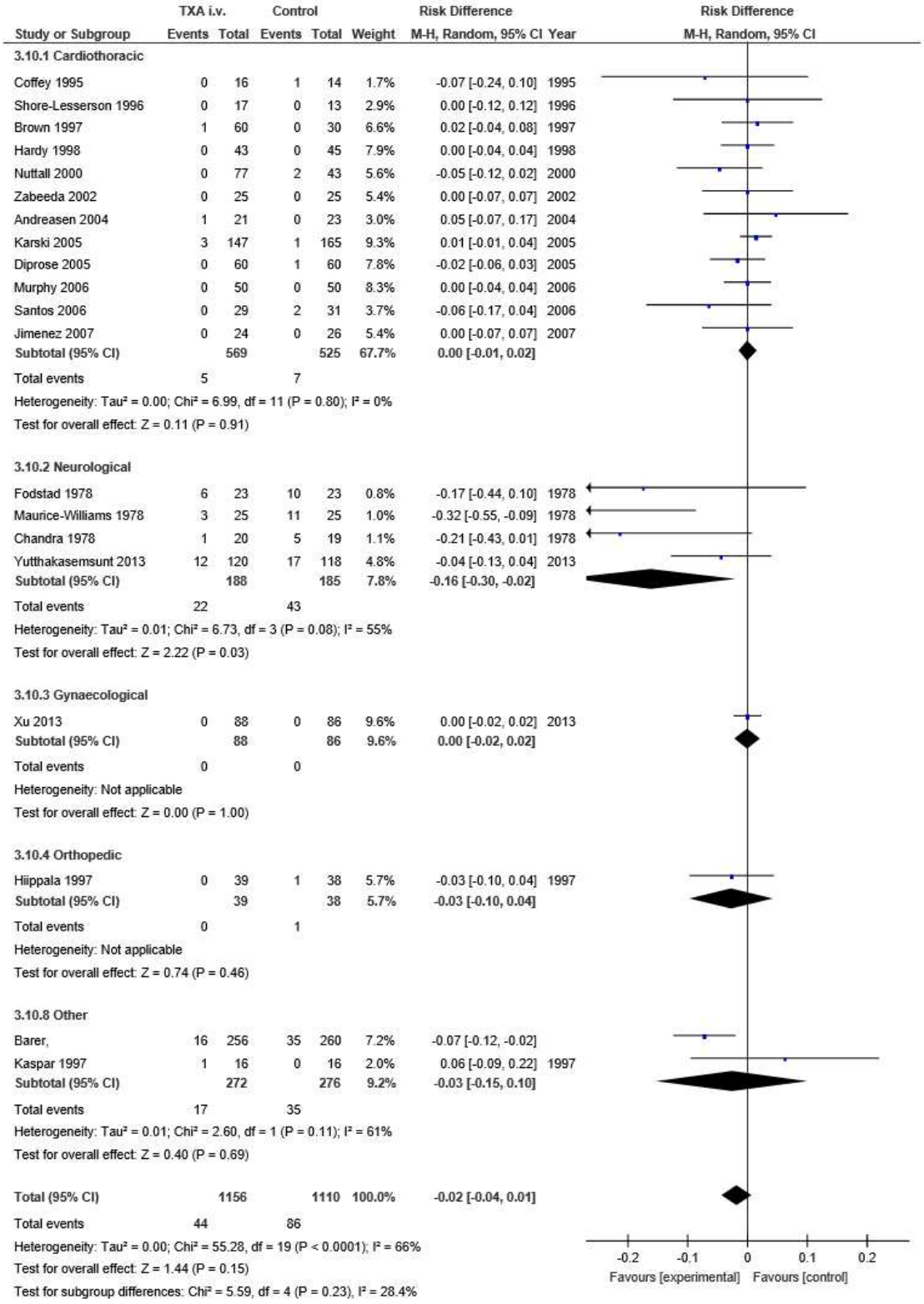
eFigure 28: Venous Thromboembolic Event Rate in High Risk Patients receiving TXA compared to Control using the Fixed-Effect Model



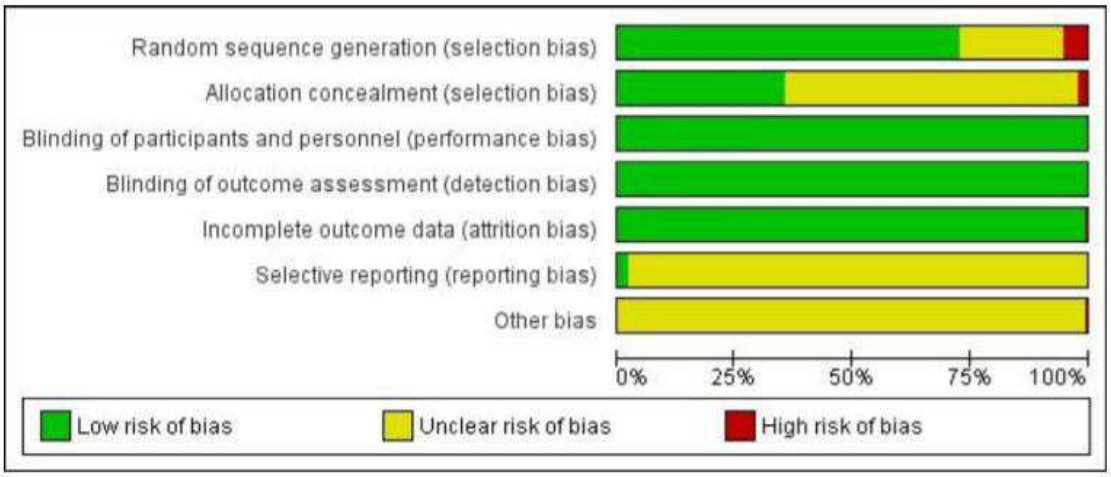
eFigure 29: Overall Mortality Rate in High Risk Patients receiving TXA compared to Control using the Fixed-Effect Model



eFigure 30: Overall Mortality Rate in High Risk Patients receiving TXA compared to Control using the Random-Effects Model



eFigure 31: Risk of Bias Summary



Review authors' judgments about each risk of bias items presented as percentages across all included studies. 192 studies are included in this meta-analysis.

eFigure 32: Risk of bias Graph

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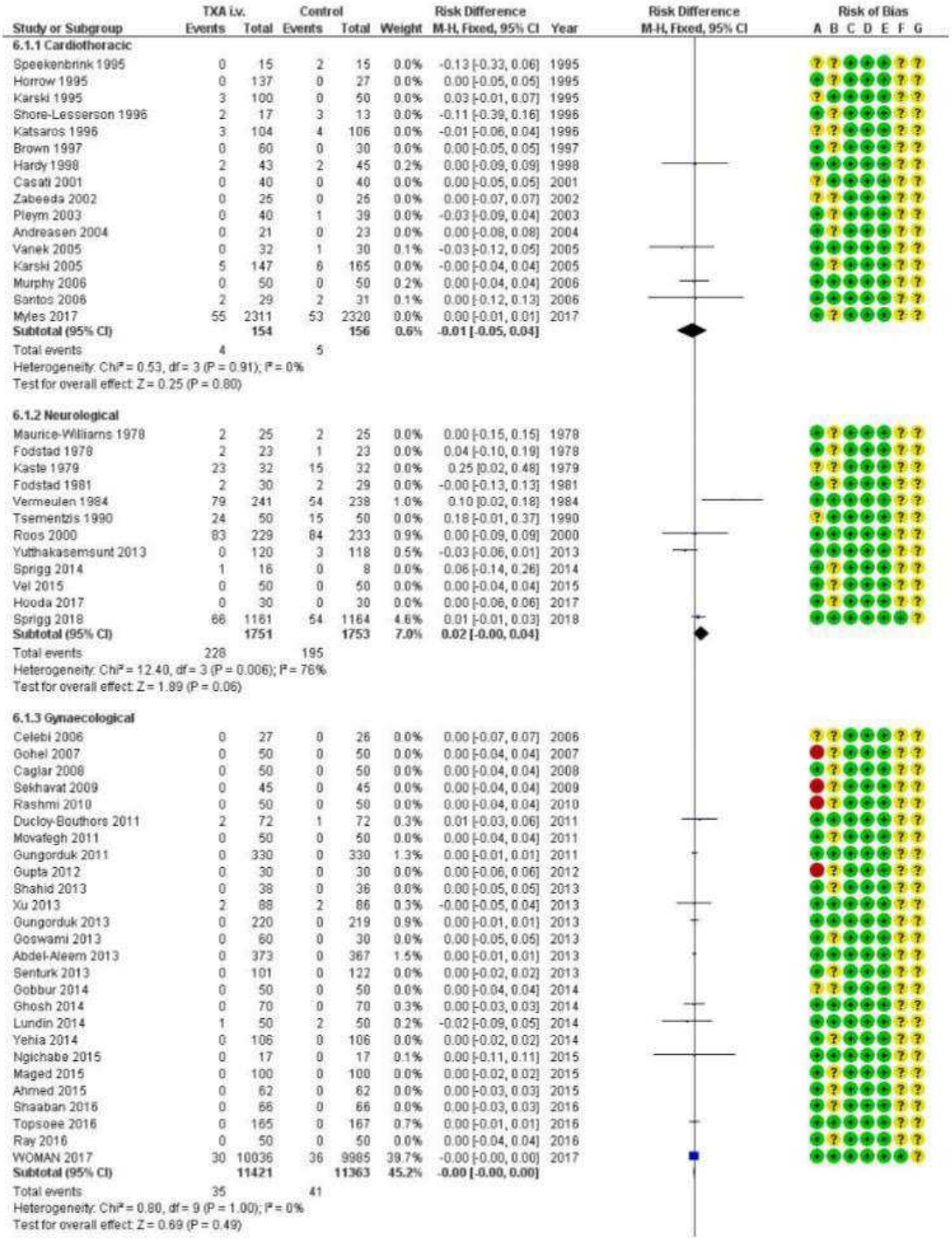
eFigure 33: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control of Studies Judged with Low Selection Bias using the Fixed-Effect Model



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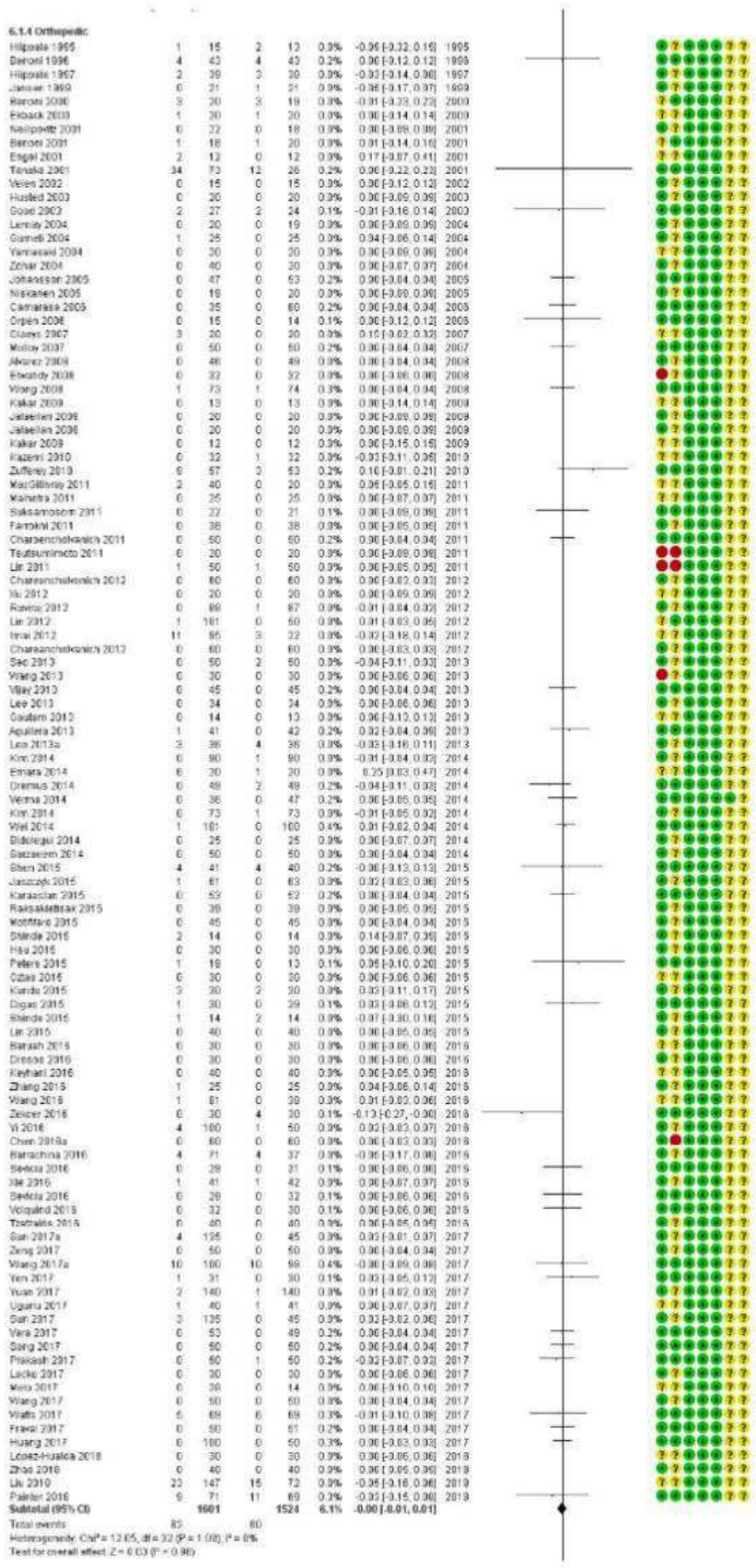

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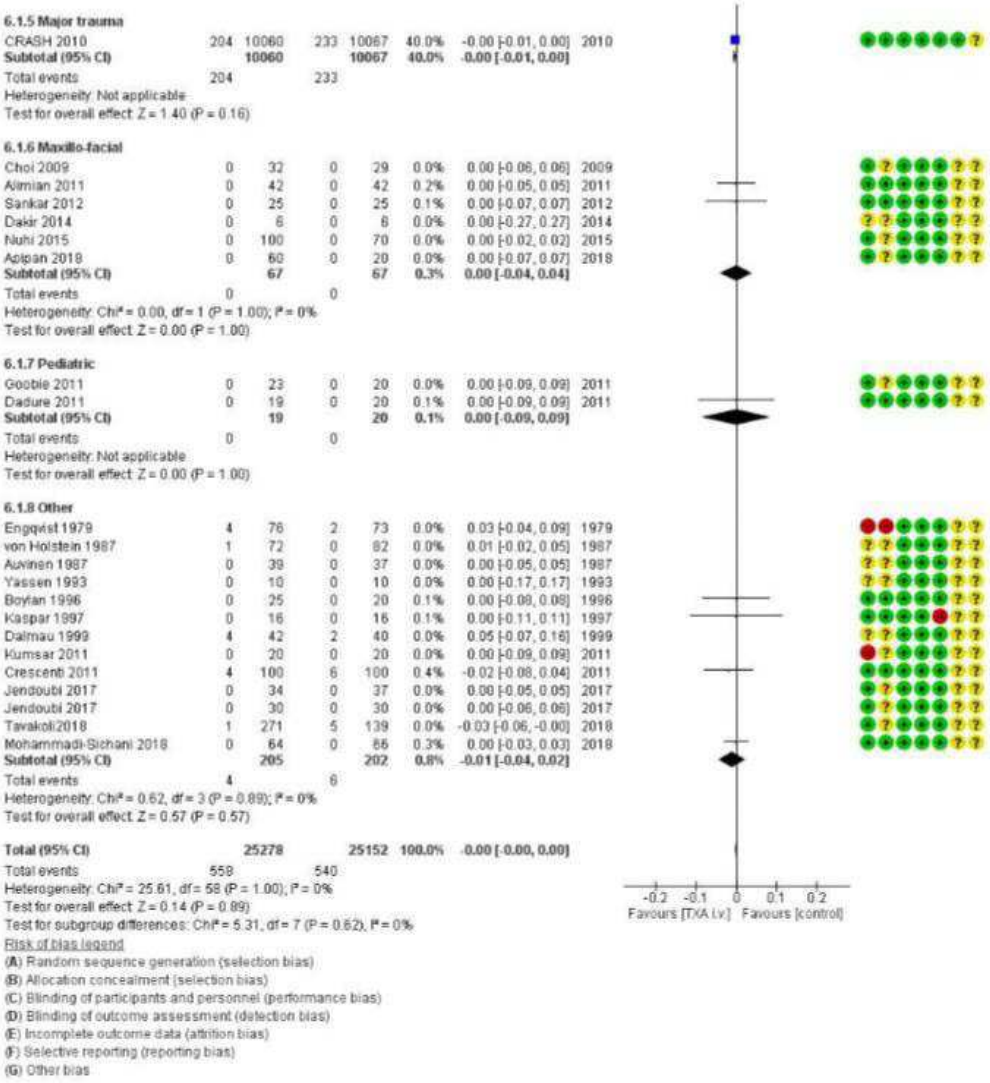
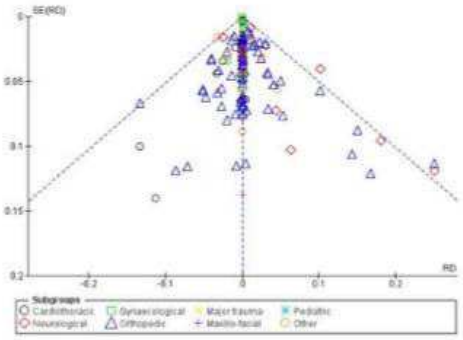
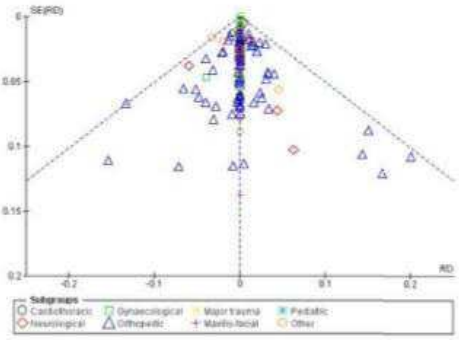


eFigure 34: Funnel Plots for Total Thromboembolic Event, Venous Thrombosis, Cerebral Infarction, and Bleeding Mortality

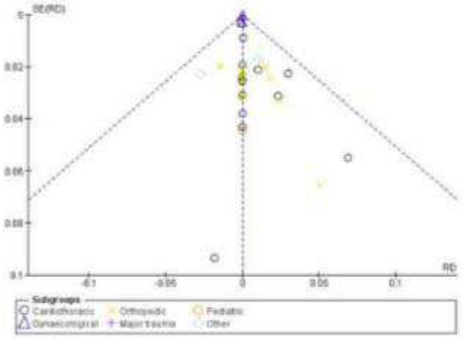
Total Thromboembolic Events



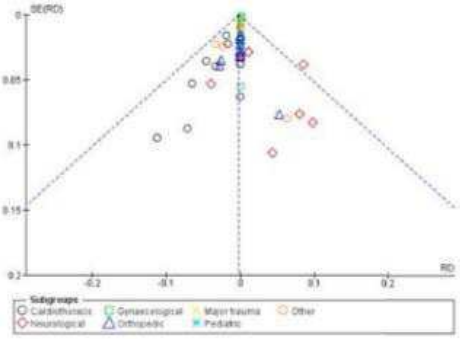
Venous Thrombosis



Cerebral Infarction or Ischaemia



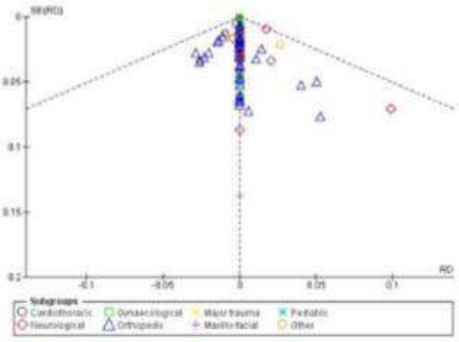
Non-Bleeding Mortality



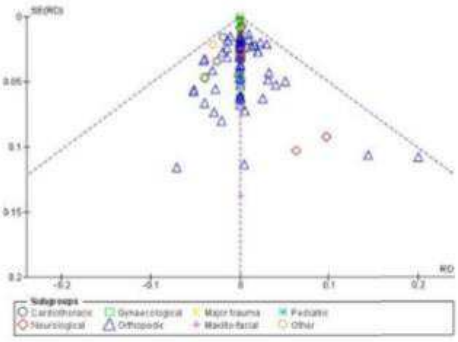
Funnel plots of intravenous tranexamic acid compared with control showing distribution of publicated studies for total TE, VT, CI and non-bleeding mortality.

eFigure 35: Funnel Plots for Pulmonary Embolism, Venous Thromboembolic Events, and Myocardial Infarction

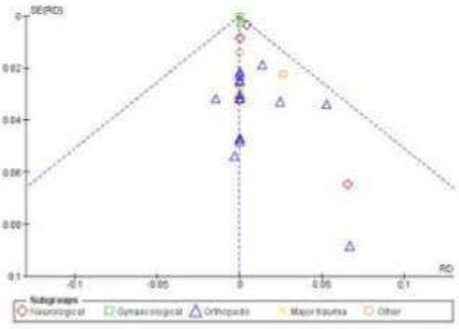
Pulmonary Embolism



Venous Thromboembolic Events

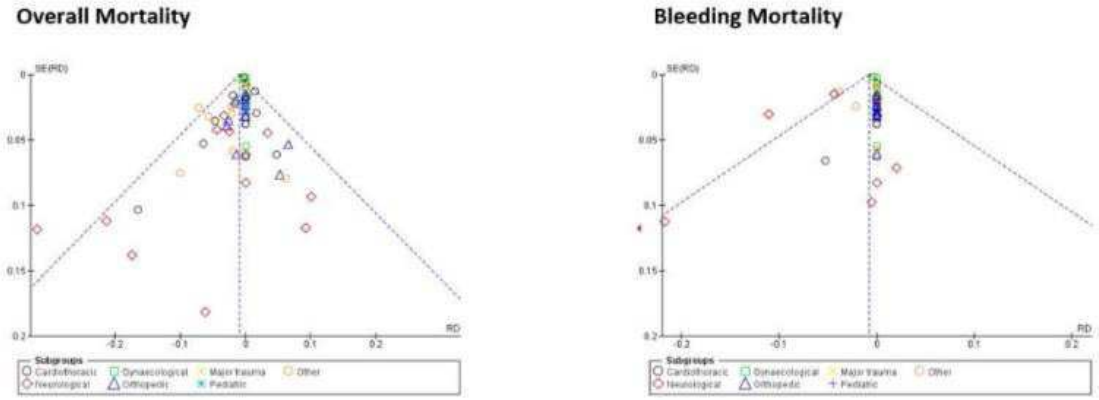


Myocardial Infarction or Ischaemia



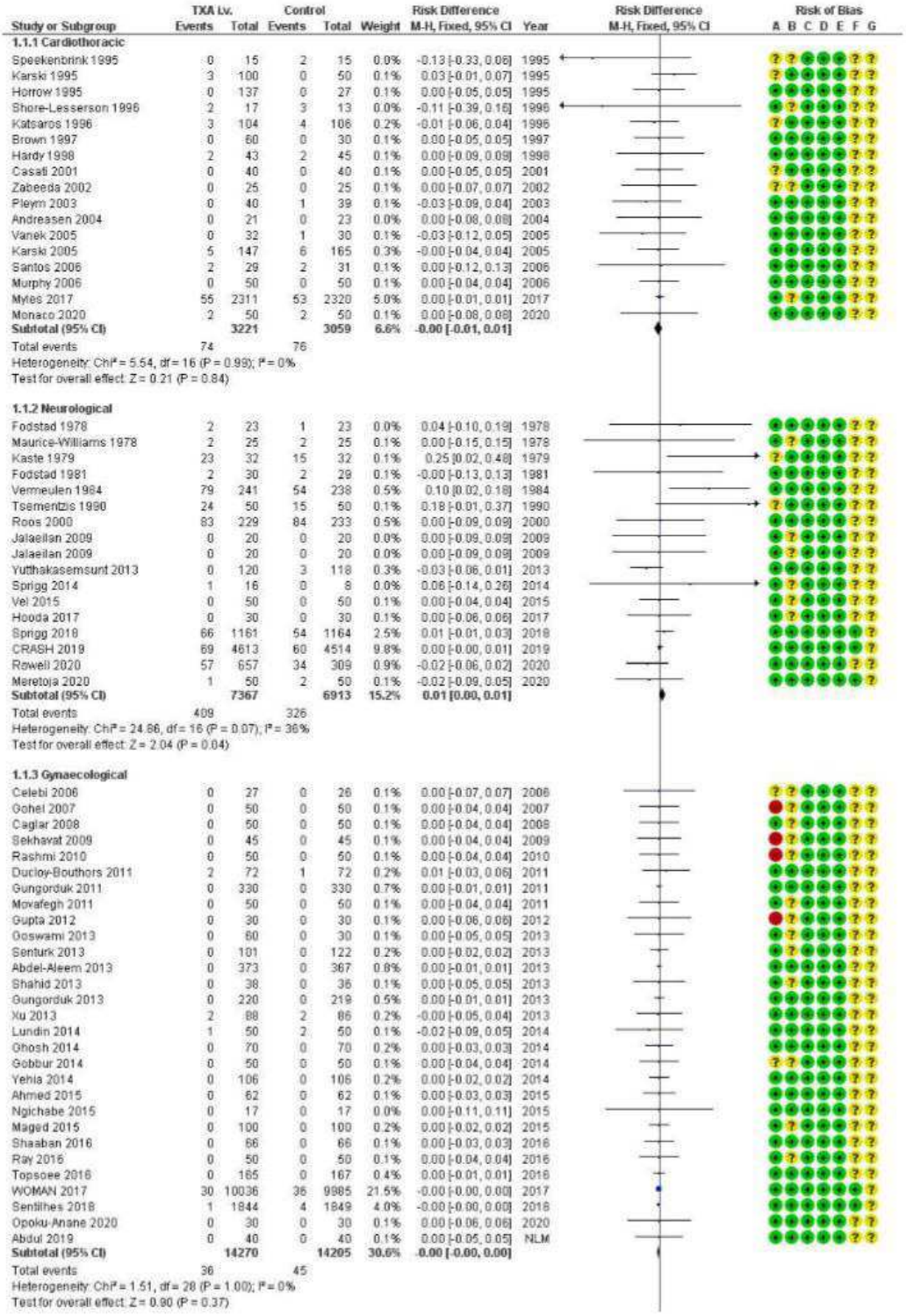
Funnel plots of intravenous tranexamic acid compared with control showing distribution of publicated studies for PE, VTE, and MI.

eFigure 36: Funnel Plots for Overall and Bleeding associated Mortality



Funnel plots of intravenous tranexamic acid compared with control showing distribution of publicated studies for overall and bleeding mortality.

eFigure 37: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model of updated Meta-Analysis



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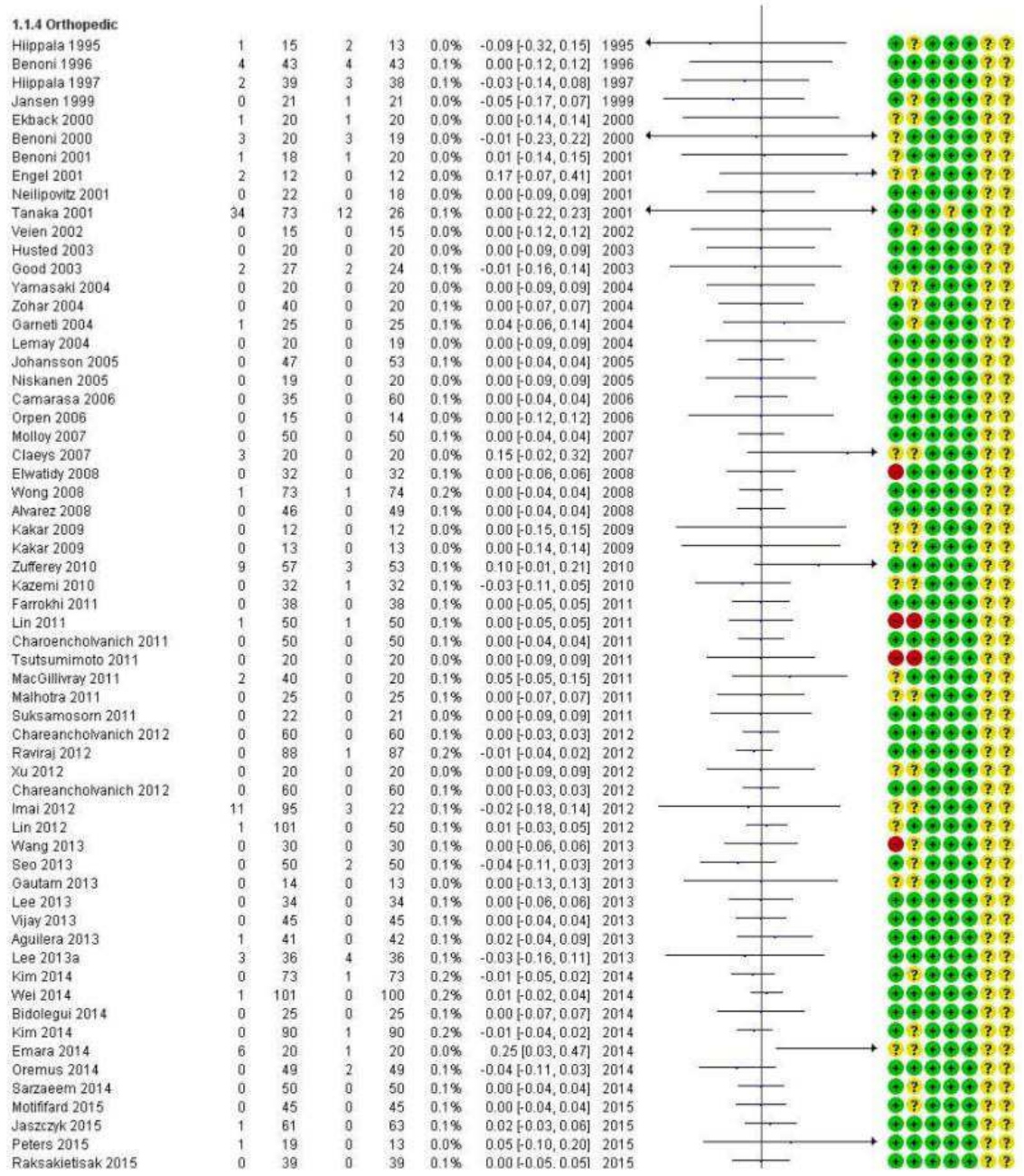

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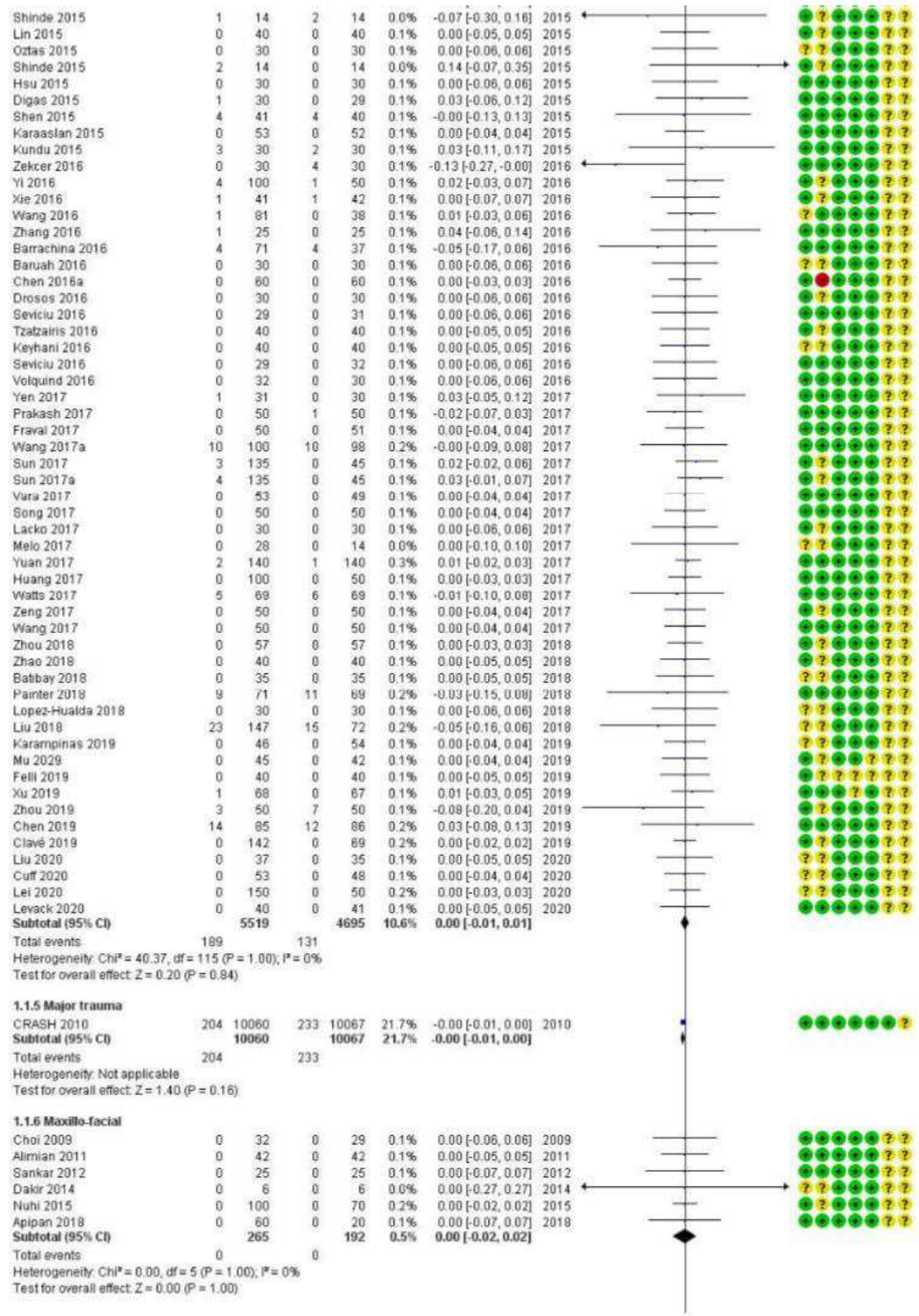

Shinde 2015	1	14	2	14	0.0%	-0.07 [-0.30, 0.16]	2015
Lin 2015	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2015
Oztas 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Shinde 2015	2	14	0	14	0.0%	0.14 [-0.07, 0.35]	2015
Hsu 2015	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2015
Digas 2015	1	30	0	29	0.1%	0.03 [-0.06, 0.12]	2015
Shen 2015	4	41	4	40	0.1%	-0.00 [-0.13, 0.13]	2015
Karaaslan 2015	0	53	0	52	0.1%	0.00 [-0.04, 0.04]	2015
Kundu 2015	3	30	2	30	0.1%	0.03 [-0.11, 0.17]	2015
Zekcer 2016	0	30	4	30	0.1%	-0.13 [-0.27, -0.00]	2016
Yi 2016	4	100	1	50	0.1%	0.02 [-0.03, 0.07]	2016
Xie 2016	1	41	1	42	0.1%	0.00 [-0.07, 0.07]	2016
Wang 2016	1	81	0	38	0.1%	0.01 [-0.03, 0.06]	2016
Zhang 2016	1	25	0	25	0.1%	0.04 [-0.06, 0.14]	2016
Barrachina 2016	4	71	4	37	0.1%	-0.05 [-0.17, 0.06]	2016
Baruah 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Chen 2016a	0	60	0	60	0.1%	0.00 [-0.03, 0.03]	2016
Drosos 2016	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Seviciu 2016	0	29	0	31	0.1%	0.00 [-0.06, 0.06]	2016
Tzatzairis 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Keyhani 2016	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2016
Seviciu 2016	0	29	0	32	0.1%	0.00 [-0.06, 0.06]	2016
Volquind 2016	0	32	0	30	0.1%	0.00 [-0.06, 0.06]	2016
Yen 2017	1	31	0	30	0.1%	0.03 [-0.05, 0.12]	2017
Prakash 2017	0	50	1	50	0.1%	-0.02 [-0.07, 0.03]	2017
Fraval 2017	0	50	0	51	0.1%	0.00 [-0.04, 0.04]	2017
Wang 2017a	10	100	10	98	0.2%	-0.00 [-0.09, 0.08]	2017
Sun 2017	3	135	0	45	0.1%	0.02 [-0.02, 0.06]	2017
Sun 2017a	4	135	0	45	0.1%	0.03 [-0.01, 0.07]	2017
Vara 2017	0	53	0	49	0.1%	0.00 [-0.04, 0.04]	2017
Song 2017	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2017
Lacko 2017	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2017
Melo 2017	0	28	0	14	0.0%	0.00 [-0.10, 0.10]	2017
Yuan 2017	2	140	1	140	0.3%	0.01 [-0.02, 0.03]	2017
Huang 2017	0	100	0	50	0.1%	0.00 [-0.03, 0.03]	2017
Watts 2017	5	69	6	69	0.1%	-0.01 [-0.10, 0.08]	2017
Zeng 2017	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2017
Wang 2017	0	50	0	50	0.1%	0.00 [-0.04, 0.04]	2017
Zhou 2018	0	57	0	57	0.1%	0.00 [-0.03, 0.03]	2018
Zhao 2018	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2018
Batibay 2018	0	35	0	35	0.1%	0.00 [-0.05, 0.05]	2018
Painter 2018	9	71	11	69	0.2%	-0.03 [-0.15, 0.08]	2018
Lopez-Hualda 2018	0	30	0	30	0.1%	0.00 [-0.06, 0.06]	2018
Liu 2018	23	147	15	72	0.2%	-0.05 [-0.16, 0.06]	2018
Karampinas 2019	0	46	0	54	0.1%	0.00 [-0.04, 0.04]	2019
Mu 2029	0	45	0	42	0.1%	0.00 [-0.04, 0.04]	2019
Felli 2019	0	40	0	40	0.1%	0.00 [-0.05, 0.05]	2019
Xu 2019	1	68	0	67	0.1%	0.01 [-0.03, 0.05]	2019
Zhou 2019	3	50	7	50	0.1%	-0.08 [-0.20, 0.04]	2019
Chen 2019	14	85	12	86	0.2%	0.03 [-0.08, 0.13]	2019
Clavé 2019	0	142	0	69	0.2%	0.00 [-0.02, 0.02]	2019
Liu 2020	0	37	0	35	0.1%	0.00 [-0.05, 0.05]	2020
Cuff 2020	0	53	0	48	0.1%	0.00 [-0.04, 0.04]	2020
Lei 2020	0	150	0	50	0.2%	0.00 [-0.03, 0.03]	2020
Levack 2020	0	40	0	41	0.1%	0.00 [-0.05, 0.05]	2020
Subtotal (95% CI)		**5519**		**4695**	**10.6%**	**0.00 [-0.01, 0.01]**	
Total events	189		131				

Heterogeneity: Chi² = 40.37, df = 115 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

1.1.5 Major trauma

CRASH 2010	204	10060	233	10067	21.7%	-0.00 [-0.01, 0.00]	2010
Subtotal (95% CI)		**10060**		**10067**	**21.7%**	**-0.00 [-0.01, 0.00]**	
Total events	204		233				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)

1.1.6 Maxillo-facial

Choi 2009	0	32	0	29	0.1%	0.00 [-0.06, 0.06]	2009
Alimian 2011	0	42	0	42	0.1%	0.00 [-0.05, 0.05]	2011
Sankar 2012	0	25	0	25	0.1%	0.00 [-0.07, 0.07]	2012
Dakir 2014	0	6	0	6	0.0%	0.00 [-0.27, 0.27]	2014
Nuhi 2015	0	100	0	70	0.2%	0.00 [-0.02, 0.02]	2015
Apipan 2018	0	60	0	20	0.1%	0.00 [-0.07, 0.07]	2018
Subtotal (95% CI)		**265**		**192**	**0.5%**	**0.00 [-0.02, 0.02]**	
Total events	0		0				

Heterogeneity: Chi² = 0.00, df = 5 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

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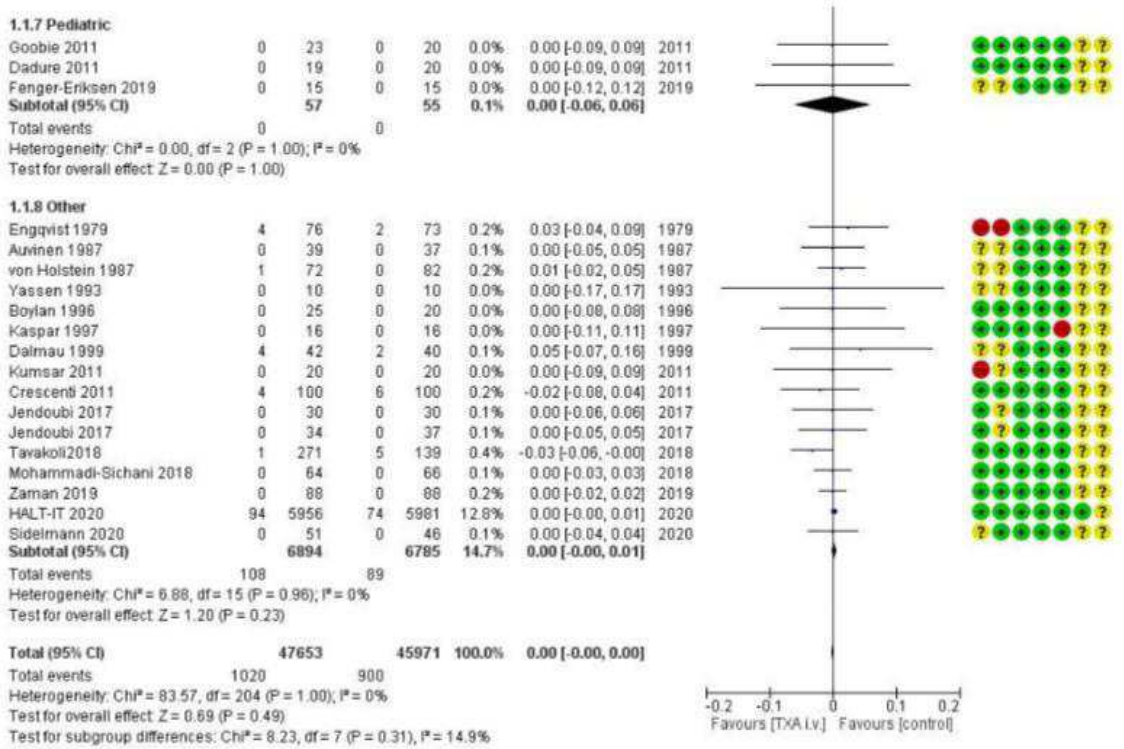
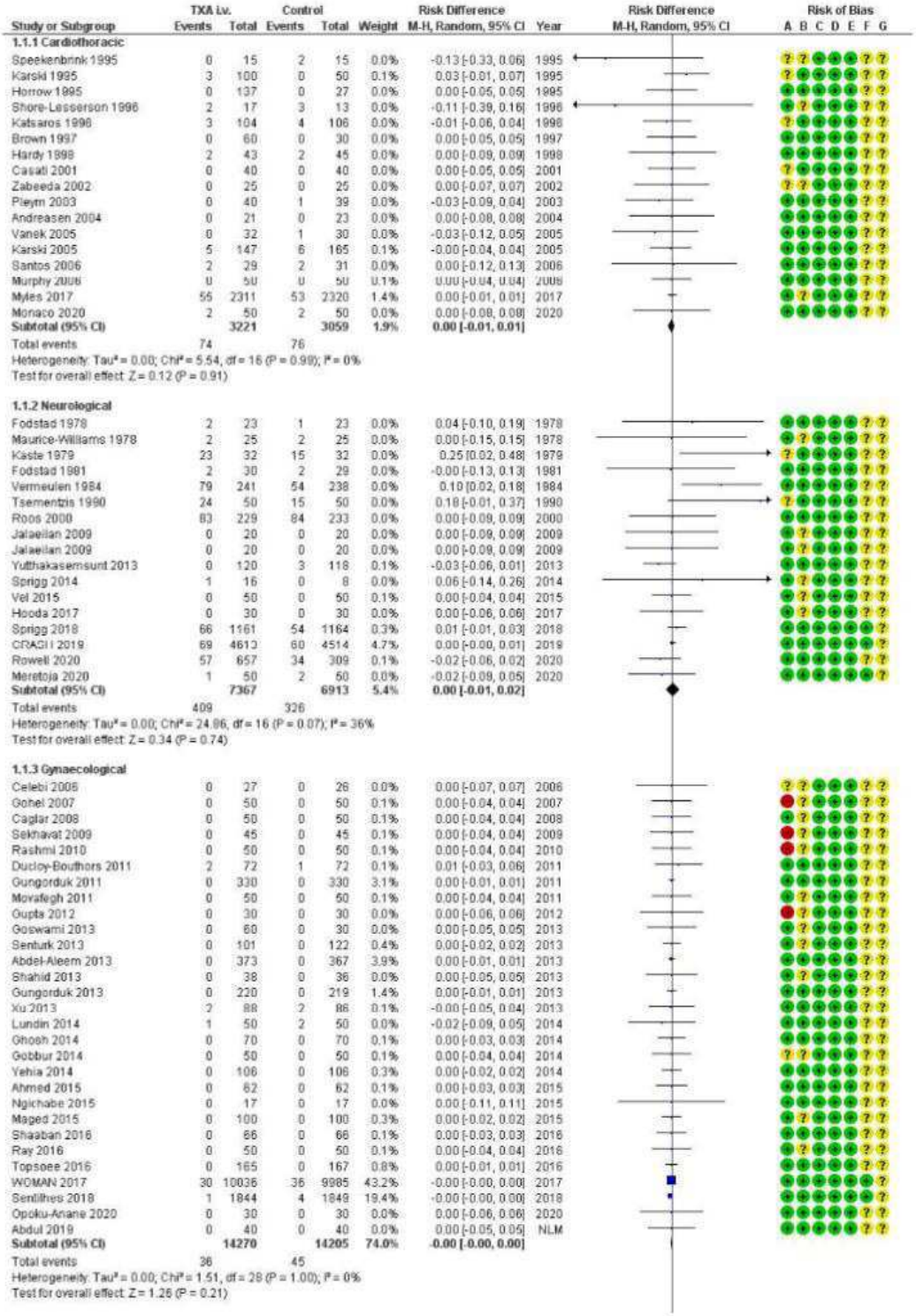


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

eFigure 38: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model updated Meta-Analysis



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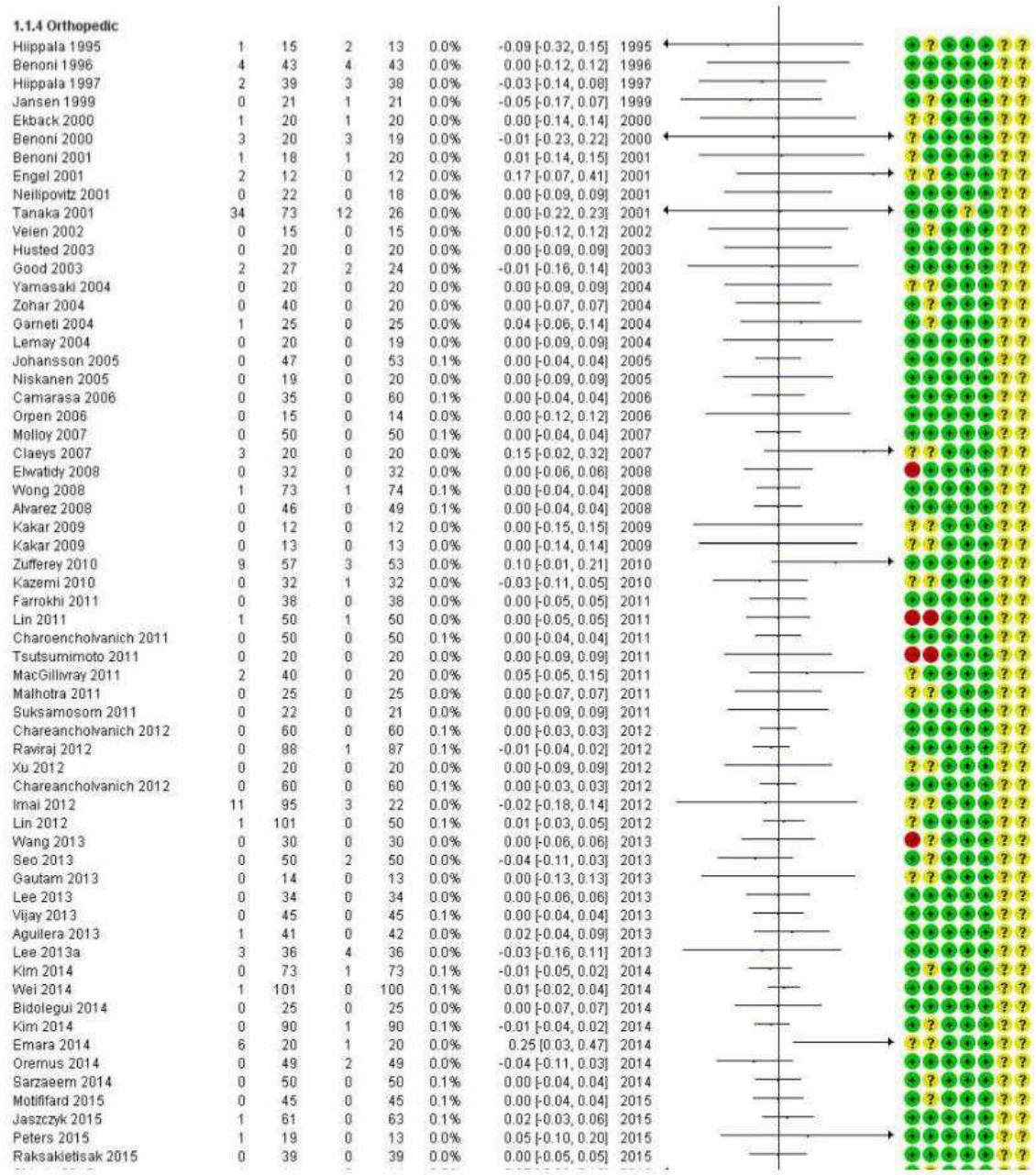

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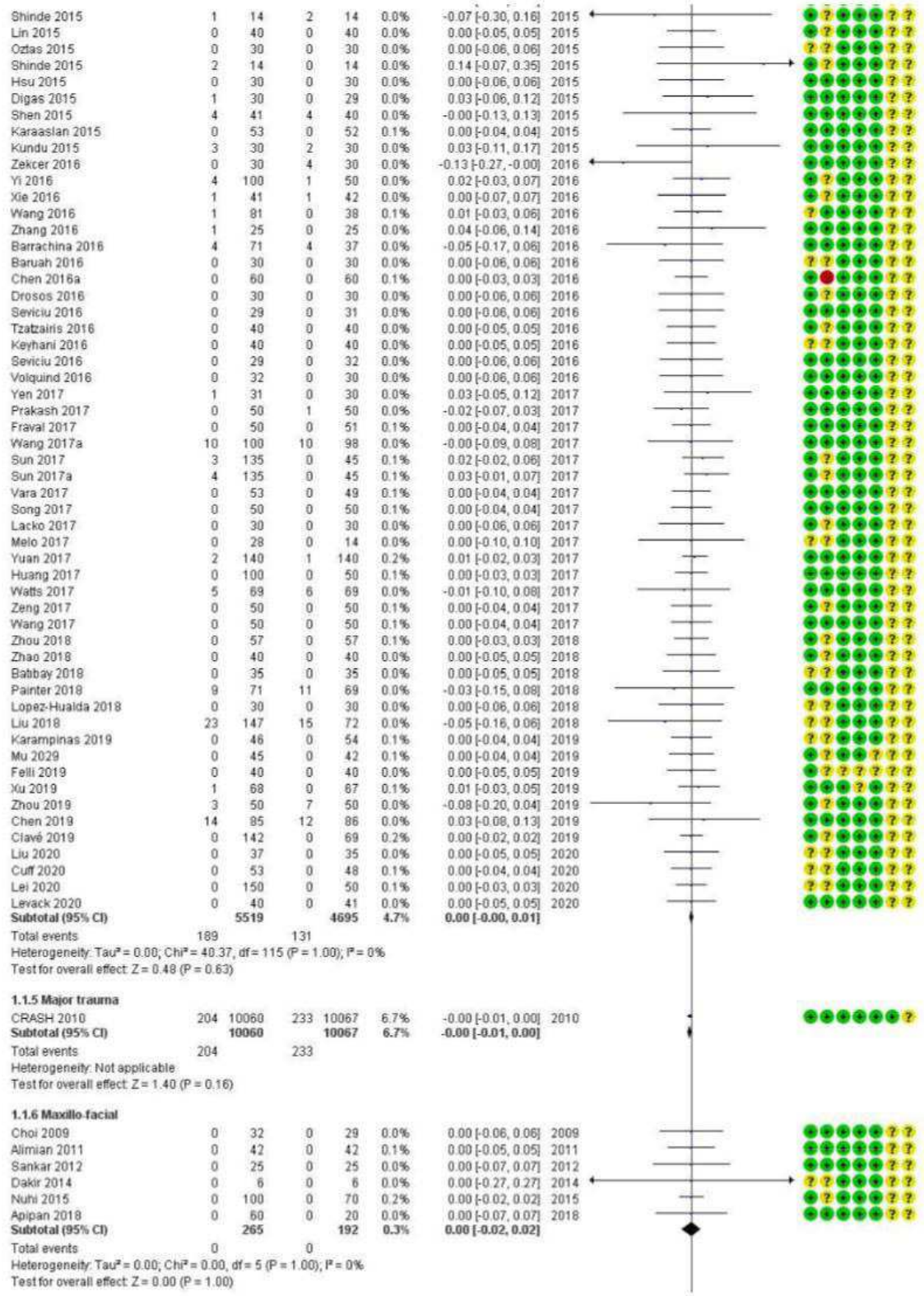

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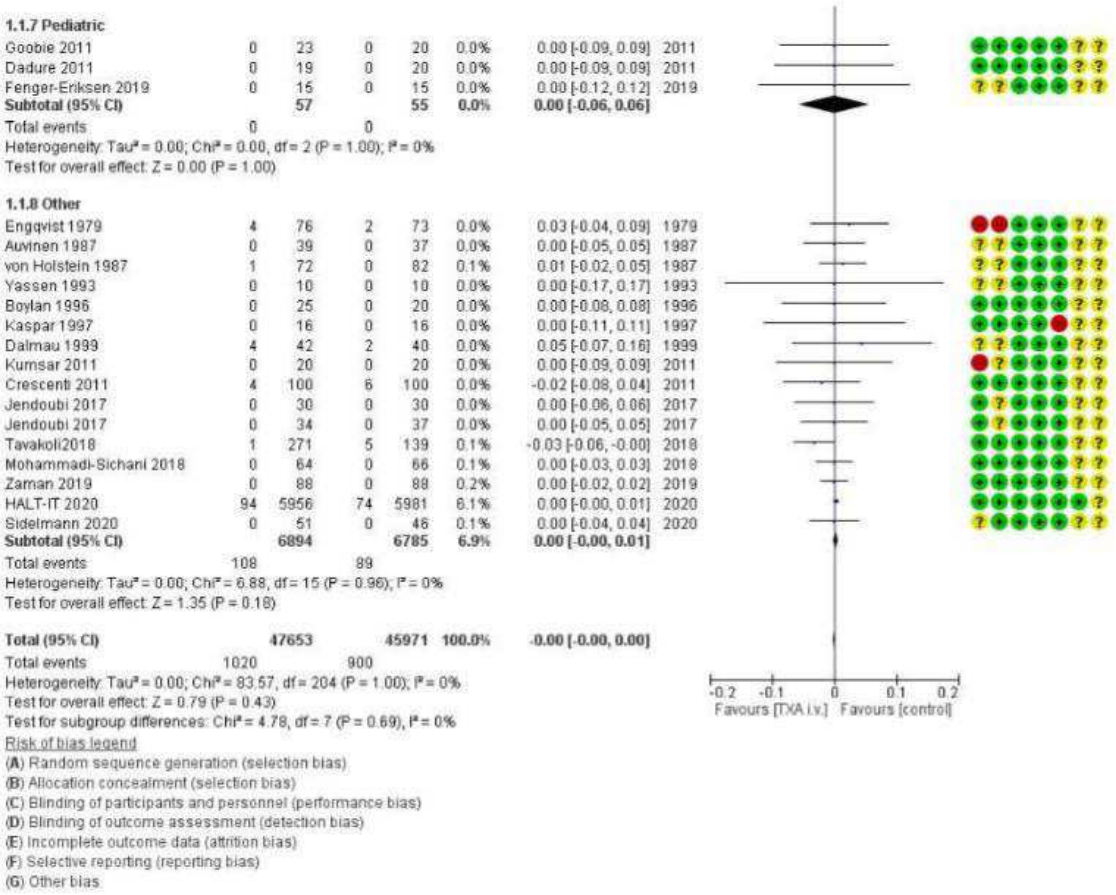
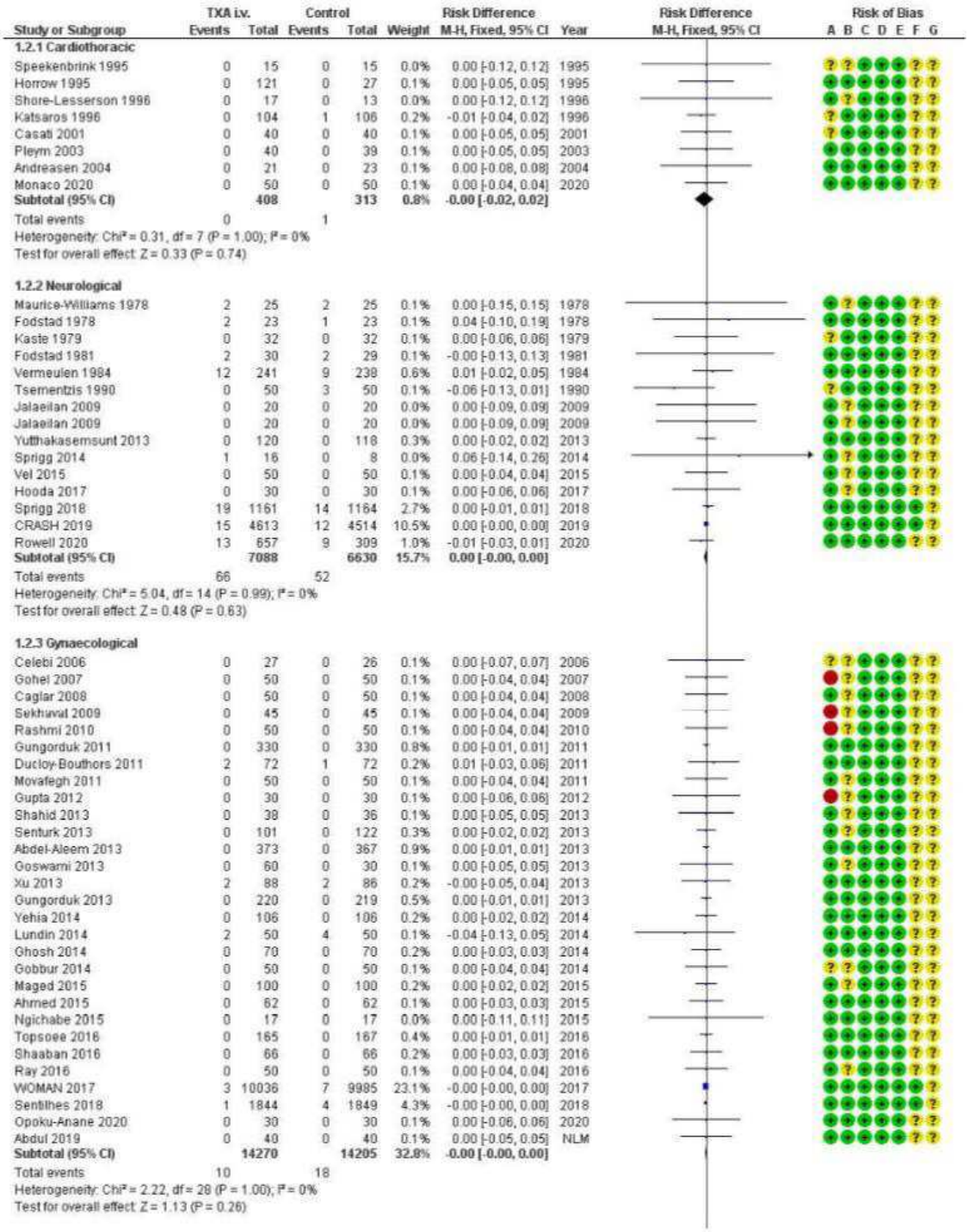


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

eFigure 39: Venous Thrombosis Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model of updated Meta-Analysis



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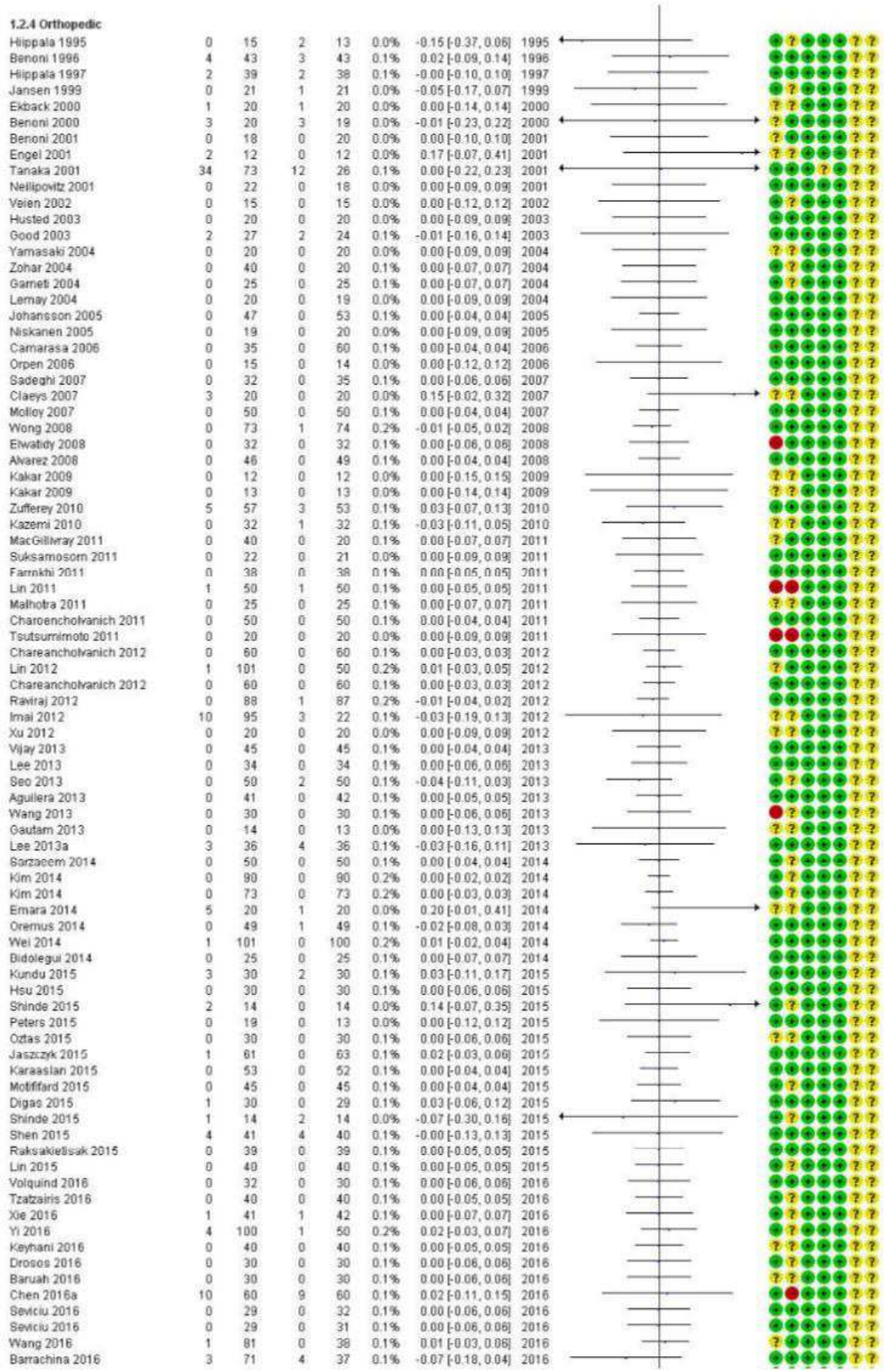

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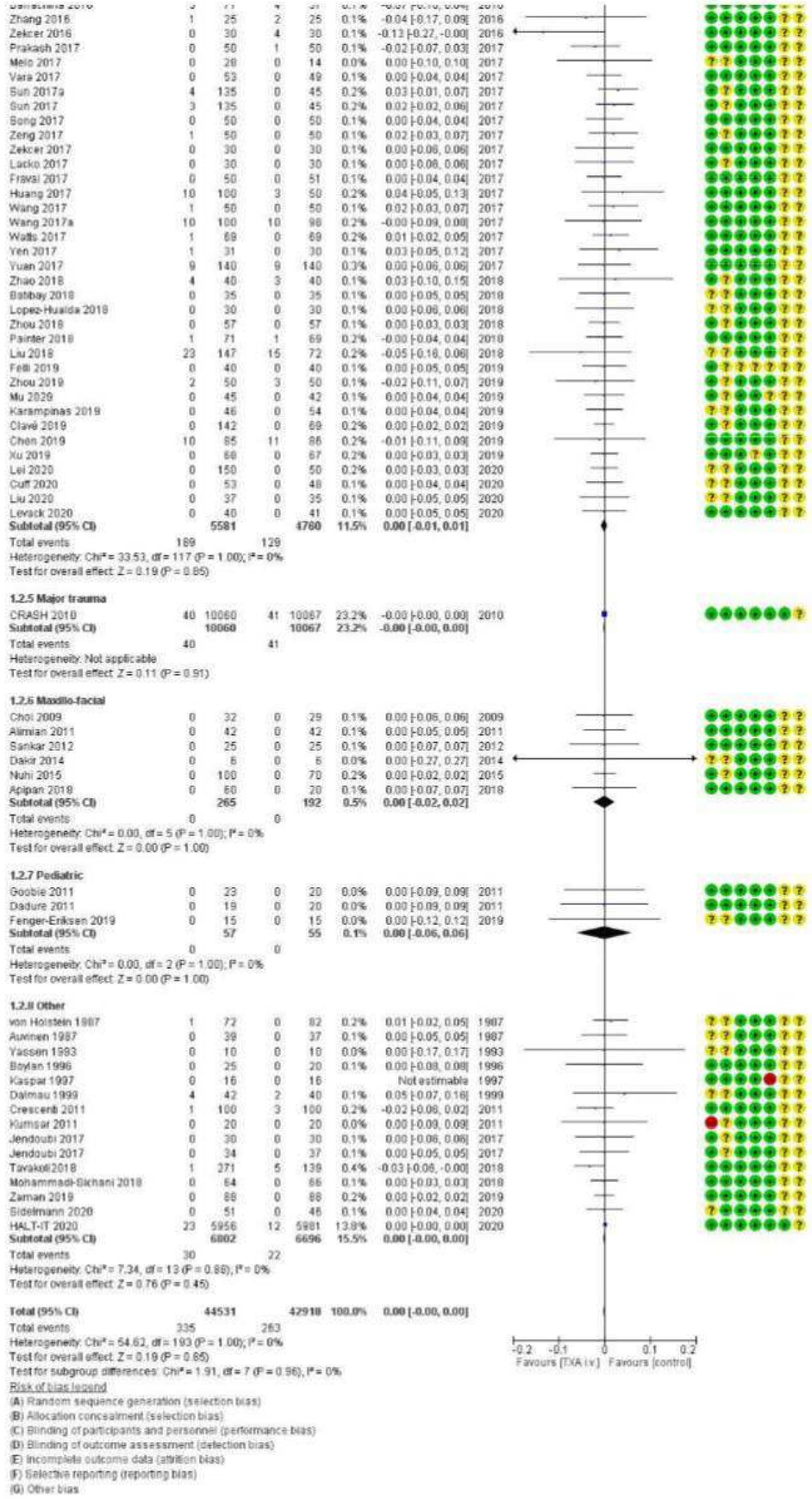
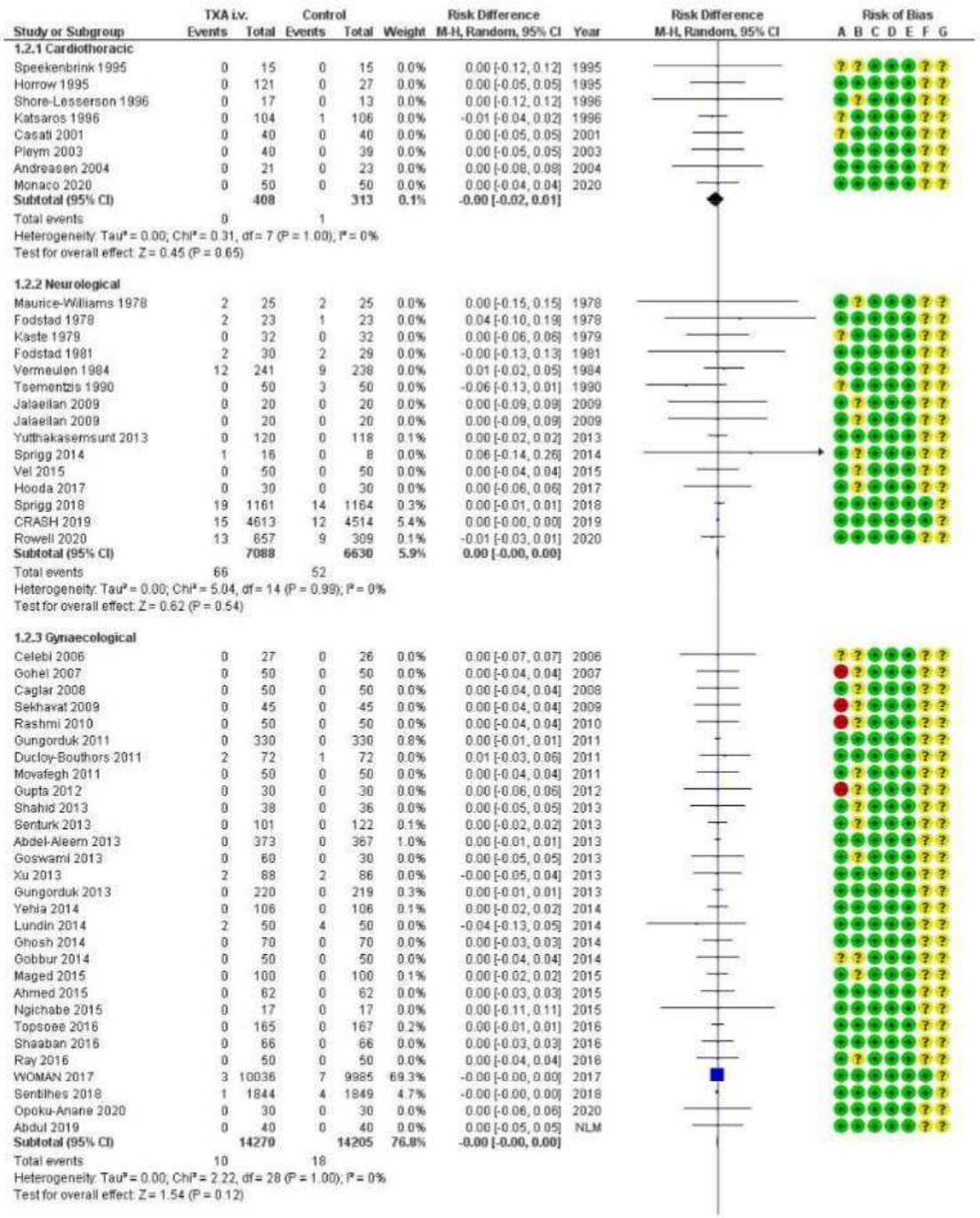


eFigure 40: Venous Thrombosis Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model of updated Meta-Analysis



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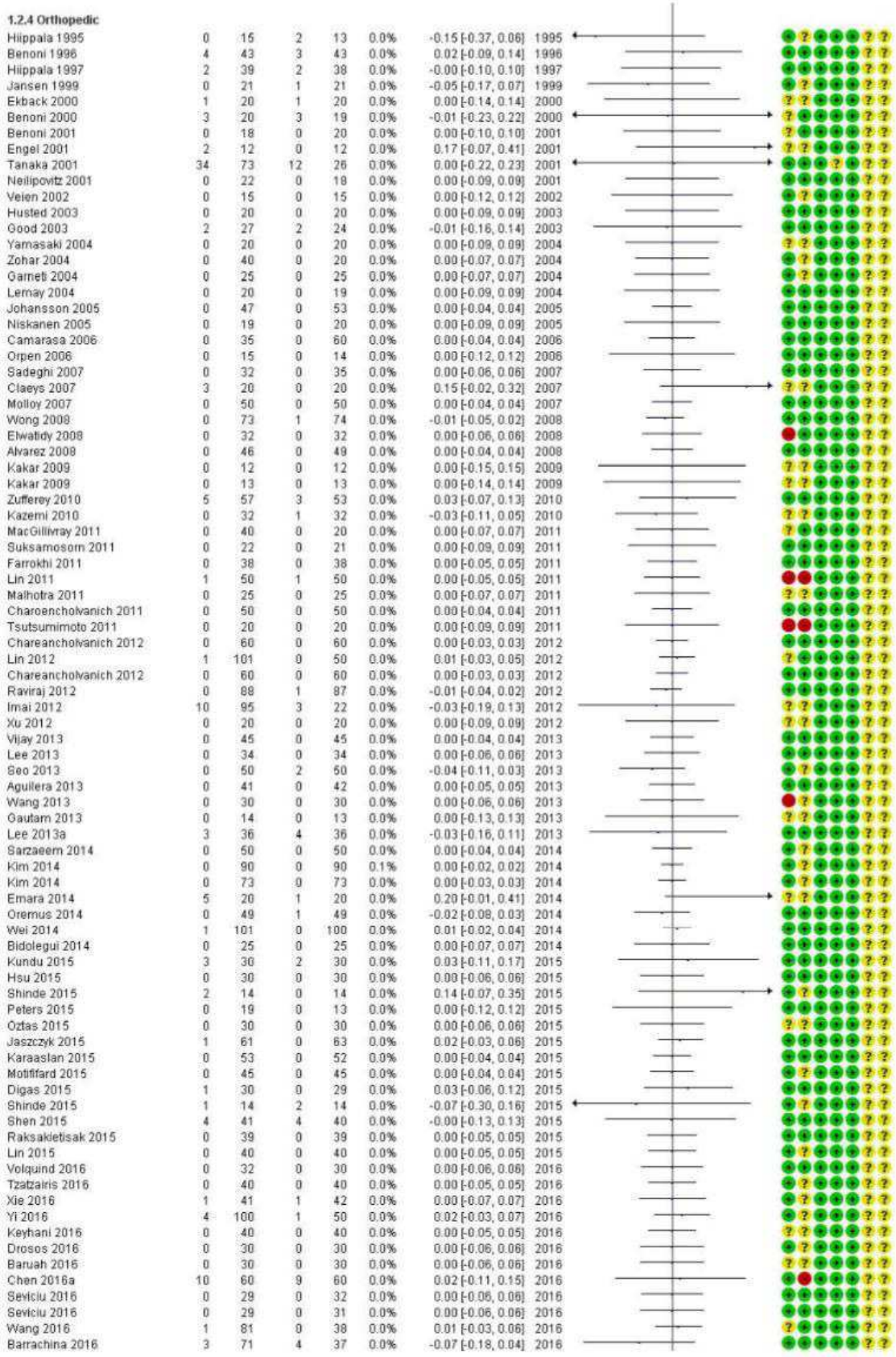

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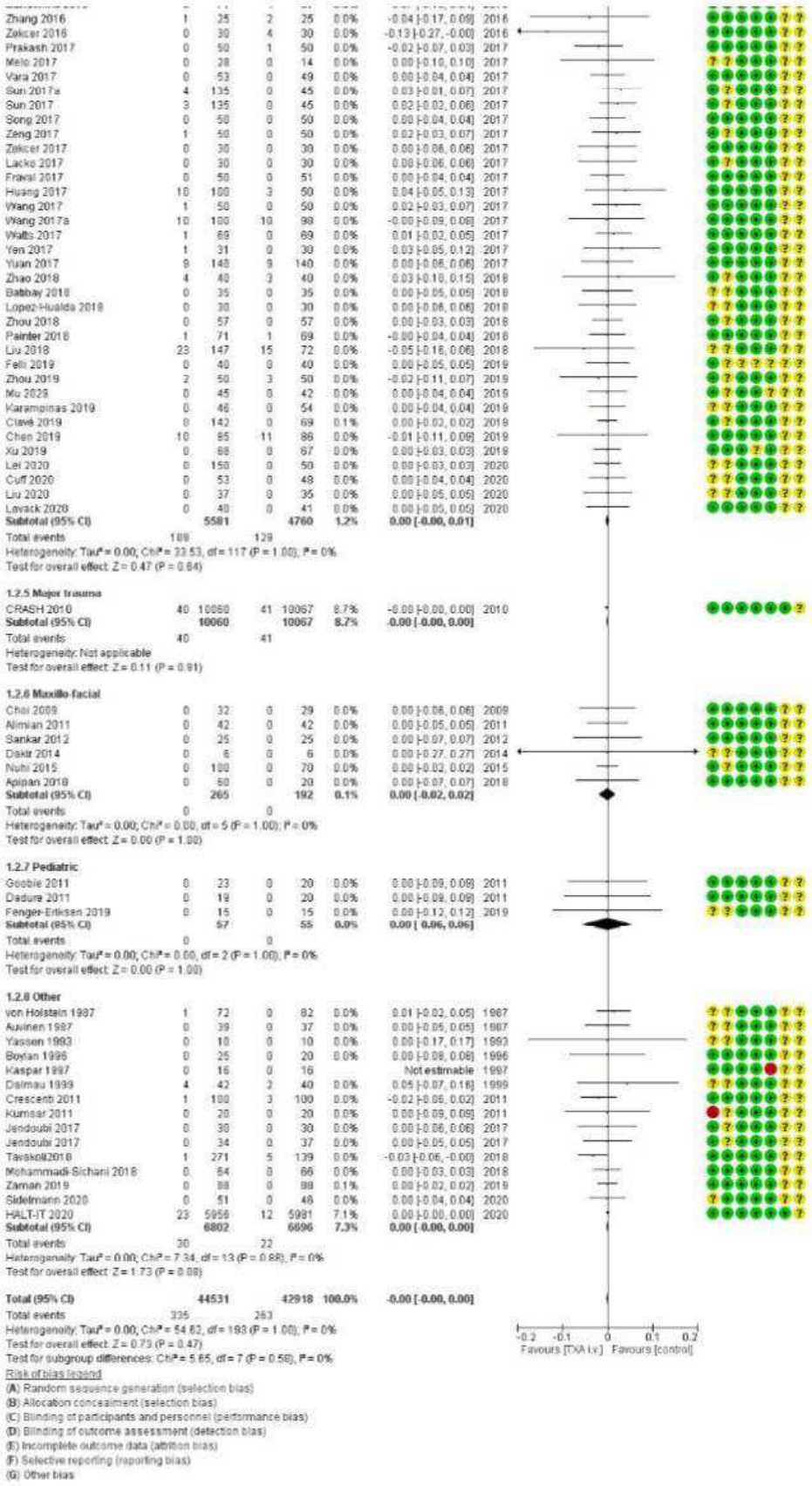
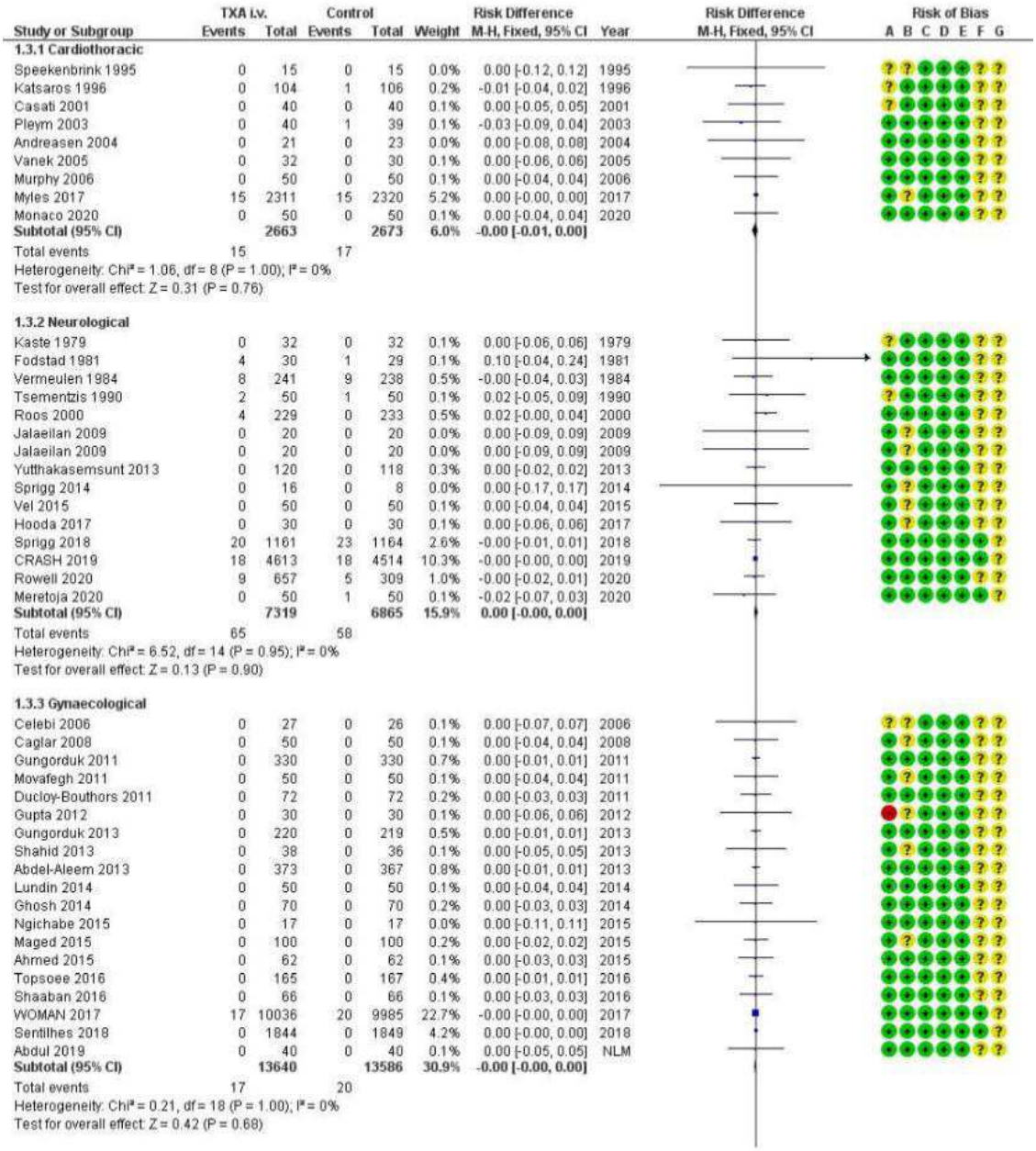


eFigure 41: Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model of updated Meta-Analysis



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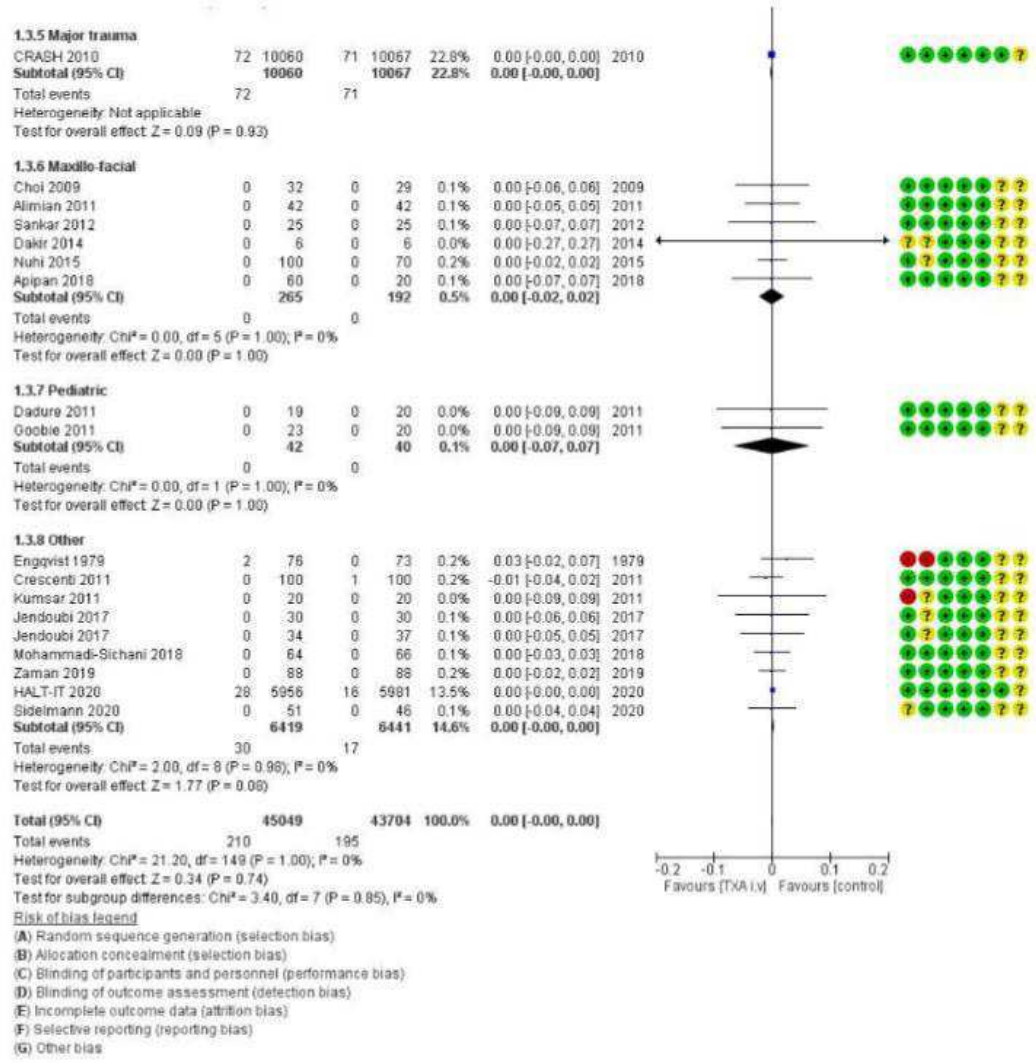
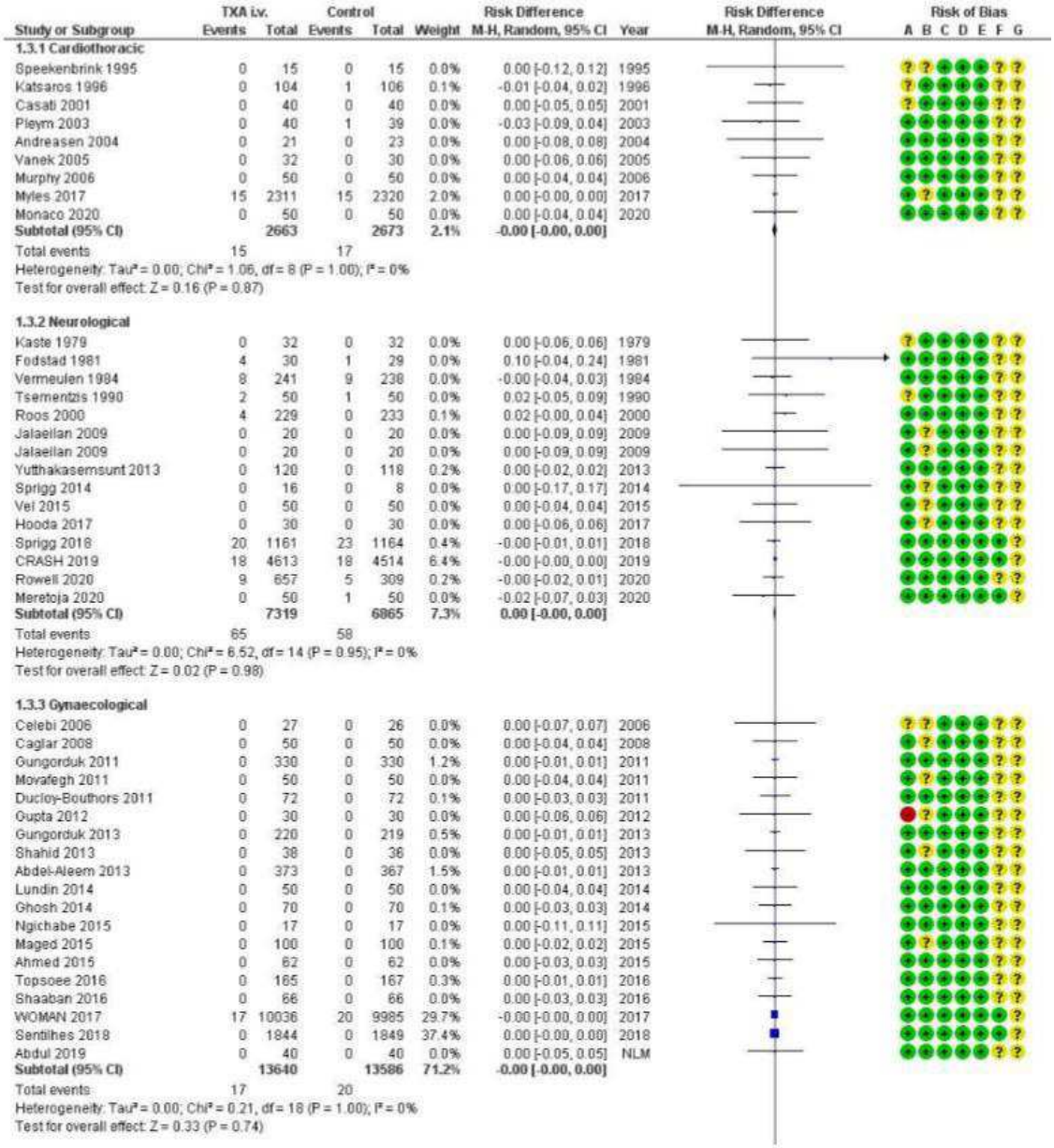


eFigure 42: Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model of updated Meta-Analysis



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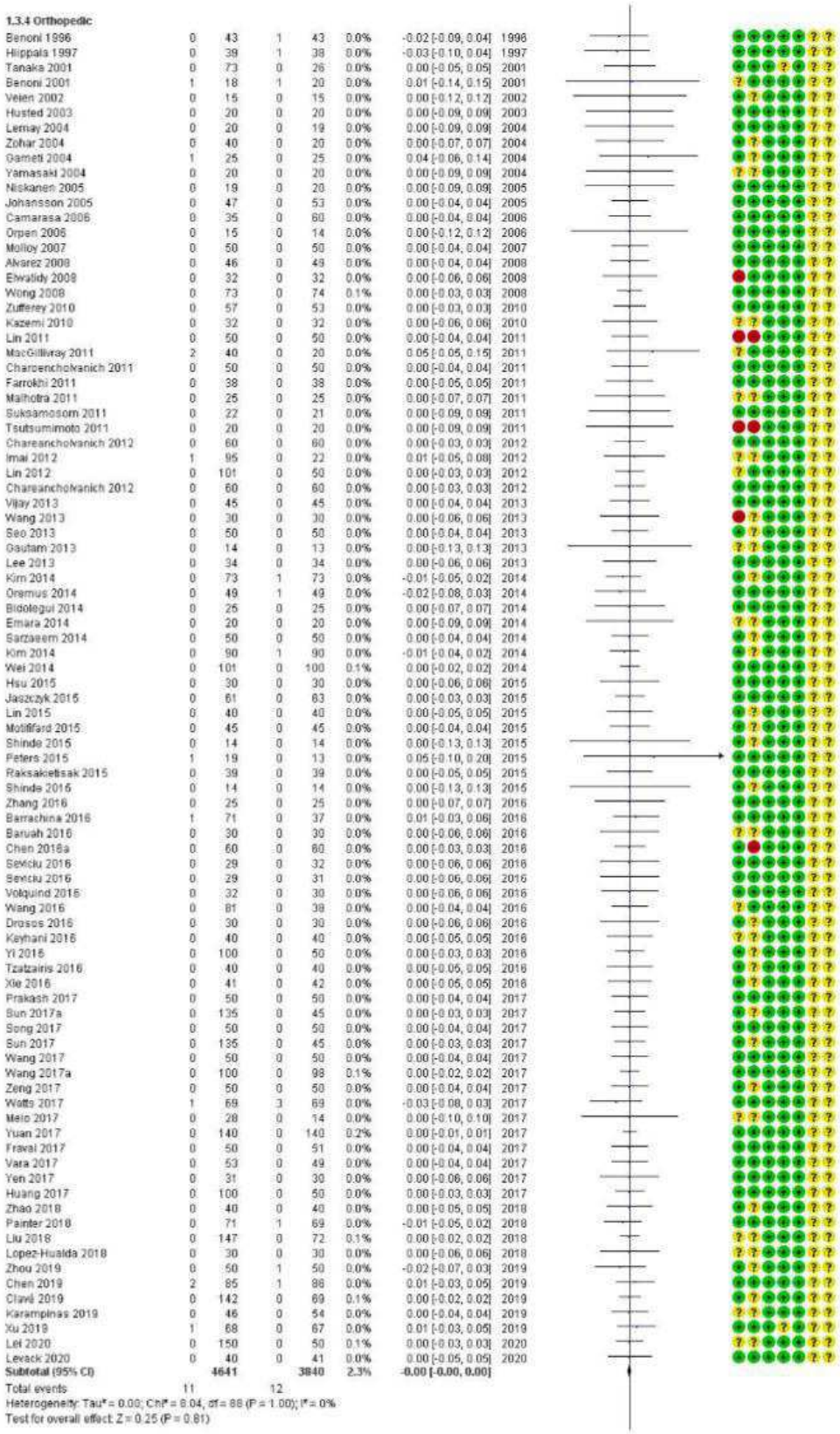

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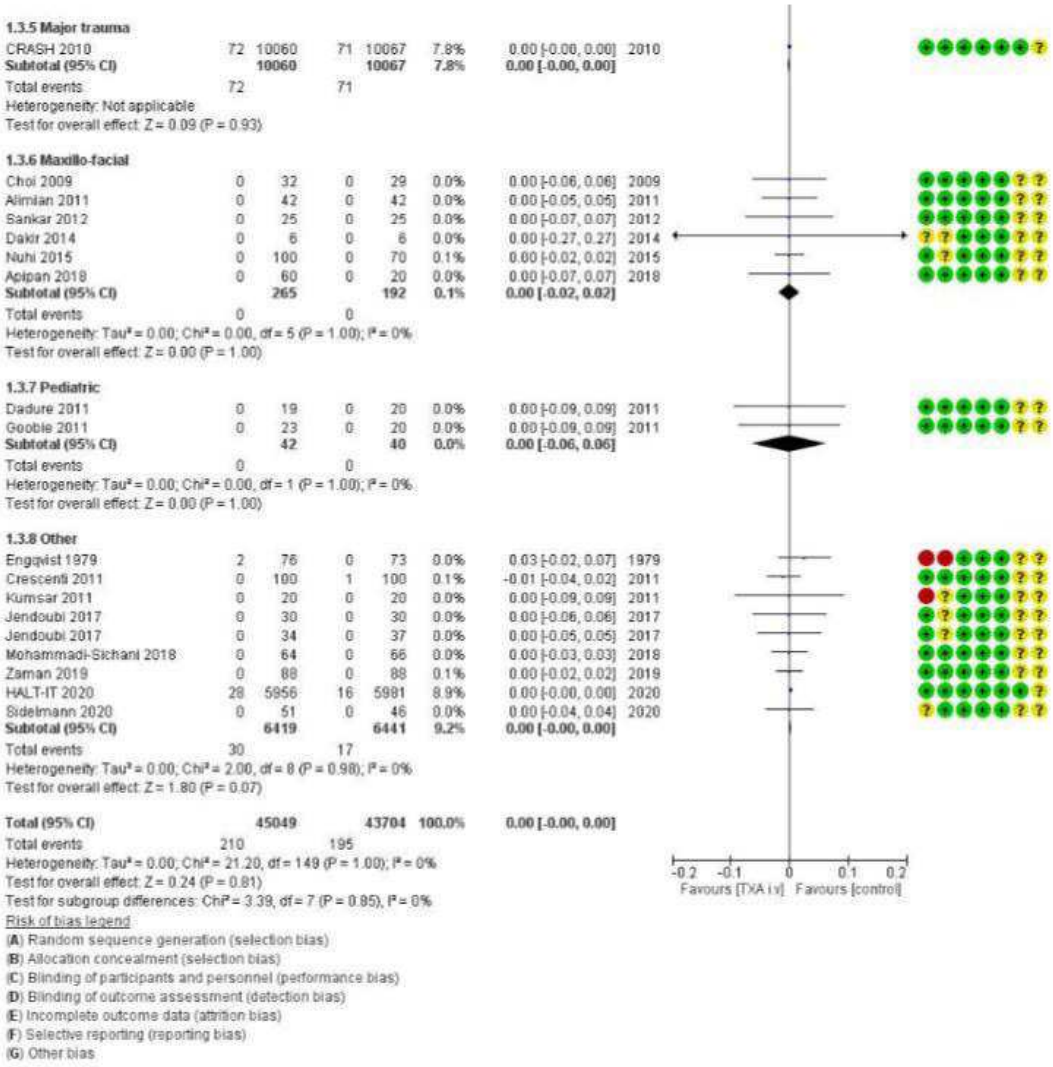
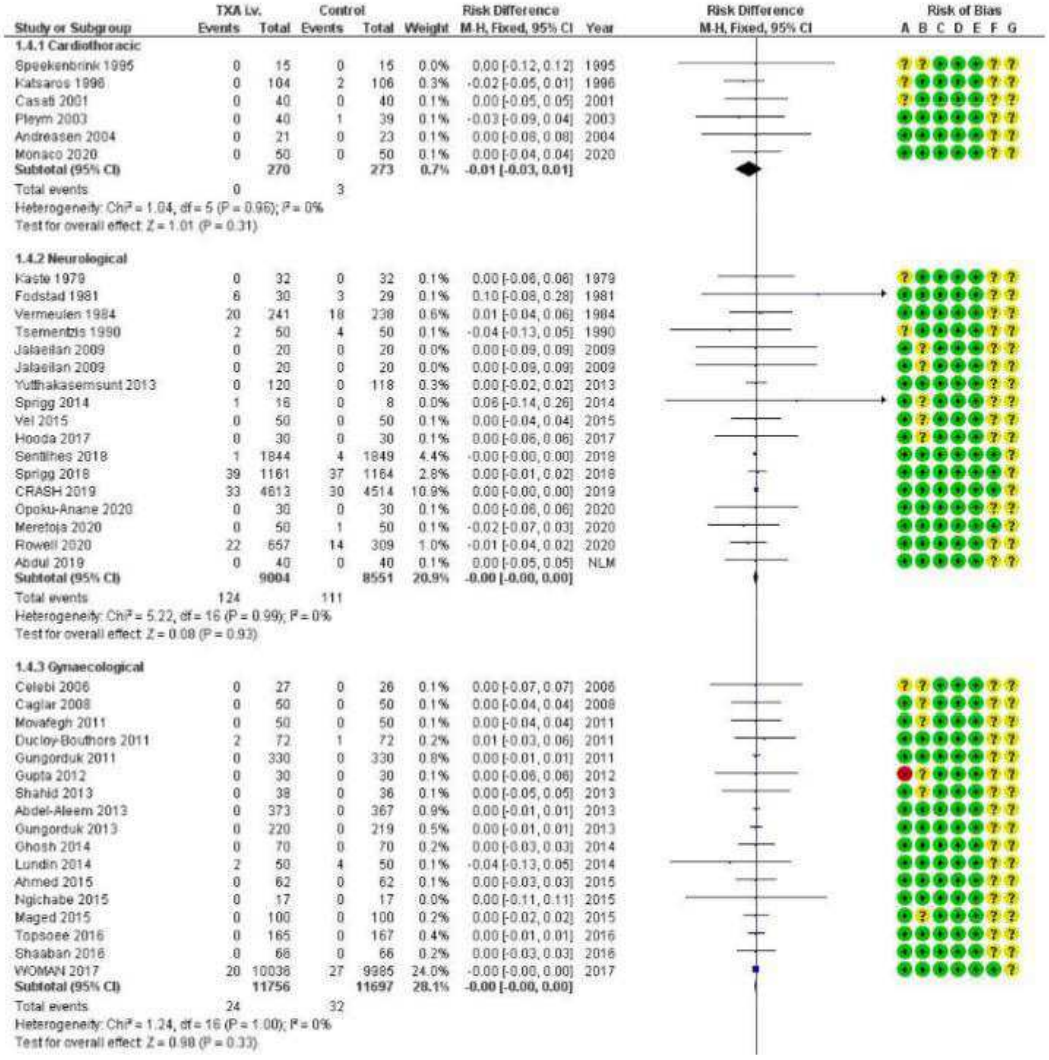


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

eFigure 43: Venous Thromboembolic and Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model of updated Meta-Analysis



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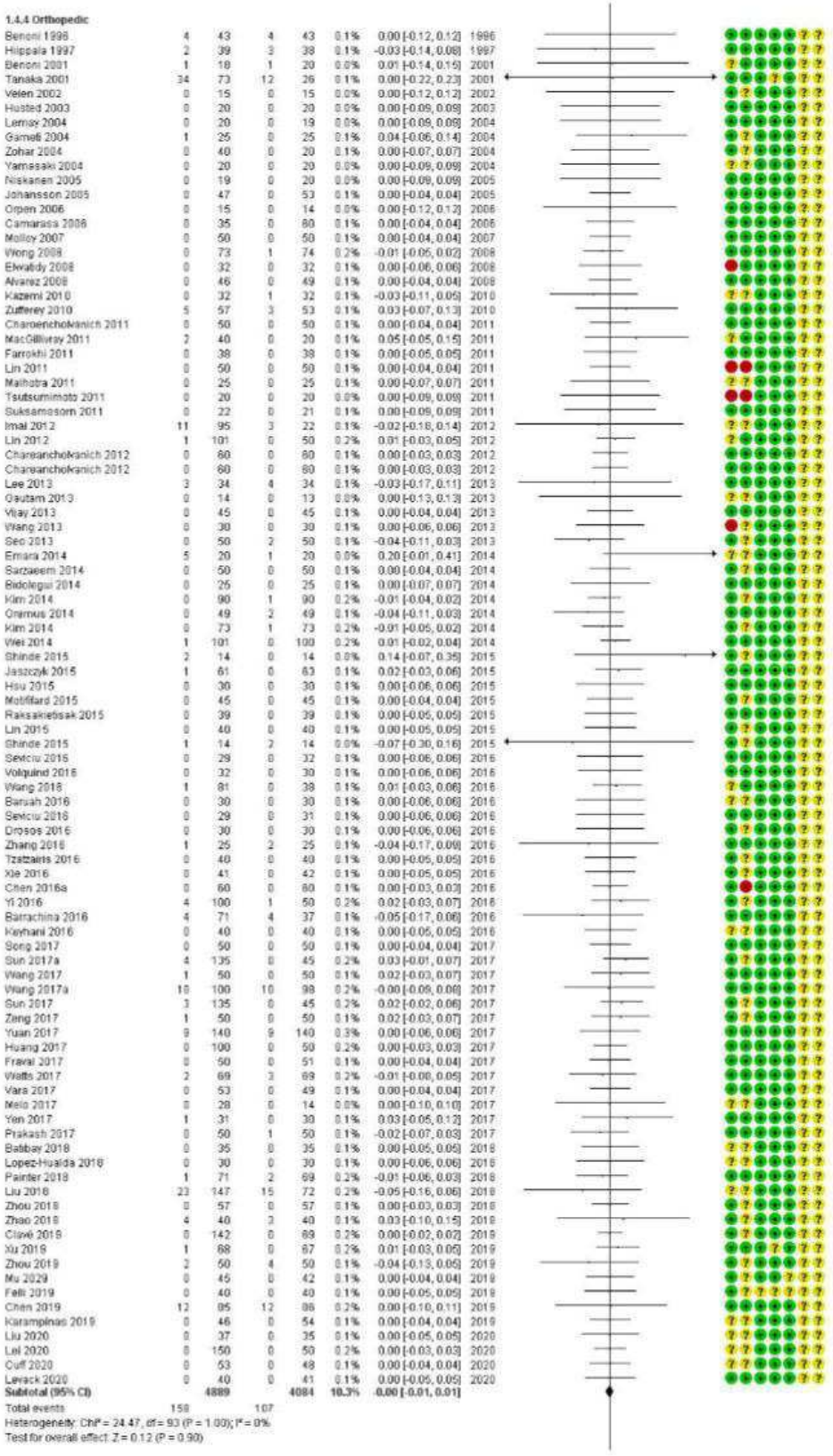

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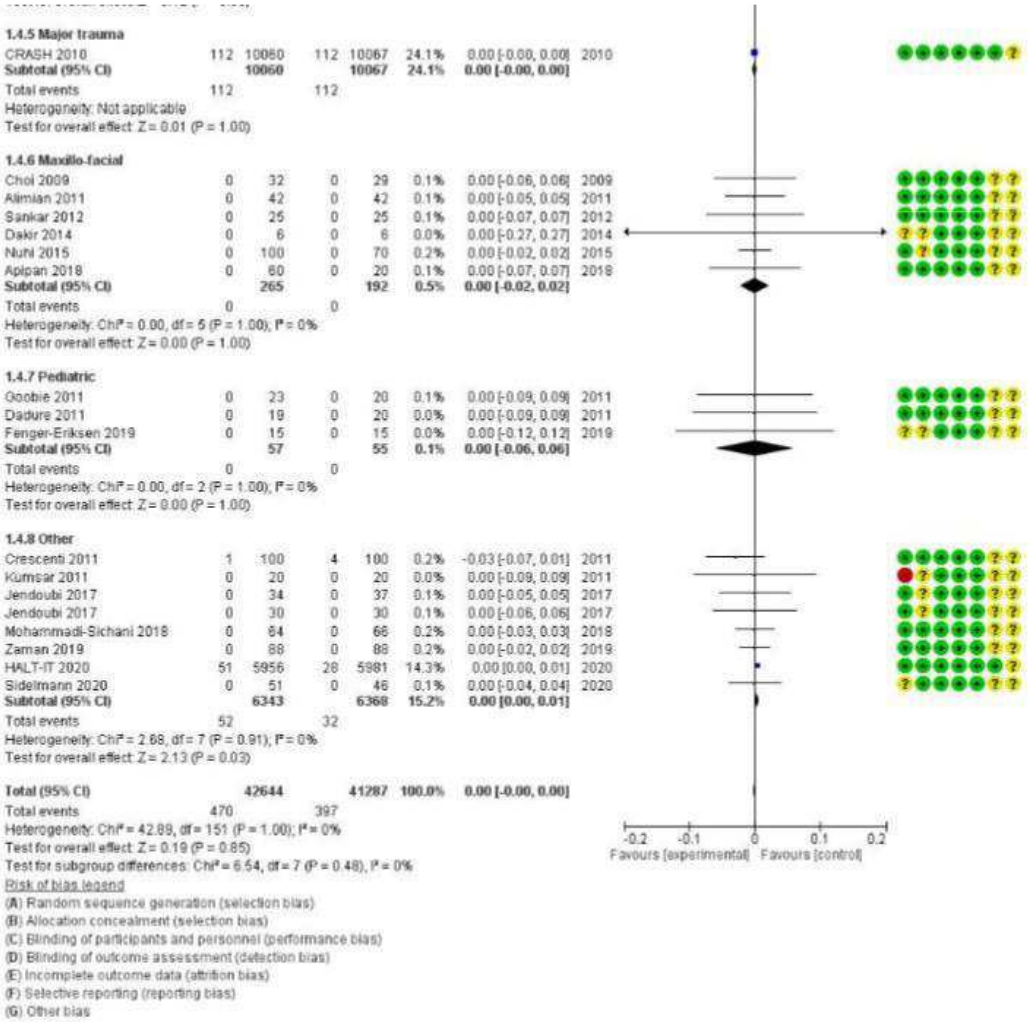
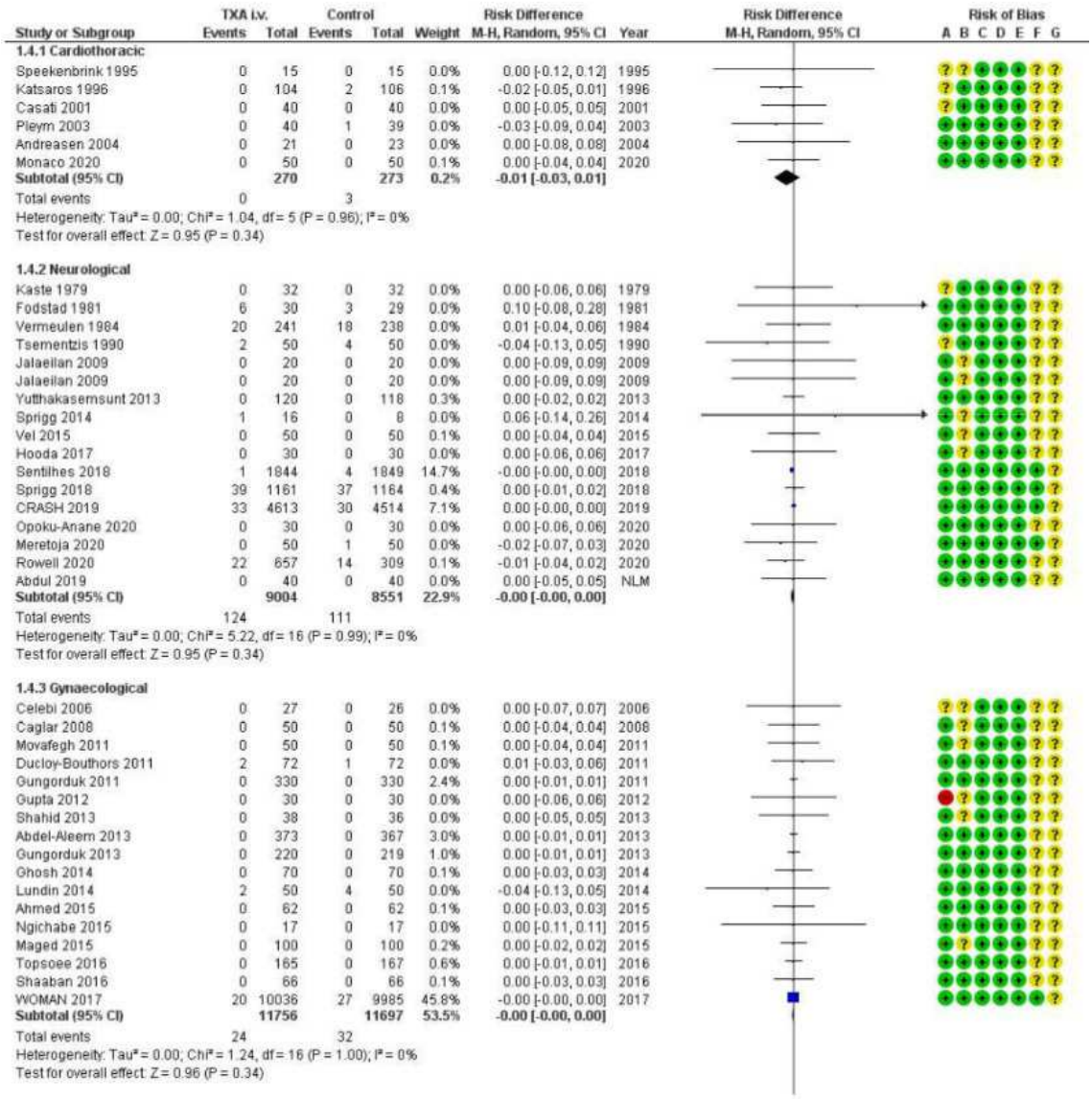


eFigure 44: Venous Thromboembolic and Pulmonary Embolism Event Rate in Patients receiving TXA compared to Control using the Random-Effects Model of updated Meta-Analysis



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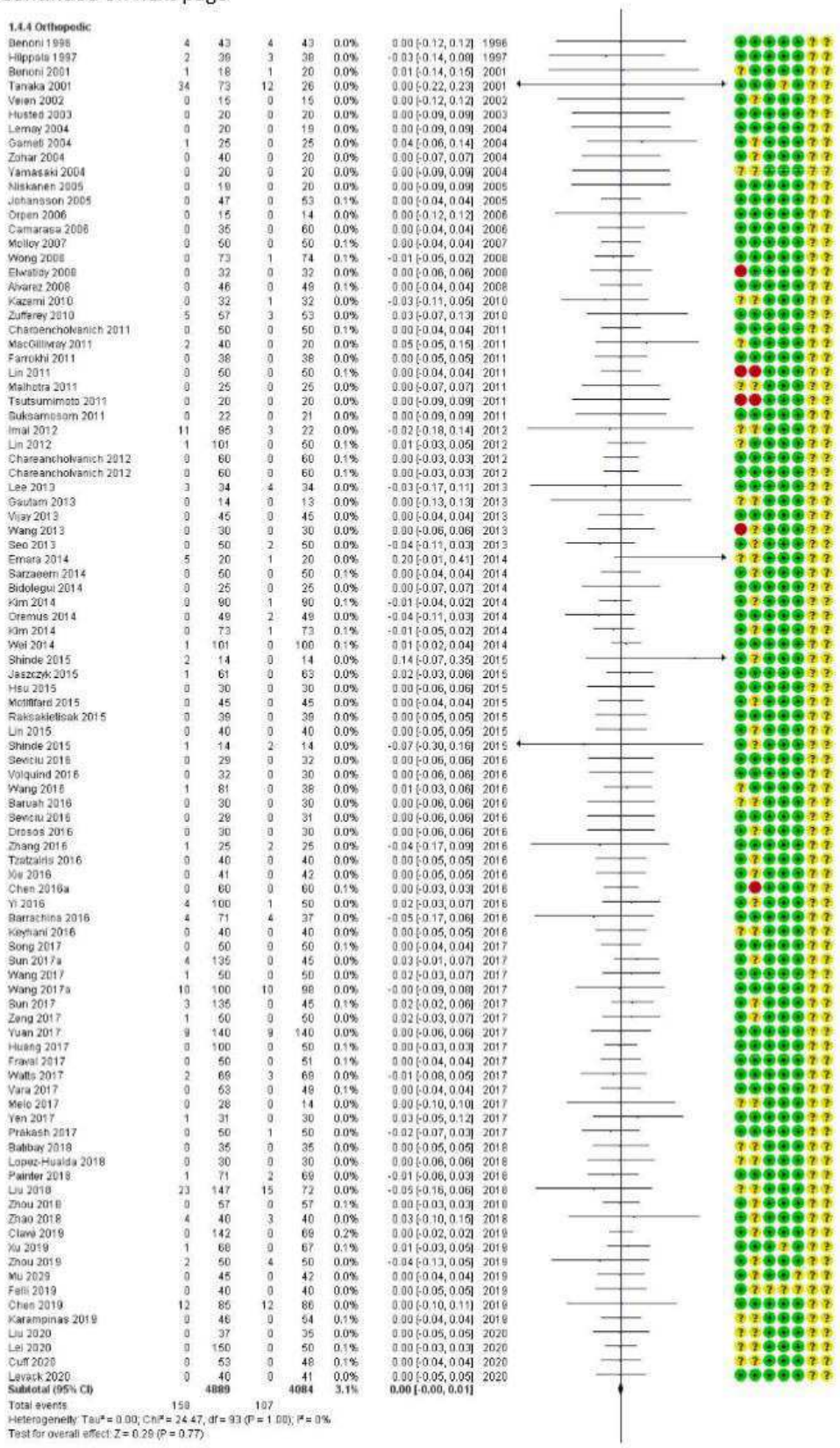

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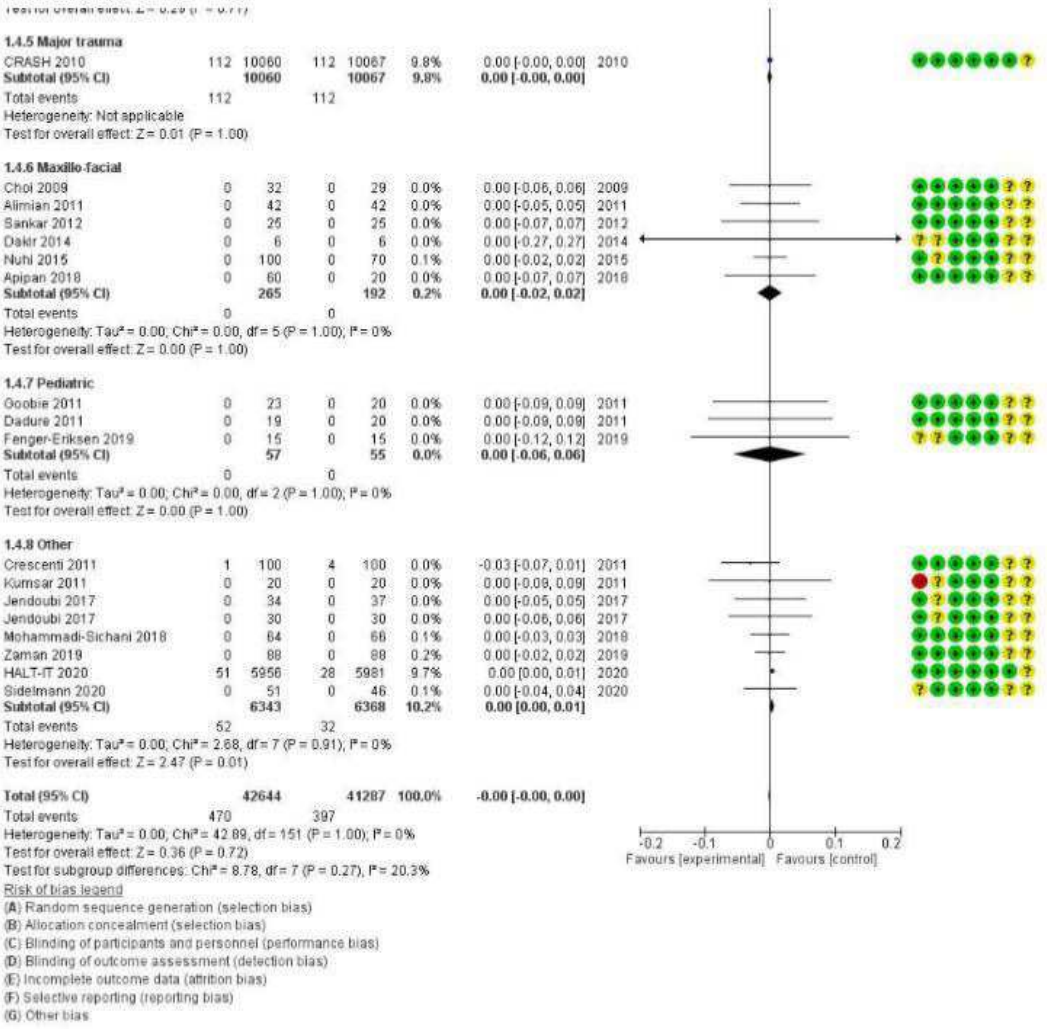
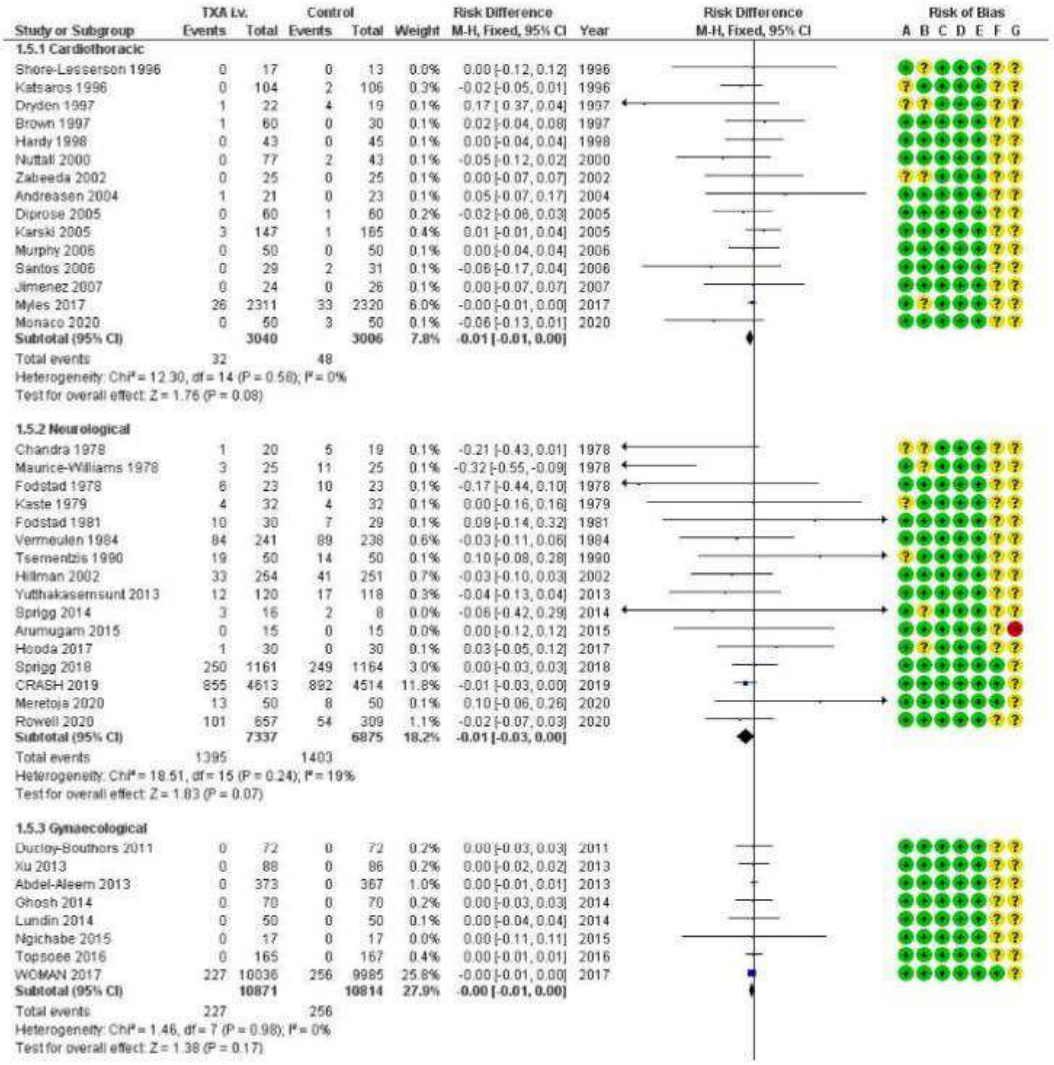


eFigure 45: Overall Mortality Rate in Patients receiving TXA compared to Control using the Fixed-Effect Model of updated Meta-Analysis



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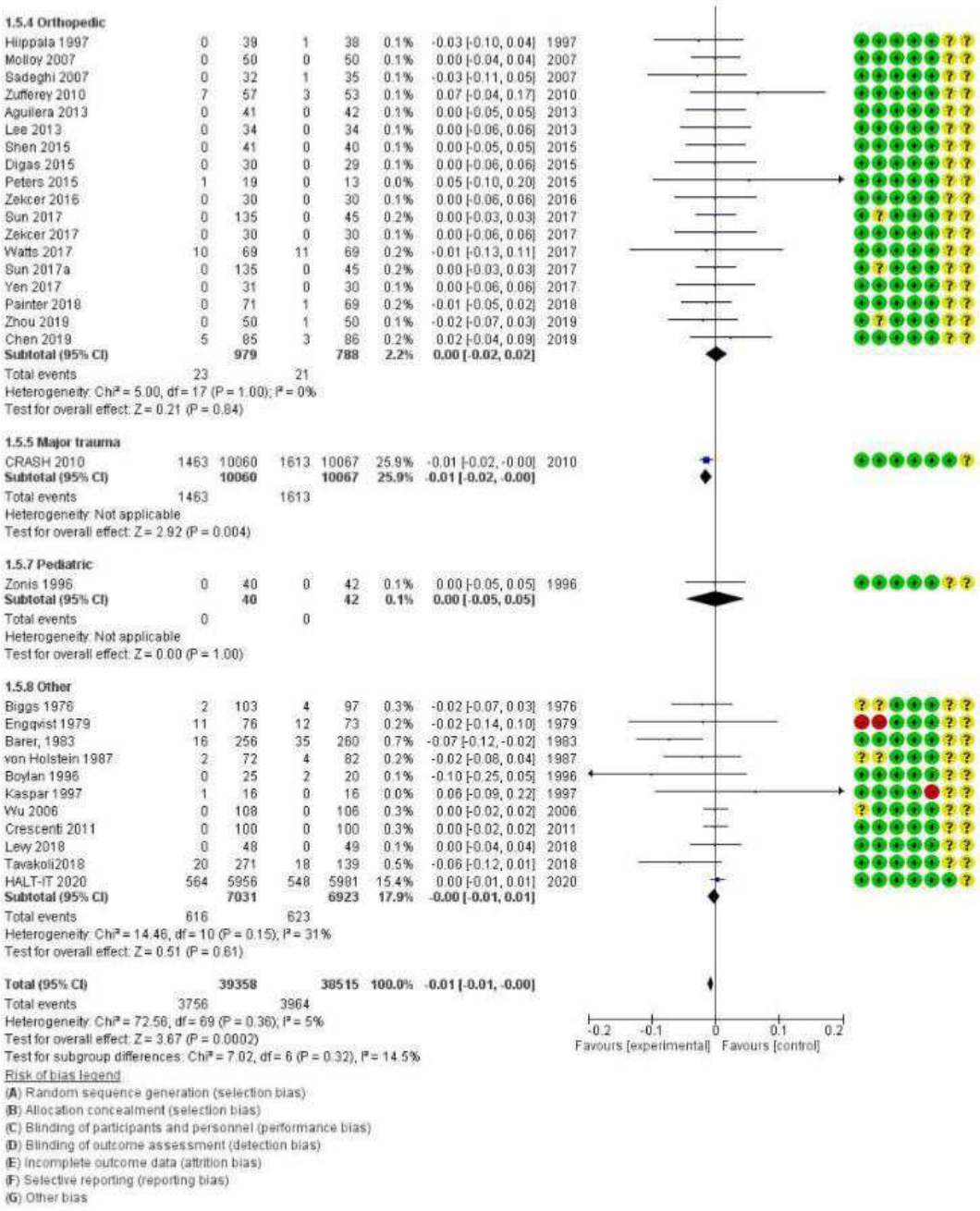
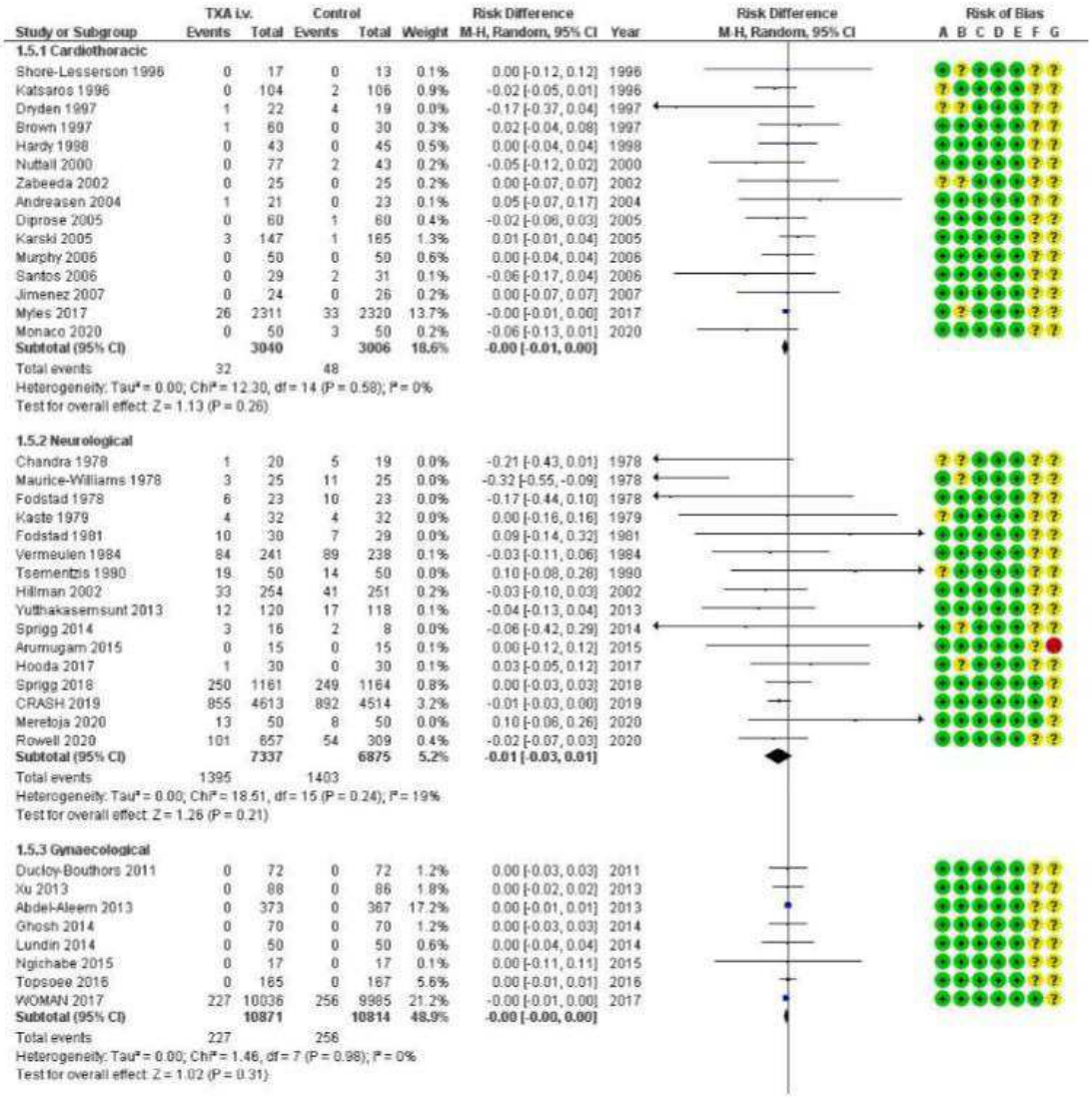


eFigure 46: Overall Mortality Rate in Patients receiving TXA compared to Control using the Random-Effects Model of updated Meta-Analysis



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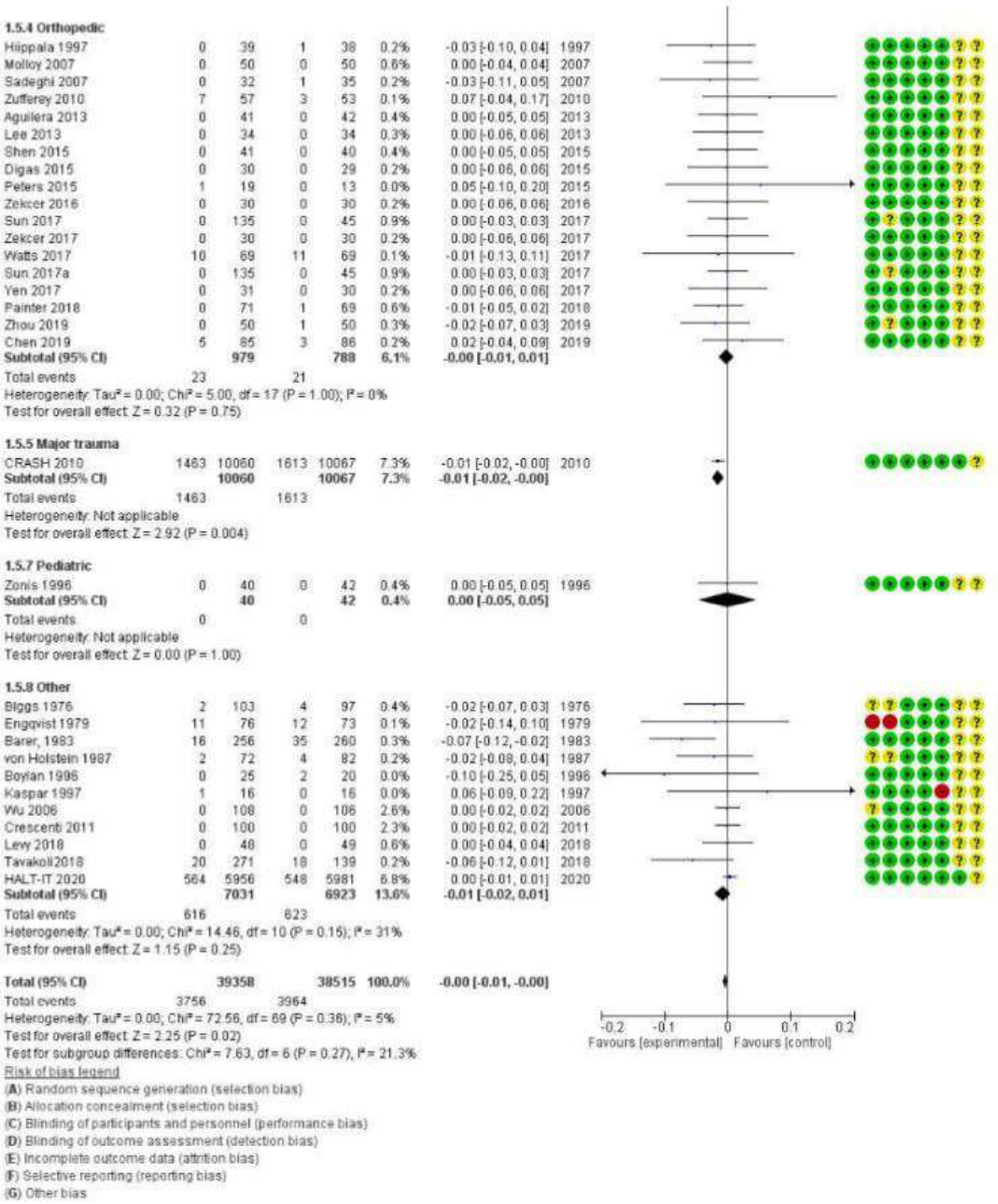
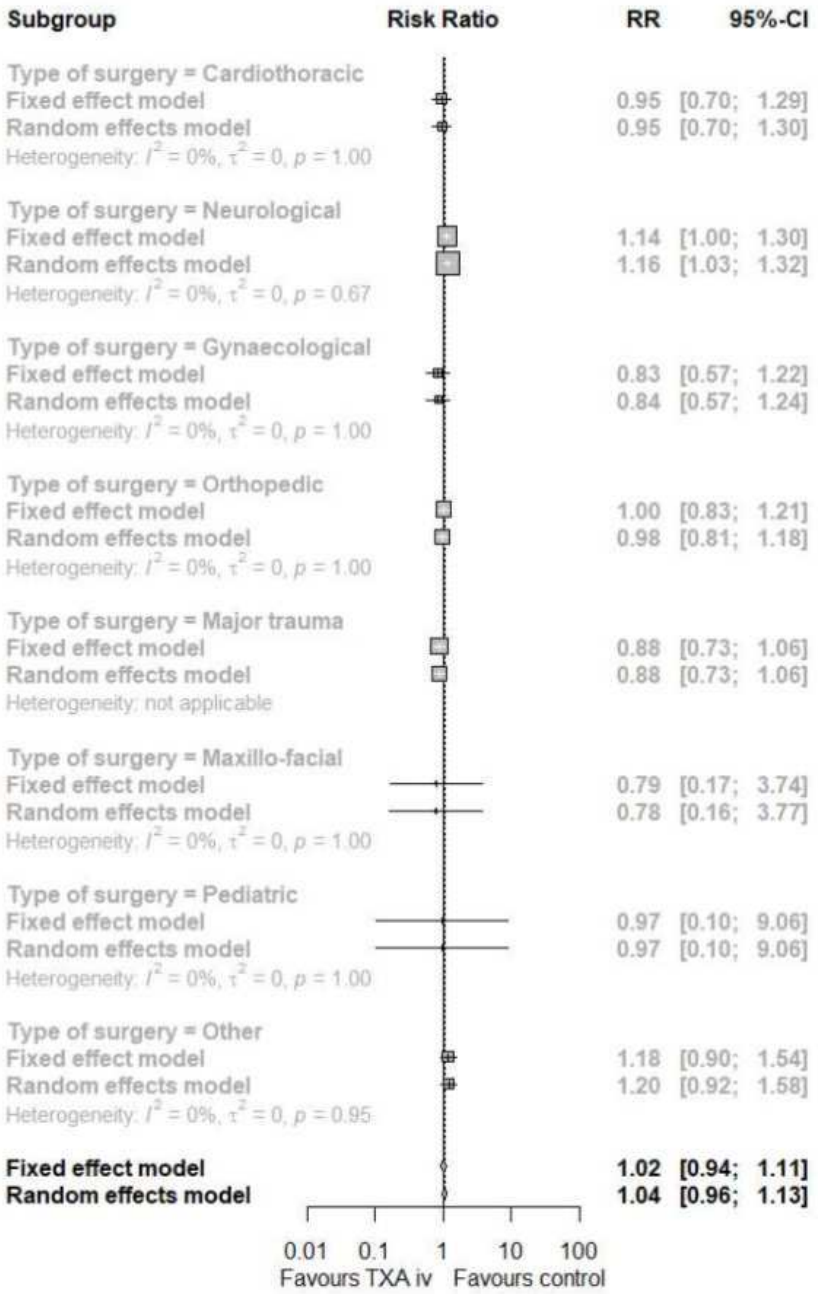
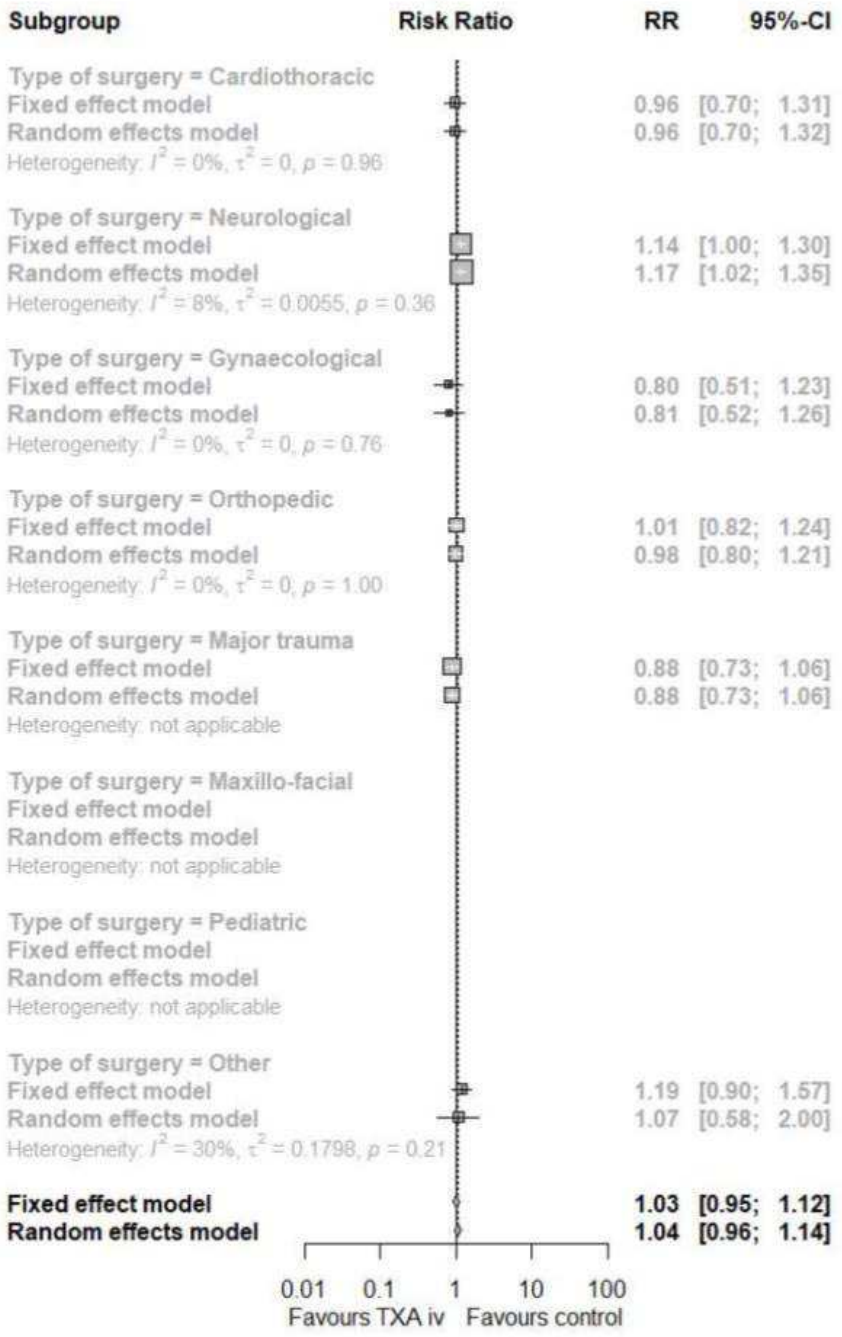


eFigure 47: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control analysed with Risk Ratio in Studies with Zero Events of updated Meta-Analysis



eFigure 48: Total Thromboembolic Event Rate in Patients receiving TXA compared to Control analysed with Risk Ratio in Studies without Zero Events of updated Meta-Analysis



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8. Darstellung des eigenen Anteils

Zur Planung der vorliegenden Analyse fand 2018 ein initiales Treffen mit Prof. Dr. Patrick Meybohm, Dr. Suma Choorapoikayil und mir statt. Hierbei wurden der Suchterm, die Ein- und Ausschlusskriterien sowie die Endpunkte festgelegt. Ich befasste mich intensiv mit den verschiedenen Analysemöglichkeiten und erstellte einen Analyseplan nach Rücksprache mit Prof. Patrick Meybohm, Prof. Eva Herrmann und Dr. Suma Choorapoikayil. In den folgenden Monaten führte ich die Literaturrecherche, Datenanalyse und -auswertung sowie die Erstellung von Tabellen und Grafiken durch: In einem ersten Schritt las ich alle Abstracts (ca. 700) der durch unseren Suchterm identifizierten Studien und schloss Studien von unserer Analyse aus, die unseren Einschlusskriterien nicht entsprachen (ca. 400). Bei allen übrigen Studien las ich die Volltexte und markierte Textstellen zu unseren Endpunkten (ca. 300). Um eine möglichst vollständige Analyse der Datenlage zu ermöglichen, screente ich auch alle Referenzlisten der durch den verwendeten Suchterm identifizierten Metaanalysen und Reviews nach weiteren einzuschließenden Studien. Hier verglich ich jede einzelne Referenz mit der Liste der bereits identifizierten Studien. Im nächsten Schritt extrahierte ich Daten zu 219 Studien in eine Excel-Tabelle und übertrug die Daten von 192 Studien in das Programm „Review Manager“ zur weiteren Analyse. In dieser Zeit der Datenextraktion und -analyse fanden weitere Treffen zur Klärung von Fragen in Bezug auf die eingeschlossenen Studien und deren berichteten Endpunkte zwischen Dr. Suma Choorapoikayil, Prof. Patrick Meybohm und mir statt. In statistischen Fragen wurden wir durch Prof. Eva Herrmann und Dr. Stephanie Weibel unterstützt. Ein erster Entwurf des Manuskriptes wurde von mir verfasst und durch Dr. Suma Choorapoikayil, Prof. Patrick Meybohm und Dr. Stephanie Weibel bearbeitet. Nach Einreichung meines Manuskriptes wurde von einem Reviewer die Frage gestellt, ob die Möglichkeit bestehe eine Literaturrecherche für den Zeitraum 2018 bis Ende 2020 durchzuführen, welche dann von mir ausgeführt wurde. Für die aktualisierte Metaanalyse wiederholte ich die bereits oben genannten Schritte. Das Manuskript ergänzte ich durch die neu gewonnenen Ergebnisse. Im Rahmen des Peer Review Verfahrens wurde das Manuskript

durch Dr. Suma Choorapoikayil und mich in Rücksprache mit Prof. Patrick Meybohm und Dr. Stephanie Weibel revidiert. Für die Veröffentlichung gestaltete ich zudem einen visuellen Abstract, welcher auf den Social-Media-Accounts des Journals zu finden ist (https://twitter.com/JAMASurgery/status/1382363056773210115?s=20; https://www.facebook.com/JAMASurgery/). Innerhalb von 4 Wochen wurde das Manuskript circa 7.500-mal gelesen. Auf Grundlage der Publikation unseres Manuskriptes im JAMA Surgery erfolgte die Einladung zu einem Vortrag auf dem „Swiss Oncology & Hematology Congress“, dem drittgrößten Medizinkongress der Schweiz, welchen ich am 20. November 2021 in Zürich gehalten habe. Nach Veröffentlichung des Manuskriptes erreichte uns ein „Letter to the Editor“ (siehe Sentilhes L, et al. Importance of the Assessment Time Window for Intravenous Tranexamic Acid and Thromboembolic Events. *JAMA Surg.* Published online September 01, 2021.). Um die hier angesprochene Thematik auf der Grundlage unserer Daten zu beantworten, führte ich eine zusätzliche Subanalyse durch und verfasste mit der Unterstützung von Prof. Patrick Meybohm und Dr. Suma Choorapoikayil einen „Reply Letter“ (siehe Taeuber I, Choorapoikayil S, Meybohm P. Importance of the Assessment Time Window for Intravenous Tranexamic Acid and Thromboembolic Events—Reply. *JAMA Surg.* Published online September 01, 2021.). Aufgrund meiner strukturierten Arbeitsweise und meiner gewonnenen Expertise konnte ich Dr. Florian Piekarski und seiner Doktorandin Lara Gerdessen bei der Datenanalyse ihres Projektes zu Methoden der Erfassung von perioperativen Blutverlusten unterstützen (siehe Gerdessen L, Meybohm P, Choorapoikayil S, Herrmann E, Taeuber I, et al. Comparison of common perioperative blood loss estimation techniques: a systematic review and meta-analysis. J Clin Monit Comput. 2021;35(2):245-58). Weiterhin habe ich Prof. Patrick Meybohm und Dr. Suma Choorapoikayil bei der Durchführung einer Kosteneffektivitätsanalyse zum Thema Patient Blood Management unterstützt (siehe Meybohm P, Straub N, Fullenbach C, Judd L, Kleineruschkamp A, Taeuber I, et al. Health economics of Patient Blood Management: a cost-benefit analysis based on a meta-analysis. Vox Sang. 2020;115(2):182-8.).

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12. Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Erhöht die Gabe intravenöser Tranexamsäure die Wahrscheinlichkeit für thromboembolische Ereignisse?

in der Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie unter Betreuung und Anleitung von Prof. Dr. Patrick Meybohm mit Unterstützung durch Dr. Suma Choorapoikayil ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht*. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden in folgendem Publikationsorgan veröffentlicht:

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