ONLINE SUPPLEMENTAL MATERIALS:

Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomized and observational studies. Hutton B, Joseph L, Fergusson D, Mazer D, Shapiro S, Tinmouth A (2012).

Contents of Online Supplement:

The first material provided in this supplement is a full list of the randomized controlled trials included in our systematic review from the recent Cochrane systematic review of antifibrinolytic agents for cardiac surgery. Following this, the supplement contains additional information in the form of tables and figures referred to in the main text to present study characteristics and report results from our data analyses. The following information is provided:

List of Included Randomized Controlled Trials

(1) Alderman EL, Levy JH, Rich JB, et al. Analyses of coronary graft patency after aprotinin use: results from the international multicenter aprotinin graft patency experience (IMAGE) trial. J Thorac Cardiovasc Surg 116, 716-730. 1998.

(2) Alvarez JM JLC, Jackson LR, Chatwin C, Smolich JJ. Low-dose postoperative aprotinin reduces mediastinal drainage and blood product use in patients undergoing primary coronary artery bypass grafting who are taking aspirin: a prospective, randomized, double-blind, placebo-controlled trial. The Journal of Thoracic and Cardiovascular Surgery 122(3):457-63, 2001 Sep.

(3) Alvarez JM, Quiney NF, McMillan D, Joscelyne K, Connelly T, Brady P, et al. The use of ultra-low-dose aprotinin to reduce blood loss in cardiac surgery. Journal of Cardiothoracic & Vascular Anesthesia 9(1):29-33, 1995 Feb.

(4) Andreasen J, Nielsen C. Prophylactic tranexamic acid in elective, primary coronary artery bypass surgery using cardiopulmonary bypass. European Journal of Cardio-Thoracic Surgery 26[2], 311-317. 2004.

(5) Armellin G, Casella S, Guzzinati S, Pasini L, Marcassa A, Giron G. Tranexamic acid in aortic valve replacement. Journal of Cardiothoracic & Vascular Anesthesia 15[3], 331-335. 2001.

(6) Ashraf S, Tian Y, Cowan D, et al. "Low-dose" aprotinin modifies hemostasis but not proinflammatory cytokine release. The Annals of Thoracic Surgery 63(1):68-73, 1997 Jan.

(7) Asimakopoulos G, Kohn A, Stefanou D, Haskard D, Landis R, Taylor K. Leukocyte integrin expression in patients undergoing cardiopulmonary bypass. Annals of Thoracic Surgery 69, 1192-1197. 2000.

(8) Baele PL, Ruiz Gomez J, Londot C, Sauvage M, Van Dyck MJ, Robert A. Systematic use of aprotinin in cardiac surgery: influence on total homologous exposure and hospital cost. Acta anaesthesiologica Belgica 43(2):103-12, 1992.

(9) Bernet F. Reduction of blood loss and transfusion requirements after coronary artery bypass grafting: similar efficacy of tranexamic acid and aprotinin in aspirin-treated patients. Journal of Cardiac Surgery 14(2):92-7, 1999 Mar;-Apr.

(10) Bidstrup B, Underwood S, Sapsford RN, Streets EM. Effect of aprotinin (Trasylol) on aorta-coronary bypass graft patency. The Journal of Thoracic and Cardiovascular Surgery 105(1):147-52; discussion 153, 1993 Jan.

(11) Bidstrup BP, Royston D, Sapsford RN, Taylor KM. Reduction in blood loss and blood use after cardiopulmonary bypass with high dose aprotinin (Trasylol). The Journal of Thoracic and Cardiovascular Surgery 97(3):364-72, 1989 Mar.

(12) Bidstrup BP, Hunt BJ, Sheikh S, et al. Amelioration of the bleeding tendency of preoperative aspirin after aortocoronary bypass grafting. The Annals of Thoracic Surgery 69(2):541-7, 2000 Feb.

(13) Blauhut B, Harringer W, Bettelheim P, Doran JE, Spath P, Lundsgaard-Hansen P. Comparison of the effects of aprotinin and tranexamic acid on blood loss and related variables after cardiopulmonary bypass. J Thorac Cardiovasc Surg 108, 1083-1091. 1994.

(14) Brown R, Thwaites B, Mongan P. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary artery bypass operations: A double-blind, randomized, placebo-controlled trial. Anesth Analg 85[5], 963-970. 1997.

(15) Carrera A, Martinez M, Garcia Guiral M, et al. High doses of aprotinin in cardiac surgery. Revista Espanola de Anestesiologia y Reanimacion 41, 13-19. 1994.

(16) Casas JI, Zuazu-Jausoro I, Mateo J, et al. Aprotinin versus desmopressin for patients undergoing operations with cardiopulmonary bypass. J Thorac Cardiovasc Surg 110, 1107-1117. 1995.

(17) Casati V, Guzzon D, Oppizzi M, et al. Hemostatic effects of aprotinin, tranexamic acid, and epsilon aminocaproic acid in primary cardiac surgery. Ann Thorac Surg 68, 2252-2257. 1999.

(18) Casati V, Sandrelli L, Speziali G, et al. Hemostatic effects of tranexamic acid in elective thoracic aortic surgery: a prospective, randomized, double-blind, placebo-controlled study. Journal of Cardiothoracic & Vascular Surgery 123[6], 1084-1091. 2002.

(19) Casati V. Tranexamic acid compared with high-dose aprotinin in primary elective heart operations: effects on perioperative bleeding and allogeneic transfusions. The Journal of thoracic and Cardiovascular Surgery 120(3):520-7, 2000 Sep.

(20) Cicek S, Demirkilic U, Kuralay E, Ozal E, Tatar H. Effect on blood loss and transfusion requirements in cardiac operations. Annals of Thoracic Surgery 61, 1372-1376. 1996.

(21) Cicek S, Demirkilic U, Ozal E, et al. Postoperative use of aprotinin in cardiac operations: An alternative to its prophylactic use. Journal of Thoracic and Cardiovascular Surgery 112[6], 1462-1467. 1996.

(22) Cicekcioglu F, Cagli K, Emir M, et al. Effects of minimal dose aprotinin on blood loss and fibrinolytic system-complement activation in coronary artery bypass grafting surgery. Journal of Cardiac Surgery 21(4):336-41, 2006 Jul;-Aug.

(23) Coffey A, Pittmam J, Halbrook H, et al. The use of tranexamic acid to reduce postoperative bleeding following cardiac surgery: A double-blind randomized trial. American Surgeon 61[7], 566-568. 1995.

(24) Cohen G, Ivanov J, Weisel RD, et al. Aprotinin and dipyridamole for the safe reduction of postoperative blood loss. Ann Thorac Surg 65, 674-683. 1998.

(25) Cosgrove D, Heric B, Lyttle B, et al. Aprotinin therapy for reoperative myocardial revascularization: a placebo-controlled study. Ann Thorac Surg 54[6], 1031-1036. 1992.

(26) D'Ambra MN, Akins CW, Blackstone EH, et al. Aprotinin in primary valve replacement and reconstruction: a multicenter, double-blind, placebo-controlled trial. The Journal of Thoracic and Cardiovascular Surgery 112(4):1081-9, 1996 Oct.

(27) Daily P, Lamphere J, Dembitsky W, Adamson R, Dans N. Effect of prophylactic epsilon-aminocaproic acid on blood loss and transfusion requirements in patients undergoing first-time coronary artery bypass grafting. A randomized, prospective, double-blind study. Journal of Thoracic and Cardiovascular Surgery 108[1], 99-106. 1994.

(28) Del Rossi A, Cernaianu A, Botros S, Lemole G, Moore R. Prophylactic treatment of postperfusion bleeding using EACA. Chest 96[1], 27-30. 1989.

(29) Dietrich W, Barankay A, Hahnel C, Richter JA. High-dose aprotinin in cardiac surgery: three years' experience in 1,784 patients. J Cardiothorac and Vasc Anesth 6[3], 324-327. 1992.

(30) Dietrich W, Dilthey G, Spannagl M, et al. Influence of high-dose aprotinin on anticoagulation, heparin requirement, and celite- and kaolin-activated clotting time in heparin-pretreated patients undergoing open-heart surgery. A double-blind, placebo-controlled study. Anesthesiology 83(4):679-89; discussion 29A-30A, 1995 Oct.

(31) Dietrich W, Spannagl M, Boehm, et al. Tranexamic acid and aprotinin in primary cardiac operations: an analysis of 220 cardiac surgical patients treated with tranexamic acid or aprotinin. Anesth Analg 107, 1469-1478. 2008.

(32) Dignan RJ, Law DW, Seah PW, Manganas CW, et al. Ultra-low dose aprotinin decreases transfusion requirements and is cost effective in coronary operations. Ann Thorac Surg 71, 158-164. 2001.

(33) Diprose P, Herbertson MJ, O'Shaughnessy D, Deakin CD, Gill RS. Reducing allogeneic transfusion in cardiac surgery: a randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage. British Journal of Anaesthesia 94(3):271-8, 2005 Mar.

(34) Dryden P, O'Connor J, Jamieson W, et al. Tranexamic acid reduces blood loss and transfusion in reoperative cardiac surgery. Canadian Journal of Anesthesia 44[9], 934-941. 1997.

(35) Eberle B, Mayer E, Hafner G, et al. High-dose epsilon-aminocaproic acid versus aprotinin: antifibrinolytic efficacy in first-time coronary operations. Ann Thorac Surg 65[3], 667-673. 1998.

(36) Ehrlich M, Grabenwoger M, Cartes-Zumelzu F, et al. Operations on the thoracic aorta and hypothermic circulatory arrest: is aprotinin safe? The Journal of Thoracic and Cardiovascular Surgery 115(1):220-5, 1998 Jan.

(37) Englberger L, Markart P, Ekstein FS, Immer FF, Berdat PA, Carrel TP. Aprotinin reduces blood loss in off-pump coronary artery bypass (OPCAB) surgery. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 22(4):545-51, 2002 Oct.

(38) Englberger L, Kipfer B, Berdat PA, Nydegger UE, Carrel TP. Aprotinin in coronary operation with cardiopulmonary bypass: does "low-dose" aprotinin inhibit the inflammatory response? The Annals of Thoracic Surgery 73(6):1897-904, 2002 Jun.

(39) Feindt P, Seyfert U, Volkmer I, et al. Is there a phase of hypercoagulability when aprotinin is used in cardiac surgery? Eur J Cardiothorac Surg 8, 308-314. 1994.

(40) Fergusson DA, Hebert PC, Mazer CD, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. New England Journal of Medicine 358[22], 2319-2331. 2008.

(41) Gherli T, Porcu A, Padua G, et al. Reducing bleeding during extracorporeal circulation interventions by high doses of aprotinin. Minerva Cardioangiologica 40[4], 121-126. 1992.

(42) Golanski R, Golanski J, Chizynski K, et al. Low doses of aprotinin in aortocoronary bypass surgery--advantages and disadvantages. Med Sci Mon 6[4], 722-728. 2000.

(43) Gott J, Cooper W, Schmidt F, et al. Modifying risk for extracorporeal circulation: trial of four antiinflammatory strategies. Ann Thorac Surg 66[3], 747-753. 1998.

(44) Green D, Sanders J, Eiken M, et al. Recombinant aprotinin in coronary artery bypass graft operations. The Journal of Thoracic and Cardiovascular Surgery 110(4 Pt 1):963-70, 1995 Oct.

(45) Greilich PE, Jessen ME, Satyanarayana N, et al. The effect of epsilon-aminocaproic acid and aprotinin on fibrinolysis and blood loss in patients undergoing primary, isolated coronary artery bypass surgery: a randomized, double-blind, placebo-controlled, noninferiority trial. Anesth Analg 109[1], 15-24. 2009.

(46) Harder M, Eijsman L, Roozendaal K, van Oeveren W, Wildevuur C. Aprotinin reduces intraoperative and postoperative blood loss in membrane oxygenator cardiopulmonary bypass. Annals of Thoracic Surgery 51[6], 936-941. 1991.

(47) Hardy JF, Desroches J, Belisle S, et al. Low-dose aprotinin infusion is not clinically useful to reduce bleeding and transfusion of homologous blood products in high-risk cardiac surgical patients. Can J Anaesth 40[7], 625-631. 1993.

(48) Hardy JF, Belisle S, Dupont C, et al. Prophylactic tranexamic acid and epsilonaminocaproic acid for primary myocardial revascularization. Annals of Thoracic Surgery 65[2], 371-376. 1998.

(49) Hayashida N. Effects of minimal-dose aprotinin on coronary artery bypass grafting. The Journal of Thoracic and Cardiovascular Surgery 114(2):261-9, 1997 Aug.

(50) Hekmat K, Zimmermann T, Kampe S, Kasper SM, et al. Impact of tranexamic acid vs. aprotinin on blood loss and transfusion requirements after cardiopulmonary bypass: a prospective, randomised, double-blind trial. Current Medical Research and Opinions 20[1], 121-126. 2004.

(51) Horrow J, Hlavacek J, Strong M, et al. Prophylactic tranexamic acid decreases bleeding after cardiac operations. Journal of Thoracic and Cardiovascular Surgery 99[1], 70-74. 1990.

(52) Horrow J, van Riper D, Strong M, Brodsky I, Parmet JL. Hemostatic effects of tranexamic acid and desmopressin during cardiac surgery. Circulation 84[5], 2063-2070. 1991.

(53) Jamieson WR, Dryden PJ, O'Connor J, et al. Beneficial effect of both tranexamic acid and aprotinin on blood loss reduction in reoperative valve replacement surgery. Circulation 96[9 Supp], 96-100. 1997.

(54) Jimenez J, Iribarren J, Lorente L, et al. Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. Critical Care 11[6], R117. 2007.

(55) Kalangos A, Tayyareci G, Pretre R, Di Dio P, Sezerman O. Influence of aprotinin on early graft thrombosis in patients undergoing myocardial revascularization. European Journal of Cardio-Thoracic Surgery 8[12], 651-656. 1994.

(56) Karski J, Teasdale S, Norman P, et al. Prevention of bleeding after cardiopulmonary bypass with high-dose tranexamic acid. Double blind, randomized clinical trial. Journal of Thoracic and Cardiovascular Surgery 110[3], 835-842. 1995.

(57) Karski J, Djaiani G, Carroll J, et al. Tranexamic acid and early saphenous vein graft patency in conventional coronary artery bypass graft surgery: a prospective randomized controlled clinical trial. 130. Journal of Thoracic and Cardiovascular Surgery , 309-314. 2005. 2.

(58) Katoh J, Tsuchiya K, Sato W, Nakajima M, Iida Y. Additional postbypass administration of tranexamic acid reduces blood loss after cardiac operations. Journal of Thoracic and Cardiovascular Surgery 113[4], 802-804. 1997.

(59) Katsaros D, Petricevic M, Snow NJ, Woodhall D, Van Bergen R. Tranexamic acid reduces postbypass blood use: a double-blinded, prospective, randomized study of 210 patients. Annals of Thoracic Surgery 61[4], 1131-1135. 1996.

(60) Kipfer B, Englberger L, Gygax E, Nydegger U, Carrel T. Is reduced systemic heparinization justified with heparin-bonded bypass circuits in cardiac surgery?--Experience with and without aprotinin. Transfusion and apheresis science: 29(1):17-24, 2003 Aug.

(61) Klein M, Keith PR, Dauben H, et al. Aprotinin counterbalances an increased risk of peri-operative hemorrhage in CABG patients pre-treated with Aspirin. European Journal of Cardio-Thoracic Surgery 14[4], 360-366. 1998.

(62) Kluger R, Olive D, Stewart A, Blyth C. Epsilonaminocaproic acid in coronary artery bypass graft surgery: preincision or postheparin?. Anesthesiology 99[6], 1263-1269. 2003.

(63) Koster A, Huebler S, Merkle F, et al. Heparin-level-based anticoagulation management during cardiopulmonary bypass: a pilot investigation on the effects of a half-dose aprotinin protocol on postoperative blood loss and hemostatic activation and inflammatory response. Anesth Analg 98[2], 285-290. 2004.

(64) Kuepper F, Dangas G, Mueller-Chorus A, Kulka PM, Zenz M, Wiebalck A. Fibrinolytic activity and bleeding after cardiac surgery with cardiopulmonary bypass and low-dose aprotinin therapy. Blood coagulation & Fibrinolysis 14(2):147-53, 2003 Feb.

(65) Kuitunen A, Hiippala S, Vahtera E, Rasi V, Salmenpera M. The effects of aprotinin and tranexamic acid on thrombin generation and fibrinolytic response after cardiac surgery. Acta anaesthesiologica Scandinavica 49(9):1272-9, 2005 Oct.

(66) Kunt A, Darcin O, Avdin S, Demir D, Selli C, Andac MH. Mini-dose pump-prime aprotinin inhibited enhanced fibrinolytic activity and reduced blood loss and transfusion requirements after coronary artery bypass surgery. J Thromb Thrombolysis 19[3], 197-200. 2005.

(67) Landymore RW, Murphy JT, Lummis H, Carter C. The use of low-dose aprotinin, epsilon-aminocaproic acid or tranexamic acid for prevention of mediastinal bleeding in patients receiving aspirin before coronary artery bypass operations. European Journal of Cardio-Thoracic Surgery 11(4):798-800, 1997 Apr.

(68) Lass M, Welz A, Kochs M, Mayer G, Schwandt M, Hannekum A. Aprotinin in elective primary bypass surgery. Graft patency and clinical efficacy. European Journal of Cardio-Thoracic Surgery 9(4):206-10, 1995.

(69) Later A, Maas JJ, Engbers F, et al. Tranexamic acid and aprotinin in low- and interediate risk cardiac surgery: a non-sponsored, double-blind, randomised, placebo-controlled trial. European journal of Cardio-Thoracic Surgery 36, 322-329. 2009.

(70) Lemmer JH, Stanford W, Bonney SL, et al. Aprotinin for coronary bypass operations: efficacy, safety, and influence on early saphenous vein graft patency. A multicenter, randomized, double-blind, placebo-controlled study. The Journal of Thoracic and Cardiovascular Surgery 107(2):543-51.

(71) Lemmer JH, Dilling EW, Morton JR, et al. Aprotinin for primary coronary artery bypass grafting: a multicenter trial of three dose regimens. The Annals of Thoracic Surgery 62(6):1659-67.

(72) Levy JH, Pifarre R, Schaff HV, et al. A multicenter, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion in patients undergoing repeat coronary artery bypass grafting. Circulation 92(8):2236-44, 1995 Oct.

(73) Liu B, Belboul A, Radberg G, et al. Effect of reduced aprotinin dosage on blood loss and use of blood products in patients undergoing cardiopulmonary bypass. Scand J Thor Cardiovasc Surg 27, 149-155. 1993.

(74) Maccario M, Fumagalli C, Deangelis R, et al. Comparison between low and high doses of aprotinin in heart surgery. Minerva Anestesiol 60[6], 315-320. 1994.

(75) Maddali M, Rajakumar M. Tranexamic acid and primary coronary artery bypass surgery: a prospective study. Asian Cardiovascular and Thoracic Annals 15[4], 313-319. 2007.

(76) Maineri P, Covaia G, Realini M, et al. Postoperative bleeding after coronary revascularization. Comparison between tranexamic acid and epsilonaminocaproic acid. Minerva Cardioangiologica 48[6], 155-160. 2000.

(77) Misfeld M. Fibrinolysis-adjusted perioperative low-dose aprotinin reduces blood loss in bypass operations. The Annals of thoracic surgery 66(3):792-9, 1998 Sep.

(78) Mohr R, Goor DA, Lusky A, Lavee J. Aprotinin prevents cardiopulmonary bypass-induced platelet dysfunction. Circulation 85 (Supp II), II405-II409. 1992.

(79) Mongan PD, Brown RS, Thwaites BK, et al. Tranexamic acid and aprotinin reduce postoperative bleeding and transfusions during primary coronary revascularization. Anesthesia and analgesia 87(2):258-65, 1998 Aug.

(80) Moran SV. Comparison of two doses of aprotinin in patients receiving aspirin before coronary bypass surgery. Perfusion 15(2):105-10, 2000 Mar.

(81) Murkin J, Lux J, Shannon NA, et al. Aprotinin significantly decreases bleeding and transfusion requirements in patients receiving aspirin and undergoing cardiac operations. Journal of thoracic and cardiovascular surgery 107[2], 554-561. 1994.

(82) Nuttall GA, Oliver WC, Ereth MH, et al. Comparison of blood-conservation strategies in cardiac surgery patients at high risk for bleeding. Anesthesiology 92(3):674-82, 2000 Mar.

(83) Parvizi R, Azarfarin R, Hassanzadeh S. Ultra-low dose aprotinin effects on reducing the need for blood transfusion in cardiac surgery. Saudi Medical Journal 28[1], 49-53. 2007.

(84) Ranaboldo CJ, Thompson JF, Davies JN, et al. Prospective randomized placebo-controlled trial of aprotinin for elective aortic reconstruction. The British journal of surgery 84(8):1110-3, 1997 Aug.

(85) Rao B, Saxena N, Chauhan S, Sashikanth M. Use of EAminocaproic acid in the management of aspirin related postoperative bleeding in patients undergoing coronary revascularization. Journal of Anaesthesiology Clinical Pharmacology 15[3], 261-264. 1999.

(86) Rocha E, Hidalgo F, Llorens R, et al. Randomized study of aprotinin and DDAVP to reduce postoperative bleeding after cardiopulmonary bypass surgery. Circulation 90, 921-927. 1994.

(87) Rodrigus IE, Vermeyen KM, De Hert SG, Amsel BJ, Walter PJ. Efficacy and safety of aprotinin in aortocoronary bypass and valve replacement operations: a placebo-controlled randomized double-blind study. Perfusion 11(4):313-8, 1996 Jul.

(88) Royston D. Effect of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet 2(8571):1289-91, 1987 Dec.

(89) Sadeghi M, Mehr-Aein A. Does a single bolus dose of tranexamic acid reduce blood loss and transfusion requirements during hip fracture surgery? A prospective randomized double blind study in 67 patients. Acta Medica Iranica 45[6], 437-442. 2007.

(90) Santamaria A, Mateo J, Oliver A, et al. The effect of two different doses of aprotinin on hemostasis in cardiopulmonary bypass surgery: similar transfusion requirements and blood loss. Haematologica 85[12], 1277-1284. 2000.

(91) Santos A, Kalil R, Bauemann C, Pereira JB, Nesralla IA. A randomized, double-blind, and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary artery bypass grafting. Brazilian Journal of Medical and Biological Research 39[1], 63-69. 2006.

(92) Schweizer A, Hohn L, Morel DR, Kalangos A, Licker M. Aprotinin does not impair renal haemodynamics and function after cardiac surgery. British Journal of Anaesthesia 84[1], 16-22. 2000.

(93) Shore-Lesserson L, Reich D, Vela-Cantos F, Ammar T, Ergin M. Tranexamic acid reduces transfusions and mediastinal drainage in repeat cardiac surgery. Anesth Analg 83[1], 18-26. 1996.

(94) Speekenbrink RG, Vonk AB, Wildevuur CR, Eijsman S. Hemostatic efficacy of dipyridamole, tranexamic acid, and aprotinin in coronary bypass grafting. The Annals of thoracic surgery 59(2):438-42, 1995 Feb.

(95) Speekenbrink RG, Wildevuur CR, Sturk A, Eijsman L. Low-dose and high-dose aprotinin improve hemostasis in coronary operations. The Journal of thoracic and cardiovascular surgery 112(2):523-30, 1996 Aug.

(96) Stammers AH. The antiinflammatory effects of aprotinin in patients undergoing cardiac surgery with cardiopulmonary bypass. Journal of Extra-Corporeal Technology 29(3):114-122, 1997.

(97) Swart MJ, Gordon PC, Hayse-Gregson PB, Dyer RA, Swanepoel AL, Buckels NJ. High-dose aprotinin in cardiac surgery--a prospective, randomized study. Anaesthesia and intensive care 22(5):529-33, 1994 Oct.

(98) Taggart D, Djapardy V, Naik M, Davies A. A randomized trial of aprotinin (Trasylol) on blood loss, blood product requirement, and myocardial injury in total arterial grafting. Journal of thoracic and cardiovascular surgery 126[4], 1087-1094. 2003.

(99) Trinh-Duc P. [Comparison of the effects of epsilon-aminocaproic acid and aprotinin on intra- and postoperative bleeding in heart surgery]. Annales de chirurgie 46(8):677-83, 1992.

(100) van der Linden J, Lindvall G, Sartipy U. Aprotinin decreases postoperative bleeding and number of transfusions in patients on clopidogrel undergoing coronary artery bypass graft surgery: a double-blind, placebo-controlled, randomized clinical trial. Circulation 112(9 Suppl):I276-80, 2005 Aug.

(101) Vander-Salm T, Kaur S, Lancey R, et al. Reduction of bleeding after heart operations through the prophylactic use of epsilon-aminocaproic acid. Journal of thoracic and cardiovascular surgery 112[4], 1098-1107. 1996.

(102) Wei M, Jian K, Guo Z, Li P, et al. Effects of half dose aprotinin in coronary artery bypass grafting. World J Surg 30[6], 1108-1114. 2006.

(103) Wong BI, McLean R, Fremes S, et al. Aprotinin and tranexamic acid for high transfusion risk cardiac surgery. The Annals of thoracic surgery 69(3):808-16, 2000 Mar.

(104) Zabeeda D, Medalion B, Sverdlov M, et al. Tranexamic acid reduces bleeding and the need for blood transfusion in primary myocardial revascularization. Annals of Thoracic Surgery 74[3], 733-738. 2002.

(105) Wendel HP HW. Lower cardiac troponin T levels in patients undergoing cardiopulmonary bypass and receiving high-dose aprotinin therapy indicate reduction of perioperative myocardial damage. The Journal of thoracic and cardiovascular surgery 109(6):1164-72, 1995 Jun.

(106) Casati V, Della VP, Benussi S, et al. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: comparison between on-pump and off-pump techniques. Journal of thoracic and cardiovascular surgery 128[1], 83-91. 2004.

Literature Search Summary For RCTs and Observational Studies

A recent Cochrane systematic review of aprotinin, tranexamic acid and epsilon aminocaproic acid was used as the basis for identification of randomized controlled trials. A search of Medline, EMBASE and the Cochrane Register of Controlled Trials was conducted in November 2011 to identify any subsequent RCTs published at any time during 2011. The same databases were also searched with no date restrictions to identify relevant propensity score matched or propensity score adjusted observational studies. Provided below are the strategies implemented for these searches.

E-Table 1: Summary of Literature Searches for RCT Update

Medline	EMBASE	Cochrane Register of Controlled trials
1 Randomized controlled trial.pt. 2 Controlled clinical trial.pt. 3 Randomized controlled trial.sh. 4 Random allocation.sh. 5 Double blind method.sh. 6 Single-blind method.sh. 7 or/1-6 8 (ANIMALS not HUMAN).sh. 9 7 not 8 10 Clinical trial.pt. 11 exp Clinical trial 12 (clin$ adj25 trial$).ti,ab. 13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 14 Placebos.sh. 15 placebo$.ti,ab. 16 random$.ti,ab. 17 Research design.sh. 18 or/10-17 19 18 not 8 20 19 not 9 21 COMPARATIVE STUDY.sh. 22 exp EVALUATION STUDIES/ 23 FOLLOW UP STUDIES.sh. 24 PROSPECTIVE STUDIES.sh. 25 (control$ or prospectiv$ or volunteer$).ti,ab. 26 or/21-25 27 26 not 8 28 27 not (9 or 20)	1 Clinical trial/ 2 Randomized Controlled Trial/ 3 Randomization/ 4 Single Blind Procedure/ 5 Double Blind Procedure/ 6 Crossover Procedure/ 7 Placebo/ 8 Randomi?ed controlled trial$.tw. 9 Rct.tw. 10 Random allocation.tw. 11 Randomly allocated.tw. 12 Allocated randomly.tw. 13 (allocated adj2 random).tw. 14 Single blind$.tw. 15 Double blind$.tw. 16 ((treble or triple) adj blind$).tw. 17 Placebo$.tw. 18 Prospective Study/ 19 or/1-18 20 Case Study/ 21 Case report.tw. 22 Abstract report/ or letter/ 23 or/20-22 24 19 not 23 25 aprotinin/ 26 (antilysin or aprotinin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or traskolan or trasylol or zymofren).mp.	(antilysin or aprotinin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or traskolan or trasylol or zymofren) and (heart or cardiac or coronary) in Record Title, Abstract or Keywords**,** in 2011

E-Table 1: Summary of Literature Searches for RCT Update		
29 9 or 20 or 28 30 Aprotinin/ 31 (antilysin or aprotinin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or traskolan or trasylol or zymofren).mp. 32 heart/ or (heart or cardiac or coronary).tw. 33 (30 or 31) and 32 34 29 and 33 35 limit 34 to yr="2011"	27 heart/ or (heart or cardiac or coronary).tw. 28 (25 or 26) and 27 29 24 and 28 30 limit 29 to yr="2011"	

E-Table 2: Summary of Searches for Eligible Cohort Studies		
Medline	**EMBASE**	**Cochrane Register of Controlled trials**
1. Aprotinin 2. (antilysin or aprotinin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or traskolan or trasylol or zymofren).mp. 3. heart/ or (heart or cardiac or coronary).tw 4. (1 or 2) and 3 5. (logistic or propensity).mp 6. 4 and 5	1 aprotinin/ 2 (antilysin or aprotinin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or traskolan or trasylol or zymofren).mp. 3 heart/ or (heart or cardiac or coronary).tw. 4 (1 or 2) and 3 5 (logistic or propensity).mp. 6 4 and 5	(antilysin or aprotinin or contrical or contrykal or dilmintal or iniprol or kontrikal or kontrykal or pulmin or traskolan or trasylol or zymofren) and (heart or cardiac or coronary) in Title, Abstract or Keywords and (logistic or propensity) in Cochrane Central Register of Controlled Trials

E-Table 3: Study characteristics of additional studies identified beyond Cochrane review						
First author (year)	**Study Design**	**Patients' Inclusion criteria**	**Interventions compared (with dosages where available)**	**Sample size of groups from included analyses**	**Quality score (Newcastle Ottawa Scale)**	**Summary of study findings (based on propensity matched sample where available)**
Mangano (2006)	Propensity-adjusted cohort	Patients undergoing CABG at one of 69 centers	APRO versus TXA versus EACA versus no therapy	APRO: 1295; TXA: 822; EACA: 883; No therapy: 1374	9/9	Following propensity score adjustments, increased risks of death, MI, stroke, renal dysfunction with APRO vs no therapy. No such differences when TXA, EACA were compared to no therapy.
Karkouti (2006)	Propensity-matched cohort	Patients undergoing cardiac surgery between 1999-2004. CABG and other procedures and those with prior surgeries were enrolled.	APRO (Hammersmith dose) versus TXA (50-100mg/kg)	APRO: 449; TXA: 449	9/9	Aprotinin was associated with elevated risk of renal dysfunction (24% vs 17%) and renal failure (5.6% vs 3.1%). rates of death (7% vs 7%), MI (3% vs 2%), stroke (3% vs 3%) weren't significantly different.
Karkouti (2010)	Propensity-matched cohort	Patients undergoing cardiac surgery between 2000-2008	APRO (Hammersmith dose) versus TXA (50-100mg/kg)	APRO: 772; TXA: 772	9/9	No significant differences between APRO and TXA for death (7% vs 7.4%), MI (3% vs 2.3%), stroke (3.6% vs 2.3%) or dialysis (5.6% vs 3.6%)
Olenchock (2008)	Propensity-adjusted cohort (stratification)	Patients undergoing single CABG surgery between 1994-2006.	APRO (Hammersmith dose) versus EACA (10g bolus, 2g/hr)	APRO: 1507; EACA: 1830	9/9	Post-operative renal failure was found to be higher with aprotinin (6.2% vs 2.7%), as was newly required dialysis (2.1% vs 0.7%). Neurologic complication was higher with EACA (3.7% vs 5.1%). 30-day (4.1% vs 1.0%) and 5-year mortality (26.8% vs 12.8%) were higher with aprotinin. MI was similar between groups (0.3% vs 0.3%). Renal failure and mortality remained higher with aprotinin after propensity score stratification.
Shaw (2008)	Propensity-matched cohort	Patients undergoing CABG (some with valve procedures also) between 1996-2005.	APRO versus no therapy (data not available for EACA group)	APRO: 996 No therapy: 996	9/9	30-day and one-year mortality rates were comparable between groups (4.74% vs 4.24%; 13.1% vs 11.5%).
Schneeweiss (2008)	Propensity-matched cohort	Patients undergoing CABG between 2003-2006	APRO (variable dose) versus EACA (at least 10g)	APRO: 4799; EACA: 4799	9/9	Estimated differences between APRO and EACA were: death (4.4% vs 3.3%), stroke (2% vs 8%), and need for dialysis (2.5% vs 2.4%)
Stamou	Propensity	Patients undergoing	APRO (hammersmith	APRO: 570;	9/9	No significant differences between APRO and EACA for

E-Table 3: Study characteristics of additional studies identified beyond Cochrane review						
First author (year)	**Study Design**	**Patients' Inclusion criteria**	**Interventions compared (with dosages where available)**	**Sample size of groups from included analyses**	**Quality score (Newcastle Ottawa Scale)**	**Summary of study findings (based on propensity matched sample where available)**
(2009)	matched cohort	CABG, isolated valve surgery or valve and CABG between 2002-2006	dose) versus EACA (total dose 10g)	EACA: 114		death (4% vs 1%), MI (0.9% vs 0.9%), stroke (1.9% vs 2.6%), renal failure (6.8% vs 2.6%) or haemodialysis (1.4% vs 1.8%)
Ngaage (2008)	Propensity-matched cohort	Patients undergoing CABG, AVR, MVR as isolated or combined procedure between 1998-2007.	No therapy versus APRO (hammersmith dose)	no therapy: 341; APRO: 341	9/9	Rates of death (2% vs 1%) , stroke (2% vs. 1%), renal insufficiency (3.5% vs 3.8%) were similar between aprotinin and no aprotinin groups
Jakobsen (2009)	Propensity matched cohort	Patients undergoing cardiac surgery (including multiple procedures and repeat procedures) between 2003-2006	APRO versus TXA	APRO:534; TXA: 534	9/9	Differences between APRO and TXA groups were: death (8.1% vs 7.1%), MI (7.2% vs 7.2%), stroke (5.1% vs 3.4%), dialysis 10.3% vs 5.4%)
Wang (2010)	Propensity matched cohort	Chinese patients undergoing isolated primary CABG between 1999-2005.	APRO (10,000 KIU test dose, $2x10^6$ KIU loading dose, $1x10^6$KIU maintenance dose) vs no therapy	APRO: 981; no therapy: 981	9/9	No significant differences between APRO and no therapy for renal failure (0.7% vs 0.5%), stroke (0.1% vs 0.6%), MI (2.1% vs 1.6%) or death (3.9% vs 3.8%)
Gillespie (2005)	Propensity matched cohort	Patients undergoing cardiac surgery between 1999-2003	APRO (mean dose $2.75x10^6$ KIU) vs no therapy	APRO: 219; no therapy: 219	9/9	None of the following comparisons between groups achieved conventional statistical significance: death (14.2% vs 16.9%), MI (3.2% vs 4.1%), stroke (1.8% vs 4.1%), renal failure (14.2% vs 10%).

CABG=coronary artery bypass graft; APRO=aprotinin; TXA=tranexamic acid; EACA=epsilon-aminocaproic acid; AVR=aortic valve repair; MVR=mitral valve repair. For the Newcastle Ottawa Scale, a maximum of 9 points can be achieved and scores are based on the elements of patient selection, comparability, and outcome assessment. All observational studies achieved the maximum number of points possible.

Summary of Ranking Probabilities by Intervention and Outcome

E- Figures 1a-1d:
Summary of estimated probabilities of rankings by clinical outcome from MTC meta-analyses of all available data

LEGEND:

Aprotinin Placebo TXA EACA

Figure 1a: death

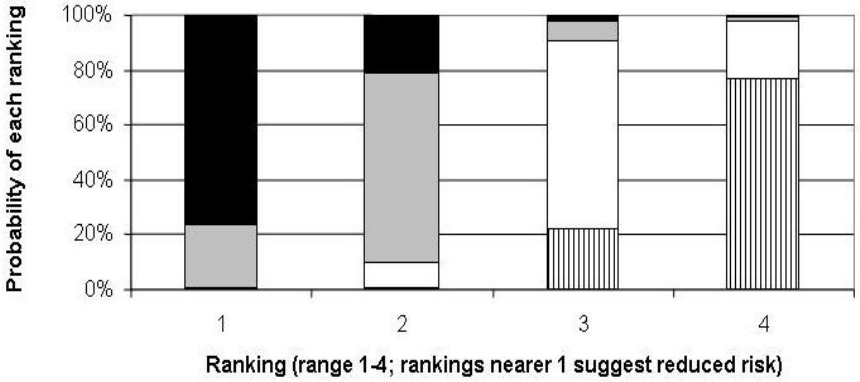


Figure 1b: myocardial infarction

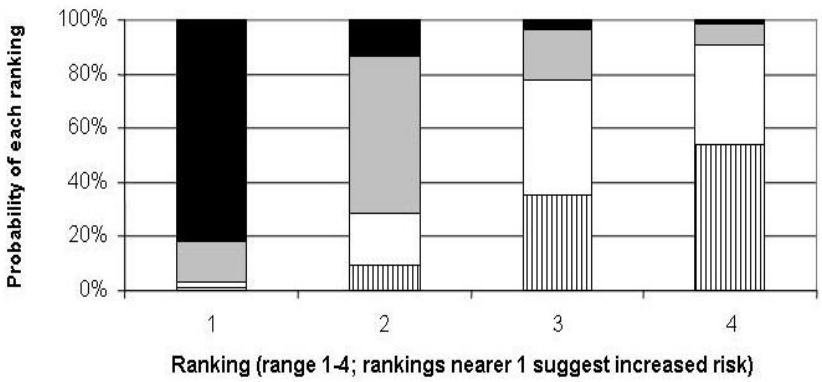
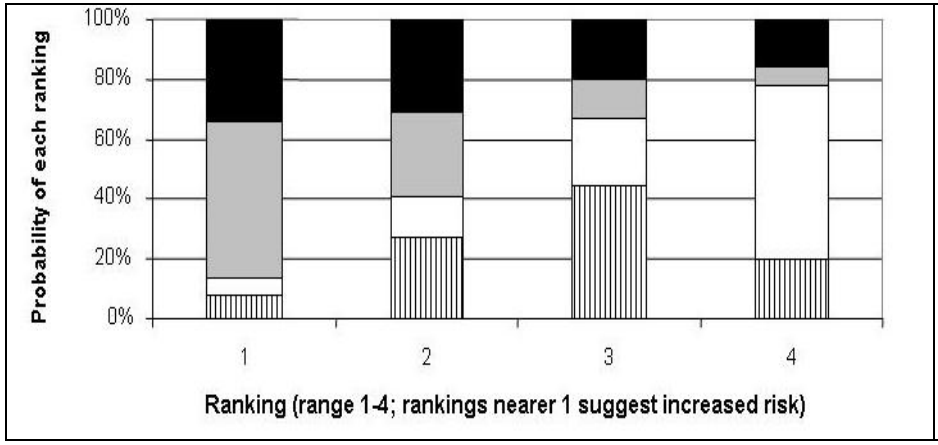
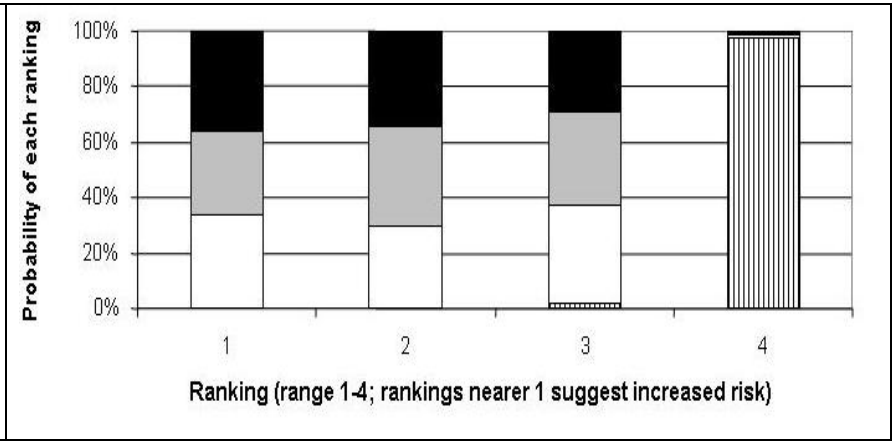


Figure 1c: stroke

Figure 1d: renal failure / dysfunction


Probability of each ranking
100%
80%
60%
40%
20%
0%
1
2
3
4
Ranking (range 1-4; rankings nearer 1 suggest increased risk)


Probability of each ranking
100%
80%
60%
40%
20%
0%
1
2
3
4
Ranking (range 1-4; rankings nearer 1 suggest increased risk)

Summary of prediction intervals for network meta-analyses of all available data, by outcome

E-Table 4: 95% Prediction Intervals for Pairwise Comparisons based on All Available Data, by Outcome								
Comparison (reference group listed first)	**Death**		**MI**		**Stroke**		**Renal**	
	Estimate and 95% Prediction Interval	**P(OR<1)**	**Estimate and 95% Prediction Interval**	**P(OR<1)**	**Estimate and 95% Prediction Interval**	**P(OR<1)**	**Estimate and 95% Prediction Interval**	**P(OR<1)**
Aprotinin versus placebo	0.91 (0.43 to 1.92)	61.8%	0.97 (0.70 to 1.49)	57.9%	1.14 (0.29 to 4.23)	41%	0.66 (0.32 to 1.43)	87.8%
Aprotinin versus TXA	0.72 (0.32 to 1.52)	83%	0.88 (0.61 to 1.34)	78.1%	0.80 (0.21 to 3.15)	65%	0.67 (0.31 to 1.38)	88.6%
Aprotinin versus EACA	0.61 (0.28 to 1.35)	90.8%	0.77 (0.53 to 1.21)	90.3%	0.89 (0.22 to 3.45)	57.9%	0.65 (0.30 to 1.33)	89.9%
Placebo versus TXA	0.78 (0.35 to 1.70)	75.5%	0.90 (0.59 to 1.33)	74.5%	0.71 (0.18 to 2.92)	71.5%	1.01 (0.44 to 2.15)	49.1%
Placebo versus EACA	0.66 (0.30 to 1.50)	86.3%	0.80 (0.51 to 1.20)	89.9%	0.78 (0.19 to 3.23)	65.7%	0.99 (0.42 to 2.09)	51.3%
TXA versus EACA	0.84 (0.38 to 2.02)	67.4%	0.88 (0.57 to 1.36)	75.9%	1.10 (0.26 to 4.44)	43.7%	0.98 (0.44 to 2.10)	50.0%

Summary data reported represent the summary estimate and corresponding 95% prediction interval for each pairwise comparison, as well as the probability that each predicted summary estimate is below 1 (suggesting an increased risk of harm with aprotinin). OR=odds ratio, TXA=tranexamic acid, EACA=epsilon-aminocaproic acid.

Supplement of Full Results of Network Meta-Analyses of Randomized Trials Only

Provided below is a summary of results obtained from network meta-analyses based on evidenced from randomized controlled trials, excluding all observational evidence.

E-Table 5: Full Results from Analyses Limited to Randomized Studies

Pairwise comparison	Odds Ratio and 95% Credible Interval			
	Death	Myocardial Infarction	Stroke	Renal failure/ dysfunction
APRO vs no therapy	1.00 (0.72 to 1.36)	1.14 (0.89 to 1.47)	1.05 (0.40 to 2.23)	0.83 (0.50 to 1.37)
APRO vs TXA	0.63 (0.40 to 0.96)	0.95 (0.66 to 1.44)	1.06 (0.33 to 2.63)	0.82 (0.31 to 1.68)
APRO vs EACA	0.80 (0.48 to 1.53)	0.79 (0.50 to 1.30)	0.72 (0.15 to 2.02)	0.74 (0.23 to 1.44)
no therapy vs TXA	0.64 (0.39 to 1.01)	0.84 (0.55 to 1.28)	1.00 (0.38 to 2.58)	0.98 (0.36 to 2.17)
no therapy vs EACA	0.80 (0.46 to 1.63)	0.69 (0.43 to 1.16)	0.67 (0.17 to 2.10)	0.88 (0.28 to 1.89)
TXA vs EACA	1.27 (0.73 to 2.66)	0.81 (0.50 to 1.44)	0.68 (0.15 to 2.25)	0.92 (0.31 to 2.08)

For all estimates, the first treatment listed for the comparison served as the reference group. APRO= aprotinin, TXA= tranexamic acid, EACA=epsilon-aminocaproic acid

Summary of Findings from Sensitivity Analyses

Supplemental E-Table 6 summarizes findings from sensitivity analyses carried out to explore the effects of RCT quality and observational evidence in findings from network meta-analysis.

E-Table 6:
Sensitivity Analysis Results by Outcome, Odds Ratio (95% CrI)

Comparator (aprotinin is reference group)	Primary Network Meta-Analysis Result	Sensitivity Analyses Excluding:		
		Low quality RCTs	Propensity adjusted studies	Low quality RCTs & propensity adjusted studies
Mortality				
# included studies	93	41	91	39
No Therapy	0.91 (0.71 to 1.16)	0.80 (0.54 to 1.09)	1.01 (0.83 to 1.23)	0.94 (0.71 to 1.19)
TXA	0.71 (0.50 to 0.98)	0.73 (0.45 to 1.09)	0.84 (0.64 to 1.06)	0.87 (0.62 to 1.16)
EACA	0.60 (0.43 to 0.87)	0.58 (0.38 to 0.90)	0.75 (0.58 to 0.97)	0.74 (0.54 to 1.03)
Myocardial Infarction				
# included studies	75	31	73	29
No Therapy	0.98 (0.81 to 1.20)	0.87 (0.70 to 1.12)	1.09 (0.86 to 1.36)	0.97 (0.66 to 1.42)
TXA	0.89 (0.73 to 1.11)	0.86 (0.70 to 1.08)	0.92 (0.71 to 1.20)	0.89 (0.65 to 1.24)
EACA	0.78 (0.60 to 1.03)	0.77 (0.60 to 1.02)	0.76 (0.50 to 1.16)	0.79 (0.49 to 1.33)
Stroke				
# included studies	50	28	48	26
No Therapy	1.14 (0.68 to 1.89)	1.06 (0.60 to 1.87)	1.19 (0.67 to 2.02)	1.09 (0.58 to 2.07)
TXA	0.81	0.78	0.90	0.88

	(0.48 to 1.40)	(0.47 to 1.32)	(0.53 to 1.59)	(0.54 to 1.52)
EACA	0.89 (0.48 to 1.40)	0.90 (0.51 to 1.56)	0.95 (0.44 to 2.00)	0.95 (0.49 to 1.98)
Renal Failure / Dysfunction				
# included studies	37	23	35	21
No Therapy	0.66 (0.45 to 0.88)	0.60 (0.40 to 0.88)	0.78 (0.56 to 1.11)	0.72 (0.45 to 1.12)
TXA	0.66 (0.48 to 0.91)	0.66 (0.45 to 0.93)	0.69 (0.49 to 0.90)	0.68 (0.44 to 0.96)
EACA	0.65 (0.45 to 0.88)	0.64 (0.43 to 0.89)	0.78 (0.49 to 1.05)	0.76 (0.41 to 1.05)

Aprotinin was used as the reference group for all analyses. RCT=randomized controlled trial, TXA=tranexamic acid, EACA=epsilon-aminocaproic acid.

Summary of Model Fit Assessment

As recommended for conduct of network meta-analysis, model fit for our analyses was assessed by comparing the observed residual deviance to the number of unconstrained data points (i.e. total number of intervention arms across all studies) in each case. Adequate fit is suggested to be present when these two quantities are approximately equal to each other.

E-Table 7: Assessment of Model Fit

Clinical Outcome	Analyses of RCTs only		Analyses of RCTs with Observational Data	
	# unconstrained data points	Residual deviance	# unconstrained data points	Residual deviance
Death	122	137.2	146	163.0
Myocardial Infarction	112	114.6	130	129.5
Stroke	59	61.1	81	88.0
Renal dysfunction/failure	38	39.1	58	57.7

Summary of Pairwise Meta-Analyses of head-head study data

The following table summarizes meta-analytic estimates from synthesis of head-to-head direct data for all pairwise comparisons. These may be of interest to readers as a means of assessing the consistency of direct and indirect evidence used for network meta-analyses. All meta-analyses used a random effects approach with a uniform(0,10) prior distribution for the between study-standard deviation.

E-table 8: Summary estimates derived from pairwise meta-analyses of head-head study data

Pairwise Comparison	Clinical Outcome and Summary Odds Ratio (95% CrI)			
	Death	MI	Stroke	Renal
Aprotinin vs no therapy	1.00 (0.82 to 1.25)	0.99 (0.75 to 1.22)	1.18 (0.49 to 2.78)	0.66 (0.46 to 1.01)
Aprotinin vs TXA	0.78 (0.46 to 1.18)	0.88 (0.69 to 1.14)	0.64 (0.29 to 1.11)	0.68 (0.47 to 0.95)
Aprotinin vs EACA	0.48 (0.23 to 0.87)	0.74 (0.48 to 1.28)	0.96 (0.34 to 2.94)	0.63 (0.30 to 1.08)
No therapy vs TXA	0.64 (0.12 to 1.87)	0.93 (0.17 to 8.98)	0.85 (0.22 to 2.50)	0.95 (0.01 to 17.1)
No therapy vs EACA	0.39 (0.01 to 3.57)	0.92 (0.41 to 2.81)	0.43 (0.01 to 13.1)*	0.74 (0.01 to 401)*
TXA vs	0.53	0.88	1.40	1.02

EACA	(0.0001 to 5.35)	(0.43 to 2.33)	(0.05 to 304)*	(0.01 to 100)*

An OR<1 favors the second comparator listed. The symbol '*' denotes meta-analyses where model convergence based on a burn-in of 20,000 iterations and sampling of 50,000 iterations was questionable based on Gelman-Rubin plots.

Graphical Summary of Treatment Rankings Across Clinical Outcomes

Cumulative probability plots of rankings for each therapy are helpful to facilitate interpretation of findings from network meta-analysis. Summary plots for the outcomes of death, MI, stroke, and renal failure / dysfunction are provided below.

E-Figures 2a-2d: Cumulative Probability Plot for Treatment Rankings by Outcome Measure

LEGEND

Figure 2a: Mortality

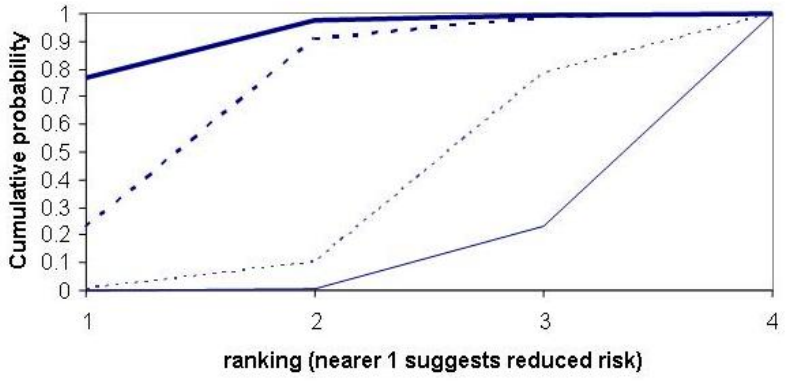


Figure 2b: Myocardial Infarction

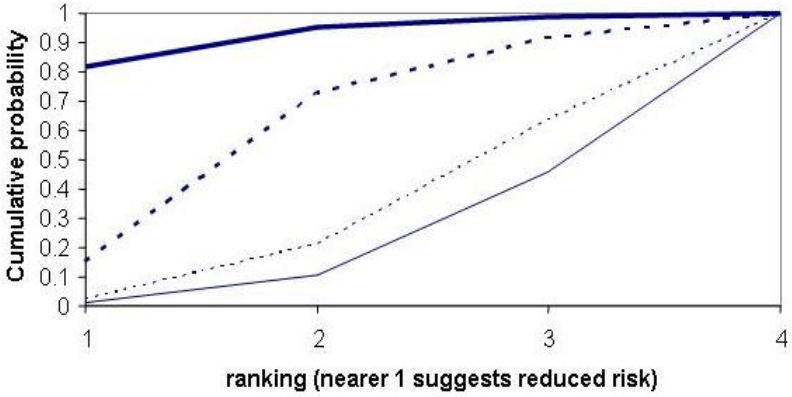
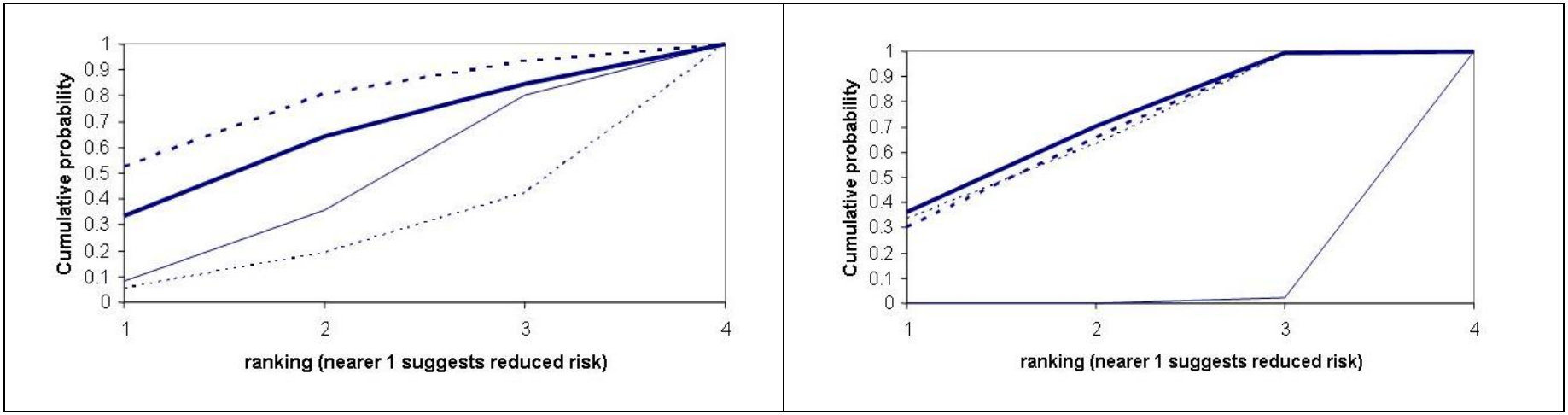


Figure 2c: Stroke

Figure 2d: Renal failure / dysfunction


Cumulative probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
ranking (nearer 1 suggests reduced risk)
Cumulative probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
ranking (nearer 1 suggests reduced risk)