Appendix 1 (as supplied by the authors): Supplementary material concerning randomized controlled trial on the effects of oral curcumin in elective abdominal aortic aneurysm repair

Version August 3, 2018

Table of Contents

Appendix to: Garg AX, Devereaux PJ, Hill A, et al.; Curcumin AAA AKI Investigators. Oral curcumin in elective abdominal aortic aneurysm repair: a multicentre randomized controlled trial. *CMAJ* 2018. DOI:10.1503/cmaj.180510.

Curcumin AAA AKI Investigators

Amit X. Garg, PJ Devereaux, Andrew Hill, Manish Sood, Bharat Aggarwal, Luc Dubois, Swapnil Hiremath, Randolph Guzman, Vikram Iyer, Matthew T. James, Eric McArthur, Louise Moist, Georges Ouellet, Chirag R. Parikh, Virginia Schumann, Sumit Sharan, Heather Thiessen-Philbrook, Sheldon Tobe, Ron Wald, Michael Walsh, Matthew Weir, Neesh Pannu

Section 1. Animal studies which demonstrate curcumin prevents toxin and ischemic reperfusion injury to the kidneys

Study	Model	Kidney Insult	Effect of Curcumin
Ischemia-Reperfusion			
Bayrak et al.	Rat	Ischemia-reperfusion from 45 minutes bilateral renal pedicle clamping	Improved renal morphology; improved urea and cystatin C levels, reduced oxidation products
Jones et al.	Rat	Ischemia-reperfusion from 30 minutes left renal pedicle occlusion with contralateral nephrectomy	Reduced renal injury; decreased tubular damage, attenuated renal inflammation, prolonged skin graft survival
Kaur et al.	Rat	Ischemia-reperfusion from 45 minutes unilateral renal pedicle occlusion	Attenuated renal dysfunction and morphological changes; reduced tubular necrosis, hyaline casts, epithelial swelling, proteinaceous debris, hemorrhage, and medullary congestion
Shoskes et al.	Rat	Ischemia-reperfusion from 30 minutes left renal pedicle occlusion with simultaneous right nephrectomy	Preserved histological integrity, decreased tubular damage and interstitial inflammation
Liu et al.	Rat	Ischemia-reperfusion from unilateral artery occlusion	Protected kidney tubules by modulating nitric oxide signaling pathway
Kaur et al.	Rat	Ischemia-reperfusion	Increased creatinine clearance and reduced blood urea and uric acid. Improved the fractional excretion of sodium, and reduced proteinuria. Reduced markers of oxidative stress. Renoprotection on histology.
Liu et al.	Rat	Ischemia-reperfusion	Attenuated renal injury in a dose-dependent way. Significant reduction in the serum creatinine, blood urea nitrogen level and also suppressed the kidney injury molecules-1. Significant inhibition of the malonaldehyde, caspase-3, myeloperoxide, lactose dehydrogenase and interferon-gamma together with enhanced interleukin-10 content
Najafi et al.	Rat	Ischemia-reperfusion	Decrease in serum concentration of creatinine, urea-nitrogen, tissue malondialdehyde level, and leukocytes infiltration, and better ferric reducing/antioxidant power levels
Aydin et al.	Rat	Abdominal aorta ischemia for 60 minutes followed by 120 minutes of reperfusion	Reduced histopathologic injury and oxidative stress (as assessed with blood serum antioxidant capacity, total oxidative status, and oxidative stress index).
Chen et al.	Rat	Bilateral occlusion of renal pedicles for 45 minutes followed by 3 hours or reperfusion	Lower serum malondialdehyde, urea, creatinine. Also improvement in cardiac parameters (serum troponin I) and TNF-alpha. Better cardiac ejection fraction and higher systolic blood pressure.
Rogers et al.	Mice	Bilateral occlusion of renal pedicles for 30 minutes.	Improved serum creatinine, reduced histological injury and cellular apoptosis and lowered Toll-like receptor-4, heat shock protein-70 and TNF-α mRNA expression. Reduced neutrophil infiltration and diminished inflammatory chemokine expression. Reduced intracellular superoxide generation and increased superoxide dismutase levels, decreased inducible NOS mRNA expression and 3-nitrotyrosine staining (consistent with limitations in nitrosative stress and inhibited renal tubular mRNA and protein expression of thioredoxin-interacting protein). Actions mediated by inhibition of NF-κB, MAPK and phospho-S6 ribosomal protein.
Nephrotoxin Injury			
Chen et al.	Rat	LPS-induced disseminated intravascular coagulation	Prevented fibrin deposition in glomeruli, decreased circulating TNF-α levels
Farombi et al.	Rat	Gentamicin-induced renal oxidative damage	Attenuated lipid perodixative damage, decreased CAT, GSH-Px, and GSH levels
Kuhad et al.	Rat	Cisplatin nephrotoxicity	Dose-dependently restored renal function, reduced serum TNF-α and lipid peroxidation
Okada et al.	Mouse	Ferric nitrilotriacetate (Fe-NTA)-induced oxidative renal damage	Suppressed oxidative stress, induced antioxidant enzymes
Tirkey et al.	Rat	Cyclosporine-induced renal dysfunction and oxidative stress	Attenuated renal dysfunction, normalized renal morphology, reduced elevated levels of thiobarbituric

			acid reactive substances (TBARS), increased antioxidant enzymes
Verma et al.	Mouse	Aflatoxin-induced hepatic and renal lipid peroxidation	Decreased lipid peroxidation, increased enzymatic and non-enzymatic antioxidants
Chen et al.	Rat	Glycerol-induced acute kidney injury (rhabdomyolysis)	Reduced oxidative stress, apoptosis, cleaved Capase-3 and GRP-78 expression
Akinyemi et al.	Rat	Cadmium-induced renal toxicity	Increased nonexymatic antioxidant status and nitric oxide in the kidney, with a concomitant decrease in the levels of malondialdehyde and renal biomarkers (serum urea, creatinine)
Wu et al.	Rat	Glycerol-induced acute kidney injury (rhabdomyolysis)	Significant reduction in blood urea, serum creatinine and creatinine kinase levels. Significant increase in kidney tissue superoxide dismutase enzyme activity and glutathione peroxidase levels and a reduction in malondialdehyde. Less severe renal lesions and renal injury on histopathology. Benefits in renal immunohistochemistry, less renal cell apoptosis, decreased mRNA expression of inflammation and kidney injury markers in renal tissue.
Ahmed et al.	Rat	Non-steroidal anti-inflammatory drug induced acute kidney injury (diclofenac)	Attenuation of fatty changes and eosinophilic casts in renal tubules.
Kumar et al.	Rat	Cisplatin-induced nephrotoxicity	Mitigated nephrotoxicity by reducing inflammatory markers TNF-α, interleukin-6, interleukin-8
Kumar et al.	Rat	Cisplatin-induced nephrotoxicity	Reduced blood urea, serum creatinine, TNF-α, interleukin-6, interleukin-8, and increased albumin and IL-10 levels. Less nephrotoxicity on histopathology.
Topcu-Tarladacalisir et al.	Rat	Cisplatin-induced nephrotoxicity	Ameliorated the development of kidney injury (histopathology), inflammatory responses [myeloperoxidase (MPO) and tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, IL-10 levels], the degree of lipid peroxidation [malondialdehyde (MDA) level], renal tubular cell apoptosis (active caspase-3) and expression of related proteins [p53, Fas, and Fas ligand (Fas-L)] by immunohistochemistry, and renal dysfunction (serum urea and creatinine)
Molina-Jijon et al.	Rat	Maleate-induced kidney injury	Curcumin prevented maleate-induced proteinuria, increased heat shock protein of 72 KDa (Hsp72) expression, and decreased plasma glutathione peroxidase activity. Ameliorated measures of oxidative stress, and epithelial damage. Decreased mitochondrial fission and autophagy.
Cuce G et al.	Mouse	Methanesulfonate induced kidney injury	Improved congestion and vacuole formation in the kidney and reduced apoptosis.
Hismiogullari AA et al.	Rat	Carbon tetrachloride induced kidney injury	Renoprotective effect; reduced inflammation and cell apoptosis
He et al.	Rat	Gentamycin-induced nephrotoxicity	Lower blood urea and serum creatinine; significant reduction of kidney injury biomarkers plasma NGAL and KIM-1. Less tubular damage on histology, attenuated apoptosis of tubule cells and oxidative stress of the kidney. Upregulated expression of Nrf2, HO-1, and Sirt1 expression (which protects against oxidative stress).
Ugur et al.	Rat	Cisplatin-induced nephrotoxicity	Lower serum urea, creatinine and malondialdehyde levels. Higher resistance to stress (higher nicotinamide phosphoribosyltransferase (NAMPT) and sirtuin (SIRT) proteins)
Tapia E at al.	Rat	Maleate-induced nephrotoxicity	Prevented oxidative stress and preserved mitochondrial oxygen consumption and activity of respiratory complex I
Buyuklu M et al.	Rat	Contrast-induced injury	Lower serum urea and creatinine levels. Significant increase in tissue antioxidant profiles and a significant reduction in tissue lipid peroxidation. Less necrotic and degenerative changes, and less intertubular hemorrhage on histopathology. Reduced iNOS expression, LC3/B and active caspace 3. Less apoptotic and autophagic cell death.

Ueki M et al.	Mouse	Cisplatin-induced nephrotoxicity	Anti-inflammatory effects (lower serum concentration of TNF-alpha; lower TNF-alpha and MCP-1 concentrations and ICAM-1 mRNA expression in kidney). Attenuation of renal dysfunction and renal tubular necrosis.
Zhong F et al.	Mouse	Endotoxin-induced kidney inflammation	A change in gene expression as assessed with gene chip technology. Most of the genes were found to be related to the genes of regulation of macrophage activation and macrophage activation-associated genes.
Manikandan R et al.	Rat	Gentamicin-induced nephrotoxicity	Reduced kidney lipid peroxidation (LPO), nitric oxide synthase, nuclear factor-kB, increased activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST) and glutathione (GSH).
Molina-Jijon et al.	Rat	Renal oxidant damage induced by hexavalent chromium	Reduced renal dysfunction, histological damage, oxidant stress, and the decrease in antioxidant enzyme activity both in kidney tissue and in mitochondria. Reduced mitochondrial dysfunction.
Zhong F et al.	Mice	Lipopolysaccharide-induced renal inflammation	Protective effect on renal inflammation, potentially attributed to its inhibitory effects on MCP-1 mRNA expression and DNA-binding activity of NF-κB.
Ahminda	Rat	Vancomycin induced nephrotoxicity	Reduction in induction levels of thiobarbituric acid reactive substances in plasma and kidney, urea and creatinine. Improved antioxidant enzymes and GSH.

References

1. Bayrak O, Uz E, Bayrak R, *et al*. Curcumin protects against ischemia/reperfusion injury in rat kidneys. *World J Urol* 2008 June;26:285–91.
2. Jones EA, Shoskes DA. The effect of mycophenolate mofetil and polyphenolic bioflavonoids on renal ischemia reperfusion injury and repair. *J Urol* 2000 March;163:999–1004.
3. Kaur H, Satyanarayana PSV, Singh D, Chopra K. Bioflavonoids in salvage of ischemic renal failure. *Emerging Drugs* 2003;2:118–31.
4. Shoskes DA. Effect of bioflavonoids quercetin and curcumin on ischemic renal injury: a new class of renoprotective agents. *Transplantation* 1998 July 27;66:147–52
5. Liu F, Ni W, Zhang J, Wang G, Li F, Ren W. Administration of Curcumin Protects Kidney Tubules Against Renal Ischemia-Reperfusion Injury (RIRI) by Modulating Nitric Oxide (NO) Signaling Pathway. *Cell Physiol Biochem.* 2017 Nov 13;44:401–411.
6. Kaur A, Kaur T, Singh B, Pathak D, Singh Buttar H, Pal Singh A. Curcumin alleviates ischemia reperfusion-induced acute kidney injury through NMDA receptor antagonism in rats. *Ren Fail.* 2016 Oct;38:1462–1467.
7. Liu FH, Ni WJ, Wang GK, Zhang JJ. Protective role of curcumin on renal ischemia reperfusion injury via attenuating the inflammatory mediators and Caspase-3. *Cell Mol Biol (Noisy-le-grand)*. 2016 Sep 30;62:95–99.
8. Najafi H, Changizi Ashtiyani S, Sayedzadeh SA, Mohamadi Yarijani Z, Fakhri S. Therapeutic effects of curcumin on the functional disturbances and oxidative stress induced by renal ischemia/reperfusion in rats. *Avicenna J Phytomed*. 2015 Nov-Dec;5:576–86.
9. Aydin MS, Caliskan A, Kocarslan A, *et al.* Intraperitoneal curcumin decreased lung, renal and heart injury in abdominal aorta ischemia/reperfusion model in rat. *Int J Surg.* 2014;12:601–5.
10. Chen TH, Yang YC, Wang JC, Wang JJ. Curcumin treatment protects against renal ischemia and reperfusion injury-induced cardiac dysfunction and myocardial injury. *Transplant Proc.* 2013;45:3546–9.
11. Rogers NM, Stephenson MD, Kitching AR, Horowitz JD, Coates PT. Amelioration of renal ischaemia-reperfusion injury by liposomal delivery of curcumin to renal tubular epithelial and antigen-presenting cells. *Br J Pharmacol.* 2012 May;166:194–209. doi: 10.1111/j.1476-5381.2011.
12. Chen HW, Kuo HT, Chai CY, Ou JL, Yang RC. Pretreatment of curcumin attenuates coagulopathy and renal injury in LPS-induced endotoxemia. *J Endotoxin Res* 2007;13:15–23.
13. Farombi EO, Ekor M. Curcumin attenuates gentamicin-induced renal oxidative damage in rats. *Food Chem Toxicol* 2006 September;44:1443–8.
14. Kuhad A, Pilkhwal S, Sharma S, Tirkey N, Chopra K. Effect of curcumin on inflammation and oxidative stress in cisplatin-induced experimental nephrotoxicity. *J Agric Food Chem* 2007 December 12;55:10150–5.
15. Okada K, Wangpoengtrakul C, Tanaka T, Toyokuni S, Uchida K, Osawa T. Curcumin and especially tetrahydrocurcumin ameliorate oxidative stress-induced renal injury in mice. *J Nutr* 2001 August;131:2090–5.
16. Tirkey N, Kaur G, Vij G, Chopra K. Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys. *BMC Pharmacol* 2005;5:15.
17. Verma RJ, Mathuria N. Curcumin ameliorates aflatoxin-induced lipid-peroxidation in liver and kidney of mice. *Acta Poloniae Pharmaceutica* 2008;65:195–202
18. Chen X, Sun J, Li H, *et al*. Curcumin-Loaded Nanoparticles Protect Against Rhabdomyolysis-Induced Acute Kidney Injury. *Cell Physiol Biochem.* 2017 Oct 24;43:2143–2154.
19. Akinyemi AJ, Onyebueke N, Faboya OA, Onikanni SA, Fadaka A, Olayide I. Curcumin inhibits adenosine deaminase and arginase activities in cadmium-induced renal toxicity in rat kidney. *J Food Drug Anal.* 2017 Apr;25:438–446.
20. Wu J, Pan X, Fu H, *et* al. Effect of curcumin on glycerol-induced acute kidney injury in rats. *Sci Rep.* 2017 Aug 31;7:10114. doi: 10.1038/s41598-017-10693-4.

21. Ahmed AY, Gad AM, El-Raouf OMA. Curcumin ameliorates diclofenac sodium-induced nephrotoxicity in male albino rats. *J Biochem Mol Toxicol.* 2017 Oct;31.

22. Kumar P, Barua CC, Sulakhiya K, Sharma RK. Curcumin Ameliorates Cisplatin-Induced Nephrotoxicity and Potentiates Its Anticancer Activity in SD Rats: Potential Role of Curcumin in Breast Cancer Chemotherapy. *Front Pharmacol.* 2017 Apr 4;8:132. doi: 10.3389/fphar.2017.00132.

23. Kumar P, Sulakhiya K, Barua CC, Mundhe N. TNF-α, IL-6 and IL-10 expressions, responsible for disparity in action of curcumin against cisplatin-induced nephrotoxicity in rats. *Mol Cell Biochem.* 2017 Jul;431:113–122.

24. Topcu-Tarladacalisir Y, Sapmaz-Metin M, Karaca T. Curcumin counteracts cisplatin-induced nephrotoxicity by preventing renal tubular cell apoptosis. *Ren Fail.* 2016 Nov;38:1741–1748.

25. Molina-Jijón E, Aparicio-Trejo OE, Rodríguez-Muñoz R, *et al*. The nephroprotection exerted by curcumin in maleate-induced renal damage is associated with decreased mitochondrial fission and autophagy. *Biofactors.* 2016 Nov 12;42:686–702.

26. Cuce G, Cetinkaya S, Isitez N, *et al*. Effects of curcumin on methyl methanesulfonate damage to mouse kidney. *Biotech Histochem.* 2016;91:122–7.

27. Hismiogullari AA, Hismiogullari SE, Karaca O, *et al*. The protective effect of curcumin administration on carbon tetrachloride (CCl4)-induced nephrotoxicity in rats. *Pharmacol Rep.* 2015 Jun;67:410–6.

28. He L, Peng X, Zhu J, *et al*. Protective effects of curcumin on acute gentamicin-induced nephrotoxicity in rats. *Can J Physiol Pharmacol.* 2015 Apr;93:275–82.

29. Ugur S, Ulu R, Dogukan A, *et al*. The renoprotective effect of curcumin in cisplatin-induced nephrotoxicity. *Ren Fail.* 2015 Mar;37:332–6.

30. Tapia E, Sánchez-Lozada LG, García-Niño WR, *et al*. Curcumin prevents maleate-induced nephrotoxicity: relation to hemodynamic alterations, oxidative stress, mitochondrial oxygen consumption and activity of respiratory complex I. *Free Radic Res.* 2014 Nov;48:1342–54.

31. Buyuklu M, Kandemir FM, Ozkaraca M, Set T, Bakirci EM, Topal E. Protective effect of curcumin against contrast induced nephropathy in rat kidney: what is happening to oxidative stress, inflammation, autophagy and apoptosis? *Eur Rev Med Pharmacol Sci.* 2014;18:461–70.

32. Ueki M, Ueno M, Morishita J, Maekawa N. Curcumin ameliorates cisplatin-induced nephrotoxicity by inhibiting renal inflammation in mice. *J Biosci Bioeng*. 2013 May;115:547–51.

33. Zhong F, Chen H, Jin Y, Guo S, Wang W, Chen N. Analysis of the gene expression profile of curcumin-treated kidney on endotoxin-induced renal inflammation. *Inflammation.* 2013 Feb;36:80–93

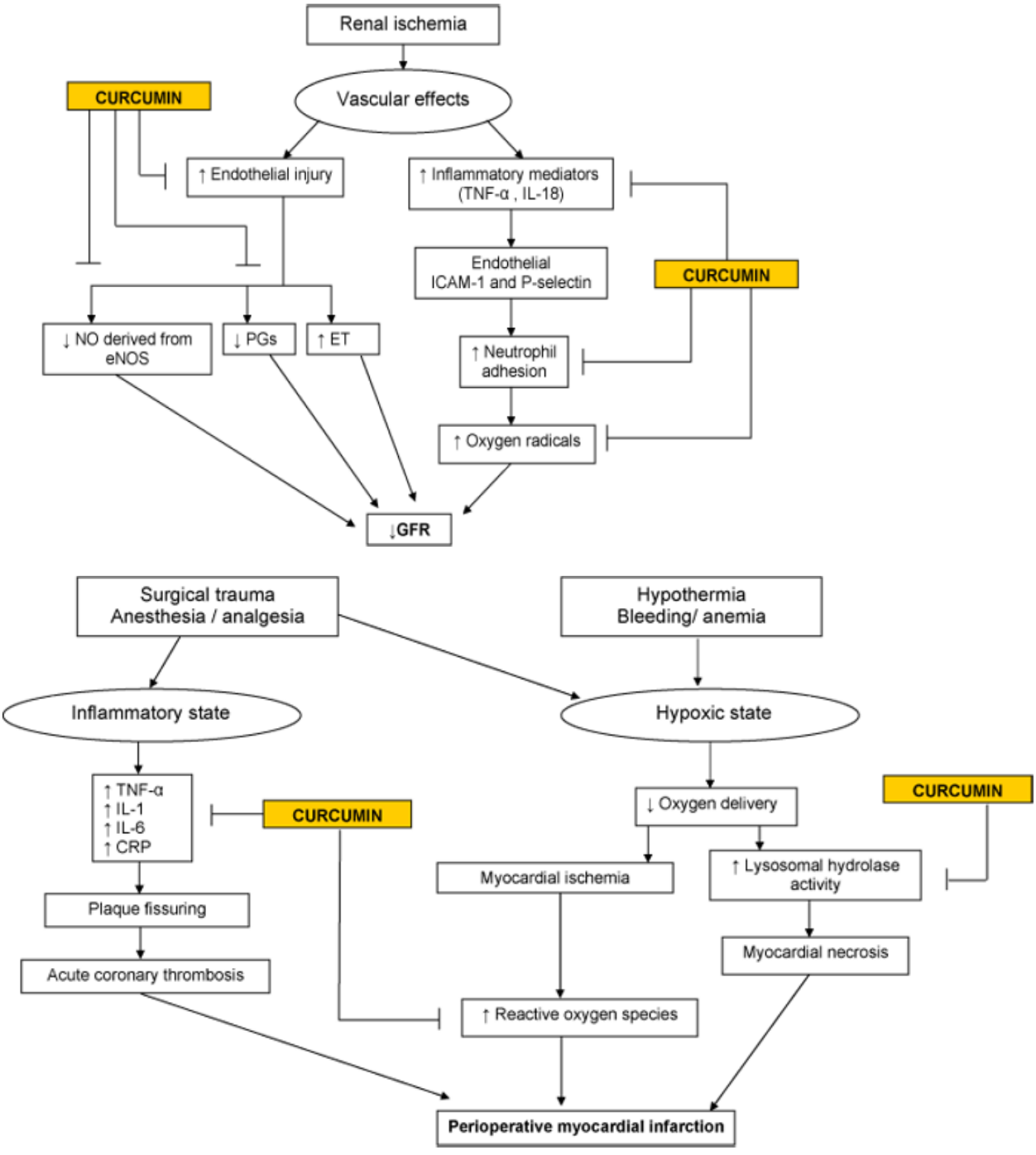
34. Manikandan R, Beulaja M, Thiagarajan R, Priyadarsini A, Saravanan R, Arumugam M. Ameliorative effects of curcumin against renal injuries mediated by inducible nitric oxide synthase and nuclear factor kappa B during gentamicin-induced toxicity in Wistar rats. *Eur J Pharmacol.* 2011 Nov 30;670:578–85.

35. Molina-Jijón E, Tapia E, Zazueta C, *et al*. Curcumin prevents Cr(VI)-induced renal oxidant damage by a mitochondrial pathway. *Free Radic Biol Med.* 2011 Oct 15;51:1543–57.

36. Zhong F, Chen H, Han L, Jin Y, Wang W. Curcumin attenuates lipopolysaccharide-induced renal inflammation. *Biol Pharm Bull.* 2011;34:226–32.

37. Ahmida MH. Protective role of curcumin in nephrotoxic oxidative damage induced by vancomycin in rats. *Exp Toxicol Pathol.* 2012 Mar;64:149–53.

Section 2. A graphical presentation of the mechanisms by which curcumin may prevent peri-operative kidney and cardiac injury



TNF-α - tumor necrosis factor alpha; NO – nitric oxide, eNOS – endothelial nitric oxide synthase; IL-19 – interleukin 18, PG – prostaglandin, ET – endothelin, ICAM-1 – intercellular adhesion molecule 1, P-selectin – platelet selectin, GFR – glomerular filtration rate, IL-1 – interleukin 1, IL-6 – interleukin 6, CRP - C-reactive protein

Section 3. Full eligibility criteria for the trial

Hospital sites:
Patients were recruited at the following 10 academic hospitals: London Health Sciences Centre, London, Ont.; The Ottawa Hospital, Ottawa, Ont.; St. Michael's Hospital, Toronto, Ont.; Sunnybrook Health Sciences Centre, Toronto, Ont.; Hamilton General Hospital, Hamilton, Ont.; Sudbury Regional Hospital, Sudbury, Ont.; University of Alberta Hospital, Edmonton, Alta.; Peter Lougheed Centre, Calgary, Alta.; St. Boniface Hospital, Winnipeg, Man.; Hôpital Maisonneuve-Rosemont, Montréal, Que.

Inclusion criteria
Patients have an elective repair of an unruptured abdominal aortic aneurysm (AAA) (excludes thoracic and thoracoabdominal aneurysms). At the time of pre-operative assessment scheduled for an:

- open surgery
- endovascular repair, where the patient had at least one of the following risk factors for post-operative complications: i) diabetes mellitus treated with insulin or oral hypoglycemic agents, ii) age > 70 years, or iii) an elevated preoperative serum creatinine (> 177 μmol/L (2.0 mg/dL) in men or > 146 μmol/L (1.6 mg/dL) in women).

> 18 years of age
able to provide written consent
if diabetic willing to monitor and record glucose levels at home

Exclusion criteria
Elective abdominal AAA repair expected to occur in ≤ 3 days
Prior kidney transplant
Pregnant or breastfeeding
Current active gastrointestinal reflux disease, gastrointestinal ulcer, or hepatobiliary disease
Evidence of acute kidney injury in prior 30 days
Participating in another study that could conflict with the intervention or outcomes of this trial
Received ≥ 1 dialysis treatment (hemodialysis or peritoneal dialysis) in past week
Previous participation in this trial
A history of a major bleeding event in the prior 6 months
A bleeding disorder: a diagnosis of hemophilia, von Willibrand disease, platelets <70
An allergy to turmeric, ginger, curry, cumin, cardamom, yellow or red food coloring, gelatin or cellulose
A history of hypoglycemia in the past 6 months (<3.5 mmol/L or < 135.0 mg/dL)

Section 4. Study regimen and justification

500 mg capsule of curcumin and placebo manufactured for the trial

The curcumin capsules contained finished product 95% curcumin, which was extracted from the rhizome of curcuma longa (turmeric) [which was ground, extracted, separated, concentrated, sieved and packaged]. The curcumin capsules were free of impurities (no lead, arsenic, cadmium, mercury, bacteria and fungi). The placebo capsules looked, smelled and tasted the same as the curcumin capsules, and were made of yellow food colouring, gelatin and cellulose. All the specifications for both curcumin and placebo were submitted to Health Canada, which included the results of testing confirming stability of the capsules.

	2 days before repair	**1 day before repair**	**Day of repair**	**1 day after repair**
Morning	2000mg	2000mg	2000mg	2000mg
			2000mg On call to the OR	
Evening	2000mg	2000mg	2000mg 6 hours after repair	

In the 2 days prior to repair patients were instructed to take the capsules with food to improve curcumin absorption (which occurred for all doses in over 85% of patients in both groups based on their self-report). If a patient was unable to swallow the capsule (as occurred for some patients 6 hours after repair) the protocol indicated the capsule was not to be opened as curcumin can stain materials yellow, and could result in patients and providers becoming aware of the treatment allocation.

The regimen of curcumin was pragmatic and feasible accounting for the realities of how surgeries are booked into busy operating room suites. Our justification for the curcumin regimen used is as follows: a) there is consensus that a daily oral dose of 4000 mg is reasonable; although many trials are using doses as low as 500 mg/day, 4000 mg/day is about the average dose used in current registered clinical trials, b) this dose has proven safe and is well tolerated by patients with no report of any major adverse event, c) although young adults have taken up to 12 g of curcumin at a single time most older patients scheduled for AAA repair would not tolerate taking more than four 500 mg capsules at a given time, d) the dose of 4000 mg/day is expected to have pharmacodynamic effects as demonstrated in a trial done in the setting of coronary artery bypass graft surgery, e) providing the capsules for two days before repair (vs. as a single dose on the day of repair) may 'prime' the body for an insult and cause accumulation of curcumin at the gastrointestinal mucosal interface resulting in more free curcumin delivered to systemic sites, f) we started the regimen two days before AAA repair (rather than for a longer duration prior to the repair) as knowledge of the repair date according to operating room schedule is usually only confirmed a few days before repair; in an animal study curcumin use three days before a major septic insult attenuated tissue injury and reduced mortality, g) the amount and dose given on call to the operating room suite is the last feasible time curcumin can be given before an AAA repair, the time where the 'insult' occurs. The regimen used in this trial is also guided by the known uptake and half-life of serum curcumin and its major metabolites (curcumin glucuronide, curcumin sulphate).

References

1. Cheng AL, Hsu CH, Lin JK *et al*. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res* 2001 July;21:2895–900.
2. Sharma RA, McLelland HR, Hill KA *et al*. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clin Cancer Res* 2001 July;7:1894–900.
3. Sharma RA, Euden SA, Platton SL *et al.* Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin Cancer Res* 2004 October 15;10:6847–54.
4. Siddiqui AM, Cui XX, Wu RQ *et al*. The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-gamma. *Critical Care Medicine* 2006;34:1874–82.
5. Wongcharoen W, Jai-Aue S, *et al*. Effects of curcuminoids on frequency of acute myocardial infarction after coronary artery bypass grafting. *Am J Cardiol.* 2012 Jul 1;110:40–4
6. Strimpakos AS, Sharma RA. Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid Redox Signal* 2008 March;10:511–45.
7. Hsu CH, Cheng AL. Clinical studies with curcumin. *Adv Exp Med Biol* 2007;595:471–80.
8. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int J Biochem Cell Biol* 2009 January;41:40–59.
9. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem Pharmacol* 2008 February 15;75:787–809.

Section 5. Details of the study outcomes.

Four Biomarkers: The first three markers listed below were measured on biosamples carefully processed and stored at minus 80 degrees in a biorepository; when the trial was completed samples were shipped on dry ice to an experienced laboratory at Yale University for analysis. We observed <10% intra assay CV and <10% inter assay CV for all the standards and the assays covered 4-5 log concentrations in terms of range. All samples were within the detection range for all the biomarkers measured.

Urine kidney injury biomarker IL-18 was measured using a prototype assay on Meso Scale Diagnostics (MSD) platform.

Plasma NT ProBNP was measured using an assay on the MSD platform. We remeasured 48 samples on the Roche machine at the Yale hospital. The correlation between the Roche and MSD measurements was good (0.8988). Using the measurements from both platforms, a correction factor was calculated to align samples measured on MSD to provide standard measurements on Roche as: NTProBNP_Roche = (NTProBNP_MSD + 335.07)/12.647

Plasma high-sensitivity C-reactive protein was measured using the singleplex assay from MSD.

Serum creatinine was as mesaured in routine care, where in Canada this is with the reference method of isotope-dilution mass spectrometry (IDMS).

Acute kidney injury: Defined as a $\geq$ 0.3 mg/dL (or 26.5 umol/L) increase of in serum creatinine in the 48 hours following surgery from the pre-operative value, or a $\geq$ 50% increase in serum creatinine the 7 days following surgery from the pre-opreative value (some of the criteria that feature in the KDIGO defintion; urine output was not used to define acute kidney injury in our study because the measurement is often unreliable).

Clinical Event Definitions (the protocol contains additional details on the reporting timelines and required source documents; all clinical events were centrally adjudicated by a committee unaware of the treatment allocation).

The composite of clinical events in this study was any of the following events within 30 days of surgery: death, new acute dialysis, myocardial infarction, receipt of percutaneous coronary artery intervention (PCI), receipt of coronary artery bypass graft surgery (CABG), sepsis, pneumonia, non-fatal cardiac arrest, stroke, deep vein thrombosis, pulmonary embolism, lower limb amputation, ischemic bowel or congestive heart failure.

New Acute Dialysis: Dialysis is defined as the use of a hemodialysis machine or peritoneal dialysis apparatus, intermittent or continuous.

Myocardial infarction: The diagnosis of MI requires any one of the following 3 criterion:

1. A typical rise of troponin or a typical fall of an elevated troponin detected at its peak post-surgery in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism). This criterion also requires that 1 of the following must also exist:
    - A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema)
    - B. development of pathologic Q waves present in any two contiguous leads that are $\geq$ 30 milliseconds
    - C. ECG changes indicative of ischemia (i.e., ST segment elevation [$\geq$ 2 mm in leads V_1, V_2, or V_3 OR $\geq$ 1 mm in the other leads], ST segment depression [$\geq$ 1 mm], or symmetric inversion of T waves $\geq$ 1 mm) in at least two contiguous leads
    - D. coronary artery intervention (i.e., PCI or CABG surgery)
    - E. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging
2. Pathologic findings of an acute or healing myocardial infarction
3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

Sepsis/Infection: Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms. Sepsis is a clinical syndrome defined by the presence of BOTH: 1) infection, AND 2) a systemic inflammatory response. Systemic inflammatory response

requires 2 or more of the following factors: core temperature > 38°C or < 36°C; heart rate > 90 bpm; respiratory rate > 20 breaths/min; white blood cell count > 12 x 10^9/L or < 4 x 10^9/L.

Pneumonia: Requires A or B: A) Rales or dullness to percussion on physical examinations of chest AND any of the following: 1) New onset of purulent sputum or change in character of sputum; 2) Isolation of organism from blood culture; or 3) Isolation of pathogen from specimen obtained by transtracheal (across the trachea) aspirate, bronchial brushing, or biopsy. B) Chest radiography showing new or progressive infiltrate, consolidation, cavitation (formation of bubbles/cavities) , or pleural effusion AND any of the following: 1) New onset of purulent sputum or change in character of sputum; 2) Isolation of organism from blood culture; 3) Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy; 4) Isolation of virus or detection of viral antigen in respiratory secretions; 5) Diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen; or 6) Histopathologic evidence of pneumonia (evidenced by changes in tissue samples)

Nonfatal cardiac arrest: Nonfatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulse less electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

*Stroke***:** Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours or leading to death.

Deep venous thrombosis (DVT) of leg or arm: The diagnosis of DVT requires any one of the following:
1. A persistent intraluminal filling defect on contrast venography
2. No compressibility of one or more venous segments on B mode compression ultrasonography
3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography

Pulmonary Embolus (PE): The diagnosis of PE requires any one of the following:
1. A high probability ventilation/perfusion lung scan
2. An intraluminal filling defect of segmental or larger artery on a helical CT scan
3. An intraluminal filling defect on pulmonary angiography
4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following:
A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan
B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan

Lower Limb Amputation: Defined as amputation of any part of a lower limb.

Acute Ischemic Bowel: A sudden reduction in blood flow to the intestine (small bowel or large bowel) frequently resulting in severe abdominal pain. This is due to occlusive or nonocclusive obstruction of arterial or venous blood flow.

Congestive heart failure: The definition of congestive heart failure requires at least one of the following clinical signs (elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) *and* at least one of the following radiographic findings (vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).

Safety Events (Adverse events that may occur with curcumin)

Serious Adverse Event (SAE) Reporting: The protocol defines SAEs as events which are fatal, life threatening or fulfill a definition of being clinically important, that is not one of the efficacy or safety outcomes where detailed information is already collected. These events will not be considered unexpected unless their course, severity or other specific features are such that the investigator, according to his/her best medical judgment, considers these events as exception in the context of the patient's medical condition.

Clinically Important Bleeding
All bleeds are to be reported that meet the following criteria:
>Fatal (also complete death CRF),
>Leads to: a drop of hemoglobin of $\geq$ 5 g/dL, significant hypotension that requires inotrope therapy,

>Re-operation for reason of bleeding (other than superficial vascular repair),
> Intracranial hemorrhage, or requiring transfusion of ≥ 4 units of red blood cells or equivalent of whole blood,
> Intraocular bleeding,
> Bleeding requiring ≥ 2 units of red blood cells or equivalent of whole blood PLUS one of: post-operative hemoglobin ≤ 70 g/L (≤7.0 g/dL) OR results in a hemoglobin drop of ≥ 50 g/L (≥ 5.0 g/L),
> Transfusion of ≥ 4 units of red blood cells within a 24 hour period,
> Leads to any other intervention (i.e. embolization, superficial vascular repair, nasal packing)
> Is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging)

New acute peptic ulcer: A new acute peptic ulcer is defined as a mucosal lesion of the stomach or duodenum detected on endoscopy or upper GI x-ray.

Nausea: Participants rated the intensity of nausea in the 2 days prior to surgery based on a visual analogue scale (0=no nausea, 5=distressing nausea, 10=worst nausea imaginable). The results from the analogue scale was dichotomized into 0 as "No Nausea" and 1-10 as "Any Nausea".

Diarrhea: Defined as ≥3 episodes of loose or liquid stools in the 24 hours after repair.

Hypoglycemic event: Defined as any glucose reading <4mmol/L in the 2 days prior to repair, day of repair or day after repair.

Section 6. Statistical power to detect meaningful differences in our outcomes.

Outcomes	Standard deviation, or event rate (%)	Minimal Detectable Between Group Difference, or Odds Ratio	Between group difference observed in simulated scenarios in data from coronary artery bypass graft setting *		
			A longer (versus shorter) pump duration	CABG & valve (vs. CABG)	statin held (vs. not held)
Primary Outcomes					
Post-operative urine IL-18, pg/mL	72	16.6	99	126	52
Post-operative minus pre-operative change in plasma NTPro-BNP (log-transformed), mesoscale pg/mL	0.55	0.1	-0.15	0.11	-0.05
Post-operative minus pre-operative change in plasma HsCRP (log-transformed), ug/mL	0.37	0.1	…	…	…
Post-operative minus pre-operative change in serum creatinine, umol/L	45	10	15	13	2
Secondary Outcomes					
Acute kidney injury, %	13	OR 1.84	OR 2.3 (1.26, 4.38)	OR 1.70 (1.00, 2.88)	OR 1.29 (0.73, 2.28)
Hospital Length of Stay, days	5.4	1.2	5.25	2.7	0.26
Composite of 14 clinical events, %	9	OR 2.01	…	…	…

Assumptions: 2-group comparison with equal number of participants in each group (300 each), equal variation in both groups (SD) or event rate in control group, alpha of 5% and power of 80%.

OR – odds ratio. Pump Time: Treatment – CPB Time < 80 minutes and Control – CPB Time > 120 minutes

* The Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) NIH-funded multi-centre study prospectively enrolled and followed 1219 adults undergoing cardiac surgery. Urine and plasma samples were collected daily pre-operatively and for the first 5 days post-operatively. To simulate the effect of a possible trial, we first selected treatment and control groups (e.g. pump duration CPB Time > 120 minutes and CPB Time < 80 minutes). To simulate the effect of randomization, we used a greedy matching algorithm to select individuals with similar baseline criteria. First, we calculated a propensity score of being in the treatment group based on baseline characteristics: diabetes, hypertension, CHF, contract dye use, and pre-operative medications (ACE, Beta-blockers, Aspirin and Statins). Then patients were matched on: site (exact), age (± 10 years), gender (exact), pre-op CKD stage (exact), and propensity score (±0.25). For each simulated trial only the patients that were matched were included in the analysis (see table below). For the final groups, we calculated the observed effects.

	A longer (versus shorter) pump duration		CABG & valve (vs. CABG)		statin held (vs. not held)	
	CPB Time > 120 min	CPB Time< 80 min	CABG & Valve	CABG	Hold Statins	Continue Statins
# possible	429	183	273	567	588	206
# matched	141	141	207	207	189	189

Section 7. Patient enrollment in the trial.

	Curcumin	Placebo	Total
Patient provided informed consent and was randomized into trial	313	311	624
Excluded before repair, **before** any scheduled study capsules were to be taken			
- Surgery date changed, postponed or cancelled and patient unable to participate in trial	2	1	4
- Patient changed their mind about trial participation (sometimes in setting of surgery date change, postponement or cancellation)	3	5	7
- Patient's physician decided patient should not participate in trial	2	3	5
Excluded after repair			
Participant changed their mind about trial participation (for no medical reason) and asked for their data to be withdrawn from the trial	1	0	1
For technical reasons the AAA was not repaired during surgery and no data was available	1	0	1
Patients included in the analysis*	**304**	**302**	**606**

* The completeness of the four primary biomarker measures for the 606 patients ranged from 96.5% to 99.8%.

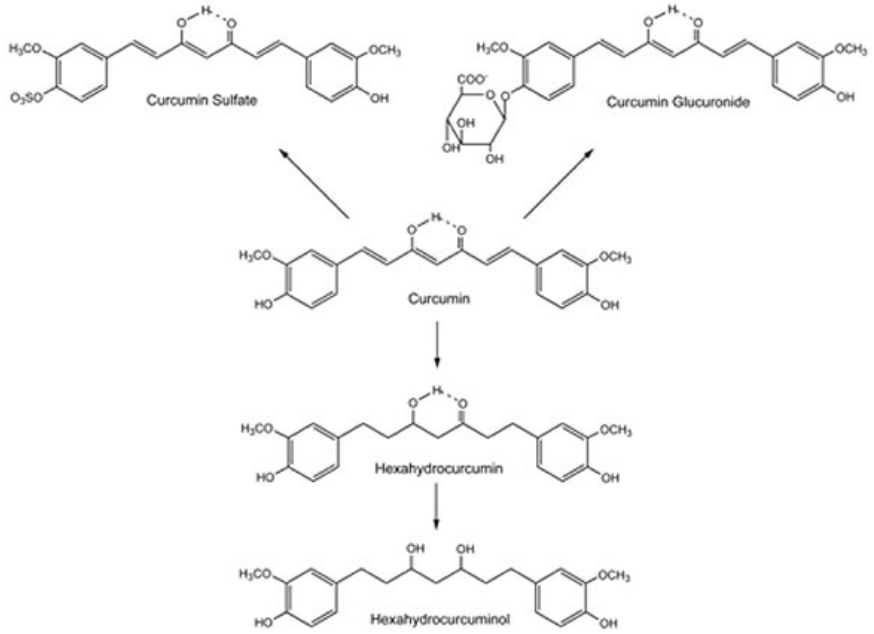
Section 8. Adherence to the allocated therapy.

Time point		Curcumin (n=304)					Placebo (n=302)				
		4 caps taken	**3 caps taken**	**2 caps taken**	**1 caps taken**	**no caps taken**	**4 caps taken**	**3 caps taken**	**2 caps taken**	**1 caps taken**	**0 caps taken**
2 days before repair	AM	286 (94)				17 (6)	294 (98)				7 (2)
	PM	285 (94)				18 (6)	293 (97)				8 (3)
1 days before repair	AM	291 (96)				12 (4)	295 (98)				6 (2)
	PM	287 (95)				16 (5)	295 (98)				6 (2)
Day of Repair	AM	282 (93)		1 (0)	1 (0)	19 (6)	287 (95)		1 (0)	0	13 (4)
	on call to OR	282 (93)		1 (0)		20 (7)	288 (96)		0		13 (4)
	6-hr post	249 (82)	0		1 (0)	53 (17)	251 (83)	1 (0)		2 (1)	47 (16)
1 day after repair	AM	251 (83)	1 (0)		0	51 (17)	265 (88)	0		2 (1)	34 (11)
total pills taken (max 32 pills)		median (25^{th},75^{th} percentile) 32 (28, 32)					median (25^{th},75^{th} percentile) 32 (32, 32)				

Cells contain n (%) unless otherwise indicated.
caps - capsules
73% of patients took all (100%) of the scheduled study capsules.
74% of patients took over 90% of the scheduled study capsules.
85% of patients took 80% of the scheduled study capsules.

Section 9. Detection of curcumin metabolites in the urine

Chemical structures of curcumin and its metabolites



Curcumin conjugates in urine were subjected to enzymatic hydrolysis as described by Vareed et al. Cancer Epidemiol Biomarkers Prev 2008;17(6):1411–7. Briefly, 200 µl of urine samples were mixed with 90 µl of water and 10 µl of Mepronil (10 µg/ml) and the samples were vortexed for 30 seconds. Following this, 20 µl of β-glucuronidase (1000 units) in 0.1 mol/L phosphate buffer pH 6.8 and 52 units of sulfatase in 0.1 mol/L sodium acetate buffer pH 5.0 was added, samples were vortexed and incubated at 37°C for 3.5 h. The samples were then extracted twice with 1 mL of ethylacetate: methanol mixture (95:5). The top organic layer was pooled and dried under a stream of nitrogen. The extracts were reconstituted in 200 µl of 100% methanol and 10 µl of the extracted was injected on the column.

Spot urine samples from sent 30 randomly selected patients were sent for analysis from the curcumin group, and 10 randomly selected patients from the placebo group. The urine samples were collected a median (25^{th}, 75^{th} percentile) of 0.8 (0.6, 1.2) hours after completion of the repair.

Curcumin was quantitated using the Agilent UHPLC-Q-TOF mass spectrometer on the Agilent Infinity 1290 UPLC system. Chromotographic separation was achieved on the Zorbax Eclipse plus RP 2.1x50 mm 1.8µ column at the flow rate of 0.6 mL/min. The mobile phase consisted of 0.1% Formic acid and 80% acetonitrile in 0.1% Formic acid. The retention time was 5.6 minutes and the total run time was 10 minutes. The detection was performed in positive ion mode. Stock solutions of Curcumin and Mepronil were prepared in 100% methanol at a concentration of 10 µg/mL. The highest standard used was 2000 ng/mL, this was further serially diluted with methanol to obtain 1000, 500, 250, 125, 62.5, and 31.5 and 15.75 ng/mL. All samples and standards were run in duplicate. Quantitation was carried using the Agilent MassHunter software.

29 of 30 urine samples from the curcumin group were successfully analyzed. The median (25^{th}, 75^{th} percentile) amount of curcumin detected in the urine in the curcumin group was 87.4 (53.6, 173.6) ng/mL. This was significantly higher than any curcumin detected in the placebo group (n=10; 20.8 (18.4, 26.8) ng/mL). We were surprised to detect any curcumin in the placebo group, as the ethnic population of the trial would not be expected to have a diet rich in turmeric. We reviewed the study procedures and documentation which confirms the curcumin and placebo capsules were allocated as expected in the trial. We attribute the detection of some curcumin metabolites in the placebo samples to imprecision in the measurement technique; there is no standard assay for curcumin metabolites and detecting it in biological samples is notoriously difficult.

Section 10. Pre-operative and post-operative values of serum and plasma biomarkers

	Pre-operative	Post-operative
serum creatinine, µmol/L		
curcumin	88 (74, 108)	92 (76, 123)
placebo	83 (71, 103)	86 (73, 106)
plasma NT Pro BNP, mesoscale pg/mL		
curcumin	158 (77, 430)	475 (216, 926)
placebo	146 (83, 359)	413 (184, 857)
plasma high-sensitivity C-reactive protein, ug/mL		
curcumin	3 (2, 8)	65 (36, 104)
placebo	3 (2, 6)	64 (35, 101)

* presented as median (25^{th}, 75^{th} percentile)

Section 11. Additional analyses

Results adjusted for baseline clinical characteristics *, manuscript Table 3.

	Curcumin n = 304	Placebo n=302	Adjusted P-value
Primary outcomes			
Post-op urine IL-18, pg/mL	13 (6, 27)	16 (7, 30)	0.12
Post-op minus pre-op change in plasma or serum			
NT Pro BNP, mesoscale pg/mL	221 (67, 511)	184 (48, 431)	0.17
Plasma high-sensitivity C-reactive protein, ug/mL	58 (28, 95)	58 (30, 90)	0.46
serum creatinine, µmol/L	1 (-7, 19)	1 (-6, 12)	0.37
Secondary outcomes			
Acute kidney injury, %	17	10	0.05
Composite of events (including death, myocardial infarction, and stroke), %	9	9	0.69
Hospital length of stay, days	5 (2,8)	5 (2, 7)	0.29

Presented as median (IQR), or Percent

Results adjusted for baseline clinical characteristics *, manuscript Table 4.

	Curcumin n = 304	Placebo n=302	Adjusted P-value
Change in post-operative minus pre-operative hemoglobin, g/L	- 33 (-46, -23)	- 32 (-43, -24)	1.00
Clinically important bleeding, %	2	3	0.48
Peptic ulcer, %	1	0	0.98
Glucose 0 to 3 hours after the repair, mmol/L	7 (6, 9)	7 (6, 9)	0.14
Hypoglycemic event, %	3	1	0.10
Diarrhea , %	5	7	0.68
Any nausea, %	12	10	0.32

Presented as median (25^{th}, 75^{th} percentiles), or Percent
* Adjusted for age, gender, BMI, ACE-I or ARB use, history of congestive heart failure, history of coronary artery disease, history of a cerebral vascular event, history of smoking in the past 30 days, planned endovascular aortic repair (EVAR vs open vs open & EVAR), pre-operative eGFR, diuretic use, NSAID use, statin use

Complete Case Results, manuscript Table 3 – Primary and secondary outcomes*

	Curcumin n = 304	Placebo n=302	unadjusted P-value	adjusted P-value
Primary outcomes				
Post-op urine IL-18, pg/mL	13 (6, 26)	16 (7, 29)	0.19	0.09
Post-op minus pre-op change in plasma or serum				
NT Pro BNP, mesoscale pg/mL	220 (65, 517)	183 (48, 431).	0.18	0.21
Plasma high-sensitivity C-reactive protein, ug/mL	58 (28, 95)	58 (30, 90)	0.44	0.30
creatinine, µmol/L	1 (-7, 19)	1 (-6, 12)	0.17	0.37
Secondary outcomes				
Acute kidney injury, %	17	10	0.01	0.05
Composite of events (including death and myocardial infarction) stroke), %	9	9	0.91	0.69
Hospital length of stay, days	5 (2,8)	5 (2, 7)	0.98	0.29

Presented as median (25^{th}, 75^{th} percentiles), or Percent

Adjusted for: Age, gender, BMI categories (<30, 30-35, >35), Congestive Heart Failure, Coronary Artery Disease, Previous Cerebral Vascular Event, History of Smoking in Last 30 Days, planned surgery, baseline eGFR, Pre-op ACE/ARB, Pre-op Diuretics, pre-op NSAIDs, pre-op Statins)
Outcomes defined in section 5 of the Supplementary Appendix

Complete Case Results, manuscript Table 4. Adverse outcomes from curcumin in prior studies *

	Curcumin n = 304	Placebo n=302	unadjusted P-value	adjusted P-value
Change in post-operative minus pre-operative hemoglobin, g/L	-33 (-46, -23)	-32 (-43, -24)	0.63	0.97
Clinically important bleeding	2%	3%	0.45	0.47
Peptic ulcer	1%	0%	0.57	0.99
Glucose 0 to 3 hours after the repair, mmol/L	7.3 (6.2, 8.7)	7.4 (6.2, 8.7)	0.71	0.16
Hypoglycemic event	3%	1%	0.10	0.10
Diarrhea	5%	7%	0.59	0.68
Any nausea	12%	10%	0.40	0.32

Adjusted for: Age, gender, BMI categories (<30, 30-35, >35), Congestive Heart Failure, Coronary Artery Disease, Previous Cerebral Vascular Event, History of Smoking in Last 30 Days, planned surgery, baseline eGFR, Pre-op ACE/ARB, Pre-op Diuretics, pre-op NSAIDs, pre-op Statins)

* Median (25^{th}, 75^{th} percentile) or percent. Outcomes defined in section 5 of Supplementary Appendix

Subgroup analyses by the type of procedure, open (curcumin n=151, placebo n=135) or endovascular (curcumin n=153, placebo n=167). Procedures that were both open and endovascular (n=4) were categorized as open procedures. The same statistical models were used as done for the primary and secondary outcome analyses.

	Curcumin	Placebo	P-value for interaction
Primary outcomes			
Post-op urine IL-18, pg/mL			
open procedure	17 (8, 51)	20 (10, 45)	0.09
endovascular procedure	10 (5, 20)	14 (6, 23)	
Post-op minus pre-op change in			
serum creatinine, µmol/L			
open procedure	7 (-5, 32)	5 (-5, 20)	0.30
endovascular procedure	-2 (-8, 7))	0 (-7, 8)	
plasma NT Pro BNP, mesoscale pg/mL			
open procedure	140 (41, 391)	123 (26, 332)	0.76
endovascular procedure	305 (113, 621)	249 (75, 551)	
plasma high-sensitivity C-reactive protein, µg/mL			
open procedure	87 (56, 112)	87 (55, 118)	0.40
endovascular procedure	33 (16, 61)	40 (19, 66)	
Secondary outcomes			
Acute kidney injury, n (%)			
open procedure	39 (26)	24 (18)	0.55
endovascular procedure	12 (8)	6 (4)	

Composite of events, n (%)			
open procedure	20 (13)	18 (13)	0.97
endovascular procedure	8 (5)	9 (5)	
Hospital length of stay, days			
open procedure	7 (6, 9)	7 (6, 9)	0.31
endovascular procedure	2 (2, 3)	2 (2, 3)	

Section 12. Kidney function 90 days after surgery

A serum creatinine laboratory value was obtained approximately 90 days after the surgical procedure. . If a value was not available in routine care a specimen was collected as per study protocol. Participant vital status was also ascertained as this time.

As shown in the table below, the data were mostly complete. We found no meaningful between-group difference in kidney function at 90 days.

	Curcumin (n=304)	**Placebo (n=302)**	**P-value**
90 day follow-up visit			
died	8	8	
no follow-up visit completed	3	2	
follow-up visit but no 90 day serum creatinine value	6	7	
follow-up visit and 90 day serum creatinine available	287	285	
Change in eGFR (90 day value – pre-op value), median (IQR)	-1.38 (-6.93, 3.66)	-1.23 (-6.07, 4.01)	0.72
Percent change in eGFR (90 day value - pre-op value), median (IQR)	-2.2 (-10.6, 5.8)	-1.6 (-8.6, 6.5)	0.57
eGFR categories at 90 days, n (%)			
≥60	174 (61)	201 (70)	0.08
45-60	56 (20)	45 (16)	
30-45	36 (13)	26 (9)	
< 30	21 (6)	13 (5)	

eGFR – estimated glomerular filtration rate reported in mL/min per 1.73 m^2