Adverse Effects and Precautions

The most frequent adverse effects with dofetilide are headache, chest pain, and dizziness. Dofetilide prolongs the QT interval and may cause severe ventricular arrhythmias, including torsade de pointes; it should not be given to patients with congenital or acquired long QT syndromes. Hypokalaemia increases the risk of arrhythmias and potassium concentrations should be corrected before starting dofetilide. The dosage of dofetilide must be individualised according to QT interval and creatinine clearance, which must be measured before starting therapy; dofetilide is contra-indicated if the corrected QT interval is above 440 milliseconds (or above 500 milliseconds in patients with ventricular conduction abnormalities) or if the creatinine clearance is less than 20 mL/minute. Treatment should begin under ECG monitoring, which must be continued for at least 3 days, and both ECG and renal function should be monitored at least every 3 months during treatment.

Interactions

Dofetilide should not be given with other drugs that prolong the QT interval. Class I or class III antiarrhythmics should be stopped at least 3 half-lives before dofetilide is given. Potassium-depleting diuretics may cause hypokalaemia or hypomagnesaemia, increasing the potential for torsade de pointes; US licensed product information for dofetilide states that hydrochlorothiazide is contra-indicated since it also causes significant increases in plasma-dofetilide concentrations. Dofetilide is metabolised to a small extent by the cytochrome P450 isoenzyme CYP3A4, and drugs or foods that inhibit this isoenzyme, such as macrolide antibacterials, HIV-protease inhibitors, diltiazem, and grapefruit juice, should be used with caution. Cimetidine, trimethoprim, ketoconazole, prochlorperazine, and megestrol, should not be given as they inhibit the renal excretion of dofetilide; verapamil is also contra-indicated as it too may substantially increase dofetilide concentrations.

◊ References.

1. Yamreudeewong W, *et al.* Potentially significant drug interactions of class III antiarrhythmic drugs. *Drug Safety* 2003; **26:** 421–38.

Pharmacokinetics

The oral bioavailability of dofetilide is more than 90%. Peak plasma concentrations occur after 2 to 3 hours and steady state concentrations after 2 to 3 days. The terminal half-life is about 10 hours. Protein binding is 60 to 70%. Dofetilide undergoes limited metabolism. About 80% of a dose is excreted in the urine, with about 80% of this as unchanged drug and 20% as 5 minimally active or inactive metabolites; metabolism may be mediated to some extent by the cytochrome P450 isoenzyme CYP3A4. Renal elimination involves both glomerular filtration and active tubular secretion via the cation transport system. The clearance of dofetilide decreases with decreasing creatinine clearance.

◊ References.

1. Allen MJ, *et al.* The pharmacokinetics and pharmacodynamics of oral dofetilide after twice daily and three times daily dosing. *Br J Clin Pharmacol* 2000; **50:** 247–53.

Uses and Administration

Dofetilide is a class III antiarrhythmic (p.1153); it selectively blocks one of the potassium channels involved in repolarisation and therefore prolongs the action potential. It is used in the treatment of atrial fibrillation and flutter (p.1160) in patients who are highly symptomatic. The initial oral dose in patients with a corrected QT interval of 440 milliseconds or less is 500 micrograms twice daily; the maintenance dose must be reduced if the QT interval becomes prolonged after the first dose, and treatment should be stopped if the QT interval exceeds 500 milliseconds. Doses should be reduced in renal impairment (see below).

◊ References.

1. McClellan KJ, Markham A. Dofetilide: a review of its use in atrial fibrillation and atrial flutter. *Drugs* 1999; **58:** 1043–59.
2. Kalus JS, Mauro VF. Dofetilide: a class III-specific antiarrhythmic agent. *Ann Pharmacother* 2000; **34:** 44–56.
3. Mounsey JP, DiMarco JP. Dofetilide. *Circulation* 2000; **102:** 2665–70.
4. Roukoz H, Saliba W. Dofetilide: a new class III antiarrhythmic agent. *Expert Rev Cardiovasc Ther* 2007; **5:** 9–19.

Administration in renal impairment. Doses of dofetilide should be reduced in patients with renal impairment based on creatinine clearance (CC). Initial doses are:

- CC 40 to 60 mL/minute: 250 micrograms twice daily
- CC 20 to 39 mL/minute: 125 micrograms twice daily
- CC below 20 mL/minute: contra-indicated

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Tikosyn.

Dopamine Hydrochloride

(BANM, USAN, pINNM)

ASL-279; Dopamiinihydrokloridi; Dopamin Hidroklorür; Dopamine, chlorhydrate de; Dopamin-hidroklorid; Dopamin-hydrochlorid; Dopaminhydroklorid; Dopamini hydrochloridum; Dopamino hidrochloridas; Dopaminy chlorowodorek; Hidrocloruro de dopamina; 3-Hydroxytyramine Hydrochloride. 4-(2-Aminoethyl)pyrocatechol hydrochloride.

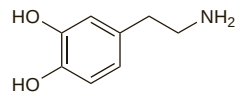
Допамина Гидрохлорид

$C_8H_{11}NO_2$,HCl = 189.6.

CAS — 51-61-6 (dopamine); 62-31-7 (dopamine hydrochloride).

ATC — C01CA04.

ATC Vet — QC01CA04.



(dopamine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US.*
Ph. Eur. 6.2 (Dopamine Hydrochloride). A white or almost white crystalline powder. Freely soluble in water; soluble in alcohol; sparingly soluble in acetone and in dichloromethane. Store in airtight containers. Protect from light.
USP 31 (Dopamine Hydrochloride). A white to off-white crystalline powder that may have a slight odour of hydrochloric acid. Freely soluble in water and in aqueous solutions of alkali hydroxides; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 4% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Dopamine is inactivated in alkaline solutions such as sodium bicarbonate 5% and is incompatible with alkaline drugs such as furosemide[1] and thiopental sodium;[1] incompatibility with insulin[2] and with alteplase[3] has also been reported, and licensed product information states that it is incompatible with ampicillin and with amphotericin B, and that mixtures with gentamicin sulfate, cefalotin sodium, or oxacillin sodium should be avoided.

1. Chiu MF, Schwartz ML. Visual compatibility of injectable drugs used in the intensive care unit. *Am J Health-Syst Pharm* 1997; **54:** 64–5.
2. Yamashita SK, *et al.* Compatibility of selected critical care drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1996; **53:** 1048–51.
3. Lee CY, *et al.* Visual and spectrophotometric determination of compatibility of alteplase and streptokinase with other injectable drugs. *Am J Hosp Pharm* 1990; **47:** 606–8.

Adverse Effects and Treatment

As for Sympathomimetics, p.1407; dopamine may have adverse effects relating to both its alpha- and beta-agonist properties.

Dopamine has a short duration of action and most adverse effects respond to stopping the infusion or reducing its rate; infiltration with phentolamine may relieve pain and prevent necrosis following extravasation.

Effects on the CNS. Movement disorders are well known adverse effects of the dopamine precursor, levodopa (p.804) but do not usually occur with dopamine since it does not enter the CNS. However, there has been a report[1] of choreoathetosis in a patient receiving dopamine infusion; it was suggested that there must have been disruption to her blood-brain barrier to allow this to occur.

1. Walker VA, Massoumi M. Choreoathetosis with dopamine. *Ann Intern Med* 2005; **142:** 478–9.

Effects on the endocrine system. Dopamine has complex actions on the anterior pituitary[1] and dopamine infusion is associated with a number of endocrine effects, including suppression of prolactin, growth hormone, and thyroid hormone release. In postoperative or critically ill patients, dopamine infusion may affect the endocrine response to stress, even when given in low doses. Depression of serum-prolactin concentrations has been reported[2] in critically ill patients given dopamine in a dose of 2.5 micrograms/kg per minute to maintain renal blood flow, while a study[3] in postoperative patients given dopamine 5 micrograms/kg per minute to maintain splanchnic blood flow found that serum concentrations of both prolactin and thyroid stimulating hormone were decreased. It was suggested that these changes could adversely affect immunological function and add to morbidity in such patients.

1. Van den Berghe G, de Zegher F. Anterior pituitary function during critical illness and dopamine treatment. *Crit Care Med* 1996; **24:** 1580–90.
2. Bailey AR, Burchett KR. Effect of low-dose dopamine on serum concentrations of prolactin in critically ill patients. *Br J Anaesth* 1997; **78:** 97–9.
3. Schilling T, *et al.* Endocrine effects of dopexamine vs. dopamine in high-risk surgical patients. *Intensive Care Med* 2001; **27:** 1908–15.

Effects on the heart. For mention of the arrhythmogenic effects of dopamine on the heart, see p.1407.

Ischaemia and gangrene. Dopamine is converted to noradrenaline, a powerful vasoconstrictor, and there have been reports[1-3] of ischaemia and gangrene of the extremities in patients receiving dopamine infusion, as well as local necrosis after extravasation.[4] Extravasation of catecholamines is usually treated with an alpha blocker such as phentolamine, but there have also been reports of the use of topical glyceryl trinitrate ointment to improve capillary blood flow in patients with dopamine-induced ischaemia of the digits. The ointment was applied either to the affected area,[5] or to the warmest area of skin,[6] such as the chest or abdominal wall.

1. Alexander CS, *et al.* Pedal gangrene associated with the use of dopamine. *N Engl J Med* 1975; **293:** 591.
2. Julka NK, Nora JR. Gangrene aggravation after use of dopamine. *JAMA* 1976; **235:** 2812–13.
3. Maggi JC, *et al.* Gangrene in a neonate following dopamine therapy. *J Pediatr* 1982; **100:** 323–5.
4. Boltax RS, *et al.* Gangrene resulting from infiltrated dopamine solution. *N Engl J Med* 1977; **296:** 823.
5. Gibbs NM, Oh TE. Nitroglycerine ointment for dopamine induced peripheral digital ischaemia. *Lancet* 1983; **ii:** 290.
6. Coakley J. Nitroglycerin ointment for dopamine-induced peripheral ischaemia. *Lancet* 1983; **ii:** 633.

Precautions

As for Sympathomimetics, p.1407.

Children. There have been reports of increased pulmonary artery pressure with the use of dopamine in children after cardiac surgery,[1] and in premature infants with hypotension.[2] It has therefore been suggested that dopamine should be used with caution in children at risk of developing pulmonary hypertension.

1. Booker PD, *et al.* Comparison of the haemodynamic effects of dopamine and dobutamine in young children undergoing cardiac surgery. *Br J Anaesth* 1995; **74:** 419–23.
2. Liet J-M, *et al.* Dopamine effects on pulmonary artery pressure in hypotensive preterm infants with patent ductus arteriosus. *J Pediatr* 2002; **140:** 373–5.

Interactions

As for Sympathomimetics, p.1407. Dopamine has both direct and indirect actions and may therefore interact with MAOIs; the dose of dopamine should be substantially reduced in patients taking MAOIs, and an initial dose of one-tenth the usual dose has been suggested.

Antiepileptics. Following a report in 1976 to the FDA of hypotension in patients given *phenytoin* in addition to dopamine infusion, a study[1] of this potential interaction found that dopamine given by intravenous infusion with phenytoin infusion to *dogs*, did not alter the CNS effects of phenytoin nor result in hypotension and cardiovascular collapse. Large doses of phenytoin alone had a reproducible hypotensive effect that was reduced by dopamine, suggesting a possible supportive role in phenytoin-induced hypotension.

1. Smith RD, Lomas TE. Modification of cardiovascular responses to intravenous phenytoin by dopamine in dogs: evidence against an adverse interaction. *Toxicol Appl Pharmacol* 1978; **45:** 665–73.

Dopaminergics. Severe hypertension occurred[1] in a patient who had been receiving *selegiline* for Parkinson's disease when a dopamine infusion was started. Although selegiline is considered to be a selective monoamine oxidase type B inhibitor, at higher doses it also affects monoamine oxidase type A and could

have reduced the metabolism of dopamine in this patient. Caution may be necessary if dopamine is given to patients who have been receiving selegiline within the previous 2 weeks.

1. Rose LM, *et al.* A hypertensive reaction induced by concurrent use of selegiline and dopamine. *Ann Pharmacother* 2000; **34:** 1020–4.

Pharmacokinetics

The vasoconstrictor properties of dopamine preclude its use by the subcutaneous or intramuscular route. Like adrenaline (p.1204) it is inactive when given orally, and it is rapidly inactivated in the body by similar processes, with a half-life of about 2 minutes. Dopamine is a metabolic precursor of noradrenaline and a proportion is excreted as the metabolites of noradrenaline. Nevertheless, the majority appears to be directly metabolised into dopamine-related metabolites.

◊ References.

1. Steinberg C, Notterman DA. Pharmacokinetics of cardiovascular drugs in children: inotropes and vasopressors. *Clin Pharmacokinet* 1994; **27:** 345–67.
2. Juste RN, *et al.* Dopamine clearance in critically ill patients. *Intensive Care Med* 1998; **24:** 1217–20.
3. MacGregor DA, *et al.* Pharmacokinetics of dopamine in healthy male subjects. *Anesthesiology* 2000; **92:** 338–46.
4. Johnston AJ, *et al.* Pharmacokinetics and pharmacodynamics of dopamine and norepinephrine in critically ill head-injured patients. *Intensive Care Med* 2004; **30:** 45–50.

Uses and Administration

Dopamine is a catecholamine sympathomimetic (p.1408) with both direct and indirect effects. It is formed in the body by the decarboxylation of levodopa, and is both a neurotransmitter in its own right (notably in the brain) and a precursor of noradrenaline. Dopamine differs from adrenaline and noradrenaline in dilating renal and mesenteric blood vessels and increasing urine output, apparently by a specific dopaminergic mechanism. This effect is predominant at low infusion rates (about 2 micrograms/kg per minute); at slightly higher infusion rates (around 2 to 10 micrograms/kg per minute) it also stimulates $beta_1$-adrenergic receptors in the myocardium, and at 10 to 20 micrograms/kg per minute the effects of alpha-adrenergic stimulation, such as vasoconstriction, predominate. The inotropic action of dopamine on the heart is associated with less cardiac-accelerating effect, and a lower incidence of arrhythmias, than that of isoprenaline.

Dopamine also inhibits release of prolactin from the anterior pituitary.

Dopamine is used in acute heart failure, as occurs in cardiogenic shock (p.1183) and myocardial infarction (p.1175); it is also used in renal failure (but see below, under Surgery and Intensive Care), in cardiac surgery, and in septic shock.

Dopamine is given as the hydrochloride by intravenous infusion as a dilute solution (usually 1.6 or 3.2 mg/mL, although more dilute solutions may be used where fluid expansion is not a problem), in glucose 5%, sodium chloride 0.9%, or other suitable diluents; many fluids are suitable and licensed product information should be consulted. The initial rate is 1 to 5 micrograms/kg per minute, gradually increased by up to 5 to 10 micrograms/kg per minute according to the patient's blood pressure, cardiac output, and urine output. Up to 20 to 50 micrograms/kg per minute may be required in seriously ill patients; higher doses have been given. A reduction in urine flow, without hypotension, may indicate a need to reduce the dose. To avoid tissue necrosis dopamine is best given via a large vein high up in a limb, preferably the arm. When gradually stopping dopamine it is advised that care be taken to avoid undue hypotension associated with very low dosage levels, where vasodilatation could predominate.

Surgery and intensive care. Dopamine has an established role as an inotrope in cardiogenic shock and in cardiac surgery; it has also been used as a **renal protectant,** due to the apparently beneficial effects of lower doses on renal function. Studies in healthy *animals* and human subjects have shown that low-dose dopamine increases renal blood flow, natriuresis, diuresis, and possibly glomerular filtration rate. Low doses of dopamine (sometimes termed 'renal-dose' dopamine) have therefore been widely used in patients at risk of renal failure, such as those undergoing major surgery or in intensive care, as well as for the treatment of acute renal failure. However, clinical studies have failed to convincingly demonstrate that low-dose dopamine is effective in either preventing acute renal failure in patients at high risk, or in improving renal function or outcome in patients with established acute renal failure. A placebo-controlled, randomised study[1] in critically-ill patients with early renal dysfunction and meta-analyses[2,3] including studies of varying design, failed to show any clinical benefit in those receiving dopamine. It is now generally considered[2,4,5] that low-dose dopamine has no place as a renal protectant in the routine management of critically ill patients.

Dopexamine, which like dopamine acts as a peripheral dopamine agonist, has been used similarly but evidence of benefit is limited and it is generally not recommended (see Critical Care under Dopexamine, p.1274).

1. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000; **356:** 2139–43.
2. Kellum JA, Decker JM. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; **29:** 1526–31.
3. Friedrich JO, *et al.* Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; **142:** 510–24.
4. Galley HF. Renal-dose dopamine: will the message now get through? *Lancet* 2000; **356:** 2112–13. Correction. *ibid.* 2001; **357:** 890.
5. Holmes CL, Walley KR. Bad medicine: low-dose dopamine in the ICU. *Chest* 2003; **123:** 1266–75.

Preparations

BP 2008: Dopamine Intravenous Infusion;
USP 31: Dopamine Hydrochloride and Dextrose Injection; Dopamine Hydrochloride Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Dopatropin; Hettytropin†; Inotropin; Megadose; ***Belg.:*** Dynatra; ***Braz.:*** Constriction; Dopabane; Dopacris; Revimine; Revivan; Vasomine†; ***Canad.:*** Intropin†; ***Cz.:*** Tensamin; ***Denm.:*** Abbodop; Dopmin; Giludop; ***Fin.:*** Abbodop; Dopmin; ***Gr.:*** Giludop; ***Hong Kong:*** Intropin†; ***India:*** Dopinga; ***Indon.:*** Cetadop; Dopac; Indop; ***Israel:*** Docard; ***Ital.:*** Revivan; ***Jpn:*** Inovan; Pre Dopa; ***Malaysia:*** Dopmin; ***Mex.:*** Clorpamina†; Drynalken; Flemina†; Inotropisa; Miocina; Zetarina; ***Neth.:*** Dynatra; ***Norw.:*** Abbodop; ***Philipp.:*** Docard; Myocard; ***Port.:*** Cordodopa; Medopa; ***S.Afr.:*** Dynos; Intropin; ***Singapore:*** Dopmin†; ***Swed.:*** Abbodop; Giludop; Intropin†; ***Thai.:*** Dopamex; Dopaminex; Dopmin; Inopin; ***Turk.:*** Dopmin; ***USA:*** Intropin†; ***Venez.:*** Dopina; Rascordin†.

Dopexamine Hydrochloride

(BANM, USAN, rINNM) ⊗

Dopeksamiinihydrokloridi; Dopeksamin Hidroklorür; Dopéxamine, Chlorhydrate de; Dopexamine, dichlorhydrate de; Dopexamine dihydrochloride; Dopexaminhydroklorid; Dopexamini dihydrochloridum; Dopexamini Hydrochloridum; FPL-60278 (dopexamine); FPL-60278AR; Hidrocloruro de dopexamina. 4-{2-[6-(Phenethylamino)hexylamino]ethyl}pyrocatechol dihydrochloride.

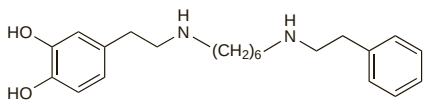
Допексамина Гидрохлорид

$C_{22}H_{32}N_2O_2,2HCl$ = 429.4.

CAS — 86197-47-9 (dopexamine); 86484-91-5 (dopexamine dihydrochloride).

ATC — C01CA14.

ATC Vet — QC01CA14.



(dopexamine)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dopexamine Dihydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol and in methyl alcohol; practically insoluble in acetone. A 1% solution in water has a pH of 3.7 to 5.7. Protect from light.

Incompatibility. Dopexamine is inactivated in alkaline solutions such as sodium bicarbonate 5%.

Adverse Effects and Precautions

As for Sympathomimetics, p.1407. Dopexamine has mainly beta-agonist and dopaminergic actions; its most common adverse effect is tachycardia, and transient hypotension may also occur. Dopexamine may cause a small reduction in platelet counts and should not be given to thrombocytopenic patients.

Interactions

As for Sympathomimetics, p.1407. The interactions of dopexamine are mainly due to its beta-agonist and dopaminergic actions; it may also potentiate the effects of noradrenaline and some other sympathomimetics by inhibiting neuronal uptake of noradrenaline.

Pharmacokinetics

Dopexamine has a short half-life in blood of about 6 to 7 minutes. It is excreted as metabolites in bile and in urine.

Uses and Administration

Dopexamine is a sympathomimetic (p.1408) with direct and indirect effects. It stimulates $beta_2$ adrenoceptors and peripheral dopamine receptors and also inhibits the neuronal reuptake of noradrenaline. These actions result in an increased cardiac output, peripheral vasodilatation, and an increase in renal and mesenteric blood flow.

Dopexamine hydrochloride is used to provide short-term haemodynamic support, for example after cardiac surgery or in exacerbations of chronic heart failure. It is given as an intravenous infusion of either 400 or 800 micrograms/mL in glucose 5%, sodium chloride 0.9%, or other suitable diluents, through a central or large peripheral vein; more concentrated solutions may be given via a central vein but concentrations should not exceed 4 mg/mL. The initial dose is generally 0.5 micrograms/kg per minute and is then increased to 1 microgram/kg per minute; further increases, in increments of 0.5 to 1 microgram/kg per minute at intervals of not less than 15 minutes, may be made up to a total of 6 micrograms/kg per minute if necessary. Heart rate, blood pressure, urine output, and cardiac output should be monitored. On withdrawal, the dose should be reduced gradually.

◊ References.

1. Fitton A, Benfield P. Dopexamine hydrochloride. *Drugs* 1990; **39:** 308–30.
2. Anonymous. Dopexamine after cardiac surgery. *Drug Ther Bull* 1995; **33:** 30–2.

Critical care. Dopexamine has been reported to increase splanchnic blood flow and it has been used with the aim of preventing renal and gastrointestinal dysfunction in critically-ill patients.[1] Although there may be a reduction in ischaemic damage to the gut,[2] a study[3] in critically-ill patients failed to show any improvement in outcome with the use of dopexamine. Studies[4,5] using dopexamine to increase oxygen delivery in high-risk surgical patients have also failed to show any benefit in terms of postoperative mortality or organ function, and a systematic review[6] found insufficient evidence to recommend the use of dopexamine in either patient group. A later meta-analysis[7] found that overall, perioperative dopexamine infusion reduced the length of hospital stay in patients having major surgery, but showed no survival benefit; however, at low doses (up to 1 microgram/kg per minute) dopexamine infusion seemed also to be associated with improved survival.

Use of low-dose dopamine for renal protection is not recommended (see Surgery and Intensive Care, p.1274).

1. Lisbon A. Dopexamine, dobutamine, and dopamine increase splanchnic blood flow: what is the evidence? *Chest* 2003; **123** (suppl): 460S–463S.
2. Baguneid MS, *et al.* A randomized study to evaluate the effect of a perioperative infusion of dopexamine on colonic mucosal ischemia after aortic surgery. *J Vasc Surg* 2001; **33:** 758–63.
3. Ralph CJ, *et al.* A randomised controlled trial investigating the effects of dopexamine on gastrointestinal function and organ dysfunction in the critically ill. *Intensive Care Med* 2002; **28:** 884–90. Correction. *ibid*; 1001. [dose]
4. Takala J, *et al.* Effect of dopexamine on outcome after major abdominal surgery: a prospective, randomized, controlled multicenter study. *Crit Care Med* 2000; **28:** 3417–23.
5. Stone MD, *et al.* Effect of adding dopexamine to intraoperative volume expansion in patients undergoing major elective abdominal surgery. *Br J Anaesth* 2003; **91:** 619–24.
6. Renton MC, Snowden CP. Dopexamine and its role in the protection of hepatosplanchnic and renal perfusion in high-risk surgical and critically ill patients. *Br J Anaesth* 2005; **94:** 459–67.
7. Pearse RM, *et al.* Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. *Crit Care Med* 2008; **36:** 1323–9.