

Unit 4: Cardiovascular Pharmacology

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4.1 Diuretics

Diuretics increase urine output by blocking sodium reabsorption at successive nephron segments; the further downstream the site, the less sodium remains to be claimed, so potency follows anatomy:

Class	Site and mechanism	Examples	Uses and signature problems
Osmotic	Proximal tubule and loop, water held osmotically	Mannitol	Raised intracranial pressure, acute glaucoma; IV only, volume shifts first
Carbonic anhydrase inhibitors	Proximal tubule, block bicarbonate reabsorption	Acetazolamide	Glaucoma, altitude sickness, metabolic alkalosis; weak diuresis, acidosis, paraesthesia
Loop diuretics	Thick ascending limb, block Na-K-2Cl cotransporter	Furosemide, bumetanide, torasemide	The most potent class: acute heart failure, oedema, hypercalcaemia. Hypokalaemia, hypomagnesaemia, ototoxicity at high IV doses, gout
Thiazides	Distal tubule, block Na-Cl cotransporter	Hydrochlorothiazide, chlorthalidone, indapamide	Hypertension mainstay, mild heart failure; hypokalaemia, hyponatraemia, hypercalcaemia, hyperuricaemia, glucose and lipid effects
Potassium sparing: ENaC blockers	Collecting duct, block epithelial sodium channel	Amiloride, triamterene	Added to loop or thiazide to spare potassium; hyperkalaemia is the risk
Potassium sparing: aldosterone antagonists	Collecting duct, block mineralocorticoid receptor	Spironolactone, eplerenone	Heart failure with proven survival benefit, resistant hypertension, ascites; hyperkalaemia and, for spironolactone, gynaecomastia

Site teaching points: loop and thiazide diuretics waste potassium because more sodium reaches the collecting duct and is exchanged for potassium under aldosterone; thiazides reduce calcium excretion (useful in recurrent calcium stones) while loops increase it; and any diuretic fails if the patient eats enough salt to replace the losses, the commonest cause of apparent resistance, alongside NSAIDs.

4.2 The renin angiotensin aldosterone system (RAAS)

Blood pressure and volume are governed by the RAAS cascade. A fall in renal perfusion pressure, sympathetic beta1 drive or low distal sodium delivery makes the juxtaglomerular cells release **renin**, which cleaves hepatic angiotensinogen to angiotensin I; **angiotensin converting enzyme (ACE)**, largely pulmonary and endothelial, converts it to **angiotensin II**, the system's effector: a potent vasoconstrictor (AT1 receptors), a stimulus to aldosterone release (sodium and water retention, potassium and hydrogen loss), to ADH release and thirst, to sympathetic facilitation and to cardiac and vascular growth and remodelling. ACE is also the enzyme that destroys **bradykinin** (Unit 5), so ACE inhibition raises bradykinin, a fact that returns as the class cough. The counter regulatory arm, angiotensin (1-7) acting at Mas receptors and the AT2 receptor, opposes vasoconstriction and growth, and is pharmacology in development rather than in the clinic.

Every binding site in the cascade is drugged: renin directly (aliskiren), ACE (the prils), the AT1 receptor (the sartans), and the mineralocorticoid receptor (spironolactone, section 4.1), giving four pharmacological handles on one physiology.

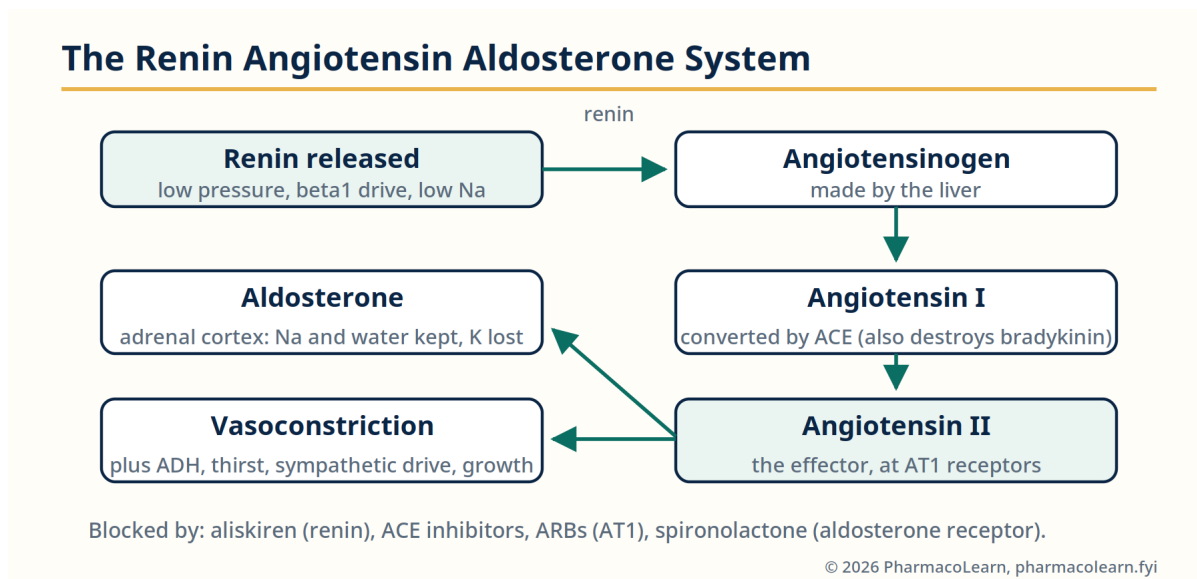


Figure: The renin angiotensin aldosterone system and the four levels at which drugs block it.

4.3 Antihypertensive drugs

Hypertension is treated to targets, usually with combinations, because each class defends against the compensations provoked by the others (a vasodilator's reflex tachycardia and salt retention are answered by a beta blocker and a diuretic).

- **ACE inhibitors** (ramipril, enalapril, lisinopril, perindopril): block angiotensin II formation. First line, with outcome benefits in heart failure, after myocardial infarction and in diabetic kidney disease, where dilating the efferent glomerular arteriole lowers intraglomerular pressure and proteinuria. Adverse effects: dry cough (bradykinin), angioedema (also bradykinin, commoner in Black patients and potentially fatal), first dose hypotension, hyperkalaemia, a reversible rise in creatinine when renal perfusion depends on angiotensin II (bilateral renal artery stenosis is the danger), and teratogenicity, so they are avoided in pregnancy.
- **Angiotensin receptor blockers** (losartan, valsartan, candesartan, telmisartan): block AT1 receptors, all the benefits with no cough, the usual substitute when ACE inhibitors are not tolerated. Never combined with an ACE inhibitor for routine hypertension (the combination trials showed harm without gain).
- **Calcium channel blockers**: dihydropyridines (amlodipine, nifedipine) block L type channels in vascular smooth muscle and dilate arteries, causing ankle oedema, flushing and headache, with short acting nifedipine's reflex tachycardia now avoided; rate limiting agents (verapamil, diltiazem) also slow AV conduction and contractility, are useful in angina and rate control, and must not be combined carelessly with beta blockers. Verapamil constipates.
- **Beta blockers** (Unit 2 for pharmacology): reduce cardiac output and renin release; no longer first choice for uncomplicated hypertension in many guidelines, but essential when there is angina, post infarction status, heart failure or rate control to treat.
- **Thiazide and thiazide like diuretics** (section 4.1): cheap, effective, outcome proven.

- **Others:** alpha1 blockers (doxazosin) as add on therapy; centrally acting alpha2 agonists (methyldopa, the traditional agent in pregnancy; clonidine); direct vasodilators (hydralazine, and minoxidil for resistant cases with hirsutism as its mark); and in hypertensive emergencies, controlled intravenous reduction with agents such as labetalol, nicardipine or sodium nitroprusside, never a precipitous fall.

4.4 Anti-ischemic drugs: treatment of angina

Angina is myocardial oxygen demand outrunning a supply narrowed by atheroma. Drugs work by cutting demand (heart rate, contractility, wall tension through preload and afterload) or, in vasospastic angina, by relieving spasm.

- **Organic nitrates** (glyceryl trinitrate, isosorbide dinitrate and mononitrate) release nitric oxide, raise cGMP and relax veins more than arteries: preload falls, wall tension and demand fall, and coronary collateral flow improves. GTN sublingual is the acute remedy (and a diagnostic one: pain relieved in minutes supports the diagnosis). Tolerance develops with continuous exposure (a daily nitrate free interval is prescribed), and phosphodiesterase 5 inhibitors such as sildenafil combine with nitrates to cause profound hypotension, an absolute contraindication pairing.
- **Beta blockers** cut rate and contractility, lengthening diastole when the coronaries fill; a mainstay of effort angina and post infarction care.
- **Calcium channel blockers** serve both effort angina (rate limiting agents) and vasospastic (Prinzmetal) angina, where they are first line and beta blockers are used cautiously.
- **Newer and adjunctive agents:** **ivabradine** blocks the funny current I_f of the sinoatrial node and slows the heart with no other cardiac action; **ranolazine** blocks the late sodium current, reducing calcium overload without changing rate or pressure; **nicorandil** opens potassium channels and donates nitrate like action; **trimetazidine** shifts cardiac metabolism toward glucose oxidation. All antianginals sit on top of the prognostic treatment of the underlying atheroma: antiplatelet drugs, statins and ACE inhibitors (sections 4.7 and 4.10).

4.5 Antiarrhythmic drugs

The Vaughan Williams classification organises antiarrhythmics by their dominant electrophysiological action, while clinical practice increasingly organises them by the arrhythmia and the state of the heart:

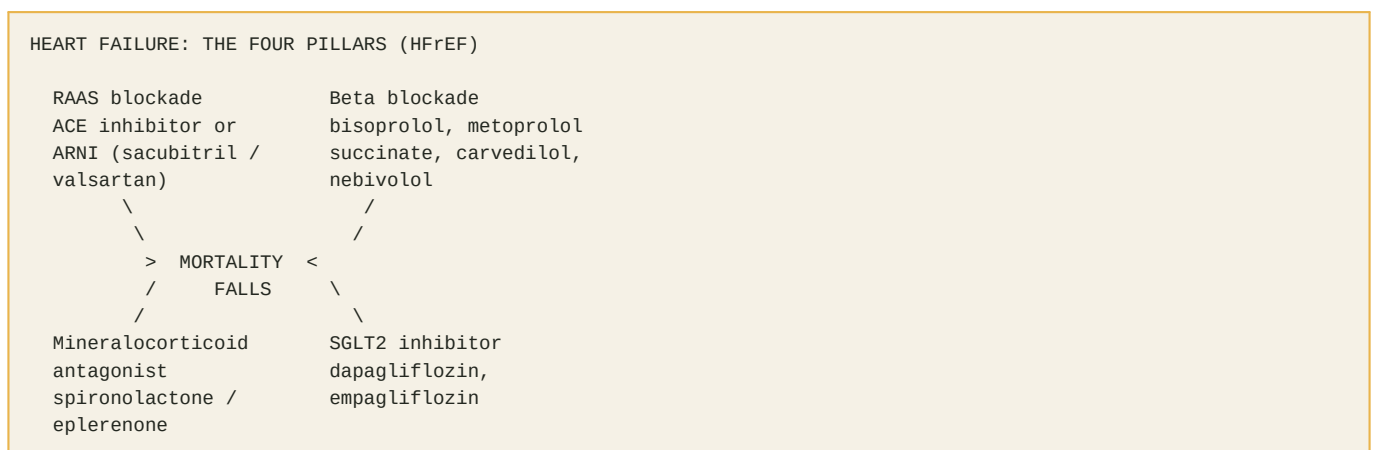
Class	Mechanism	Examples	Notes
I: sodium channel blockers	Block fast sodium channels, use dependently	Ia quinidine, procainamide (lengthen action potential); Ib lidocaine, mexiletine (shorten); Ic flecainide, propafenone (marked conduction slowing)	The CAST trial taught that suppressing post infarction ectopics with Ic drugs increased mortality; class I is now used cautiously and mainly in structurally normal hearts
II: beta blockers	Blunt sympathetic drive to the node and myocardium	Metoprolol, esmolol (IV, ultra short)	Rate control in atrial fibrillation, post infarction protection, inherited arrhythmia syndromes

Class	Mechanism	Examples	Notes
III: potassium channel blockers	Prolong action potential and refractory period	Amiodarone (the broadest agent, also blocks sodium and calcium channels and beta receptors), sotalol (with beta blockade), dofetilide, dronedarone	Amiodarone's toxicology is a syllabus in itself: thyroid both ways, pulmonary fibrosis, corneal deposits, blue grey skin, liver injury, and a half life of weeks to months
IV: calcium channel blockers	Block L type channels in nodal tissue	Verapamil, diltiazem	Terminate AV nodal tachycardias and control ventricular rate; never for wide complex tachycardia of unknown origin
Others	Various	Adenosine (A1 agonist, opens potassium channels and halts the AV node for seconds; the drug for SVT termination and a famously unpleasant few seconds), digoxin (vagal rate control), magnesium (torsades de pointes), atropine and pacing for bradycardia	Arrhythmia management is as much about anticoagulation, electrolytes and the underlying heart as about these drugs

The standing lesson is **proarrhythmia**: every antiarrhythmic can cause the arrhythmias it treats, including torsades de pointes from action potential prolonging drugs combined with hypokalaemia, so the modern trend is toward ablation and devices, with drugs holding specific niches.

4.6 Drugs for heart failure

Heart failure with reduced ejection fraction is a neurohormonal disease: the failing heart's compensations (sympathetic drive, RAAS, vasopressin) become the disease, and the drugs that improve survival all block them.



- **RAAS blockade**: ACE inhibitors, or the ARNI **sacubitril valsartan** (blocking AT1 while inhibiting neprilysin, the enzyme that degrades natriuretic peptides, so the heart's own protective peptides rise; an ACE inhibitor must be stopped 36 hours before starting, because combined ACE and neprilysin blockade invites angioedema).
- **Beta blockers** titrated slowly upward from low doses (starting during decompensation is an error; continuing through it, where possible, is not).
- **Mineralocorticoid antagonists** at low, non diuretic doses (spironolactone, eplerenone) with potassium and renal monitoring.
- **SGLT2 inhibitors** (dapagliflozin, empagliflozin), born as diabetes drugs, now pillars in heart failure with and without diabetes, by mechanisms still debated (natriuresis, metabolic and renal protection).

- **Diuretics** (section 4.1) relieve congestion and breathlessness but do not change prognosis; dose follows symptoms and weight.
- **Digoxin**, the old inotrope (Na-K ATPase inhibition raising intracellular calcium, plus vagal effects), now a niche drug for rate control and symptom relief in selected patients, with its narrow index, its toxicity (arrhythmias of nearly every kind, nausea, yellow vision) provoked by hypokalaemia and renal impairment, and its specific antidote, digoxin specific antibody fragments.
- **Others:** ivabradine when the rate stays high in sinus rhythm; hydralazine with isosorbide dinitrate in selected patients, notably those of African ancestry or intolerant of RAAS blockade; intravenous iron where deficiency limits exercise capacity; and acute decompensation managed with IV loop diuretics, vasodilators and, in low output states, inotropes (dobutamine, milrinone, levosimendan).

4.7 Drugs for hyperlipidemia

Lipid lowering is cholesterol lowering, and the axis is the hepatic LDL receptor: clear more LDL from the blood and events fall.

- **Statins** inhibit HMG-CoA reductase, the rate limiting enzyme of cholesterol synthesis; the hepatocyte responds by expressing more LDL receptors. They are the foundation (atorvastatin, rosuvastatin the potent pair; simvastatin, pravastatin older), with outcome benefits across primary and secondary prevention. Adverse effects: muscle pain and, rarely, rhabdomyolysis (risk raised by CYP3A4 inhibitors with simvastatin), transaminase rises, and a small increase in diabetes incidence. Their effect is measured in LDL percentage reduction and, in modern practice, LDL targets.
- **Ezetimibe** blocks the intestinal cholesterol transporter NPC1L1, adding a modest further LDL fall, used when statins are not enough or not tolerated.
- **PCSK9 inhibitors** (evolocumab, alirocumab, monoclonal antibodies) prevent PCSK9 from marking LDL receptors for destruction, so receptors recycle and LDL falls by more than half again; inclisiran, a small interfering RNA given twice yearly, silences PCSK9 production in the liver.
- **Fibrates** (fenofibrate, gemfibrozil) activate PPAR alpha and chiefly lower triglycerides; used for severe hypertriglyceridaemia and pancreatitis prevention rather than routine event reduction. Gemfibrozil with statins raises myopathy risk and the pair is avoided.
- **Others:** bile acid sequestrants (cholestyramine, colesevelam) bind bile acids in the gut and force hepatic cholesterol consumption, safe in pregnancy because they are not absorbed, at the price of gut side effects and binding of other drugs; bempedoic acid inhibits ATP citrate lyase upstream of HMG-CoA reductase and is activated only in the liver, limiting muscle effects; prescription omega 3 preparations and icosapent ethyl serve high triglyceride niches; niacin has effectively retired (flushing, and outcome trials without benefit on top of statins).

4.8 Hematinics

Hematinics supply what red cell production lacks. **Iron** is given orally as ferrous salts (ferrous sulfate, fumarate, gluconate) for iron deficiency, the commonest anaemia worldwide; absorption is duodenal, helped by vitamin C and an empty stomach, hindered by tea, calcium and proton pump inhibitors, and limited by hepcidin in inflammation. Side effects are gastrointestinal, and black stools are expected. Intravenous iron (ferric carboxymaltose and relatives) serves malabsorption, intolerance, chronic kidney disease and heavy ongoing losses, with modern preparations safe enough for routine use under supervision; acute iron poisoning in children is treated with the chelator desferrioxamine. **Vitamin B12** (hydroxocobalamin or cyanocobalamin) treats megaloblastic anaemia of pernicious anaemia and other

malabsorption, given parenterally when absorption is the problem; treating B12 deficiency with folate alone corrects the blood while the spinal cord disease (subacute combined degeneration) progresses, a classic examination trap. **Folic acid** covers increased demand (pregnancy, where it also prevents neural tube defects), malabsorption and antifolate drug effects; folinic acid rescues methotrexate. **Erythropoietin** (epoetin, darbepoetin) treats the anaemia of chronic kidney disease and chemotherapy, with iron repletion first, and with hypertension and thrombosis as its risks; its abuse in sport is the same pharmacology misapplied.

4.9 Coagulation, anticoagulants and fibrinolytics

Haemostasis balances clotting against bleeding. Vessel injury exposes tissue factor and collagen; platelets adhere, activate and aggregate (section 4.10); and the **coagulation cascade** converts fibrinogen to a stabilised fibrin mesh: the extrinsic pathway (tissue factor with factor VII) initiates, the intrinsic pathway (XII, XI, IX, VIII) amplifies, and the common pathway (X, V, prothrombin (II), fibrin (I)) executes, with thrombin as the central enzyme and factors II, VII, IX and X dependent on vitamin K for their synthesis. Natural anticoagulants (antithrombin, protein C and S) and fibrinolysis (plasminogen converted to plasmin, which digests fibrin) hold the system in check.

Anticoagulants:

- **Heparin** (unfractionated) binds antithrombin and accelerates its inhibition of thrombin and factor Xa; intravenous, immediate, monitored by aPTT, reversed by protamine. **Low molecular weight heparins** (enoxaparin) are more Xa weighted, subcutaneous, weight dosed, largely unmonitored, and less prone to heparin induced thrombocytopenia, the immune prothrombotic complication that makes heparin's adverse list unique.
- **Warfarin** blocks vitamin K epoxide reductase, so factors II, VII, IX, X and proteins C and S are made in inactive form. Oral, cheap and effective, with a narrow index managed by the INR, a slow onset (days, and a brief early prothrombotic window as protein C falls first, hence heparin bridging), dozens of CYP2C9 and dietary interactions, teratogenicity, and reversal by vitamin K, prothrombin complex concentrate or plasma.
- **Direct oral anticoagulants (DOACs):** dabigatran (direct thrombin inhibitor, reversed by idarucizumab), and the factor Xa inhibitors rivaroxaban, apixaban and edoxaban (reversal by andexanet alfa or PCC). Fixed dosing, no routine monitoring, fewer interactions and less intracranial bleeding than warfarin; renal function decides eligibility and dose.
- **Fondaparinux**, a synthetic antithrombin binding pentasaccharide, fills niches including heparin induced thrombocytopenia.

Coagulants and antifibrinolytics are the other direction: vitamin K for deficiency and warfarin reversal, **tranexamic acid** blocking plasminogen activation (trauma, surgery, menorrhagia, dental bleeding in haemophilia), desmopressin releasing von Willebrand factor, and factor concentrates and bypassing agents for the haemophilias.

Fibrinolytics dissolve formed clot: alteplase and its engineered variants tenecteplase and reteplase convert plasminogen to plasmin, given within strict time windows in ST elevation myocardial infarction (where primary angioplasty is unavailable in time) and in selected ischaemic stroke and massive pulmonary embolism. Their price is major bleeding, including intracranial haemorrhage, and their use is a protocol decision, never a casual one. Streptokinase, antigenic and non specific, is now largely historical in high income practice.

The Coagulation Cascade and Its Drug Points

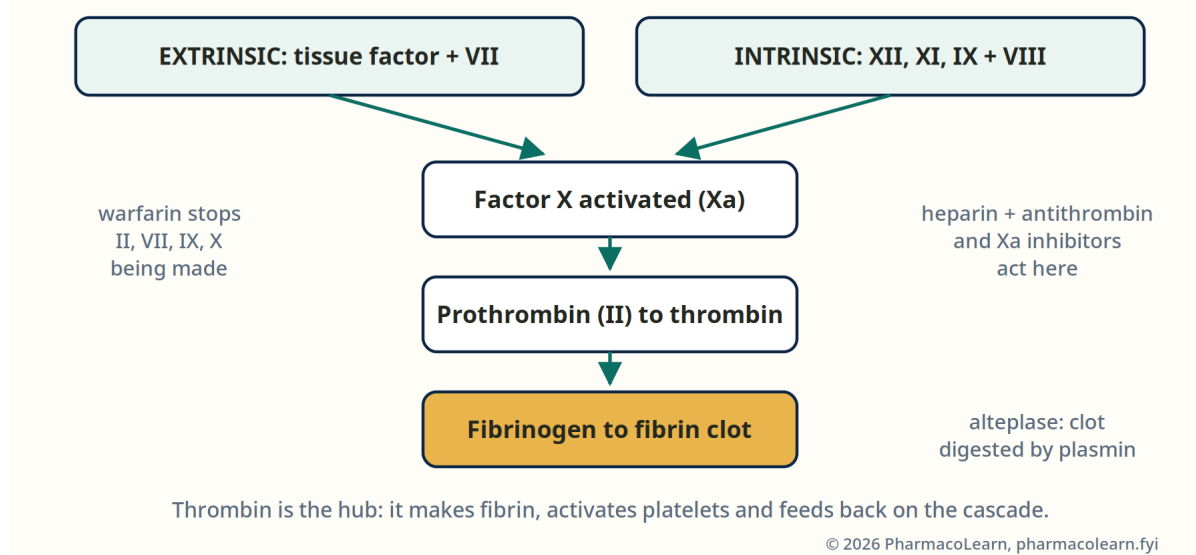


Figure: The coagulation cascade as a single convergent pathway, with the points where warfarin, heparin, the Xa inhibitors and the fibrinolytics act.

4.10 Antiplatelet drugs

Platelets are activated by collagen, thrombin, ADP and thromboxane A₂, and aggregate through the glycoprotein IIb/IIIa receptor binding fibrinogen. Each signal is a drug target:

- **Aspirin** irreversibly acetylates platelet COX-1, abolishing thromboxane A₂ production for the platelet's life. Low doses suffice because the effect is cumulative and presystemic. It is the foundation of secondary prevention after myocardial infarction and stroke, given immediately in acute coronary syndromes (chewed, for speed).
- **P2Y₁₂ blockers** prevent ADP driven activation: clopidogrel and prasugrel (prodrugs, irreversible; clopidogrel needs CYP2C19 activation, which poor metabolisers lack), and ticagrelor (direct, reversible, with dyspnoea and bradycardia among its effects). Combined with aspirin as **dual antiplatelet therapy** after coronary stenting, for a duration set by the stent and the bleeding risk.
- **Glycoprotein IIb/IIIa blockers** (abciximab, eptifibatide, tirofiban) block the final common pathway of aggregation, reserved for high risk percutaneous intervention.
- **Others:** dipyridamole (phosphodiesterase inhibition and adenosine uptake blockade, combined with aspirin for stroke prevention in some practice), cilostazol (peripheral arterial disease), and vorapaxar (thrombin receptor PAR-1 blockade) in narrow niches.

Balancing this section against section 4.9 is the daily work of cardiology: antithrombotic benefit is bought with bleeding, and combinations (dual antiplatelet therapy, or antiplatelet plus anticoagulant) multiply both sides of the bargain.

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