Q16 Define the mechanisms of action and adverse effects of metoprolol and glyceryl trinitrate when used to manage myocardial ischaemia.

METOPROLOL - a relatively cardioselective beta antagonist without intrinsic sympathomimetic actions. Used for the management of HTN, cardiac failure, migraine prophylaxis, rate control in AF, and as an adjunct in thyrotoxicosis. Can be given IV or PO.

Mechanism of action – metoprolol blocks the Gs protein of the beta 1 receptor, resulting in a reduction in cAMP and thus intracellular calcium. In doing so it reduces the catecholamine-induced rise of the prepotential (phase 4) of the cardiac pacemaker action potential, reducing automaticity and conduction through the AV node and slowing heart rate. By reducing heart rate it not only reduces oxygen demand but also allows for greater ventricular filling time, thus greater preload and consequently greater force of contraction (as per Starling's law). Prolonging diastole also results in better myocardial arterial blood supply – hence its indications in managing myocardial ischaemia.

Adverse effects – can cause bradycardia and hypotension due to decreased heart rate. Use with caution with other rate-lowering agents such as calcium channel blockers. Also use with caution in asthmatics or COPD patients as may initiate bronchospasm. May cause postural hypotension.

GLYCERYL TRINITRATE – an organic nitrate. Relatively selective for venodilatation and thus useful in the management of hypertension, myocardial ischaemia and acute pulmonary oedema. Can be given IV, S/L or transdermal.

Mechanism of action – GTN is cleaved by thiols to produce NO in smooth muscle cells, which activates soluble guanylate cyclase to increase cGMP and reduce intracellular calcium, causing vasodilatation. Most of its effects are on venous capitance vessels, resulting in a reduction in preload, venous return, ventricular end diastolic volume, and myocardial oxygen demand. Improves cardiac O2 supply via dilatation of large capitance vessels to improve subendocardial and epicardial vessel flow. The reduction in preload may lead to a reduction in cardiac output, however patients with LV dysfunction may find their output improves with the improvement in coronary blood supply.

Adverse effects –
CNS – headache due to intracerebral vasodilatation and an increase in ICP
CVS – at high doses SVR will fall, causing a reduction in afterload, however a compensatory tachycardia (baroreceptor induced) may reduce myocardial blood supply.
GIT – relaxes the sphincter of oddi
HAEM – may precipitate methaemoglobinaemia
Other – tolerance develops rapidly due to depletion of sulphydryl groups required for metabolism of GTN to NO2.