These drugs have been replaced by better tolerated and more effective drugs. Usage is limited to difficult to treat hypertension.

**Examples**  
Hydralazine  
Minoxidil

**Mechanism of action**  
Both hydralazine and minoxidil are dilators of resistance vessels with little action on venous beds. Blood pressure fall is accompanied by baroreceptor activation. Stimulation of the renin-angiotensin system together with compensatory increases in heart rate and contractility, tends to counteract the antihypertensive effects.

**Pharmacokinetics**  
- Hydralazine is rapidly and completely absorbed after oral administration. Pre-hepatic and hepatic metabolism, mainly by acetylation, is extensive. The acetylation pathway is subject to genetic polymorphism. Elimination is more rapid in “fast acetylators” while slow acetylators” have higher plasma concentrations with greater antihypertensive effects and greater risk of side effects. Elimination half-life is 2 – 4 hours.  
- Minoxidil also exhibits complete oral absorption and undergoes extensive liver metabolism. A sulphated metabolite is pharmacologically active and probably accounts for most of the activity.

**Adverse effects**  
Side effects common to both agents include headache, nasal stuffiness, fluid retention and oedema. These latter effects can lead to pseudotolerance. Other serious side effects include:

- **Hydralazine**  
  - peripheral neuropathy due to pyridoxine deficiency  
  - lupus reaction/raised ANA titres  
  - decreased white cell count
- **Minoxidil**  
  - hirsutism  
  - coarsening of facial features
- diabetes mellitus
- angina in those with ischaemic heart disease due to reflex tachycardia
- pericardial or pleural effusions (resolves on withdrawal of minoxidil)

**Practical issues**

Potent vasodilators are effective antihypertensive agents but are associated with unacceptable adverse reactions. With the advent of newer and better tolerated antihypertensive agents, use has declined dramatically.

Fall in total peripheral resistance and arterial pressure results in reflex cardio stimulation with frequent tachycardia and palpitation unless cardiac reflex responses are offset by concomitant beta-blockade. Sodium retention requires co-treatment with diuretic in most. A loop diuretic, sometimes at high dosage, may be necessary, particularly if there is renal impairment. These agents should not be administered to hypertensive patients with heart failure, myocardial infarction, angina or aortic dissection because the reflex cardiac effects will aggravate the underlying condition.

During chronic treatment with hydralazine, periodic full blood counts and ANA titres are recommended. The incidence of side effects can be reduced if dose is kept below 100 mg daily but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis or malaise.

Much of the early information demonstrating that antihypertensive therapy can diminish morbidity and mortality involved hydralazine-treated patients. A combination of reserpine, hydrochlorothiazide and hydralazine was used in the landmark Veterans Administration Cooperative Study which established unequivocally the merits of antihypertensive therapy not only in severe but in moderate hypertension. Because of the severity of adverse effects, however, usage of potent vasodilators is now limited to severe hypertension unresponsive to other treatments.