
Hypertension

Management is according to guidelines proposed by the British Hypertension Society¹. Similar sets of guidelines have been produced in other countries, and by the WHO.

The NICE guidelines (www.nice.org.uk) make some recommendations that are at odds with BTS guidelines

- Thiazide-like diuretics are recommended as first line treatment irrespective of patient demographics and presence/absence of ISH; this is not supported by best evidence²

ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)

- C (amlodipine) ± A (perindopril) vs. B (atenolol) ± D (bendroflumethiazide)
- α-blocker (doxazosin) added if target not reached
- Halted early as C ± A group did better
 - 10% lower rate of CHD, and 11% lower all-cause mortality
 - 30% lower incidence in DM
- Now needed: cost effectiveness analysis, joint BHS/NICE guidelines³

Measurement of blood pressure

Frequency

- Routinely every 5 years
- Annually if 'high normal' BP, or any high previous BPs

Method

- Patient seated (and standing if diabetic or elderly to exclude orthostatic hypotension)
- Support arm at heart level, remove tight clothing, avoid talking
- Use a calibrated device with an appropriate bladder size (NB the traditional mercury manometer is being phased out due to concerns about the safety of liquid mercury)
- Record to nearest 2mmHg
- Diastolic taken at disappearance of sound (phase V)
- If discrepancy between arms, use higher reading
- Average of two readings at each visit
- Three separate visits to determine BP thresholds (?still valid)
 - In mild hypertensives and older hypertensives with isolated systolic hypertension, but no target organ damage, take BP recordings over 3-6 months
 - In severe hypertensives, or where target organ damage is present, take BP measurements more often (e.g. weekly for 1 month)

Potential indications for ambulatory BP monitoring

- Possible white coat HT
- Unusual variability of BP (?episodic HT)
- Nocturnal HT, nocturnal dipper status (non-dippers are at higher risk)
- Drug-resistant HT
- Determining the efficacy of drug treatment over 24h
- Symptomatic hypotension

Mean daytime readings are preferred and can be expected to be 10/5mmHg lower than office readings; this also applies to treatment targets.

Definitions

BP distribution is unimodal ('skewed normal'), thus any definitions of HT are arbitrary

¹ WILLIAMS, B. ET AL. (2004): BHS guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* **328**:634-40.

WILLIAMS, B. ET AL. (2004): Guidelines for the management of hypertension: report of the fourth working party of the BHS. *J Hum Hypertens* **18**:139-85.

² POULTER, N.R. (2004): NICE and BHS guidelines on hypertension differ importantly. *BMJ* **329**:1289.

³ MCDUGALL, C. ET AL. (2005): ASCOT: a tale of two treatment regimens. *BMJ* **331**:859-60.

New European Society of Hypertension classification

Blood pressure

Optimal	<120	<80
Normal	<130	<85
High normal	<140	<90

Hypertension

Grade 1 (mild)	<160	<100
Grade 2 (moderate)	<180	<110
Grade 3 (severe)	>180	≥110

Isolated systolic hypertension

Grade 1	<160	<90
Grade 2	≥160	<90

Rationale for Rx

HT causes

- Heart
 - IHD
 - LVH
 - HF
 - AF
- Vessels
 - Increased rate of atherosclerosis, risk of thromboembolism
 - Fibrinoid necrosis if malignant HT
- Kidney
 - Hypertensive nephropathy (→ vicious circle)
- Brain
 - Intraparenchymal (Charcot-Bouchard aneurysms) and subarachnoid (berry aneurysms) haemorrhage

Trial evidence of benefit

MRC young/elderly hypertensive trial (1985, 1992)

SHEP: Systolic HT in the Elderly Program (1991)

>80 years: stay on existing treatment - little evidence for benefit from initiating treatment, although trial data is awaited

Aetiology

Primary (95%)

Secondary

- Pre-renal (renal artery stenosis), renal (glomerulonephritis, PKD), post-renal
- Endocrine (Cushing's, Conn's, pheochromocytoma, acromegaly, hyperthyroidism)
- Drugs (NSAIDs, OCP, steroids)
- Coarctation

Investigations

- Urine dipstick for protein and blood
- Blood for crea/e'lytes, glucose, lipid profile (both fasting), TFT
- ECG (?LVH, arrhythmias)
- Consider renal US

Aim to assess

- Cause of HT
- Associated cardiovascular risk factors

- Target organ damage

Non-pharmacological treatment

Can reduce blood pressure by 11/8

- May obviate need for drugs or reduce need for high dose/multiple drug therapy

Blood pressure lowering

- Reduce calorie intake to achieve target body weight
- Take regular exercise
- Avoid excess alcohol consumption (above 20U/wk BP rises linearly with intake)
- Reduce salt intake (may also lower cardiovascular risk independent of reduction in BP – TOHP studies),
?substitute potassium salt

Cardiovascular disease prevention

- Stop smoking
- Reduce total fat and proportion of saturated fat in diet
- Increase fresh fruit and vegetables (folate deficiency may elevate plasma homocysteine⁴)

Drug treatment

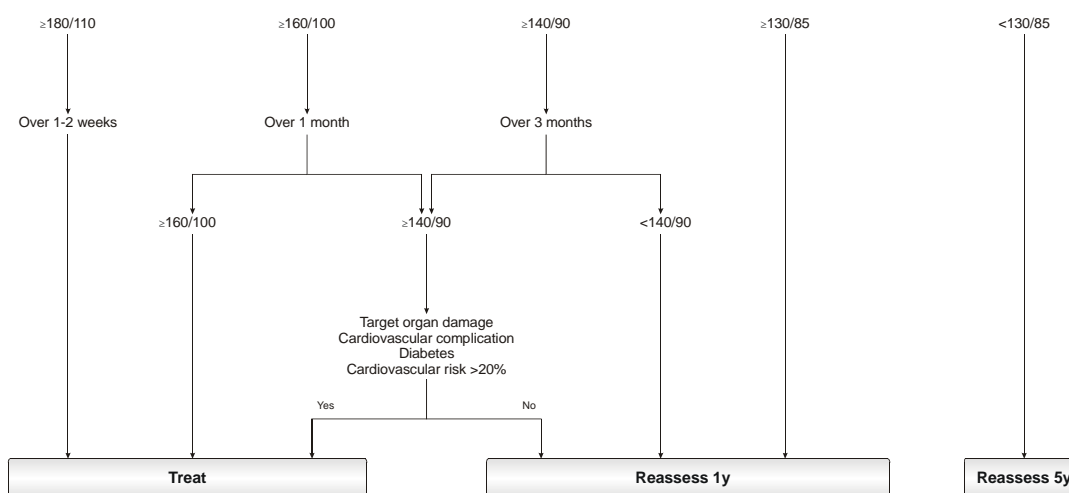
Indications

Initiate treatment in patients with sustained DBP at or above 100mmHg

Decide on treatment in patients with sustained DBP between 90 and 99mmHg according to the presence of target organ damage or absolute cardiovascular risk⁵

Decide on treatment in patients with sustained SBP at or above 160 according to the presence of target organ damage, value of DBP and magnitude of SBP elevation

Treat elderly patients of 60-80 years with SBP at or above 160mmHg and/or diastolic at or above 90mmHg



Target BP

Non-diabetics $<140/85$

Diabetics $<130/80$

Evidence for targets is limited

- SHEP (1991) – systolic
- HOT (1998) – both, no J shape
- UKPDS (1998) – diastolic (in type 2 DM)

⁴ Contentious cardiovascular risk factor: European Concerted Action Project (1997) found elevated levels in those afflicted by thromboembolic disease, but measurements were made after the event – is the elevation cause or effect?

⁵ New Joint British Societies' cardiovascular disease risk chart (www.bhsoc.org); assesses 10 year risk of all cardiovascular disease rather than coronary heart disease alone

Aims of treatment

Achieve target BP on single or multiple drug therapy with minimal side-effect profile

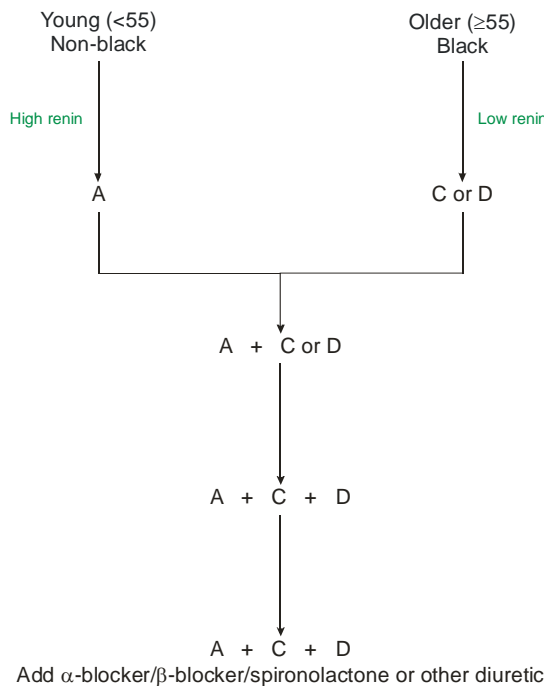
Choice of first-line agent

a) Compelling indication (simplified)

	Compelling indication	Possible indication	Relative contraindication	Absolute contraindication
ACE-Is	Heart failure LV dysfunction Type 1 diabetic nephropathy	Chronic renal disease Type 2 diabetic nephropathy	Renal impairment PVD	Renal artery stenosis Pregnancy
AT-II blockers	ACE-I intolerance Type 2 diabetic nephropathy LVH	Chronic renal disease Heart failure	PVD	Renal artery stenosis Pregnancy
Ca-channel blocker (DHP)	Elderly, ISH			
Ca-channel blocker (non-DHP)	Angina		Combination with β -blockers	Heart failure Heart block
Thiazides	Elderly, ISH			Hypokalaemia Hypercalcaemia Gout
Alpha-blocker	Prostatism		Postural hypotension	Urinary incontinence

β -blockers are no longer recommended as first or second-line agents, as they are less effective at lowering BP and cardiovascular risk⁶

b) If no compelling indication, use AB/CD rule



Several notes

- Allow 4 weeks to observe full response
- Two meta-analyses by the Blood Pressure Lowering Trialists' Collaboration show that 'newer' therapies (ACE-Is and CCBs) were as effective as, but no more effective than, conventional therapy (β -blockers and

⁶ Hypertension: management of hypertension in adults in primary care (partial update), NICE; referred to in *BMJ* 333:8

diuretics) at preventing mortality and morbidity. The main benefit is from blood pressure lowering, but little evidence exists of class-specific additional benefits.

- HOT (1998): <1/3 controlled on monotherapy; >1/3 require 3+ agents

Dosing

Start with lowest recommended dose

- If **partially effective** but well tolerated then increase dose (except thiazides which have a flat dose response curve)
- If **ineffective or partially effective** and/or not well tolerated (expect in some 50% of cases) then change drug **OR** add drug from another pharmacological class based on possibility of complementary action or countering reflex action of the first drug as above

c) Minimise side-effects (to maximise compliance)

- HT is usually asymptomatic, so patients will not readily accept side-effects
- Avoidance of side-effects associated with higher dose of single agent

d) Aim for 24h BP control with once daily administration

Class	Example	t _{1/2}
ACE-I	lisinopril	12h
β-blocker	bisoprolol	11h
CCB	amlodipine	40h
Thiazide	bendrofluzide	4h (but much longer duration of action)
α-blocker	doxazosin	11h

e) All things being equal use least expensive drug: usually thiazides (which also have best trial evidence)

Elderly

- Absolute benefit greater than at young age
- Target same as at young age
- Antihypertensives tolerated as well as in young age
- Low-dose thiazides are drug of choice

Other medications

Primary prevention

- Aspirin: use 75mg if
 - Age ≥ 50
 - BP controlled to <150/90mmHg
 - Target organ damage/DM/≥20% 10-year cardiovascular risk
- Statin: use sufficient dose to reach target (TC<4.0/25%, LDL<2.0/30%) if
 - ≥20% 10-year cardiovascular risk
 - TC ≥ 3.5mmol/l

Secondary prevention (incl. type 2 DM)

- Aspirin: use for all patients unless contraindicated
- Statin: use sufficient dose to reach target (TC<4.0/25%, LDL<2.0/30%) if
 - TC ≥ 3.5mmol/l

Remember to treat overall cardiovascular risk

Indications for specialist referral

Urgent treatment needed

- Accelerated phase hypertension
- Impending complications (e.g. TIA, CCF)

Possible underlying cause

- Young age (any HT<20; requiring treatment <30)
- Any clue re secondary cause
- Elevated crea, proteinuria/haematuria

Therapeutic problems

- Resistant to multidrug regime (3+ drugs)
- Multiple contraindications

Special situations

- Pregnancy
- Variable HT
- Possible white coat HT

Drugs used

β-blockers

See β-blockers.

Mechanism of action (HT)

Short term: ↓CO

Long term: ↓TPR

- Negative chronotropic and inotropic action
- Inhibition of sympathetically mediated hormone release
 - NorAdr (brainstem and pre-synaptic peripheral receptors)
 - Renin (also renal receptors)
- Increased baroreceptor sensitivity
- Decrease in plasma volume by unknown mechanism

Thiazide diuretics

E.g. bendrofluzide, hydrochlorothiazide

Mechanism

- Low-grade natriuretic, inhibiting distal tubular sodium reabsorption (early, short-lived effect)
- Reduce responsiveness of resistance vessels to endogenous vasoconstrictors e.g. NorAdr (later, long-lasting effect)
 - May be related to sodium loss
 - May be due to action on unidentified membrane ion channel

Loop diuretics focus on the first mechanism and their brisk action provokes reflex RAAS activation.

Adverse effects

Dose-dependent

- Hypokalaemia
- Hyponatraemia
- Hypochloreaemic alkalosis (rare)
- Hypomagnesaemia
- Hypercalcaemia (rare), decreased urinary calcium excretion
- Hyperlipidaemia
- Impaired glucose tolerance (by impaired insulin secretion + insulin resistance)
- Hyperuricaemia
- Impotence
- Photosensitive rashes
- Thrombocytopenia

Dose-independent

- Pancreatitis
- Agranulocytosis
- Thrombocytopenia

Note

- Adverse metabolic profile of thiazides less likely to occur with current lower doses than used previously since now appreciate that the dose response curve is quite flat (i.e. 1.25-2.5 mg bendrofluzide versus 10-20mg)
- Cheapest of all agents
- Best long-term mortality data for cardiovascular and cerebrovascular disease prevention

ACE-Is

First generation e.g. lisinopril/enalapril (long), captopril (short duration of action)

Second generation e.g. ramipril, quinapril, perindopril

Under development: ACE-Is with endopeptidase inhibition/natriuretic peptide action

Mechanism

Competitively inhibit the enzyme responsible for converting biologically inert angiotensin I to active angiotensin II, which acts predominantly via *AT₁ receptors*

- Vasoconstriction
- ↑aldosterone release
- ↑ADH release
- ↑thirst
- Facilitation of NorAdr release/↓NorAdr reuptake
- ↑cardiac and vascular smooth muscle growth
 - LVH
 - Blood vessel changes that lead to persistence of hypertension

Stimulation of *AT₂ receptors* is associated with antiproliferative action and teratogenicity (expressed in fetus and placenta)

ACE-Is also block degradation of kinins, which are potent vasodilators (kininase II = ACE).

Thus benefit in hypertension

- Vasodilatation – but no reflex cardioacceleration
- ↓aldosterone production and natriuresis
- Reversal of cardiac and vascular remodelling

Particularly useful in

- High-renin HT; may cause a severe BP drop in such subjects (should omit diuretics before starting, and warn of risk of hypotension; more of a problem when used in patients with CCF)
- Diabetics with proteinuria

Adverse effects

- First dose hypotension
- Dry cough
 - About 5% of patients, F>M, ethnic variability in incidence, genetically determined
 - ACE-Is inhibit kininase II and thus potentiate bradykinin and substance P near airway C fibres
- Hyperkalaemia
- Deterioration in renal function in patients with RAS
 - Suggested by ↑crea by ≥30% ± large fall in BP
 - Smaller rises in crea usually indicate that intraglomerular pressure has been successfully lowered
- Angioneurotic oedema = ACE-I hypersensitivity (rare but can be fatal; commonest in first week but may occur after years, more common in Afro-Caribbean; also due to bradykinin)
- Altered taste/stomatitis, agranulocytosis (only with older agents containing –SH group, e.g. captopril)

Contraindications

Hyperkalaemia, RAS/AS, hypotension, pregnancy

AT-II antagonists

E.g. losartan, irbesartan (longer $t_{1/2}$)

Mechanism

Non-competitive antagonism of AT-II at *AT₁ receptors* – thus longer duration of action than suggested by half-life alone

AT-II antagonists vs. ACE-Is

May eventually replace ACE-Is in both HT and heart failure?

Advantages

- Better tolerated (do not cause cough or angioneurotic oedema)
- Theoretically prevent AT-II action regardless of the mode of AT-I conversion (many tissues can convert AT-I to AT-II independently of ACE)
- Theoretically may have further benefit in causing regression of vascular and cardiac changes (LVH) due to stimulation of antiproliferative *AT₂ receptors*

Disadvantages

- Paradoxical increase in MIs (e.g. VALUE trial) although on a par with ACE-Is for BP reduction – why?

Otherwise very similar contraindications/adverse effects

Calcium channel blockers

See CCBs.

Mechanism of action

- ↓ afterload
- ↓ inotropic
- ↓ chronotropic (non-DHPs)

α -blockers

E.g. doxazosin (long-acting), prazosin (short-acting – largely obsolete)

Mechanism

Competitive α_1 antagonists
Result in arteriolar vasodilatation

Adverse effects

- First dose postural hypotension
- Nasal stuffiness
- Ejaculatory failure
- Detrusor relaxation: may alleviate outflow obstruction in men with BPH, but can cause urinary incontinence in females

Note

- Usually advise to start low dose and increase after a week
- Take medication at bedtime

Phenoxybenzamine

Irreversible non-selective α -blocker – blockade cannot be overcome by high catecholamine levels
Used only in patients with pheochromocytoma

Centrally-acting anti-hypertensive agents

These agents cannot be considered first-line/alternative first-line due to

- Side-effect profile
- Lack of good long-term outcome data

Mechanism

- CNS action to reduce sympathetic outflow
- Target receptors (probably α_2 and not I_1) in hindbrain vasomotor nuclei that project to spinal sympathetic efferents
- All are associated with sedation
- Risk of worsening or precipitating depression

Clonidine

- Post-synaptic central α_2 receptor agonist
- Not used in UK due to risk of rebound hypertension in patients with poor compliance (dry mouth, sedation)

Moxonidine

- α_2 agonist *and* imidazole receptor agonist
- Fewer adverse effects than older agents
- Longer acting and less risk of rebound hypertension

Methyldopa

- Converted by enzymes that synthesise noradrenaline to alpha-methylnoradrenaline and hence stimulation of α_2 receptors
- Usual side-effects of depression, sedation, nightmares; immunological effects including pyrexia, hepatitis, positive Coombs test or full-blown Coombs positive haemolytic anaemia, SLE
- Still commonly used in pregnancy as known to be safe

Vasodilators

IV

Diazoxide

- Arteriolar dilatation due to activation of ATP-dependent potassium channel

Sodium nitroprusside

- Arteriolar and venous vasodilatation due to production of nitric oxide

Hydralazine

- Dilates arterioles by still unknown mechanism (independent of nitric oxide)
- Hepatic metabolism by genetically determined acetylator pathway
- Sometimes used for IV treatment of hypertensive crises
- Hydralazine is used in pregnancy-induced hypertension

PO

Minoxidil

- Potent activator of ATP-dependent potassium channel
- Causes profound rebound sodium retention and may need large doses (several hundred mg) of loop diuretic
- Causes profound reflex tachycardia and need to β -block
- Used by specialists in very severe refractory HT

Pregnancy-induced hypertension

Eclampsia

- IV magnesium (hypotensive and anticonvulsant (NMDA blocker))

Pre-eclamptic HT

- First line: IV hydralazine
- Second line: PO methyldopa

Underlying HT

- First line: PO methyldopa
- Second line: CCBs, IV hydralazine
- Third line: labetalol, other β -blockers, α -blockers

Virtually all 'normal' antihypertensives are CI as they lack safety data in pregnancy.

Left ventricular hypertrophy

Is an important independent risk factor for cardiovascular mortality (i.e. independent of BP) – RR=3-5 (!)

Diagnosis

- ECG voltage criteria (poor)
- Echo

Pathology

Histologically distinct from the hypertrophy seen with exercise/training

- Diastolic dysfunction (ventricular stiffening)
- ↑incidence of angina (increased oxygen demand of big heart)
- ↑incidence of sudden death (lowers threshold for VF)

Presence of LVH suggests need for more aggressive BP control

Treatment

- All first line/alternative first-line agents lead to LVH reversal
- ACE-Is are probably most effective (AT-II is a potent growth promoter)
- AT-II antagonists have a theoretical advantage over ACE inhibitors due to stimulation of AT₂ receptors (antiproliferative action)

Malignant hypertension

It is rarely required to reduce BP rapidly and to do so may be dangerous.

Malignant HT derives its name from the poor median survival when left untreated (12-15 months). It is now more commonly referred to as 'accelerated phase' HT, reflecting the fact that the severe BP elevation comes at the end of a longer, more gradual rise.

Pathological hallmark = arteriolar fibrinoid necrosis:

- Grade III hypertensive retinopathy
- Microscopic haematuria
- Damage to small cerebral vessels and hence loss of cerebral autoregulation → risk of infarction if BP reduced rapidly
- Features of microangiopathy (fragmented RBCs and low platelets on blood film)

Management

- Bed rest
- Rx
 - Usually: oral, e.g. loop diuretic, labetalol; aiming to bring BP down over days
 - If end-organ failure (e.g. encephalopathy, ARF, LVF): IV loop diuretic or labetalol under arterial pressure monitoring; aiming for DBP of ca. 110mmHg in 4h

General comments and open questions

Patient groups/aetiology

1. Black patients tend not to respond to ACE-Is or β -blockers (low renin HT) but do tend to respond to diuretics; converse is true for Caucasians. However, a recent metaanalysis showed no significant response difference between these groups (*Hypertension* (2004) **43**:566-72; mentioned in *BMJ* (2004) **328**:602).
2. Is there benefit in treating HT over the age of 80yrs?
3. Will reversal of LVH, a known poor prognostic factor, result in better outcomes? If so, current guidelines would require overhaul.
4. What is the importance of white coat hypertension? Should it be treated and if so with which agents?
5. Severe uncontrolled HT is associated with a considerable morbidity and mortality. Stroke, MI etc. are associated with considerable health care costs. Such patients warrant expensive drug therapy on medical and arguably economic grounds to prevent subsequent expenditure on health care for complications of HT

Targets

1. Does an ideal target BP exist, and if so, what is it? Addressed by only a few trials, yet all present treatment is based on these findings

Drugs

1. New drugs tend to be expensive whilst old drugs are cheap
Should use cheapest alternative unless a particular benefit
cost per year (old)

bendrofluzide 2.5mg daily	£2.18
lisinopril 10mg daily	£153.79
atenolol 50mg daily	£13.78
bisoprolol 5mg daily	£111.28
nifedipine LA 60mg daily	£134.65
amlodipine 5mg daily	£154.05
doxazosin 4mg daily	£228.80
methyldopa 125mg tds	£34.02
moxonidine 200mcg daily	£135.85
2. Will AT-II antagonists maintain their advantage over ACE-Is in causing LVH regression in large-scale trials?
3. Role of spironolactone (non-aldosteronism spironolactone-sensitive HT)
4. Hypertension results from the failure of several homeostatic BP maintaining mechanisms in the face of an environmental insult. Current medications fail to address some of these mechanisms effectively. Drugs are in development that e.g. act via natriuretic peptide and may benefit patients with currently resistant hypertension

Outcome

1. Treatment of hypertension appears to eliminate the excess risk of stroke (reduction by 40%) but only half of the excess risk of cardiovascular disease (15% versus predicted 30%). Why is this?
2. Remember the rule of halves
50% hypertensives who need treating never get diagnosed
50% diagnosed hypertensives are inappropriately not treated
50% of those treated fail to reach target BP

Future

1. Endothelin and vasopressin antagonists, AT-II vaccines

2. Gene therapy based on overexpression of vasodilatory genes or inhibition of vasoconstrictory genes
 3. Pharmacogenetics
 - Causes and potential treatment of essential HT
 - BRIGHT (British Genetics of HT) study ongoing
 - Probably too multifactorial to target
 - Influence of individual genetic make-up on drug choice
 4. Are new classes of drugs required? Tamargo (2002): 'Hypertension is poorly controlled in a high proportion of patients, despite the availability of a variety of antihypertensive agents. Thus, there is a great need for new antihypertensive drugs that better control blood pressure and reduce other risk factors. Recent advances in the understanding of the pathogenesis of hypertension has led to the development of a large number of new antihypertensive drugs that target receptors, enzymes and channels. These agents should prevent target-organ damage independently of blood pressure reductions, as well as extend therapeutic options for patients inadequately controlled with current hypertension pharmacotherapy.'
- (<http://www.prous.com/journals/mf/20022413/html/mf240013/mf240013.html>)
5. Research needs to be paired with the dissemination of the newly found knowledge by continuous education of health care professionals. The current level of detection and treatment leaves much to be desired, and only a fraction of patients enjoys the benefits of today's established knowledge.
 6. Polypill (thiazide, ACE-I, β -blocker, statin, aspirin, folate)⁷
 - Proposed synergistic benefit
 - Controversial whether it could be used in primary prevention (everyone >55)
 - Non-specific scattershot approach, massive medicalisation of asymptomatic patients
 - Cost-effectiveness of treating low risk patients

⁷ FAHEY, T. ET AL. (2005): The polypill and cardiovascular disease. *BMJ* **330**:1035-6.