

Triple Aim: Optimising CVD medicines

Key messages

HIGH INTENSITY STATINS

People with established CVD get a further 16% reduction in CVD events by using high intensity statins. NICE recommends atorvastatin 80mg as first line treatment for ischaemic CVD and people should switch to atorvastatin 80mg or 40mg if appropriate.

HYPERTENSION

The 2019 NICE guidance endorses thiazide-like diuretics, home BP self-monitoring and medicines review. These interventions improve BP control.

BLEEDING WITH ANTICOAGULANTS/ ANTIPLATELETS

Upper GI bleeding caused by anticoagulants and/or antiplatelet medicines for AF or CVD is a major cause of death, disability or hospital admission.

In people age 65 years or older or anyone at high bleeding risk, bleeding can be reduced by 70% using proton pump inhibitors (PPI) and avoidance of interacting drugs.

Triple Aim guidance for 10% improvement in 3 years

In addition to further support for lifestyle changes, consider the following:

STATINS FOR CVD: IHD, STROKE/TIA or PAD

Increase high intensity statins:
Use atorvastatin 80mg or 40mg.

HYPERTENSION BP >140/90mmHg

Add thiazide-like diuretic.
Support adherence
Home BP monitor + management plan
Low-cost combination pills.

BLEEDING: AF or CVD on anticoagulants or antiplatelet agents

Add PPI to reduce GI bleeding.
Review duration of dual antiplatelets and/or
anticoagulants medicines.
Review interacting medicines

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Guidance

This document is a guide to decision making and not a replacement for clinical judgement. We have based this guidance largely on NICE and European Society of Cardiology guidance. Unless stated otherwise, guidance conforms to national NICE guidance. This guideline has been endorsed by the Waltham Forest and East London Medicines Optimisation and Commissioning Committee.

Additional information on the CEG Website

This guideline is available on the CEG website

<https://www.qmul.ac.uk/blizard/ceg/realhealth/>

In addition we have also prepared a set of summary position papers giving further information about the strengths and weaknesses of the evidence on which guidance is based and additional detail for those wishing to check out some of the issues around data presented in this summary as well as information leaflets for GPs targeting specific areas of our recommendations (e.g. ACE/ARB use for hypertension in women of child bearing age). These can be found on the CEG Website under REAL- HEALTH CARDIOVASCULAR

Why the Aim

A 10% improvement in the Triple Aim goals will provide internationally leading and equitable delivery of improved CVD outcomes in east London.

There are approximately 100,000 people in 3 CCGs in inner east London with either hypertension, CVD (heart attack, stroke or peripheral arterial disease) or atrial fibrillation. At least one-third of these are not on optimal medication. If an additional 10% (10,000) of these people were optimally treated, heart attack, stroke and bleeding events and hospital admissions would be reduced by 200, saving ~£6M in NHS costs over 3 years.

HYPERTENSION

Reduction of blood pressure by 10mmHg using antihypertensive medicines will reduce stroke and myocardial infarction by 25%. East London already does well for BP control. In the national Quality and Outcomes Framework 2018, City and Hackney ranked first nationally out of 209 CCGs in England in BP control, with 86% of hypertension controlled <150/90mmHg. The other inner east London CCGs ranked in the top 5%.

However, using a target of systolic blood pressure (SBP) <140mmHg, our 2019 baseline audit of nearly 90,000 hypertensive patients in City and Hackney, Tower Hamlets and Newham CCGs shows that 27% were uncontrolled with a SBP above 140mmHg.

Among these uncontrolled hypertensive patients, 17% were not on any blood-pressure treatment (although some of these may not 'qualify' for treatment on the basis of a low QRisk). 30% of the uncontrolled hypertensives were on only one blood pressure medication. Hence 47% of those with poor control are effectively undertreated and medicines could be added – most commonly a thiazide-like diuretic.

HIGH INTENSITY STATINS

Atorvastatin 40mg/80mg reduce CVD events by an additional 16% over lower intensity statins¹ – the absolute benefit is greatest in those with existing CVD who are at highest risk.

In 2019, our baseline audit in the three CCGs of Tower Hamlets, City and Hackney and Newham, showed that only 60% of people with ischaemic stroke/TIA, IHD or PAD are on high intensity statins, 26% are on lower intensity statin and 14% are not on any statin. In short, 40% are undertreated and for most, high intensity statins are appropriate.

NB. We have defined high intensity statins as atorvastatin 40mg or 80mg, rosuvastatin 20mg or 40mg and simvastatin 80mg (though this latter is not now recommended). This differs from the NICE definition which includes atorvastatin 20mg and rosuvastatin 10mg.

Statin intolerance is uncommon (<5%) and atorvastatin 80mg and 40mg are off-patent, very cheap and recommended by NICE. Negative media coverage has been a major factor and wide variation in statin use between clinical providers indicate that improvement is achievable.

BLEEDING

GI bleeding is an unwanted safety hazard of CVD prevention using anticoagulants in AF or antiplatelet agents in people with established CVD. Major GI bleeding risk increases very rapidly over age 75 years and is likely to be as disabling or fatal as a recurrent ischaemic stroke.

Our 2019 baseline east London audit showed that in patients age 75 years and older on anticoagulants/antiplatelet for Atrial Fibrillation or CVD, only 50% of AF patients and 60% of CVD patients were on a PPI.

Bleeding can be reduced by 70% or more, using PPIs, or avoiding interacting medicines, adjusting anticoagulant dose for renal impairment or frailty and avoiding over extended use of dual therapies.

SUPPORTING ADHERENCE

Fewer than half those who start medication - including anticoagulants, statins and BP medication - are taking it as prescribed after 6 months and adherence gets worse over time, with many missing doses or stopping medication altogether. A facilitative approach is advised including ascertainment of patients concerns such as:

- What do you already know about these medicines?
- How do your medicines make you feel?
- Does someone or something, help you, or remind you to take your medicine?
- Has anything changed with regards to your medicines since we last spoke?
- Ask about the extent of tablet taking – do you miss tablets occasionally or for several days on end?
- Have you considered a dosette box?
- Would reminders or more frequent review by a member of staff help?
- For new starters, the community pharmacists support the New Medicines Service. For people on anticoagulants, antiplatelets or those on four or more drugs, a pharmacist Medicines Use Review may be helpful.

Supporting adherence

At routine reviews ask about:

- Side effects - consider lower dose, switching meds
- Simplifying dose regimes and timing of doses
- Ways to reduce cost of prescription charges

Encouraging lifestyle modifications

Smoking cessation reduces CVD risks by 50% and tops the list of behavioural risk factors with a range of effective cessation alternatives. Increasing physical activity of any kind is universally beneficial and underrated for its overall health benefits. Increased activity should be incorporated into routine daily activities of which more walking and stair climbing are the simplest to achieve.

Dietary advice


Dietary advice should continue to stress the importance of a diet low in meat and animal fat, and of a reduction in dietary salt. Processed meats - sausages, pies, burgers, kebabs - are very high in saturated fats. Avoid butter, ghee, full-fat milk and pastries. All processed food is high in salt and intake should be limited, as should the use of salt in cooking.

Recommended vegetable oils include polyunsaturated sunflower and corn oils. Palm and coconut oils are saturated and should be avoided. An increase in green vegetables and fruit is beneficial. Advise use of alcohol within safe limits and reduce calories if overweight, targeting a normal-range BMI and weight. The 2019 NICE hypertension guideline advises preventive lifestyle advice at least annually, if not more often².

APL-CVD Tool


CEG has developed a new Active Patient Link APL-CVD tool that enables ‘virtual patient reviews’ using the GP practice electronic records. It identifies everyone with Hypertension, or with CVD/ AF who may benefit from medicines optimisation. It shows both the overall results for the GP practice and an individual patient.

The tool has all three main targets – **statins in people with established CVD, BP control in people with hypertension and bleeding reduction in people with CVD/AF on antiplatelets or anticoagulants**. Patients can be selected depending on disease, medication or risk and it displays a “virtual patient review” for the patients own characteristics, medicines and risks.



APL - CVD Cardiovascular Disease Tool v1

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Date of last run: 19/Jul/2019

CVD (IHD, Stroke/TIA and PAD) Prescribed Statin Page

Filters

Disease: IHD Stroke/TIA PAD AF Hypertension Diabetes CKD

Statin: Any Statin High Intensity Statin Mod/Low Statin Not on Statin

Frailty: Severe Moderate Mild Other Risks SMI Learning Difficulty

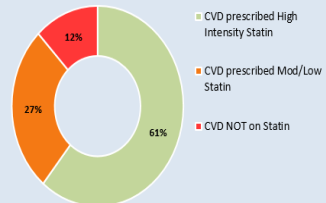
Total Cholesterol: Greater Than Or Equal To Less Than Age: >= <

Statin Exclusion: Contraindicated Declined Reset Filters

Practice Summary

Denominator Population (CVD)	420
CVD prescribed ANY Statin	369
CVD prescribed High Intensity Statin	256
CVD prescribed Mod/Low Statin	113
CVD NOT on Statin	51
CVD Statin Contraindicated	14
CVD Statin Declined	5

Prescribing CVD patients



CVD prescribed High Intensity Statin	12%
CVD prescribed Mod/Low Statin	27%
CVD NOT on Statin	61%

Full Name	Patient Reference no.	Usual GP	Age	Sex	Statin Prescription	Statin Intensity (High, Mod/Low, None)	Presc. Ezetimibe	Presc. Fibrate	Frailty Breakdown	Statin Exclusion	Blood Pressure	Total Cholesterol	Medication Review (Pharmacist or detailed GP review)
245265b8-afcb-f941-6c3b-b1d059cb7767	xxxxxxx	JP	28	Male	None	None	No	No	None	NO			
f92dcad7-e471-e185-b943-80e2788381792	xxxxxxx	KB	44	Female	None	None	No	No	None	NO	140/83	5	
ba5af7b5-98a5-3b34-b645-572d339ebbd1	xxxxxxx	SA	45	Male	None	None	No	No	None	NO	115/47	4.7	GP 30-Oct-12
2316e84e-009b-19e6-d1c6-e601631cd4d4	xxxxxxx	SA	46	Male	None	None	No	No	None	NO	122/68	4	
ae1b3b58-d2d6-c45e-485d-75259893a691	xxxxxxx	KP	50	Female	None	None	Yes	No	None	Declined	113/69	5.2	GP 14-Jan-15
cf61c8b6-0d5d-68cd-8a4f-726b1158f084	xxxxxxx	JT	51	Male	None	None	No	No	None	NO	105/78	3.9	
cb3af926-62a7-c310-da55-f29d68c062e7	xxxxxxx	JP	52	Female	None	None	No	No	None	NO	132/86	6.1	
e456e9c5-4ca8-295b-63f2-de6df44920ae	xxxxxxx	JL	54	Male	None	None	No	No	None	NO	113/64	6.2	

Statin optimisation

Patients with CVD on simvastatin 20 or 40mg should be considered for switching to atorvastatin 80mg or atorvastatin 40mg if clinically preferred.

This can easily be achieved at the next repeat prescription or annual review.

% LDL cholesterol lowering is:

- Atorvastatin 80mg/40mg/20mg: 55%, 49% and 43% respectively
- Simvastatin 40mg/20mg: 37% and 32% respectively
- Rosuvastatin 20mg/10mg: 48% and 43% respectively

STATIN INTOLERANCE

Statin intolerance due to adverse effects is uncommon. Minor but troublesome symptoms may include muscle pains, headache, gastrointestinal effects or blocked nose/sore throat and less commonly sleep disturbances, sexual dysfunction, depression, skin rash or hair loss).

True intolerance is in the order of 5% or less; if clinically appropriate, a re-challenge with low-dose pravastatin, rosuvastatin or atorvastatin may be successful. If tolerated, further up-titration to atorvastatin 20mg may be possible. Pravastatin at low dose is considerably better than no statin at all. Weekly low dose rosuvastatin may also be effective as it has a longer duration of action, though this dosing is unlicensed.

A meta-analysis of statins, for primary and secondary prevention, demonstrated that “Only a small minority of symptoms reported on statins are genuinely due to the statins: almost all would occur just as frequently on placebo” (including muscle pain and rhabdomyolysis)³. There is a small increase in Type 2 diabetes (possibly 1 new case for every 100 patients treated for 5 years) but statins remain associated with a reduction in cardiovascular events and benefits far outweigh any possible harm.

If patients have pre-existing muscle pain before starting a statin, check creatine kinase and do not start statins if >5 upper limit of normal. If muscle symptoms occur after treatment with statins, and do not resolve within 3 weeks after discontinuation, then statins are unlikely to be the cause. Check creatine kinase is < 3x upper limit of normal and exclude other causes of such symptoms (e.g thyroid function). Statins can be restarted at low dose and uptitrated.

For a more detailed paper on statins see the CEG website:

www.qmul.ac.uk/blizard/ceg/realhealth/

If symptoms do resolve within 3 weeks, then re-challenge at lower doses.

- Patients should be advised that statin therapy is a safe and well tolerated therapy – a trial of low dose pravastatin, rosuvastatin or atorvastatin may convince sceptical patients to uptitrate further in the absence of side effects.
- If no statin is tolerated record “adverse reaction to statin” in CEG template.

If no statin is tolerated, ezetimibe is an option. If lipid control remains a major issue, referral to a lipid clinic may be advisable. PCSK9 inhibitors evolocumab or alirocumab are highly effective but given by injection every two weeks, at a cost of £1800-4000 per year which may not be cost effective. Decrease in LDL cholesterol with PCSK9 was 53% compared with 17% reduction with ezetimibe.⁴ Omega fish oils should not be prescribed as they are ineffective.

STATIN MONITORING

At statin initiation check **non-fasting lipids** including total cholesterol, HDL cholesterol and triglycerides and a single ALT. For routine annual monitoring, total cholesterol alone is all that is required.

At initiation a single ALT is required by NICE - do not routinely request an entire 7 analyte LFT – NICE advises recheck at 3 months and 12 months but do not routinely measure again, unless clinically indicated. Statins do not cause liver disease but transitory low rises in liver function are common; increases in ALT up to 3x upper-limit of normal are acceptable and do not need further monitoring.

The NICE 2014 target is a 40% reduction in non-HDL cholesterol at 3 months of treatment⁵. If cholesterol is not sufficiently reduced, review adherence, diet, lifestyle and statin dosage. Repeat monitoring of total cholesterol annually. This is a **non-fasting specimen and HDL cholesterol and triglycerides are not required.**

Identifying high bleed-risk patients

Our APL-CVD tool helps GP practices identify high-bleed risk patients. It flags risks using a Red/Amber/Green code, and shows their specific risk factors to enable a rapid 'virtual review' to aid decision making.

About half of patients with CVD/AF on antiplatelets or anticoagulants are not adequately protected against bleeding. Bleeding risk can be substantially reduced in these individuals.

Bleeding due to antiplatelets or anticoagulants

Anticoagulant and antiplatelet related bleeding is one of the commonest causes of hospital admission for adverse drug related events. Observational studies show PPIs reduce hospital admission for GI bleeding due to anticoagulants by 70% and antiplatelets by 35%. However, trial evidence is currently limited. There is only one trial with evidence that PPIs reduce gastroduodenal bleeding as a result of anticoagulation⁷. In CVD there is only one major trial to show PPIs reduce GI bleeding from antiplatelets^{8,9}. Observational studies are numerous and consistent in their finding of reduced bleeding using PPIs with both anticoagulants and antiplatelets⁸⁻¹⁰.

Fewer than half of those with CVD on antiplatelets at high bleeding risk are on PPIs. Bleeding increases at ages over 65 years and very rapidly over age 75.¹¹ Increased use of PPIs is advised in those at high bleeding risk.

Adverse effects of PPIs

PPIs are associated with risk of bone fractures (<2/1000 per year) and pneumonia (1/1000 per year). However, in older people, both these adverse events are ten-times less likely than anticoagulant or antiplatelet related GI bleeding (20/1000 per year). PPIs may increase Vitamin B12 deficiency, influence chronic renal disease and increase clostridial infection. Hypomagnesaemia is rare.

Age is the major determinant of bleeding risk and risks rise around 65 years and more rapidly by age 75 years and older, when bleeding risks are typically 20/1000 or more per year and this risk is reduced by more than half by PPIs.

In summary, in people at increased bleeding risk, the benefits of PPI considerably outweigh the risks. The use of PPI is a clinical decision made in the context of patients who often have polypharmacy and multimorbidity. Any upper GI inflammation, ulceration and previous GI haemorrhage increase bleeding risk, for which PPI prophylaxis is recommended. Older age, frailty, renal disease and even mild anaemia also increase bleeding risk.

- Consider a proton pump inhibitor (PPI) in all patients 65 years and older with AF or CVD on anticoagulants or antiplatelet agents and in younger people on NSAID, other interacting medicines or with other major risk factors including upper GI symptoms.
- Use a PPI in any patients with previous upper GI ulceration or GI bleeding.
- Review antiplatelet plus anticoagulant or dual antiplatelet therapy for longer than 12 months and consider a PPI.
- Avoid NSAID and Coxibs: these increase both bleeding risk as well as increasing stroke, myocardial infarction and kidney injury.
- SSRIs, oral steroids, biphosphonates, lithium and spironolactone, increase bleeding risk. PPIs may be appropriate for these patients.
- Impaired renal function and frailty both increase bleeding risk and PPIs may be indicated. Anaemia is also a risk factor for bleeding. (WHO criteria <13.0 g/dl men and <12.0g/dl in women).

Although PPIs reduce upper GI bleeding risk there may be instances at older ages where even with protection, bleeding risk outweighs CVD benefits and antithrombotic agents are not appropriate. HASBLED or QBleed may aid risk assessment.

In patients age 75 years or more on an anticoagulant or antiplatelet agent, consider a PPI. Increased bleeding risks at age 65 years or younger ages may merit PPI, especially if on dual treatments or interacting medicines or other risk factors^{11,12}.

Clopidogrel and PPIs

There is concern that some PPIs reduce clopidogrel efficacy. Omeprazole or esomeprazole should not be used with clopidogrel.¹³

Pantoprazole and Lansoprazole are preferred PPIs if used in conjunction with clopidogrel.

BNF Licensed daily doses of PPIs for gastroprotection are: Lansoprazole 15–30mg. Pantoprazole 20mg.

Anticoagulant plus antiplatelet treatment

Patients on oral anticoagulants (OAC) may also have an indication for antiplatelet treatment (e.g. AF patient with a coronary stent insertion) or patients with CVD on antiplatelet treatment can develop an indication for oral anticoagulation (e.g. AF). The combination of anticoagulant therapy with an antiplatelet is known as **dual-pathway therapy**. Triple therapy is an anticoagulant plus two antiplatelet agents. Dual-pathway therapies should be initiated in secondary care with a recorded duration of treatment.

Local cardiology advice is that after a new coronary event, patients who also have AF should be put on triple therapy (OAC + two antiplatelet agents) for up to 3 months, on dual-pathway therapy (OAC + one antiplatelet) for up to one year and anticoagulation alone thereafter.

Bleeding and dual antiplatelet therapy in CVD

Dual antiplatelet therapy, typically clopidogrel plus aspirin is recommended after an acute coronary event for up to 12m and with stents or CABG this may rarely be extended for up to 3 yrs. Particularly at older ages, the risk of bleeding may outweigh the risk of CVD benefit and use of dual therapy beyond 12m should be reviewed.

Extended dual or triple therapy beyond a year is justified in only a small minority of patients. Review with the relevant specialist.

NSAIDs and other interacting drugs

NSAIDs/Coxibs should be avoided in people with CVD, AF and heart failure and hypertension.

There are as many deaths caused by NSAIDs (due to GI bleeding and also MI or stroke), as deaths from road traffic accidents in the UK. NSAIDs cause twice as many deaths as from asthma or cervical cancer.

NSAIDs increase the risk of upper gastrointestinal bleeding by 2–4 times during both short and long-term use and should not be used with anticoagulants or in people with CVD and avoided in hypertension.

NSAIDs also increase thromboembolic stroke and heart attack because they interfere with platelet function.

Impaired renal function or frailty may reduce drug excretion requiring consideration of lower anticoagulant dose and further review for potentially interacting drugs with specialist advice.

SSRIs, oral steroids, bisphosphonates, spironolactone, and anticonvulsants such as carbamazepine or phenytoin also increase risks of bleeding with anticoagulants and review of their use or addition of PPIs may be relevant.

For more detailed paper on antithrombotic bleeding, dual therapies and PPI use, see the CEG website: www.qmul.ac.uk/blizard/ceg/realhealth/

Hypertension: improving control

- **Improve BP measurement** – Confirm new diagnoses with ABPM or HBPM.
- **Devise BP management plans** with target BP (office or home targets)
- **Home blood pressure monitoring** – use a HBPM target 5mmHg below office targets.
- **Use thiazide-like diuretics** (TLD) as second line options – 2019 NICE guidelines now include thiazide diuretics (preferably indapamide) as second line agents.
- **Improve adherence** – Consider low-cost single-pill combinations (SPCs) for patients where this may aid adherence (e.g. Lisinopril or Irbesartan+ hydrochlorothiazide < £2 per month). Use dosettes or other adherence aids or reminders.
- **Patients over 80 years of age**: treat hypertension at older ages but consider risk-benefits, frailty and co-morbidity. NICE recommends a target SBP of <150mmHg. Review medication if SBP is <120mmHg.
- **Patients under 40 years of age** – Consider secondary causes particularly if control difficult to achieve.

Appropriate BP measurement and monitoring

ABPM remains the gold-standard to diagnose hypertension and all suspected hypertensive patients should have an ABPM for confirmation. However, Home Blood Pressure Monitoring (HBPM) is easily available with cheap and accurate BP monitors and provides more accurate BP assessment than routine monitoring using annual or occasional sporadic GP office-based BP measurements.

NICE guidelines detail advice on appropriate technique for office-testing, ABPM and HBPM (Additional material on the CEG website provide details on accessing the British and Irish Hypertension Society's home-use validated device list). Record ABPM and HBPM using CEG templates.

Pharmacological treatment

New NICE guidelines (NG136 Aug 2019)² has revised treatment pathways. Unchanged is the recommendation to start with an ACEi, ARB or CCB as the first-line agent. In contrast, most other international guidelines include thiazides as an optional first line choice of medication.

Indapamide, a thiazide-like diuretic, is now approved by NICE as a second line agent.

(NB. Chlortalidone is not available in the UK except at £88 per month versus <£2 per month for a standard thiazide!).

The NICE 2019 guidelines also advise suggesting treatment initiation in stage 1 hypertension at QRisk $\geq 10\%$ (rather than the previous QRISK $\geq 20\%$) and, in patients < 40 years, to consider treatment initiation even if QRisk <10%.

Key treatment recommendations from NICE 2019 and other guidance

- Favour early use of 2nd or 3rd line agents, in preference to up-titration of existing agents. Many drugs have a poor “return on investment” from up-titration, with an increase in adverse effects. Higher doses may cause more marked biochemical changes with little advantage in blood pressure control.
- Indapamide (a thiazide-like diuretic, TLD) is the preferred second line diuretic choice. TLDs were preferred to standard thiazides hydrochlorothiazide or bendroflumethiazide, because a meta-analysis showed TLDs reduce CVD events by an additional 12% and of heart failure by 21%¹⁴.

Other considerations

The ALLHAT trial demonstrated chlortalidone superior to amlodipine or lisinopril in BP reduction and CVD prevention. Chlortalidone is either not available in the UK or unaffordable¹⁵.

Indapamide is the only UK low-cost TLD available. However, the older thiazides - bendroflumethazide and hydrochlorothiazide - are both highly effective low-cost anti-hypertensive agents and alternatives where indapamide is unsuitable or a single pill combination is required.

If adherence or control is poor, consider if a low-cost single-pill combination (SPC) would be helpful. NICE did not make any recommendations on SPC. Their availability and costs are shown in Table 1.

TABLE 1

Single-Pill Combination	Spc Vs. Split-Pills (28 Day Cost)
Standard Thiazide diuretic + ACEi /ARB SPC	
Lisinopril + Hydrochlorothiazide	£1.22 vs £2.50 cost saving
Irbesartan + Hydrochlorothiazide	£1.62 vs £1.60
Losartan + Hydrochlorothiazide	£1.62 vs £1.13
Valsartan + Hydrochlorothiazide*	£3.81 vs £2.91 *Cost goes up hugely with dose
Indapamide + ACEi SPC	
Perindopril + Indapamide	£9.51 vs £5.66
Standard Thiazide diuretic + ACEi + CCB SPC	
Olmesartan + Amlodipine + Hydrochlorothiazide	£16.95 vs £2.91

TABLE 2

Condition	1st line	Comment
CKD and ACR \geq 30 CKD and diabetes and ACR \geq 3	ACEi/ARB*	NICE CG182 (CKD) [2015]
CKD and ACR $<$ 30 (non-diabetic)	ACEi/ARB* or CCB	NICE GC182 (CKD) [2015] NICE NG136 (HTN) [2019]
Pregnant patient	Labetolol (BB)	NICE NG 133 (HTN in preg.) [2019]
Diabetes (any ethnicity)	ACEi/ARB*	NICE NG136 (HTN) [2019]
Heart failure	Thiazide-like diuretic (in addition to ACE/ARB/BB)	NICE NG136 (HTN) [2019]
Beta-blocker treated co-morbidity (HF, angina, post-MI, AF)	BB + ACE or CCB or diuretic all acceptable	Nil specific recommendation in NICE 2019

* favour an ARB, in adults of African and Caribbean ethnicity

Many SPCs including chlortalidone are unavailable or very costly in the UK. The cheapest SPC with indapamide is double the cost of the 'split-pill' alternative. **Other thiazide SPC combinations are low cost and may be better value for money. Lisinopril + hydrochlorothiazide is the only cost saving SPC** (Table 1). Other combinations are more expensive and cost-effectiveness is doubtful.

- **Review the young (<40 year old) hypertensives.** Exclude secondary causes where control remains poor. In patients with resistant hypertension consider spironolactone.

- **Consider co-morbidities**

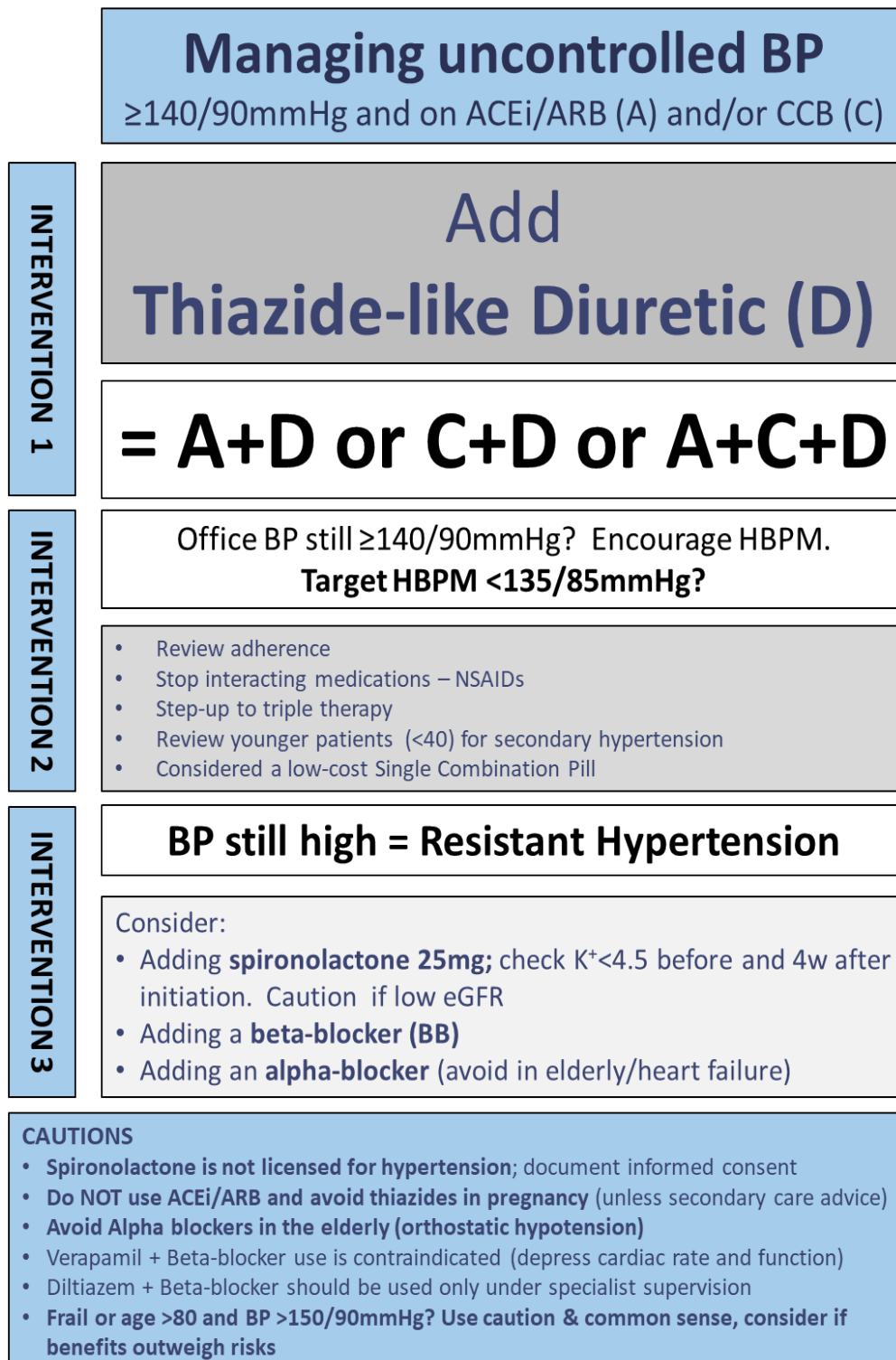
Table 2 shows recommended 1st line treatment in specific cases.

Summary Of Management

NICE 2019 guidance recommends a target BP of <140/90mmHg for all people with hypertension under age 80 years and 80 years and older of <150/90mmHg irrespective of their underlying co-morbidities such as CVD or diabetes.

The exceptions are T1 diabetes and CKD with diabetes or proteinuria (See Table 3).

FIGURE 1: Management of uncontrolled hypertension >140/90mmHg in patients already at step 1 of NICE NG136’s treatment ladder.



The general “audit” target for controlled hypertension is <140/90mmHg (office based) and this is the general treatment target in the NICE NG136 guidelines.² In patients aged 80 and over the target is relaxed to <150/90mmHg. Other NICE guidelines modify the clinical target in specific clinical contexts, these are summarised in Table 3.

TABLE 3: Specific Office BP targets for hypertension (reduce by 5mmHg if ABPM or HBPM)

Condition	Target	Source NICE
≥ 80 years old	<150/90	NG136 (HTN) [2019]
General hypertensive target	<140/90	NG136 (HTN) [2019]
CKD without diabetes or significant proteinuria	<140/90	CG182 (CKD) [2015]
CKD with diabetes or significant proteinuria	<130/80	
T2DM regardless of renal, retinal or cerebrovascular damage	<140/90	NG136 (HTN) [2019]
T1DM without albuminuria or metabolic syndrome	<135/85	NG17 (T1 Diab) [2016]
T1DM with albuminuria or metabolic syndrome	<130/80	
Chronic hypertension in pregnancy	<135/85	NG 133 (HTN preg.) [2019]
Post-stroke	<130	NICE CKS [2017]

Measuring blood pressure

- Use upper arm devices.
- If postural hypotension is suspected, measure office BPs with the patient standing.
- Uncontrolled hypertension may be due to incorrect technique, concurrent illness or white-coat hypertension.
- If control is poor, encourage HBPM.
- HBPM: advise and train patients on home blood pressure monitors and give information on what to do if they are not achieving their blood pressure target.
- Refer patient to the British and Irish Hypertension Society for home-use approved BP monitors (<https://bihsoc.org/bp-monitors/for-home-use/>)

Method	Correct technique	Comments
Office-based measurement	Calibrated device Quiet room, quiet and rested patient Seated, arm outstretched and supported Appropriately sized upper arm cuff at mid-sternal height centred over artery If initial BP > goal BP: 3 readings, 1 min apart Discard 1st reading, average last 2	Automated BP measuring devices may give inaccurate results in AF. If sustained office BPs of ≥140/90mmHg, confirm diagnosis with ABPM or HBPM.
Ambulatory Blood Pressure Monitoring (ABPM)	At least 2 per hour during waking hours Use average of ≥ 14 wake-time measurements to calculate BP	Diagnosis of hypertension with ABPM is made at ≥ 135/85 mmHg ⁹
Home Blood Pressure Monitoring (HBPM)	2 measurements (≥ 1 minute apart) twice a day (ideally morning and evening) Measurements for ≥ 4 days but ideally 7 days Discard first day results and average all others	Advise self-management with a recommended upper arm device: Diagnosis of hypertension with averaged HBPM is made at ≥ 135/85 mmHg

References

1. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* **376**, 1670–1681 (2010).
2. National Institute for Health and Care Excellence. Hypertension in adults: diagnosis and management (NICE guideline NG136). (2019). Available at: <https://www.nice.org.uk/guidance/ng136>. (Accessed: 9th September 2019)
3. Finegold, J. A., Manisty, C. H., Goldacre, B., Barron, A. J. & Francis, D. P. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. *Eur. J. Prev. Cardiol.* **21**, 464–74 (2014).
4. Nissen, S. E. *et al.* Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance. *JAMA* **315**, 1580 (2016).
5. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification (NICE clinical guideline CG181) [Revised 2016]. (2016). Available at: <https://www.nice.org.uk/guidance/cg181>. (Accessed: 9th September 2019)
6. Akyea, R. K., Kai, J., Qureshi, N., Iyen, B. & Weng, S. F. Sub-optimal cholesterol response to initiation of statins and future risk of cardiovascular disease. *Heart* **105**, 975–981 (2019).
7. Moayyedi, P. *et al.* Pantoprazole to Prevents Gastrointestinal Events in Patients Receiving Rivaroxaban and/or Aspirin in a Randomized, Double-blind, Placebo-controlled Trial. *Gastroenterology* **0**, (2019).
8. Bhatt, D. L. *et al.* Clopidogrel with or without Omeprazole in Coronary Artery Disease. *N. Engl. J. Med.* **363**, 1909–1917 (2010).
9. Mo, C. *et al.* Proton pump inhibitors in prevention of low-dose aspirin-associated upper gastrointestinal injuries. *World J. Gastroenterol.* **21**, 5382 (2015).
10. Ray, W. A. *et al.* Association of Oral Anticoagulants and Proton Pump Inhibitor Cotherapy With Hospitalization for Upper Gastrointestinal Tract Bleeding. *JAMA* **320**, 2221 (2018).
11. Li, L., Geraghty, O. C., Mehta, Z., Rothwell, P. M. & Oxford Vascular Study. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *Lancet (London, England)* **390**, 490–499 (2017).
12. Sehested, T. S. G. *et al.* Reduced risk of gastrointestinal bleeding associated with proton pump inhibitor therapy in patients treated with dual antiplatelet therapy after myocardial infarction. *Eur. Heart J.* **40**, 1963–1970 (2019).
13. MHRA. Clopidogrel and proton pump inhibitors: interaction—updated advice. (2014). Available at: <https://www.gov.uk/drug-safety-update/clopidogrel-and-proton-pump-inhibitors-interaction-updated-advice>. (Accessed: 13th September 2019)
14. Olde Engberink, R. H. G. *et al.* Effects of Thiazide-Type and Thiazide-Like Diuretics on Cardiovascular Events and Mortality. *Hypertension* **65**, 1033–1040 (2015).
15. ALLHAT, T. A. & Coordinators, T. C. O. and. Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA J. Am. Med. Assoc.* **288**, 2981–2997 (2002).

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