

Hypertension: Frequently Asked Questions

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The Resolve to Save Lives *Hypertension Frequently Asked Questions* were gathered from trainees and health care providers in the countries where we work.

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A. HYPERTENSION TREATMENT PROTOCOLS, CARE PROCESS, COST CONSIDERATIONS

A1. HOW SHOULD COUNTRIES/DISTRICTS/FACILITIES CHOOSE BETWEEN THE DIFFERENT HYPERTENSION TREATMENT PROTOCOLS?

There are many different reasons to choose one hypertension treatment protocol over another, and different areas/facilities may adopt slightly different protocols.¹ We provide pros and cons for each protocol to help the decision-making process. Specific factors to consider include:

- Alignment with current treatment guidelines or clinical practice
- Cost of drugs and ease of procurement
- Simplicity
- Evidence that certain drug classes may be less effective or have more side effects in the population to be treated*

* For example, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are unsafe in women who are of child bearing potential and are contraindicated in pregnancy. There is evidence that ACE inhibitors are less effective and have more angioedema in black American populations as compared to Caucasian populations.² For the most part, however, the differential impact of blood pressure-lowering drugs in other ethnic populations has not been studied.

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A2. ARE RECOMMENDED FIRST- AND SECOND-LINE AGENTS ACCESSIBLE (I.E., AVAILABLE AND AFFORDABLE) IN ALL PRACTICE SETTINGS GLOBALLY?

While recommended first and second line agents may not be accessible in all practice settings, most health systems have access to at least one agent in each recommended drug class. Selection of an alternative drug from within the same class is reasonable, as long as the selected drug is available and affordable. (Most guideline development groups^{1,2} do not distinguish among specific drugs in a particular class because of the lack of high-quality head-to-head trials comparing drugs from the same class.)

Accessibility can be improved by specifying a limited, carefully selected and effective set of medications in a standardized treatment protocol. This facilitates large-volume purchases, reducing medication costs and improving supply chain reliability.^{3,4}

When possible, select specific drugs that are long acting (dosed once a day,) affordable, have a reliable supply of quality medication, and have been used in successful clinical trials. For example, lisinopril, amlodipine, and chlorthalidone were all used in the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial.⁵

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A3. FOR PROTOCOLS THAT START WITH A SINGLE DRUG, RESOLVE TO SAVE LIVES FREQUENTLY RECOMMENDS INTENSIFYING TREATMENT WITH THE ORIGINAL DRUG BEFORE ADDING A SECOND DRUG. WHY NOT ADD A SECOND DRUG BEFORE INTENSIFYING TREATMENT WITH THE FIRST?

Although there is evidence that adding a second drug is five times more effective than intensifying dosage of the first drug,^{1,2} adding a second drug can increase barriers to access and may not be appropriate in all settings. Dose intensification using the same medication (e.g. intensifying from one pill to two) can limit some of these barriers: the patient may have to make fewer trips to the pharmacy, and may pay less, than if a second drug were added. There may also be reduced dispensing burden to the pharmacy, thereby enhancing treatment escalation efficiency.³ The need for lab tests is different across calcium channel blockers (CCBs), ACE inhibitors, ARBs, or thiazide diuretics. For example, intensifying a CCB is likely to require fewer lab tests, which may be preferable in settings in which access to lab tests is limited.⁴ In the future, if fixed-dose combinations of anti-hypertensive medications are available in appropriate dosages, intensification with multiple drugs may be simpler for patients, health care providers, and pharmacies, and these problems would not arise.

For patients with highly elevated blood pressures, it is important to note that dosage titration and sequential addition of other agents will be required to achieve blood pressure control.³

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A4. DO ALL ANTI-HYPERTENSIVE MEDICATIONS AND DOSAGES NEED TO BE PRESCRIBED BY A PHYSICIAN OR CAN THESE PROTOCOLS USE TASK-SHARING WITH NON-PHYSICIAN HEALTH WORKERS?

There are many examples of successful task-sharing models in which non-physician health workers (NPHW) prescribe and adjust medications, and which resulted in improved hypertension control.¹⁻³ There is evidence that NPHWs can be trained to reliably and effectively assess and manage cardiovascular risks and other chronic medical conditions in primary healthcare settings.⁴

NPHW can effectively manage hypertension in the context of supportive government regulatory scope of practice regulations (e.g., approval to follow a protocol), adequate hypertension treatment training, the availability of a simplified treatment protocol, and appropriate supervision and back up by medical doctors.

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A5. WHY DOES RESOLVE TO SAVE LIVES FOCUS ON BLOOD PRESSURE LEVEL FOR TREATMENT INITIATION RATHER THAN CARDIOVASCULAR RISK?

Although some clinical guideline developers from professional societies and at the World Health Organization have emphasized hypertension treatment decisions based on predicted 10-year cardiovascular disease risk, risk-based approaches have not been evaluated rigorously, and implementation may not be feasible in many settings.

An alternative to the risk-based approach posits that large numbers of low- and moderate-risk hypertensive patients can be treated efficiently and effectively when treatment is simple and highly-standardized.¹ This approach includes focusing on a very small core of generic and inexpensive but safe and effective medications that can be made readily available in bulk to organized treatment programs. It also emphasizes developing straightforward protocols for treatment that, in initial stages, can be executed by health care workers with relatively limited oversight from costly physician/specialist groups. Long-term follow up care can also be delivered in this context. Similar models have shown that by treating large numbers of patients in this manner, within 10 to 15 years the pool of hypertensive patients advancing to high-risk status can dramatically decline, resulting in reduced rates of severe cardiovascular disease and stroke.^{2,3} Furthermore, by implementing standard treatment programs for all patients with elevated blood pressure, many systems will be able to treat more high-risk patients than they would be trying to find and separately treat these individuals.

There is evidence indicating the limitations of risk-based approach (in which predicted risk is based on not only blood pressure, but also age, sex, and presence or absence of other risk factors.) In many clinical settings, risk assessments are not performed even when recommended.¹ If treatment thresholds are based on risk assessment, treatment is not likely to be prescribed when the risk assessment has not been done or is unknown. Furthermore, some people with hypertension (~10%) have low short-term cardiovascular risk; with a risk threshold approach, they would may not receive treatment, which may lead to long-term health consequences.⁴

A further limitation of the risk-based approach is that resources are directed to a relatively small proportion of all hypertensive patients, who often require physician/specialist care, laboratory resources, and other costly measures. Focus is directed away from the large numbers of low- or moderate-risk hypertensive patients, e.g., individuals who may be in lower risk categories with systolic

blood pressure between 140 and 160 mmHg. Because 10-year risk predictions are strongly influenced by the patient's current age, the risk-based approach most often doesn't select younger adults for treatment, even though most of the adverse health consequences of uncontrolled hypertension are cumulative over time. Under the risk-based protocols, lower 10-year risk patients are followed with lifestyle recommendations. However, this may be inappropriate, as almost all international guidelines recommend treating all patients with persistent hypertension above 140/90 mmHg with medication, and in resource-poor environments, these patients will often be lost to follow up before they are ever treated. Inevitably, as high-risk patients are treated, their ranks will be refilled by current low- or moderate- risk patients who will become high-risk over time, so that the overall numbers of deaths prevented are not dramatically reduced. Nonetheless, in some settings with severe resource constraints, risk-based approaches may be used to rationally allocate scarce resources.

A separate role of cardiovascular risk assessment is to identify patients, particularly those who have had a prior cardiovascular event, who will benefit from more intensive care, potentially including statins, aspirin, and beta blockers, among other measures. This is a highly effective means of reducing individual risk, although the impact on population-wide health may be limited.

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A6. WHAT IS THE BEST PRACTICE FOR MANAGING TREATMENT INTERRUPTION/MISSED MEDICATION DOSES?

"Doctor, I usually take my high blood pressure medicine every day—but not today!" This patient story is familiar to health care workers who manage blood pressure all over the world. The only solution to the missed medication dose scenario is to instruct the patient to take their medications and repeat the blood pressure measurement while on the medication, for example one week later. Health care workers should not guess what the treated blood pressure would be, as individual patients respond differently to antihypertensive medications.

Repeat visits to physicians due to missed medication doses may not be unfeasible in busy practices. In such situations, asking non-physician health care workers to perform the repeat blood pressure measurement (task-sharing) may be a more efficient and viable solution.

A7. SHOULD THE PROTOCOL APPROACH DIFFER FOR ASYMPTOMATIC PATIENTS WITH VERY ELEVATED BLOOD PRESSURE (E.G. ≥180 MMHG SYSTOLIC BLOOD PRESSURE OR ≥110 MMHG DIASTOLIC BLOOD PRESSURE)?

Hypertension treatment protocols often do differ for patients with severely raised blood pressure. Risk for cardiovascular events associated with raised blood pressure increases as blood pressure increases; more severe hypertension (e.g. ≥180 mmHg systolic blood pressure or ≥110 mmHg diastolic blood pressure) represents a higher risk state than do lower hypertension-range blood pressures. In addition, certain sequelae of hypertension (hemorrhagic stroke, hypertensive retinopathy, acute kidney failure) are more likely to occur at severely elevated blood pressures.

Resolve to Save Lives hypertension treatment protocols recommend starting treatment the same day for blood pressure ≥160/100 mmHg. Some, but not all protocols recommend starting with a higher initial antihypertensive medication dose or multiple medications for blood pressure ≥160/100 mmHg (e.g. amlodipine 10 mg versus amlodipine 5 mg; or one full pill of telmisartan 40 mg in combination with amlodipine 5 mg).

People who have symptoms of new or worsening target organ damage related to increased blood pressure (e.g. crescendo angina, confusion, acute kidney failure etc.) represent a medical emergency and need rapid care.¹

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A8. HOW SHOULD MEDICATIONS BE MANAGED WHEN A PATIENT ON MEDICATIONS HAS LOWER THAN NORMAL BLOOD PRESSURE?

For asymptomatic patients, Resolve to Save Lives treatment protocols recommend discontinuing one medication (usually the last medication prescribed) if systolic blood pressure is below 110 mmHg.

Systolic blood pressures below 90 mmHg should trigger stopping of all antihypertensive drugs until blood pressure is re-assessed (ideally within the next seven days) if the patient is asymptomatic.

Patients with low blood pressures should return for repeat blood pressure measurement and be evaluated for factors that may lead to transient lower blood pressures, including side effects from other medications, dehydration, acute inflammatory conditions, or measurement error.

Significant symptomatic reductions in blood pressure require immediate individualized assessment and management.

A9. IS IT BETTER TO TAKE ANTIHYPERTENSIVE MEDICATIONS IN THE MORNING OR EVENING?

Currently, there is not sufficient evidence to support a preference for dosing antihypertensive medications at any particular time. Most important is help each patient identify the dosing schedule that best suits their preferences and will optimize medication adherence.

There are theoretical reasons that antihypertensive medications may be more effective if taken in the evening instead of the morning, including the morning "blood pressure surge" phenomenon

(blood pressures are generally higher in the morning,) the greater bioavailability of antihypertensive drugs when dosed at night, and evidence from observational studies that night-time blood pressure is the strongest predictor of cardiovascular disease risk. Still, overall, the evidence base is weak, and findings of trials showing greater effectiveness of medications taken in the evening¹ have not been replicable.²

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B. BLOOD PRESSURE MEASUREMENT

B1. HOW RELIABLE ARE AUTOMATED, DIGITAL BLOOD PRESSURE MEASUREMENT DEVICES?

When used correctly, automated, digital blood pressure measurement devices are highly reliable and preferable to manual blood pressure devices.¹ Blood pressure is rarely measured using recommended technique in clinical practice. Automated devices have several distinct advantages that reduce user error and facilitate accurate blood pressure readings: they simplify the measurement process; eliminate errors related to hearing deficits, parallax, incorrect initial inflation pressure and rapid deflation; enable multiple measurements to be taken sequentially; and allow unobserved measurements to be performed (reducing white-coat effect). In theory, automated blood pressure measurement also eliminates terminal digit preference (rounding of the last digit that is commonly done by observers using the auscultatory method,) but only if the exact blood pressure result displayed on the device is used for clinical decision-making.

Multiple international protocols and standards have been developed to test the accuracy of automated devices, including a recently published unified international standard.² One important accuracy requirement is that the devices produce blood pressure measurements that are within 5±8 mmHg of an auscultatory reference standard (which is meticulously performed, standardized, simultaneous, blinded two-observer auscultation performed using a sphygmomanometer known to be accurate.) It is important to use an automated device that has passed one of these standards, preferably the new unified one, in a study performed by an independent authority (i.e., not by the manufacturer themselves or an organization affiliated with the manufacturer).

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B2. MANY GUIDELINES RECOMMENDED MEASURING MULTIPLE BLOOD PRESSURES AT EACH VISIT. HOW SHOULD WE MEASURE BLOOD PRESSURE IN A BUSY CLINICAL PRACTICE AND HOW IS THE REPRESENTATIVE BLOOD PRESSURE DETERMINED?

Although many guidelines recommend measuring multiple blood pressures at each visit, this may not be practical in a primary care setting.¹ These guidelines also frequently recommend discarding certain results and averaging others, a complex computational task that may be difficult, if not impossible, to do consistently and accurately in primary care health delivery systems.

A practical approach is as follows:

- If the first blood pressure (BP) is <140/90 mmHg, then no other blood pressure measurement is needed during that encounter. Use the first (and only) BP as the recorded BP.
 - There is a 95% chance that second BP will be lower than the first, so if the first BP is <140/90 mmHg, the mean blood pressure would be <140/90 mmHg.²
- If the first BP is >140/90 mmHg, perform a second BP and use the second reading as the recorded BP for the encounter.
 - Averaging the two measurements to determine mean BP in a busy primary care setting is a time-consuming exercise and is potentially prone to errors.
 - Using the second BP measurement without averaging will result in a slightly lower recorded BP compared to mean BP, but will still result in a recording that is over goal when both readings are >140/90 mmHg.
- When the first reading is >140/90 mmHg and the second reading is <140/90 mmHg, using the second BP measurement without averaging is preferable and will result in a slightly lower recorded BP compared to mean BP.
 - Despite resulting in some blood pressures that are recorded as <140/90 mmHg when the mean BP being slightly over 140/90 mmHg, the second, lower measurement is likely closer to the actual average than the first, because the first BP measurement in a series is usually the highest and most abnormal. Subsequent repeated measurements have a tendency to be less abnormal, related to the observed phenomenon described as “regression to the mean.”
- If there is a large difference between the first and second reading (>5 mmHg), it is reasonable to do a third measurement and use the third BP as the recorded BP.
 - A third BP is often much closer to the second BP than to the first BP, moving the mean closer to the second and third BP measurements.
 - Using the second BP measurement (or third, if done) as the representative BP may misclassify a small number of individuals who have a mean BP slightly above 140/90 mmHg to a recorded BP slightly under 140/90 mmHg. However, this is preferable to the potential errors associated with manual averaging at a large scale.

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C. DIET AND LIFESTYLE INTERVENTIONS TO LOWER BLOOD PRESSURE

C1. DO PATIENTS WITH BORDERLINE HYPERTENSION NEED TO START MEDICATION? WHY NOT RECOMMEND LIFESTYLE MODIFICATIONS FOR A FEW MONTHS FIRST?

The term 'borderline' is not a good way to describe hypertension, which is one of the world's leading risks for death. If a person's usual blood pressure is $\geq 140/90$ mmHg,* they are considered to have hypertension according to most clinical guidelines and are likely to benefit from antihypertensive drug treatment.

Clinical trials indicate that more rapid blood pressure control is associated with fewer cardiovascular disease events, and in most people, this can only be achieved with antihypertensive drug treatment. Although it is important to advise lifestyle changes to people with hypertension, very few people are able to change their lifestyles extensively enough to control hypertension.

Some trials that delivered standardized diet interventions under controlled conditions (i.e., food consumed by participants was prepared by study staff, as in the Dietary Approaches to Stop Hypertension (DASH) trial) achieved systolic blood pressure reductions of ≥ 10 mmHg, which is comparable to the blood pressure-lowering effect of a single standard dose antihypertensive medication.² However, trials of lifestyle change advice delivered in real-world primary care settings, in which participants prepare their own food, have demonstrated a more modest reduction in blood pressure (about 2 mmHg systolic), and it is unclear if this effect can be sustained for more than one or two years.³ Hence drug treatment should not be delayed while waiting for lifestyle change effects on blood pressure.

Lifestyle change remains an important complement to medication. Evidence shows that adherence to a low sodium diet can potentiate the blood pressure-lowering effects of particular antihypertensive medications (e.g., diuretics and renin-angiotensin system blockers).⁴⁻⁶

* $\geq 130/80$ mmHg if they have diabetes or chronic kidney disease, according to some authorities¹

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C2. IF A PATIENT IS NOT DOING LIFESTYLE MODIFICATION, IS IT APPROPRIATE TO INCREASE THE DOSES OF DRUGS OR ADD NEW DRUG WHEN THEIR BLOOD PRESSURE IS NOT CONTROLLED?

Resolve to Save Lives treatment protocols provide guidance at sequentially increasing doses and numbers of drugs to control hypertension and prevent cardiovascular death and disability. Drug titration should be undertaken regardless of the ability of the person to follow lifestyle change advice.

Although lifestyle changes can be effective at lowering blood pressure and can potentiate the blood pressure-lowering effects of specific antihypertensive medications,¹ very few people are able to make the changes necessary to control blood pressure. Unhealthy built and nutritional environments (which are appropriate targets for population-wide public health approaches) are common and make lifestyle change very challenging.

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C3. WHAT QUANTITY AND FREQUENCY OF ALCOHOL INTAKE IS CONSIDERED UNHEALTHY?

Blood pressure starts to rise as alcohol consumption exceeds two standard drinks a day.¹ (Because women have lower levels of an important enzyme that metabolizes alcohol and on average are smaller than men, many recommendations suggest that women not exceed one standard drink per day.)² Patients who have a history of alcoholism or who have liver disease should not consume any amount of alcohol, and consuming no alcohol in a day is considered healthy for everyone.

The pattern of alcohol consumption may be more important than the cumulative yearly average consumption. A binge-drinking pattern has been associated more strongly with risk for cardiovascular disease death.³ People with hypertension are at elevated cardiovascular disease risk and should avoid binge drinking.

*One standard drink includes: 12 ounces of regular beer, which is usually about 5% alcohol, or 5 ounces of wine, which is typically about 12% alcohol, or 1.5 ounces of distilled spirits, which is about 40% alcohol. Source: U.S. National Institute on Alcohol and Alcoholism

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D. ANTIHYPERTENSIVE MEDICATIONS: SELECTION OF DRUG CLASS

D1. ARE ANGIOTENSIN RECEPTOR BLOCKERS (ARBs) EQUIVALENT TO ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS AS A FIRST LINE TREATMENT?

Most national guideline formulation committees consider angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blocker (ARB) therapy equally effective in controlling hypertension and reducing hypertension-related adverse cardiovascular outcomes.^{1,2} High quality head-to-head outcome trials comparing ACE inhibitors to ARBs are limited, leading to conflicting evidence on the equivalence of ACE inhibitors and ARBs.^{3,4,5} The decision to use either ACE inhibitors or ARBs is usually determined by availability, affordability, and tolerability.

There is a broad consensus that the combination of two renin-angiotensin-aldosterone system (RAAS) inhibitors (typically ACE inhibitor and ARB) should not be prescribed.^{1,2,6}

At present, ARBs are usually more expensive than ACE inhibitors. However, as all the major medications are off patent, it may be possible to reduce medication costs for ARBs in the future.

Many clinicians have expressed a strong preference for medications that minimize adverse events. An important distinction between ACE inhibitor and ARB is the relative frequency of the cough adverse effect – which occurs in approximately 10% of people with ACE inhibitor and < 1% with ARB.^{7,8} Approximately 3% of patients discontinue ACE inhibitors due to the known side effect of cough.⁵ Angioedema, a potentially life-threatening allergic reaction, has been reported among those on ACE inhibitors (<1%), and, to a lesser degree, those taking ARBs.^{9,10}

There is also some evidence that specific populations may have fewer side effects with ARBs than with ACE inhibitors. One study indicated that individuals of recent African descent have a higher incidence of angioedema while taking ACE inhibitors.¹¹ According to the American College of Cardiology/American Heart Association Hypertension Guidelines, ARBs may be better tolerated than ACE inhibitors in black patients, with less cough and angioedema. However, based on the limited available evidence, ARBs offer no proven advantage over ACE inhibitors in preventing stroke or cardiovascular disease in this population, making thiazide diuretics or CCBs the best initial choice for single-drug therapy in this population.⁵

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D2. HOW IMPORTANT IS THE CHOICE OF INDIVIDUAL DRUGS IN A DRUG CLASS (E.G., LISINAPRIL VS. RAMIPRIL FOR ACE INHIBITOR)?

Answer: Most guideline development groups do not distinguish amongst specific drugs in a particular class based on drug efficacy due to the absence of high-quality head-to-head trials comparing drugs from similar classes.^{1,2} In general, all antihypertensive medications lower blood pressure effectively. Affordability, availability, quality, evidence base in large trials, and duration of action (e.g., once daily dosing) are important distinctions that may guide selection of a particular drug within a drug class.

If both alternatives are available and affordable, selecting the drug found to be efficacious and safe in large clinical trials is reasonable. For example, lisinopril, amlodipine, and chlorthalidone, were all used in the large, high-quality ALLHAT trial. Once-daily antihypertensive medications also increase adherence compared with twice-daily or multiple-daily dosed medications and are therefore preferred.^{3,4}

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D3. ARE THIAZIDE-TYPE AND THIAZIDE-LIKE DIURETICS REALLY AS EFFECTIVE AS NEWER DRUGS SUCH AS ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS?

Yes. The most recent US hypertension guidelines list CCBs, ACE inhibitors, ARBs, and thiazide diuretics equally as first-line antihypertensive agents.¹

The ALLHAT study compared the effects of an ACE inhibitor (lisinopril), a CCB (amlodipine), and a thiazide-like diuretic (chlorthalidone) on the incidence of fatal CHD or non-fatal myocardial infarction among those with hypertension and at least one other CHD risk factor. There were no significant differences among groups in the rate of the primary outcome, nor in all-cause mortality. The trial found those randomized to the chlorthalidone had lower systolic blood pressure at five years and a lower rate of heart failure as compared to those randomized to the ACE inhibitor or CCB; those randomized to the thiazide diuretic also had lower incidence of total CVD and stroke. The authors of the study therefore recommended thiazide diuretics as a first-line agent, except when not tolerated, and that thiazide diuretics be included in multi-drug regimens to treat hypertension.²

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D4. WHY RECOMMEND A THIAZIDE DIURETIC/ACE INHIBITOR COMBINATION?

The evidence base supporting a thiazide diuretic/ACE inhibitor combination is strong. The ALLHAT trial showed thiazide diuretics to be generally equivalent to CCBs in monotherapy (with the exception of heart failure prevention for which thiazide diuretics were superior.)¹ The thiazide diuretic/ACE inhibitor single pill combination was used successfully in a large hypertension management program in North America that achieved a 90% hypertension control rate.^{2,3} Although the ACCOMPLISH trial found that a CCB/ACE inhibitor combination was superior to a thiazide diuretic/ACE inhibitor combination,⁴ some authors have commented that the dose of the thiazide used, hydrochlorothiazide, was lower than the 25 to 50 mg dose of hydrochlorothiazide (similar to 12.5 to 25 mg of chlorthalidone) used in thiazide trials demonstrating the favorable outcomes.^{1,5,6}

There are many reasons that the ACE inhibitor/thiazide diuretic combination remains particularly compelling. Fixed-dose combination medications (single pill combination) have been shown to increase adherence and simplicity for both doctors and patients.⁷⁻⁹ Also, the joint physiologic actions of the two components can synergistically reduce adverse event risks: thiazide diuretics counteract the risk of hyperkalemia due to ACE inhibitor and ACE inhibitor reduce the risk of hypokalemia due to thiazide diuretics. There are many fixed dose combination thiazide diuretic/ACE inhibitor products that are produced by generic manufacturers. The most important factors to consider are local/regional drug availability and affordability. If available and affordable, selecting specific drug combinations that have been used in successful clinical trials is reasonable.

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D5. IS THERE EVIDENCE THAT CERTAIN THIAZIDE DIURETICS ARE MORE EFFECTIVE THAN OTHERS (E.G., CHLORTHALIDONE VERSUS HYDROCHLOROTHIAZIDE)?

Technically, no. Most guideline development groups do not distinguish amongst specific agents in the thiazide/thiazide-like diuretic class due to the absence of high-quality head-to-head trials comparing these drugs.^{1,2}

If available and affordable, selecting the thiazide-like diuretic chlorthalidone is reasonable.³ The benefits of chlorthalidone are better documented, including in the ALLHAT trial;³ the impact of hydrochlorothiazide (HCTZ) on reducing risk for cardiovascular events has never been demonstrated against a placebo.⁴ Results from network meta-analyses suggest that, in addition to greater blood pressure-lowering potency,^{3,4} chlorthalidone reduces the risk of cardiovascular events by 21%.⁵ In one analysis, treating 10,000 patients for hypertension for five years with chlorthalidone would prevent 370 more events than using HCTZ.⁵

Another thiazide-like diuretic, indapamide, has also been shown to have greater blood pressure-lowering effects than HCTZ.⁴ Some publications have reported that, compared with HCTZ, indapamide may have less impact on glucose or lipid metabolism at doses for the same degree of blood pressure-lowering.⁴ However, most such publications have been sponsored by the pharmaceutical industry, and the validity or real-world relevance of these findings is not established. Compared to placebo, indapamide has been shown among stroke patients to reduce cardiovascular events, and in combination with perindopril, to prevent CVD among the elderly, diabetics and post-stroke.⁶⁻⁸ Chlorthalidone and indapamide have not been compared head-to-head in terms effects on clinical events or mortality.

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D6. WHY ARE BETA-BLOCKERS NOT INCLUDED AS A FIRST- OR SECOND-LINE TREATMENT FOR HYPERTENSION, EXCEPT FOR THOSE WHO JUST HAD A MYOCARDIAL INFARCTION (HEART ATTACK)?

Most major guidelines (including US, UK and Australian guidelines) no longer recommend beta-blockers across all age groups as first step drug therapy in the absence of a compelling non-BP indication.¹⁻³ Beta Blockers are generally considered to be inadequate compared with first-line antihypertensive medications.

Meta-analyses have suggested that atenolol is ineffective for the primary prevention CVD events. A recent Cochrane Review of the effects of beta-blockers as first-line therapy for hypertension on morbidity and mortality endpoints concluded that initiating monotherapy with beta-blockers leads to modest CVD reductions, with little or no effects on mortality, and that the magnitude of benefit is inferior to that of other antihypertensive drugs.⁴ Another recent meta-analysis, which did not exclude trials in patients with baseline comorbidities, found that beta-blockers are inferior to other drugs for the prevention of major cardiovascular disease events, stroke, and renal failure.⁵ However, among younger patients, outcomes among those on beta blockers may be more favorable.⁶ Age-specific treatment protocols introduce additional complexity and are not considered in detail here.

Beta-blockers other than atenolol have been less well studied. Unlike atenolol, carvedilol is a nonselective beta blocker that also blocks the alpha-1 receptor, and is favored as a beta-blocker in some contexts, for example in the treatment of heart failure with a reduced ejection fraction. Nonetheless, carvedilol has not been studied in any major event-based, randomized controlled trial of blood pressure-lowering treatment.

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D7. WHAT IS THE BENEFIT OF AN ACE INHIBITOR OR AN ANGIOTENSIN RECEPTOR BLOCKER (ARB) IN HYPERTENSIVE PATIENTS WITH DIABETES OR CHRONIC KIDNEY DISEASE (CKD)?

Answer: ACE inhibitors or ARBs are the preferred first-line agents for blood pressure treatment for hypertensive patients with chronic kidney disease (CKD), defined based on proteinuria (urinary albumin-to-creatinine ratio [UACR] >300 mg/g) and/or reduced kidney function (estimated glomerular filtration rate [eGFR] <60mL/min/1.73m²). These two renin-angiotensin-aldosterone system blockers have proven benefits for prevention of CKD progression.¹⁻⁴ For patients who cannot tolerate the common cough caused by ACE inhibitors, ARBs are as effective.⁵

In the AASK trial, among 1,094 U.S. African American patients with hypertension and CKD, treatment with an ACE inhibitor reduced risk for CKD related outcomes by 22% compared with a beta-blocker and by 38% compared to a calcium channel blocker (CCB). (CKD related outcomes defined as kidney disease death, end-stage renal disease, or decline in eGFR). Overall, these results suggest that for every 100 hypertensive patients with CKD treated with an ACE inhibitor (in place of other medication classes) prevents 1-2 CKD-related outcomes. Cardiovascular disease or all-cause mortality benefits from an ACE inhibitor or and ARB compared to other anti-hypertensive agents have not yet been shown.²

ACE inhibitors, or ARBs can be used to control blood pressure in patients with diabetes and hypertension, though they do not appear be superior to alternative classes of antihypertensive therapy in patients without CKD.⁶⁻⁸ The most recent US hypertension guidelines equally recommend CCBs, ACE inhibitors, ARBs and thiazide diuretics as first-line agents for people with diabetes and hypertension but without CKD.⁷

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D8. WHICH IS THE BEST ANGIOTENSIN II RECEPTOR BLOCKER (ARB) TO CHOOSE?

While all ARBs have similar efficacy, telmisartan has several advantages. Telmisartan has low rate of adverse effects, long duration of action, is well studied, and is available in generic forms. Compared

with some other generic ARBs, telmisartan absorption is less affected by food, more effective when combined with a diuretic, better documented to reduce cardiovascular events and has a lower incidence of serious adverse effects^{1,2,3}

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E. ANTIHYPERTENSIVE MEDICATIONS: ADVERSE EFFECTS/SIDE EFFECTS

E1. WHAT ARE EXAMPLES OF LABORATORY TESTING NEEDED FOR PATIENTS TAKING ANTIHYPERTENSIVE MEDICATIONS?

Patients newly diagnosed with hypertension should ideally obtain laboratory measurements to facilitate CVD risk factor profiling, establish a baseline for medication use, and screen for secondary causes of hypertension.¹

Monitoring of kidney function and electrolytes before and during treatment of hypertension may help identify underlying problems and help prevent serious adverse effects. Guidelines suggest the monitoring of serum electrolytes (potassium and sodium) and kidney function (usually estimated based on serum creatinine level) in patients treated with antihypertensive medications, particularly those that may alter potassium, before and after initiating treatment and after undergoing a dose increase.²

Specific laboratory testing recommendations pertain to specific medications (Table 1 below). In general, when using ACE inhibitors or ARBs, renal function and electrolyte testing should occur before initiating treatment and one week after starting treatment or any subsequent dose increase. For patients at higher risk of developing hyperkalaemia or deteriorating renal function, testing should occur at 4 and 10 days after the start of treatment or an increase in dose. Repeated and more frequent testing is needed for patients who start additional treatment or whose clinical condition worsens.²

There is a lack of consensus on the frequency of monitoring patients on thiazide diuretics, and the risks to people who are not monitored have not been quantified. Some guidelines recommend potassium, sodium and creatinine assessment at baseline, several weeks after a dose change, and periodically (every 3-12 months) thereafter.^{3,4} Testing more frequently for people with reduced renal function has also been suggested.⁵

TABLE 1. Conditions to monitor when using certain classes of hypertensive drugs.^{1,2,6}

Drug Class	Conditions to Monitor	Other Considerations
ACE Inhibitors	<ul style="list-style-type: none"> Hyperkalemia (pathologically elevated serum potassium), especially in patients with CKD or in those on potassium supplements or potassium-sparing drugs Angioedema 	<ul style="list-style-type: none"> Do not use in combination with ARBs or direct renin inhibitor. Theoretical risk of acute renal failure in patients with severe bilateral renal artery stenosis Do not use if patient has history of angioedema with ACE inhibitor. Less effective as single medication in people of African descent A persistent cough is experienced by up to 10% of patients treated with an ACE inhibitor; this risk is higher in people of recent African descent. Do not use in pregnancy.
ARBs	<ul style="list-style-type: none"> Hyperkalemia or deterioration of renal function. Acute renal failure in patients with severe bilateral renal artery stenosis 	<ul style="list-style-type: none"> Do not use in combination with ACE inhibitors or direct renin inhibitor. Do not use if patient has history of angioedema with ARBs. Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued. Avoid in pregnancy.
CCBs	<ul style="list-style-type: none"> Lower extremity edema 	<ul style="list-style-type: none"> Reduces need for monitoring of electrolytes and renal function. Ankle edema may occur in up to 10% of patients, particularly with intensification dose in the absence of an ACE inhibitor or ARB.
Thiazide Diuretics	<ul style="list-style-type: none"> Hyponatremia and hypokalemia. Uric acid and calcium levels. 	<ul style="list-style-type: none"> Probably effective for all races Has unfavorable effects of lipid and glucose measurements; clinical significance unclear. Use with caution in patients with history of acute gout unless patient is on uric acid-lowering therapy. Avoid in pregnancy.

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E2. WHAT IS THE RISK OF HYPOKALEMIA AMONG PATIENTS RECEIVING A DIURETIC?

13 percent of people taking the thiazide-like diuretic chlorthalidone 12.5-25 mg daily developed hypokalemia in the ALLHAT trial¹ However, despite this observation, overall all-cause mortality was no different when compared to individuals taking the calcium channel blocker amlodipine or the ACE-inhibitor lisinopril. The authors of a subsequent analysis of hypokalemia in the ALLHAT trial concluded that "...clinicians should feel reassured that hypokalemia associated with low-to-moderate dose diuretics (12.5–25.0 mg of chlorthalidone a day) affected 13% of patients and was easily remedied...the cardioprotective actions of diuretic use are unaffected by consequent but treatable alterations in serum potassium."¹ Further, when a diuretic is combined with an ACEI, the risk of hypokalemia is greatly reduced.²

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E3. WHAT CHANGE IN SERUM CREATININE IS ACCEPTABLE (MEANING MEDICATION DOESN'T NEED TO BE DISCONTINUED) AFTER STARTING AN ACE INHIBITOR OR ARB?

The normal physiologic response to blood pressure lowering is to increase efferent arteriole constriction and restore glomerular perfusion pressure. ACE inhibitor and ARB blunt this response and may lead to decreased kidney filtration (decreased glomerular filtration rate) and kidney function. Clinical guidelines recommend monitoring serum creatinine response in a week or two following ACE inhibitor or ARB therapy and stopping therapy and further monitoring kidney function if the serum creatinine increases by more than 30% of the baseline value. Increases below this level are usually considered acceptable.¹

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E4. WHAT IS THE BEST PRACTICE WHEN LAB TESTS ARE NOT AVAILABLE?

When laboratory testing is unavailable, the safest option is to restrict medication prescription to metabolically neutral calcium channel blockers and increase these up to maximum doses if needed to control blood pressure. If additional medication classes are still needed, one may introduce other medication classes, but keep the doses of other classes of medications in the low- to mid- dose range. Higher doses of ACEIs, ARBs, and Thiazide/Thiazide-like diuretic should be avoided when laboratory testing is not available. Generally, most side effect incidence increases with medication dose.

F. SPECIAL POPULATIONS

DIABETES

F1. WHY RECOMMEND A TARGET OF 140/90 MMHG FOR MOST PATIENTS AND CONSIDERATION OF TREATMENT TO 130/80 MMHG FOR THOSE WITH DIABETES?

There is considerable controversy concerning the ideal BP diagnostic threshold and treatment target for people with diabetes. Some recent guidelines recommend a goal of 140/90 mmHg for the general population, including those with diabetes.^{1,2} Other current guidelines recommend more aggressive treatment goals with blood pressure (BP) targets of < 130/80 mmHg for people with diabetes.³⁻⁶ From a public health point of view, it is important to keep in mind that even using target of 140/90 mmHg, the control rate of blood pressure among hypertensives is 15% or lower in many countries. Thus, Resolve to Save Lives focuses on 140/90 mmHg as a target. Individual countries, areas, or providers can set lower limits.

The goal of treating hypertension in patients with diabetes is reduction of macrovascular and microvascular complications. Ret-

spective data analyses suggest an association between a lower BP and greater cardiovascular (CV) risk reduction in patients with type 2 diabetes, as well as declines in chronic kidney disease (CKD). Although some note that such conclusions are not supported by randomized controlled trials*, when considering the weight of the evidence, it appears that more intensive blood pressure lowering may be beneficial for most people with diabetes.⁷

**The SPRINT trial demonstrated a benefit from intensive versus standard blood pressure lowering treatment in a trial that enrolled patients with high CVD risk and those with chronic kidney disease, but not patients with known diabetes or strokes.^{3,4,5,6}*

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HISTORY OF CORONARY HEART DISEASE

F2. WHAT IS THE BENEFIT OF GIVING PATIENTS WHO HAVE HAD A MYOCARDIAL INFARCTION (HEART ATTACK) A BETA-BLOCKER?

When given after a myocardial infarction (MI), beta-blockers have special cardioprotective effects, over and above blood pressure-lowering, in preventing future coronary heart disease events.¹ This effect is limited to the first few years post-MI, with the greatest benefit occurring in the first few months.¹ Treating 84 patients with a recent MI with beta-blockers for one year would prevent one death, which compares favorably with other secondary prevention approaches.² Because the vast majority of recurrent events in trials of beta-blockers for secondary prevention occur in the first (77%) or second (94%) year, the benefits of beta-blockers in the first year after MI are clear and there is a possible benefit in years two and three; there is little evidence of benefit beyond three years.¹

There is some debate regarding the benefits of beta-blockers in the reperfusion era (i.e., with angioplasty and coronary bypass operations being widely used in high-income countries). A recent meta-analysis⁴ found a significant protective effect for beta-blockers given post MI on CVD mortality in the pre-coronary artery revascularization era but not in the more recent revascularization era; the analysis did find a significant reduction in the short-term risk of subsequent MI and angina in the coronary revascularization era.

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HISTORY OF CORONARY HEART DISEASE

F3. WHAT IS THE BENEFIT OF GIVING PATIENTS WHO HAVE HAD A MYOCARDIAL INFARCTION (HEART ATTACK) AN ACE INHIBITOR?

Drug therapy for people who have had an MI includes angiotensin converting enzyme inhibitors (ACE inhibitors), antiplatelet therapy, beta-blockers, and statins. ACE inhibitors are currently routinely initiated following an MI, based upon previous evidence that ACE inhibitor therapy can improve clinical outcomes, including mortality and the development of heart failure.¹

ACE inhibitor treatment started in the acute phase (0 to 36 hours)

of MI and continued for 4-6 weeks is associated with a 7% proportional reduction (7.1% vs 7.6%) in 30-day mortality. This represents an avoidance of 5 deaths per 1,000 patients (50 per 10,000) with most benefit occurring in the first week.² While the proportional benefit is similar across subgroups, the absolute benefit is particularly large among those with anterior infarcts, mild-moderate heart failure (Killip class 2 to 3) and/or impaired ejection fraction.²

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OLDER ADULTS

F4. SOME GUIDELINES RECOMMEND TREATING ADULTS OVER 60 YEARS TO A BLOOD PRESSURE GOAL OF <150/90 MMHG. WHY DO SOME RESOLVE TO SAVE LIVES PROTOCOLS RECOMMEND TREATING TO <140/90 MMHG IN OLDER ADULTS?

There is considerable controversy concerning the ideal systolic blood pressure diagnostic threshold and treatment target for people over age 60 years. Some guideline groups suggest a treatment goal <150 mmHg¹ while others suggest <140 mmHg, and some recent trials and guidelines suggest that an even lower treatment target may be appropriate.² Jurisdictions may decide to have different targets, or different targets for different populations. Some jurisdictions might choose a goal of <140 mmHg for the general population including those over age 60; a higher optional goal (e.g., <150 mmHg) for individuals over 60 years of age without diabetes, chronic kidney disease (CKD), CVD, or high cardiovascular (CV) risk; and a lower goal (e.g., 130 mmHg) for those with these high-risk features.

Regardless of the guideline recommendation, guidelines are meant to provide clinical recommendations for the average patient, but are not meant to substitute for sound clinical judgement. Individual health care providers must assess individual patient's risk for adverse events on antihypertensive medication treatment and monitor for adverse treatment-related events, and tailor treatment goals accordingly.

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G. GLOSSARY OF TERMS AND ACRONYMS

ACCOMPLISH Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial

ACCORD-BP The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial

ACE INHIBITOR Angiotensin converting enzyme inhibitors

ALLHAT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

ANGIOEDEMA Angioedema is self-limited, localized subcutaneous (or submucosal) swelling, which results from migration of fluid from blood vessels into interstitial tissues

ARB angiotensin II receptor blocker

BP blood pressure

CCB calcium channel blocker

CKD chronic kidney disease

eGFR estimated glomerular filtration rate

HCTZ hydrochlorothiazide

HTN hypertension

HYPERKALEMIA pathologically elevated serum potassium, detected on blood testing. Common adverse effect of RAAS blockers (ACE inhibitor or ARB).

HYPOKALEMIA pathologically low serum potassium, detected

on blood testing. Common adverse effect of some diuretics, for example HCTZ.

HYPONATREMIA pathologically low serum sodium, detected on blood testing. Common adverse effect of diuretics, for example HCTZ.

HYPOTENSION Very low blood pressure, sometimes leading to symptoms or adverse events such as syncope (fainting), loss of balance, or falls.

NNT number needed to treat. Defined as the number of patients treated by a therapy to prevent the disease outcome of interest over a defined period of treatment time (usually five or ten years for chronic conditions like hypertension). NNT is a measure of treatment efficiency and it is based on absolute risk reduction.

NPHW non-physician health workers. Sometimes termed lay health worker or community health worker.

ONTARGET Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

RAAS renin-angiotensin aldosterone system. This neurohormonal feedback system regulates human blood pressure and is blocked at different arms of the feedback loop by ACE inhibitors and ARBs.

SPRINT Systolic Blood Pressure Intervention Trial

UACR urine albumin-creatinine ratio. An elevated UACR is evidence of proteinuria, or pathologically failing to filter out proteins in the kidneys, leading to “spilled” protein in the urine and high urine protein concentration