RESOLVE TO SAVE LIVES
AN INITIATIVE OF VITAL STRATEGIES

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.

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 feasible 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 evening[1] 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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B3. WHAT ARE "TERMINAL DIGIT PREFERENCE BIAS" AND "OBSERVER" BIAS WHEN RECORDING BP?

Terminal digit bias is the tendency of an observer to round up, or down, a measurement to a digit of his or her own choosing, usually to zero. For example, an observer has the tendency to record a BP reading of 144/97 mmHg as 140/100 mmHg.

Observer bias occurs when the observer has a preconceived idea of what the blood pressure ought to be, leading to an arbitrary adjustment of the reading. It usually occurs when an arbitrary threshold is applied between normal and high BP, for example 140/90 mm Hg. An observer might tend to record a more favorable (under the threshold) measurement in a young healthy man with a borderline increase in BP and a less favorable one (above the threshold) in an obese, middle aged man with a similar reading. Likewise, there might be observer bias in over-reading BP to facilitate recruitment in a hypertension registry, or under-reading if there is a need to ration medications due to a shortage of medications. Intended or not, both of these types of biases can lead to inaccurate BP recordings, even among observers who have performed many BP measurements.

Why are terminal digit bias and observer bias important clinically?

Terminal digit bias and observer bias can lead to errors in the diagnosis and treatment of hypertension by systematic under- or over-estimation of the patient's blood pressure. Because hypertension is diagnosed and treated based on blood pressure thresholds (140 mmHg systolic and 90 mmHg diastolic), terminal digit bias and observer bias can result in under- or over-diagnosis as well as under- or over-treatment of hypertension. One study found that terminal digit preference was generally associated with artificially lower recorded blood pressures and lower likelihood of being prescribed the antihypertensive medication that is indicated[1]. Delayed treatment or undertreatment of elevated blood pressure puts patients at higher risk of cardiovascular disease events. Over-diagnosis and over-treatment of hypertension results in unnecessary medication side effect risks and costs. Another study showed that terminal digit preference was associated with overdiagnosis, where raising the threshold for hypertension from ›140 to ›141 would reduce the diagnosis of hypertension from 25.9% to 13.3% in that clinical dataset[2].

How can terminal digit bias and observer bias be addressed and corrected?

Evidence shows that monitoring with regular feedback of data and training can reduce terminal digit and observer bias[3, 4].

Below are 3 steps to identify and reduce these biases across facilities and healthcare workers.

Step 1: Identify and Monitor

- Review paper or electronic blood pressure records and observe staff measuring patients' blood pressure.
- Look for two signs of bias (see the **Figure** below):
- Rounding - Proportion of systolic and diastolic readings ending in "0". The expected proportion ending in "0" should be approximately 10%.
- Gaming - High number of readings that are just above or below threshold of 140/90, e.g. 138/88, 139/89, 140/90, 141/91

Figure: example of terminal digit bias In the blood pressure data from a single clinical facility, six of ten (60%) systolic blood pressure readings and four of the ten (40%) diastolic readings below are rounded to "0". Can you find them? Without terminal digit preference bias, the expected proportion of all numbers that terminate with a zero should be about 10%.

10:29 AM	♡ 130/87	Follow-up patient
10:32 AM	♥ 150/95	Follow-up patient
10:33 AM	♡ 132/87	Follow-up patient
10:35 AM	♡ 120/80	Follow-up patient
10:36 AM	♡ 131/81	Follow-up patient
10:39 AM	♡ 133/79	Follow-up patient
10:42 AM	♥ 140/102	Follow-up patient
10:44 AM	♥ 146/100	Follow-up patient
10:46 AM	♡ 100/70	Follow-up patient
10:47 AM	♥ 150/100	Follow-up patient

Step 2: Provide feedback and training

- Provide ongoing feedback for sites that continue to have bias. Many healthcare workers may not be aware of terminal digit and observer bias.
- Ask them not to round.
- Explain how rounding and observer bias can cause errors in diagnosis and treatment, leading to adverse clinical outcomes for patients
- During training sessions, advise staff to record the exact blood pressure that is measured without rounding.

Step 3: Encourage use of automatic over manual BP devices when available

- Digital blood pressure measurement devices show the precise blood pressure numbers and discourage biased readings. Studies have demonstrated that using automated blood pressure devices reduces terminal digit bias[5,6]. Whenever validated electronic devices are available, their use should be promoted. Keep in mind that most facilities that employ digital devices still require observers to manually enter the blood pressure numbers on a paper form or computer—there is still room for error and bias!

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B4. IN STARTING A NEW HYPERTENSION CONTROL PROGRAM, HOW DO I KNOW HOW MANY BLOOD PRESSURE DEVICES TO ORDER IF I WANT TO OPPORTUNISTICALLY SCREEN ALL ADULTS VISITING THE HEALTH CARE FACILITY?

Opportunistic screening for hypertension is recommended, by conducting measurement of blood pressure (BP) for all adults visiting primary health care facilities. A commitment to comprehensive opportunistic screening means having sufficient capacity in terms of health workers trained in measurement and BP measurement devices. To estimate the number of BP devices required per facility, it is important to know three data points: 1) average daily number of adult patient visits at the facility, 2) average duration of time to screen one patient [e.g. 2 minutes], and 3) number of hours the facility is open per day.

The **average daily number of total adult patient visits** can generally be estimated by reviewing facility registers. This count should assume that a BP monitor can be positioned centrally in the facility where the maximum number of adults can be screened. This location could be at the same location as the facility entryway, registration desk or triage station. Particular patient groups, such as pediatric patients or adult trauma patients could be excluded from the count.

The **duration of time to screen one patient** can be determined by direct observation in a facility by timing the length of time it takes for a health care worker to screen a patient, measure their BP, and document any record-keeping, before moving on to the next patient. Since at many facilities, the staff who screen blood pressures also have additional tasks (e.g. documenting registers), the time per screening can be variable across hypertension programs. Therefore, it may be necessary to directly observe and measure the time per patient for opportunistic BP screening. This length of time (e.g. 2 minutes) can then be used to determine how many patients can be screened by that health care worker (and BP device) per hour (e.g. 2 minutes per patient = 30 patients screened per device per hour). Facilities can modify the number of BP devices and health care workers that need to be assigned for opportunistic BP screening at a facility by reducing the time it takes to screen each patient through decreasing documentation time and off-loading other tasks from BP screening stations.

The **number of hours the facility is open per** day can be quantified by telephone survey or in-person observation.

With the above 3 data points, the following formula can be used to estimate the number of BP devices for opportunistic screening at a facility:

Numerator	Average number # of adults seen at facility per day
Denominator	[(Number # of patients screened/device/hour) x (Number # of hours facility open per day]
Example	If a facility:
	1. Has 250 patient visits a day
	2. Each BP check takes 2 minutes (=30 patients screened/device/hr) 3. Is open for patients for 4 hours per day
	250/(30x4) = 2 devices (and 2 health care workers) needed for opportunistic BP screening at that facility

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 ›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.[2,3] 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.[4] 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).[5,6]

** ›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-threating 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., LISINOPRIL 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 rage [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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D9. WHEN TREATING HYPERTENSION, CAN A DRUG FROM ONE CLASS BE SUBSTITUTED WITH A DRUG FROM A DIFFERENT CLASS AND HOW DO I KNOW WHAT AN EQUIVALENT DOSE WOULD BE?

Patients should ideally be treated accordingly to the recommended national hypertension protocol. However, situations may arise when it becomes necessary to substitute one medication with another from a different class of drugs. For example, medications such as angiotensin-converting enzyme (ACEs) and angiotensin receptor blockers (ARBs) are contraindicated during pregnancy and it is necessary to substitute them with one that is safe during pregnancy such as a calcium channel blocker (CCB) or a diuretic. While generally well tolerated, anti-hypertensive medications may cause side effects. If the side effect is troublesome enough to the patient, it may result in non-adherence to treatment. In such cases, the *addition* of a medication from a different group may resolve the problem by allowing a reduction in the required dose of the medication associated with the side effect (refer to FAQ about benefits of combination therapy). If that fails, however, discontinuing the medication and *substituting* it with an antihypertensive from another class of drugs, may be required. And finally, a patient may present with an effectively controlled blood pressure on a medication regimen that includes a medication or class of drugs that are not reimbursed by the health insurance plan. In such a case, while there is no clinical reason to change the therapy, the patient may wish to switch to a regimen covered by his/her insurance plan to reduce out-of-pocket expenses. In such cases, substitution will be financially beneficial to the patient and likely to improve the patient's adherence to, and persistence with, therapy.

The **Table** below, based on several previous reports[1-18], maps single standard doses within and across the major, first-line antihypertensive drug classes. Standard dose means that on average, a similar degree of blood pressure-lowering is expected for each dose shown. When the equivalent ranges were cross-referenced with a large clinical trials meta-analysis[1], that independent analysis consistently considered the higher dose encountered in our literature review the standard dose (**bold type** values in the table).

The antihypertensive medication dose equivalencies in the table was based on non-systematic literature search. Using terms such as "antihypertensive drug equivalency", we identified several websites and articles online and then searched the reference papers behind those websites or articles, as appropriate. Using relevant original articles (comparing multiple antihypertensive medications regarding the change in systolic and/or diastolic blood pressure), we created the antihypertensive medication dose equivalency table. Since we recognized some discrepancy in results across different studies, some medications are expressed with their dose range. All the relevant studies used to create this table are referenced below.

It is important to note that the dose equivalency of one drug class to another is a rough estimation, as actual blood pressure response varies according to a number of factors. First, blood pressure response to specific medications is influenced by patients' individual characteristics. For example, on average, elderly patients and black patients may respond better to diuretics and calcium channel blockers (CCBs) than angiotensin converting enzyme inhibitors (ACEIs, angiotensin receptor blockers (ARBs) and beta blocker. Even within broad age or ethnicity groupings, blood pressure response will vary among individuals. Patients who are dehydrated or have a stimulated renin-angiotensin-aldosterone system (RAAS) will have an accentuated hypotensive response to angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Further, because each drug class targets a distinct, but sometimes inter-related biological mechanism, the response to a change in drug class is also influenced by other drugs the patient is taking. As an example, volume depletion by a diuretic may stimulate the RAAS; taking a RAAS-inhibitor may blunt that response, leading to a synergistic blood-pressure lowering effect. These complex interactions among medicine classes make it difficult to predict a standard blood pressure response when multiple doses of medicines are combined.

TABLE. *Resolve to Save Lives equivalent standard doses of selected common antihypertensive medications*

Disclaimer: *There are limited studies comparing drug dose equivalency, and thus this table should be considered merely as guidance but not as absolute dose converter. After medication conversion, patients should be brought back soon for close follow-up blood pressure measurement and further titration.*

CCB **(these doses are likely to be equivalent to enalapril 5 mg)**	**Thiazide** **(these doses may be considered equivalent to amlodipine 5 mg and enalapril 5 mg)**
Amlodipine 5 mg	Chlorthalidone 12.5 mg
Nifedipine 30 mg	Hydrochlorothiazide 25 mg
ACEI **(these doses are likely to be equivalent to amlodipine 5 mg)**	**ARB** **(these doses are likely to be equivalent to enalapril 5-10 mg and lisinopril 10 mg)**
Benazepril 10 mg	Candesartan 8-**16** mg
Captopril 37.5-**50** mg	Eprosartan 200-**400** mg
Cilazapril 1.25-**2.5** mg	Irbesartan 75 mg
Enalapril 5 mg	Losartan 25-**50** mg
Fosinopril 10 mg	Olmesartan 5-**20** mg
Lisinopril 5-**10** mg	Telmisartan 20-**40** mg
Moexipril 3.75-**7.5** mg	Valsartan 40-**80** mg
Perindopril 2-4 mg	
Quinapril 10 mg	
Ramipril 2.5 mg	
Trandolapril 1-**2** mg	

Dose equivalents shown in* **bold font *agree with an independently derived dose equivalence scheme proposed by Law et al*[1].

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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]

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TABLE 1. *Conditions to monitor when using certain classes of hypertensive drugs.*[1,2,6]

Drug Class	Conditions to Monitor	Other Considerations
ACE Inhibitors	• Hyperkalemia (pathologically elevated serum potassium), especially in patients with CKD or in those on potassium supplements or potassium-sparing drugs • Angioedema	• 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	• Hyperkalemia or deterioration of renal function. • Acute renal failure in patients with severe bilateral renal artery stenosis	• 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	• Lower extremity edema	• 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	• Hyponatremia and hypokalemia. • Uric acid and calcium levels.	• 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 trial.[1] 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 AND SPECIALIZED CARE FOR HYPERTENSION

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. Retrospective 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, 5,4,5,6]

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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-analysis[4] 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 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 mmHg[1] 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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SPECIALIZED CARE

F5. WHAT IS A HYPERTENSION EMERGENCY OR URGENCY? WHEN MUST PATIENTS BE REFERRED IMMEDITIELY FOR ACUTE EVALUATION AND TREATMENT?

"*Hypertensive urgency*" is defined as a systolic blood pressure ›180 mmHg or diastolic blood pressure ›120 mmHg in patients without acute end-organ damage—these patients must be asymptomatic. "*Hypertensive emergency*" is defined as systolic blood pressure ›180 mmHg or diastolic blood pressure ›120 mmHg accompanied by evidence of end-organ damage (retinopathy, cerebrovascular events, aortic dissection, myocardial infarction, heart failure, or acute kidney injury), or symptoms of end organ damage like blurry vision, chest pain, severe headaches or shortness of breath.[1]

Hypertensive urgency is not a medical emergency; blood pressure can be safely lowered with oral antihypertensive agents over a period of hours or even days in the outpatient clinic setting. Studies of patients identified with severe, asymptomatic hypertension have found no significant differences in rates of hospitalization or death at 30 days in patients managed in the outpatient clinic setting compared with those referred to the hospital.[2, 3] Standard, long-acting oral medications can be used to lower blood pressure in patients with hypertensive urgency; in fact, short-acting medications may lead to end organ damage (cerebral or kidney ischemia) due to inadequate perfusion pressures. Examples of short-acting medications that should be avoided include the sublingual or capsule forms of short-acting nifedipine or captopril or clonidine. The initial blood

pressure goal should be a be a reduction of at least 10% and avoiding ‹30% change from the baseline blood pressure within the first 24 hours of treatment. These patients should be asked to return to clinic within 24 to 72 hours for follow-up assessment. Typically, a very common reason in most patients with hypertensive urgency are due to poor medication adherence.

Hypertensive emergency is rare, estimated at 1-2 cases per million per year.[1] When patients present with severely raised blood pressure and symptoms indicating hypertensive emergency, a full history should be obtained, including a review of systems, and physical examination should be performed. Physical examination should include a fundoscopic examination. Potential underlying causes and/or sequelae may include hypertensive retinopathy, head trauma, ischemic or hemorrhagic stroke, acute coronary syndrome, heart failure, aortic dissection, acute kidney failure, or pre-eclampsia and other hypertensive complications of pregnancy. The following signs and history should be considered:

Testing for signs of acute end-organ damage will vary according to local resources and practices, and testing prioritized by the patient's symptoms. Depending on the specific symptoms, testing may include biomarkers of myocardial injury or infarction, chest X-ray, brain imaging, urinalysis, and/or serum creatinine.

Patients meeting criteria for hypertensive emergency should be referred immediately to the emergency departments/room for hospital evaluation and management. Unlike hypertensive urgency, blood pressure management in patients with hypertensive emergency varies according to the underlying condition diagnosed. For example, in acute ischemic stroke, it is recommended not to lower blood pressure unless it is ›185/110 mmHg; in the case of aortic dissection, systolic blood pressure should be rapidly lowered to a target of 100-120 mmHg. In addition to blood pressure lowering, other treatments should be delivered, targeted at the specific underlying condition.

Clinical management of the specific sequelae of hypertensive emergency are not covered here.

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TABLE: *Signs and conditions associated with causes or sequelae of hypertensive emergencies*

Clinical condition or sign	Associated sequela
Acute head injury or trauma	May lead to severe rise in blood pressure
Generalized neurologic symptoms, such as agitation, delirium, stupor, seizures, or visual disturbances	Hypertensive encephalopathy
Focal neurologic symptoms	Ischemic or hemorrhagic stroke
Fresh flame hemorrhages, exudates (cotton-wool spots), or papilledema by direct fundoscopy	grade III or IV hypertensive retinopathy and can rarely be associated with hypertensive encephalopathy
Nausea and vomiting	increased intracranial pressure
Acute chest discomfort or pain	myocardial ischemia, myocardial infarction, or aortic dissection
Acute, severe back pain	aortic dissection
Dyspnea	pulmonary edema due to heart failure
Pregnancy	preeclampsia or eclampsia
Use of drugs that can produce a hyperadrenergic state	cocaine, amphetamine(s), phencyclidine, or monoamine oxidase inhibitors, or recent discontinuation of clonidine (an antihypertensive drug that can cause rebound hypertension when discontinued

G1. DO MOBILE HEALTH (MHEALTH) DECISION SUPPORT SYSTEM (DDS) APPLICATIONS IMPROVE HYPERTENSION MANAGEMENT?

Electronic clinical decision support systems (DSS) using mHealth applications on desktop computers, digital tablets, or mobile phones may potentially improve the quality and capacity of hypertension care services in low resource settings. DSS applications can provide a variety of features to promote hypertension management including: medication initiation and titration recommendations using standard treatment protocol algorithms, referrals between healthcare workers and physicians across facilities, longitudinal electronic recording of patient blood pressure (BP) and medication data, data monitoring and feedback systems, cardiovascular disease risk assessment screening, prompts to deliver lifestyle advice, tracking of overdue patient lists via registries, automated text or voice messaging to patients to promote return appointment or medication adherence, or even remote monitoring of blood pressures taken at home or in the community.

Studies of mobile-technology DSS for hypertension[1-8] are heterogeneous in terms of the technology deployed, clinical setting, health workers targeted, and study design. Taken altogether, these studies have shown mixed results from null to modest effects on increased use of BP medications and BP reduction. Regarding BP change specifically, results have ranged from no significant change to up to 15 mmHg BP reductions. Some selected examples:

- A multicomponent, mobile technology–enabled primary health care intervention (SMARTHealth) was compared to usual care in rural Indonesia. Deployment of decision support via the mobile app was associated with greater increase in use of preventive CVD medications (15.5% intervention vs 1% control) and BP medications (56.8% intervention vs 15.7% control), and a modest reduction in BP (-8.3 mmHg between group difference in BP change)[1].
- A cluster-randomized control trial of a mobile decision support primary care intervention (mWellcare) among participants with hypertension or diabetes in India demonstrated no significant difference in BP or HbA1c between the mWellcare combined with enhanced usual care group versus enhanced usual care alone group[2]. However, both groups had similar within-group reductions in BP (-12 and -13mmHg, respectively).
- Systematic reviews and meta-analyses of the effectiveness of DSS have shown heterogeneity of effects, ranging from non-significant to modest improvements in blood pressure[7-8].
- There may be specific factors underlying the range of effects observed across these studies. Studies associated with the best hypertension outcomes involved multifaceted interventions that layered DSS on top of an enhanced primary care infrastructure. These accompanying primary care interventions included in the intervention arm, but not the comparator arm, likely contributed to the overall intervention effect. Primary health care enhancements included a greater intensity of task-sharing with nurses and CHWs, enhanced training and supervision for healthcare workers, simplified treatment algorithms, and/or ensuring consistent drug supply in the intervention arm of the study.
- Given the multifaceted nature of interventions *including* a mHealth component, it is not possible to identify the relative impact of DSS versus other intervention components on achieving positive outcomes. By the same logic, in studies that enhanced primary care in both study arms, the enhancements may have obscured the independent contribution of the mHealth component. For example, the mWellcare trial[2] in which DSS was the main intervention difference between intervention and control groups did not show significant change in BP between the groups. However, both groups received enhanced primary care interventions and had similar reductions in BP, suggesting the benefits of enhanced primary care in both groups on positive outcomes rather than DSS itself. Additionally, these studies were generally conducted among focused populations, and thus, cannot be generalized to widespread implementation.
- Overall, studies demonstrate that mobile technology DSS tools can have a modest impact on hypertension when delivered with robust primary care and a well-trained workforce, but may not impact blood pressure in settings where background primary care capacity and hypertension control programs are weak.

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G2. DO PATIENT-FACING MOBILE HEALTH (MHEALTH) APPLICATIONS IMPROVE HYPERTENSION MANAGEMENT? WHICH FEATURES OF PATIENT-CENTERED MHEALTH TECHNOLOGIES ARE MOST EFFECTIVE?

The majority of nearly 6 billion mobile phone users live in low and middle-income countries (LMICs)[1]. Patient-facing mHealth applications [including short message system (SMS) text messaging, interactive voice response (IVR), and other mobile phone tools] could address gaps in care for hypertension and other non-communicable diseases in LMICs. Studies to date of mHealth interventions for hypertension and other non-communicable diseases have shown small to modest effects on improved medication adherence, increased appointment follow-up, and reductions in blood pressure among other outcomes. A summary of selected best-quality evidence on patient-facing mHealth is included below:

1. Blood pressure (BP) control: Studies of patient-facing mobile interventions for hypertension have shown mixed to positive effects on BP control. One systematic review found three of six studies of mobile SMS messaging showed significant improvement in BP outcomes[5]. Another study from South Africa randomized patients with hypertension to receive one-way information-only text messages, 2-way interactive messages, or usual care[6]. They found a small reduction in systolic blood pressure (-2.2 mmHg with 1-way SMS and -1.6 mm Hg with 2-way SMS); an increase in the proportion of patients with controlled BP below 140/90 (65% with 1-way SMS and 2-way SMS vs. 58% with usual care); and an increased proportion of patients with over 80% adherence (62.8% with 1-way SMS, 59.7% with 2-way SMS, and 49.4% with usual care). There was no significant difference between 1-way and 2-way communication in this study.

2. Medication adherence: A meta-analysis of 16 randomized controlled trials (RCTs) using mobile text messaging for chronic diseases found an approximate doubling of the odds of self-reported patient adherence, corresponding to an absolute increase in adherence rates from 50% to 67.8%[2]. Note that a 2018 Cochrane systematic review of mHealth interventions to improve medication adherence for cardiovascular disease concluded that there is low quality evidence showing small to no benefit on adherence[3].

3. Appointment attendance: A separate Cochrane systematic review from 2013 found there was moderate quality evidence that mobile text message reminders increased follow-up appointment attendance (risk ratio 1.14, 95% CI 1.03-1.26, 67.8% attendance with no reminders, 78.6% with mobile text messages, and 80.3% with phone call, reminders)[4]. However, again the authors concluded the current evidence remains insufficient to definitively assess impact on appointment attendance.

Overall, it is not possible to make definitive conclusions about the efficacy of mHealth interventions to improve hypertension outcomes because of limitations of completed trials including heterogeneous interventions, variable results, small sample sizes, short duration, and low scientific quality of evidence reported. Most of the above studies were conducted in high and upper-middle income countries; the evidence from LMICs is even more limited.

Beyond uncertainty about overall effects, it is also not well-known which features of mHealth applications are most effective. Remaining key research questions to be answered include "Are text messages more effective if delivered daily or weekly?" "Does individualized patient-specific content help?", and "Is 1-way or interactive 2-way communication better?"

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H. 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

CKDchronic 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