

Treating Hypertension in Third World Countries

**-Information for U.S. based Medical Relief Organizations & Medical Practitioners
With a focus on treating hypertension when lab is not available.**

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The information provided here has general applicability to medical relief organizations working in third world countries seeking to provide treatment to patients with high blood pressure. Treatment guidelines for high blood pressure therapy are provided for the settings with and without the capability of providing laboratory monitoring of blood work. Using the protocols described here, treatment with an effective 3 drug regimen can be achieved for 10 cents/day. (Assuming the medications are obtained at hospital cost.)

The following information was developed while caring for hypertensive patients in Haiti six weeks after the earthquake. The medical problems present at that time in Haiti were no longer primarily the problems of acute trauma, but rather the medical needs of a displaced population. Many of the patients presenting to medical clinics had blood pressures of 200/115 and had never been on medication, or no longer had available previously prescribed medication.

Many of the medical clinics were without facilities to run blood work, including electrolytes. High blood pressure treatment protocols were devised for treating hypertension in this setting by a United States cardiologist who volunteered in Haiti.

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CAVEAT: All recommendations made here are with the understanding that the final determination of therapy is made by the clinician seeing the patient and based on their own individual clinical judgment.

1. What medications used for treating hypertension are particularly cost effective for clinics to purchase? (Since medications are long term, cost issues important.)

<u>Medication</u>	<u>dosage</u>	<u>Quantity</u>	<u>Cost to a hospital pharmacy in the USA</u>
amlodipine	10 mg	1000 pills	\$25.00 approx.
atenolol	50 mg	1000 pills	\$20.00 “
hydrochlorothiazide (HCTZ)	25mg	1000 pills	\$10.00 “
lisinopril	20mg	1000 pills	\$50.00 “

(amlodipine 2.5¢/pill, atenolol 2¢/pill, HCTZ 1¢/pill, lisinopril 5¢/pill)

2. What are some general considerations in treating hypertension in third world countries in areas of very limited resources?

- 1. All patients should be told to decrease salt intake and increase fruit and vegetable intake, if possible.**
- 2. For patients started on hydrochlorothiazide (HCTZ), advise the following:**
-Eat at least one piece of fruit daily:
Either a banana, tomato, or citrus fruit (such as an orange), or other fruit relatively high in potassium.
 (When a daily banana was initially recommended, many of the patients seen did not have access to bananas or did not like bananas, so the recommendations were broadened from one banana daily.)
 HCTZ is an effective BP medication which is a very mild diuretic and causes potassium-K⁺ loss and hence the above recommendation. (Limiting dietary sodium intake tends to decrease the potassium loss that occurs with HCTZ.)
- 3. Consider giving each medication in a separate plastic container with a label attached to the outside of the container detailing medication, dose, and frequency.** (Plastic bags may be used as containers.)
Ask the patient to bring all containers of medication back with them to the clinic approximately 5 days before the medication runs out. This ensures that the doctors will know what medications the patient has been taking and be able to give appropriate additional medications.
- 4. If ½ pills are used, consider having someone at the clinic split the pill for the patient and place them in the plastic bag or other container to increase compliance.** (Though some crumbling of the pills occurs, the expected increase in patient compliance outweighs this concern.)
- 5. Tell the patient that if they develop an infectious gastroenteritis with either profuse diarrhea or sustained nausea and vomiting, they should hold the diuretic therapy (HCTZ) and ACE inhibitor therapy (lisinopril), until the**

gastroenteritis resolves. Other blood pressure medicines may need to be held, but this issue is particularly important with HCTZ and ACE inhibitors (or angiotensin receptor blockers).

5. What are some specific medications to consider using? (Includes therapeutic considerations and equivalent dosages of other medications in the same therapeutic class.)

Amlodipine is a calcium channel blocker. There is no need for laboratory monitoring with amlodipine.

Amlodipine is very similar in effects and side effects to extended release nifedipine. Both medications are the same type of calcium channel blockers.

Side effects: Can cause lower extremity swelling (noncardiac) in a dose related fashion. A small amount of swelling is common and acceptable if not bothersome to the patient. Usually, swelling occurs during the first week. Swelling resolves if the medication is stopped. Also, can increase heart rate and provoke angina.

Amlodipine 5mg qd is the therapeutic equivalent to **nifedipine (extended release) 30mg qd.** (Amlodipine 10mg qd is the approximate therapeutic equivalent to nifedipine XR 60mg qd.) Amlodipine and extended release nifedipine are different medications but with similar efficacy and similar side effect profiles. The preferred agent is whichever is drug is cheaper. (Nifedipine that is not an extended release is not an equivalent agent.) If both drugs are similar in price, obtain amlodipine, since there are more clinical trials documenting benefit.

Atenolol is a beta blocker. There is no need for laboratory monitoring with beta blockers.

Atenolol and metoprolol are in the same class of medications with similar efficacy.

Side effects: Can cause excessively slow heart rate, fatigue, and bronchospasm (asthma)-usually in individuals who already have this tendency. **If patient has a pulse less than 60 beats per minute, would not prescribe this type of medication.** Side effects of beta blockers are apparent through either history or physical exam. Beta blockers slow the heart rate to some degree in all patients and this is an expected effect. Beta blockers can also cause impotence.

Beta blockers can be less effective for treatment of hypertension in blacks.

Atenolol 50 mg qd is the therapeutic equivalent of **metoprolol 25mg bid.** Atenolol 100mg qd is the therapeutic equivalent of metoprolol 50mg bid. (Atenolol has a longer half life and is cheaper for an equivalent therapeutic effect.)

Hydrochlorothiazide (HCTZ) is a blood pressure medication and a very mild diuretic. HCTZ can cause low potassium. Infrequently, HCTZ can cause a decrease in renal function. Usually, this is not a problem when used in low dosages. Older patients are more at risk, though HCTZ is usually tolerated even in this population at low dosages. HCTZ is ideally used with laboratory monitoring.

HCTZ tends to increase the effectiveness of other blood pressure medication when used in combination with other medications.

Recommendations: Consider using **HCTZ**, even without laboratory, in very low dosages. (HCTZ 12.5mg or ½ of 25mg pill). The higher the dosage, the more likely that low potassium will result. When HCTZ is used, recommend that the patient eat foods high in potassium.

HCTZ/triamterene tablets would be an option. Pills that can be split (rather than capsules), which allow for lower dosages of HCTZ to be used, are recommended. (The potassium losing characteristics of HCTZ are usually only partially made up by the weaker potassium sparing effects of triamterene.) However, HCTZ/triamterene combinations are considerably more expensive than HCTZ.

Lisinopril is an ACE inhibitor. Lisinopril is ideally used with laboratory monitoring.

Side effects: Can raise potassium levels excessively in some patients. Lisinopril can cause a significant decrease in renal function in some patients. Risk for adverse renal effects greatly increases with age. Highest risk is for a patient with bilateral renal stenosis which most commonly occurs in the older patient with diffuse atherosclerosis.

Side effect summary:

Excessively elevated potassium.

Decreased renal function.

Non productive cough. Occurs in approximately 1 out of 20 patient and begins 1-2 weeks after starting the medication. The cough is annoying and but will resolve approximately one week after the medication is stopped. **Not to be used in pregnancy.**

Recommendations: Lisinopril can be considered for patients less than 55 years of age, even if lab is not available, if needed in addition to other medication to control severe hypertension. The risk and benefits for each individual patient need to be considered, but severe hypertension that is not well controlled has major risks.

If a patient has *recently* previously taken enalapril without a problem in a lab monitored setting, then lisinopril can usually be restarted regardless of age.

Lisinopril is in the same class of medication as enalapril. Lisinopril 10mg qd is the therapeutic equivalent of enalapril 5mg bid. Lisinopril 20mg qd is the therapeutic equivalent of enalapril 10mg bid. (Lisinopril has a longer duration of action.) Enalapril is equally good for hypertensive control, but to achieve an equivalent effective dose, the expense of enalapril tends to be significantly more, at least in the United States.

Captopril is also an ACE inhibitor and has the shortest half life. Captopril is similarly more expensive than lisinopril, with captopril 25mg bid being the approximate equivalent of lisinopril 10mg qd.

Angiotensin receptor blockers: As a footnote, there may be various small amounts of various **angiotensin receptor blockers** at some volunteer clinics (as a result of samples given to doctors in the USA).

Angiotensin receptor blockers have essentially the same effects as ACE inhibitors on the patient in regards to therapeutic effects. Angiotensin receptor blockers also have the same side effect profile except no problem with cough and a somewhat decreased risk of rare allergic reactions compared to ACE inhibitors. **Angiotensin receptor blockers are not to be used during pregnancy.**

Currently, there are no generic versions of these in the United States. When they initially become available, these generic versions will tend to be much more expensive than lisinopril. **Except for using up the samples of angiotensin receptor blockers as a temporary equivalent to lisinopril, they do not have much of a role in third world countries because of the cost.**

In order to allow the identification of these sample medications that may be present in some volunteer medical clinics, the following names are provided.

Brand names/(generic): Atacand/(candesartan), Avapro/(irbesartan), Diovan/(valsartan), Micardis/(telmisartan), Teveten (eprosartan). (These are often combined with low dose hydrochlorothiazide--HCTZ.)

Effective combinations of medications for hypertension (when laboratory monitoring available):

Amlodipine/ HCTZ

Amlodipine/Lisinopril

Lisinopril/HCTZ

Amlodipine/Lisinopril/HCTZ

(A beta blocker can be used with any of the above combinations.)

HIGH BLOOD PRESSURE TREATMENT PROTOCOLS INCLUDING WHEN LABORATORY MONITORING IS NOT AVAILABLE

There are a number of ways to approach the treatment of the patient with high blood pressure when laboratory testing is not available. The following is one approach.

Naturally, the particular circumstances of the individual patient and the experience and clinical judgment of the individual medical practitioner will lead to modifications of this protocol or even a different treatment protocol altogether. However, in the hope of providing concrete and usable information to the volunteer medical health care provider working in Haiti, the following treatment protocol is offered as a potential starting point.

The medications that are used in this protocol are very cost effective in order to increase the feasibility of a making a sustained effort to treat hypertension in this setting.

(At wholesale prices, the cost of a 3 drug regimen is 10 cents/day.)

PLEASE READ CAREFULLY:

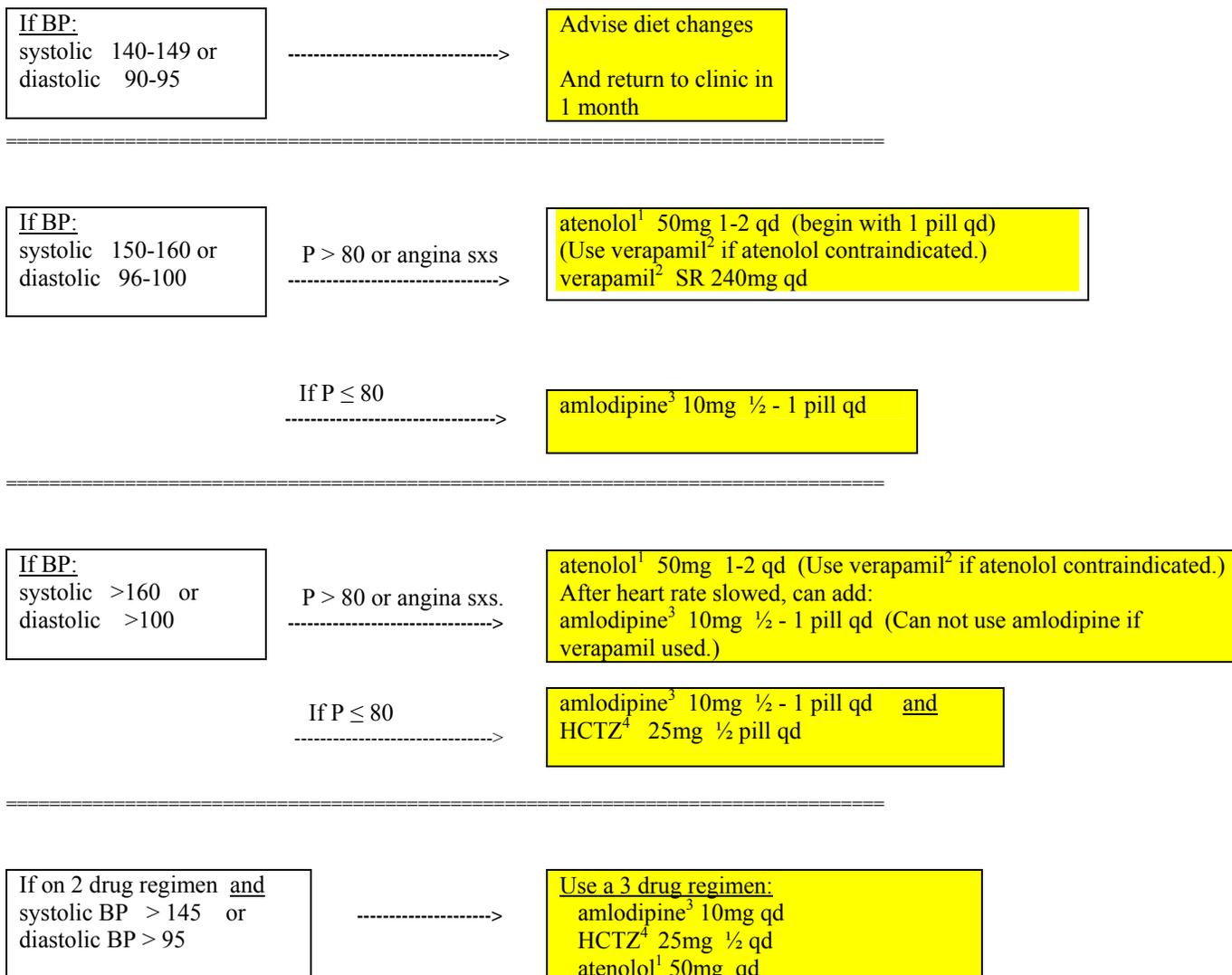
Prior to the use of any treatment protocol for hypertension, the medical practitioner should be personally knowledgeable of the complete side effect profile of every medication that is prescribed.

The following protocol is simply an approach to consider, with the final treatment decision to be made by the medical care provider seeing the individual patient while taking into account the particular clinical conditions that exist.

HIGH BLOOD PRESSURE TREATMENT PROTOCOL WHEN LAB MONITORING IS NOT AVAILABLE

- If a patient has a contraindication or develops a significant side effect with a medication, delete that medication from the protocol.
- The prescribing health care provider must be personally knowledgeable about the complete side effect profile of every medication prescribed. Final treatment decisions are to be made by the health care provider in the context of the particular conditions that exist for the individual patient.
- All patients treated for hypertension should be advised to decrease salt intake and increase fruit and vegetable intake.
- *If the patient develops profuse diarrhea or sustained nausea and vomiting, hold both the diuretic (HCTZ) and the ACE inhibitor therapy (lisinopril) until gastroenteritis resolves. (It may be necessary to hold other blood pressure medications as well.)*

HTN TREATMENT FLOW CHART- IF NO LAB AVAILABLE:



**TREATMENT PROTOCOL FOR HTN RX WHEN LAB
MONITORING NOT AVAILABLE (continued)**

If on 3 drug regimen and
systolic \geq 150 or
diastolic \geq 100

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Have patient seen by a practioner experienced in the
treatment of hypertension in order to consider adding
lisinopril⁵ 20mg ½ - 1 pill qd

Footnotes to medications:

Atenolol¹ use can be limited by the development of bronchospasm or excessive slowing of heart rate, particularly if accompanied by lightheadness. (Atenolol always slows heart rate.)

Beta blockers can also cause impotence.

Beta blockers can be less effective for the treatment of hypertension in blacks.

Verapamil² can not routinely be combined with atenolol (a beta blocker) or amlodipine.

The slow release formulation of verapamil which is needed for hypertension is relatively much more expensive than the other medications in this protocol.

Verapamil can cause excessive slowing of heart rate, constipation, and GI upset.

Amlodipine³ can at times cause the development of increased heart rate and angina.

HCTZ⁴ (**hydrochlorothiazide**) use in the unmonitored lab setting should be limited to a maximum dose of 25mg ½ pill qd. In the lab monitored setting, HCTZ can be used at a dose of 12.5- 50mg. The higher the dose, the greater the tendency for potassium loss. Using a dose of 12.5 mg minimizes potassium loss and side effects. HCTZ use should be accompanied by the advice to eat 1 additional piece of fruit daily (banana, tomato, or citrus fruit) to minimize potassium loss.

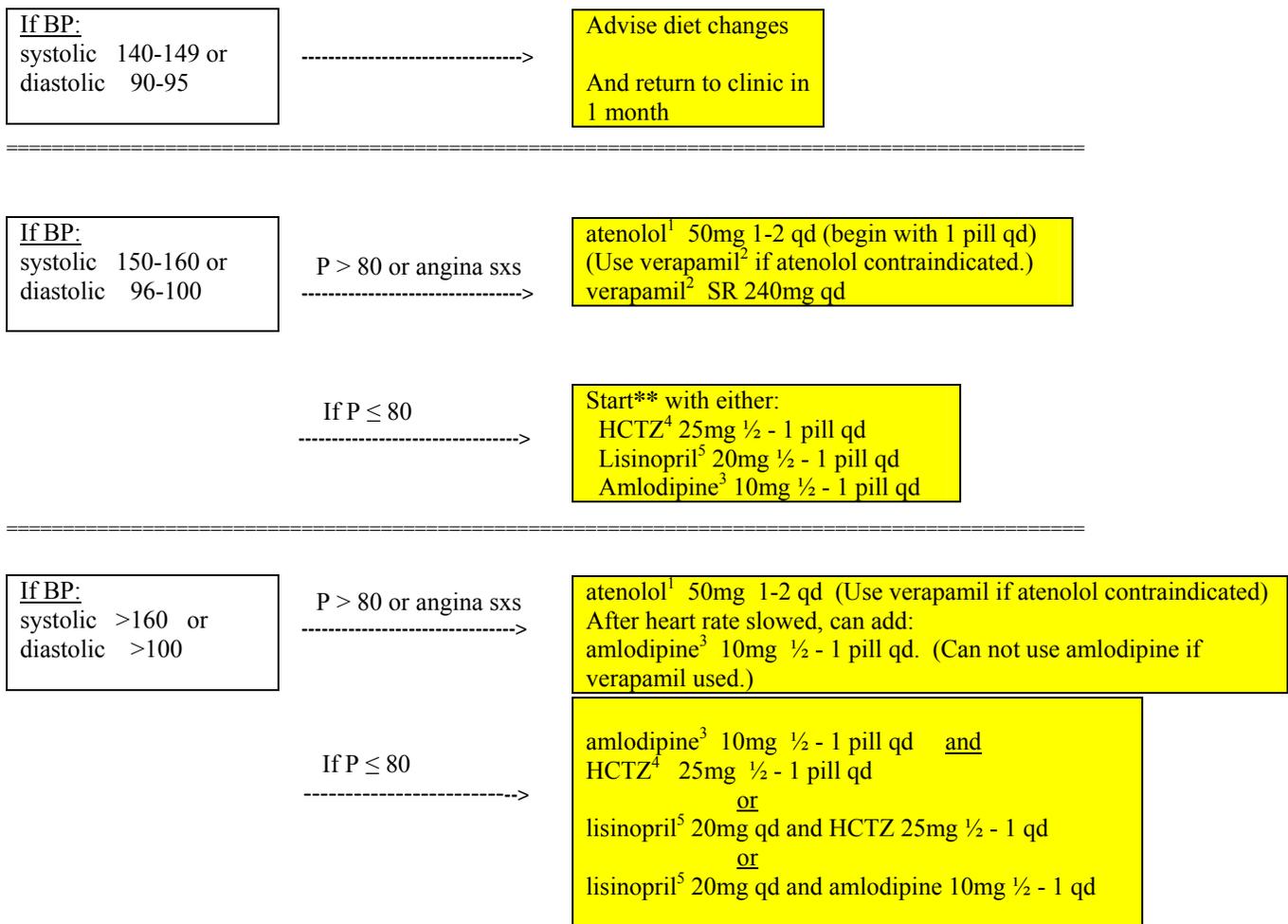
Lisinopril⁵ in this setting should not be used in patients with dehydration because of the increased risk of renal dysfunction. Lisinopril tends to increase potassium levels.

Lisinopril (as well as any other ACE inhibitor) is not to be used during pregnancy.

HIGH BLOOD PRESSURE TREATMENT PROTOCOL WHEN LAB MONITORING IS AVAILABLE

- If a patient has a contraindication or a significant side effect develops with a medication, delete that medication from the protocol.
- The prescribing health care provider must be personally knowledgeable about the complete side effect profile of every medication prescribed. Final treatment decisions are to be made by the health care provider in the context of the particular conditions that exist for the individual patient.
- All patients treated for hypertension should be advised to decrease salt intake and increase fruit and vegetable intake.
- *If the patient develops profuse diarrhea or sustained nausea and vomiting*, hold the diuretic (HCTZ) and the ACE inhibitor therapy (lisinopril) until gastroenteritis resolves. (May need to hold other blood pressure medications as well.)

HTN TREATMENT FLOW CHART- LAB MONITORING AVAILABLE:



If on 2 drug regimen and
systolic BP > 145 or
diastolic BP > 95

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Use a 3 drug regimen for difficult to control HTN:

amlodipine³ 10mg qd
lisinopril⁵ 20mg qd
HCTZ⁴ 25mg qd

A 4th medication can subsequently be added if needed:

atenolol¹ 50mg 1-2 pills qd

Footnotes to medications:

Atenolol¹ use can be limited by the development of bronchospasm or excessive slowing of heart rate, particularly if accompanied by lightheadness. (Atenolol always slows heart rate.) Beta blockers can also cause impotence.

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Lisinopril (as well as any other ACE inhibitor) is not to be used during pregnancy.

** Concerning the initial treatment of hypertension

Many advocate routinely using HCTZ as the initial drug of choice in the treatment of hypertension on the basis of the ALLHAT trial and that trial's effect on subsequent meta analyses. However, this appears to be an inappropriate overgeneralization of the ALLHAT trial results. The ALLHAT trial had particular requirements for treatment protocols that do not mimic routine clinical practice. These include the prohibition of using lisinopril (an ACE inhibitor) with a diuretic as a second agent, the prohibition of using amlodipine with a diuretic as a second agent, and the prohibition from using amlodipine in combination with lisinopril which is a synergistic combination frequently used in clinical practice. For further details see:

<http://www.improvingmedicalstatistics.com/ALLHAT%20Trial%20Critique.htm>

In fact, the subsequent ACCOMPLISH trial found that the combination of an ACE inhibitor with amlodipine compared favorably with HCTZ for the initial treatment of hypertension.

For details: <http://content.nejm.org/cgi/content/short/359/23/2417>

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Why were verapamil, diltiazem, and clonidine not recommended as primary drugs in this treatment protocol for hypertension?

They were not included for reasons of cost, compliance, and compatibility with other agents. It is worthy to note that short acting generic drugs that require a long acting formulation are almost always significantly more expensive than generic drugs in the same class of medication with an intrinsically long half life.

VERAPAMIL and DILTIAZEM are both calcium channel blockers, but affect the body so differently compared to amlodipine or nifedipine, that it is best to consider these drugs as being functionally a completely different type of medication.

The reasons for not including these medications as primary medications in this protocol will be detailed with verapamil.

Verapamil is an option for treatment of a patient in a setting without laboratory monitoring.

VERAPAMIL is useful for the treatment of the patient with hypertension with an elevated heart rate or in the presence of angina when beta blockers can not be used.

Verapamil can also be useful for patients with hypertension and palpitations resulting from SVT or atrial ectopy.

However, it is not used more widely in this protocol for the following reasons:

1. Verapamil slows heart rate, though less than a beta blocker. Verapamil should not used in combination with a beta blocker for the treatment of hypertension in this setting (Verapamil can be used in combination with a beta blocker in a closely monitored situation by an experienced clinician for a condition such as angina.)
2. Verapamil can not routinely be used with amlodipine or nifedipine because they are in the same class of medications (even though they have different effects).
3. Verapamil formulations which are not long acting need to be given as a bid or tid dosage which decreases compliance. Long acting formulations are preferable for the treatment of hypertension, having better documentation in the literature of benefit.
4. Long acting verapamil is much more expensive than amlodipine.

DILTIAZEM is not useful as a primary drug in this protocol for similar reasons. In addition, long acting verapamil has much better evidence from clinical trials compared to diltiazem that it favorably affects clinical endpoints when used for hypertension.

CLONIDINE:

Clonidine is potentially useful as a drug for hypertension in the unmonitored setting.

Side effects of dry mouth, fatigue, and postural hypotension can all be assessed without any laboratory monitoring which is a beneficial feature. **A reasonable case can be made for including this medication for the treatment of hypertension with or without laboratory monitoring.**

However, clonidine was not included as an initial drug of choice in this protocol because of the following.

1. The bothersome side effects of postural hypotension, dry mouth, and fatigue are common with this medication. If side effects occur early on in treatment, the patient

will be less likely to continue with any blood pressure treatment or even return for follow up, particularly when there is not a broad public campaign to increase the awareness of the need for maintaining a good blood pressure.

2. Clonidine is short acting and optimally given on a bid or tid schedule. This dosing frequency will lead to decreased patient compliance.
3. Long acting transdermal formulations of clonidine are available which significantly decrease the frequency of annoying side effects to the patient, but these are much more expensive and not suitable in this setting for that reason.
4. **For resistant, hypertension not responsive to other agents, an initial trial of clonidine 0.1-0.2mg qhs or clonidine 0.1mg bid added to other medications is a reasonable option.**

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I hope this information is helpful in the care of patients with hypertension in third world countries being seen by medical relief organizations. In this setting cost effective treatment is essential and resources are often limited.

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