**Please**

* review with Track Changes on (it is currently on ).
* Save copy with your name/initials at the end
* Priority to errors/gaps in recommendations and evaluation of meds
* Please return by Monday Dec 17 by 9am so that I can review for Tuesday clinical meeting

**Notes:**

Appendix F (no med scenario examples) and Appendix G (one med scenario examples) were discussed at clinical meeting

**Unanswered** **Questions:**

1. Need to encode more drug classes? (see list of non-encoded drugs in Appendix)

**Document is missing:**

ICD9/10 codes for CKD and HTN not yet added

**Reminder to Connie KB encoding to do’s**

Bad drug partner wrt Samson’ updated drugs in same class; now have 2 messages when 2 BB.

Rules Document for Hypertension Control

# Summary

This document describes the contents–the “encoding”–of the Protégé Hypertension Control KnowledgeBase; that is, the patient characteristics, including diagnoses, conditions, laboratory values, and medications, that are used to evaluate each patient for therapeutic hypertension drug options.

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# Overview

## Background

The Hypertension control Protégé KnowledgeBase (KB) captures the recommendations for the management of hypertension (HTN) described in the 2014 “VA/DOD Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care Setting” version 3. Knowledge from this guideline was augmented by the 2017 “ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults”. Links to these references, as well as other documents and papers used, can be found in [References](#_References) section.

This “Rules Document” has been created for the MedSafe Quality Enhancement Research Initiative (QUERI) Clinical Decision Support (CDS) project. Contributors to the Rules document and KB are Connie Oshiro, PhD, Michael Ashcraft MD, Omar Usman, MD, MBA, Vishal Duggal, MD, and Susana Martins, MD, MSc; contributor to the encoding of the KB are Connie Oshiro and Samson Tu, MSc. The project Principal Investigator is Mary Goldstein, MD. The MedSafe CDS project is one of 3 projects in the VA HSR&D MedSafe QUERI project with Principal Investigators Paul Heidenreich, MD and Mary Goldstein, MD.

The KB was created to encode the clinical knowledge for a CDS system intended to provide recommendations to primary care professionals who are caring for patients with HTN who did not meet HTN blood pressure goals (described in the next section). These patients will be identified via the VISN 21 Pharmacy Benefits Management (PBM) Clinical Dashboard, a panel management tool. The VISN21 Clinical Dashboard for PACT teams draws on VA structured data to identify patients who are not meeting Healthcare Effectiveness Data and Information Set (HEDIS) performance measures for specific chronic diseases. The Clinical Dashboard displays the data used to determine whether or not the patient is meeting these measures. In the MedSafe QUERI project, we are linking CDS to the Clinical Dashboard to provide recommendations for patients who are not meeting their performance measures. Patients who fail the HTN Performance measure for poor blood pressure control will be identified by the Clinical Dashboard and will be the starting set of patients who *could* receive CDS recommendations. Therefore, the CDS does not provide recommendations regarding care management when patients are already meeting measures. The recommendations will be integrated with the VISN 21 Clinical Dashboard. A brief description of the Clinical Dashboard can be found in references (3) and (4) in [References](#_References) section.

The KB is only one part of an overall architecture for the CDS which also includes processes for extracting and preparing patient data, an execution engine (aka guideline interpreter) to process the patient data against the KB, generation of recommendations from the execution engine, and presentation of the recommendations in a user interface on the Clinical Dashboard. The overall structure follows the EON model, a component-based approach to automation of protocol-directed therapy.

This Rules Document specifies the expected behavior of the CDS. It defines the clinical knowledge about HTN that is included in the CDS. This document is akin to the Requirements Document of Software Development. Unlike the Software Requirements Document, however, the Rules Document can and does change any time before the deployment of the KB. Of note, this description of the behavior is specific to the HTN KB, and the behavior, including the terms and definitions, may not be exactly the same as in other disease KBs.

## Use of the Rules Document

The primary way to test the encoding of a KB and the execution engine is by comparing the CDS output to the recommendations from a Domain Expert (DE), using real patients, and in accordance with the agreed rules as specified in this document. We refer to this process as “offline testing.” This Rules Document was created, in part, for clarity about the guideline knowledge encoded in the KB and the recommendations that should be made given specific patient clinical data.

This Rules Document is a record of what clinical knowledge is—or what should have been—encoded in the KB. This document is used by the DE when offline testing in two ways:

1. To provide recommendations consistent with the Rules Document. A comparison of the DE recommendations with the output of the CDS will verify that what was intended to be encoded has been encoded (recognizing that CDS output is determined not only by the KB encoding but also by patient data entered to the system, the execution engine, and the output display).
2. To identify gaps in or extensions to the KB that become clear in the context of real patients.

While we have included messages that will be displayed, messages per se are not part of the offline testing. And, while we have interspersed some messages throughout the Rules document, all messages can be found in their own Messages section, [5.0 Messages and text displayed in GUI](#_Messages_and_text) .

**The following sections describe what has been encoded in the HTN Control KB**

# Eligibility, Goals, Restrictions, Out of Scope and Limitations

## Eligibility

Eligible patients are those patients who –could- receive recommendations. They have

* A diagnosis of hypertension based on ICD-9 and ICD-10 codes. (See [Appendix X](#_Appendix_H:_ICD-9) for list of codes)

AND

* Age >= 18 and <=75

AND

* Have Systolic Blood Pressure (SBP) measurement

A patient who is eligible will be evaluated for drug recommendations. Those who are not eligible (ineligible) will not be evaluated for drug recommendations and are indicated simply as “ineligible.” An ineligible patient differs from a patient who is “out of scope” (described in “[Section 2.4 Out of Scope](#_Out_of_scope)”) in that there is no message displayed explaining why the patient is ineligible, whereas the “out of scope” patient receives a message why therapeutic recommendations are not given.

### Pregnant Patients

Pregnant women are not eligible, but this information cannot be easily captured at the VA. Therefore, therapeutic recommendations will be given to women of child bearing ages (18-50) with the assumption that they are not pregnant.

The following primary recommendation will be issued regarding these women: “*Warning: recommendations do not apply to pregnant women.*”

## Goals

The CDS goals for HTN control are, for patients withOUT Ischemic Heart disease (IHD)

* BP<140/90

And, for patients with IHD

* SBP<140 and 60<=DBP<90

These goals were set to be consistent with PBM dashboard goals, which are based upon the goals set by the VHA Office of Reporting, Analytics, Performance, Improvement, and Deployment (RAPID) Performance Measurements. The second goal (patients with a diagnosis of IHD) was set to insure patient safety.

## Restrictions

## Subset of HTN drugs (“encoded drugs”)

We provide recommendations for all first line and second line HTN drug classes, per VA/DoD Guidelines. We also provide recommendations for some third line drug classes, those that are commonly used for the treatment of HTN. However, we do *not* provide recommendations for all third line drugs. The drug classes where we do provide recommendations are:

* First and second line drug classes
  + Thiazide Diuretics
  + Angiotensin Converting Enzyme (ACE) Inhibitors
  + Angiotensin Receptor Blockers (ARB)
* Second and third line drug class
  + Long acting Dihydropyridine Calcium Channel Blocker (DHP CCB)
* Third line drug classes
  + Long Acting Non Dihydropyridine Calcium Channel Blocker (NDHP CCB)
  + Cardioselective Beta Blocker (BB)
  + Non Cardioselective BB
  + Alpha-beta blocker

We refer to this list of drug classes (and drugs) as “encoded drugs”; they can be found in [Appendix A](#_Appendix_A:_). Medication cut off values, such as Maximum dose values and an increase dose ceiling, that are included in the KB for many of these drugs are in [Appendix B](#_Appendix_B:_).

The list of HTN drug classes where recommendations are not provided—referred to as “non-encoded drugs” -- are also in [Appendix A](#_Appendix_A:_). No medication cut off values encoded.

There are also drugs that have anti-hypertensive effects, but are not considered by the VA Guidelines for the treatment of HTN. These drugs are also included in [Appendix A](#_Appendix_A:_) and are:

* + Aliskiren
  + Sotalol
  + Loop Diuretics (bumetanide, ethacrynic acid, furosemide, torsemide)

For patients whose active prescriptions include non-encoded HTN drugs, or the drugs with anti-hypertensive effects, recommendations are still provided, but only for the encoded drugs. Neither the non-encoded drugs, nor the drugs with anti-hypertensive effects are evaluated.

If the patient has an active prescription for non-encoded drug that we do not evaluate, the following message is displayed:

*Pt has Rx for HTN med ?nonEncodedDrug that we have not evaluated.*

Where ?nonEncodedDrug is a 3rd line non-encoded HTN medication OR sotalol OR aliskiren OR a loop diuretic.

And, if the patient has an active prescription of sotalol or aliskiren or a loop diuretic, there will be an additional message:

*?otherDrug is not a drug primarily used for the treatment of HTN.*

Where ?otherDrug is either sotalol or aliskiren or a loop diuretic.

## Out of scope

CDS evaluates all eligible patients (defined above). However, therapeutic options are not provided for all patients. Messages associated with these Out of Scope conditions can be found in the Section “[5.0 Messages and text displayed in GUI](#_Messages_and_text)”.

Therapeutic recommendations are NOT provided:

1. If a patient is at goal (described above).

OR

1. If a patient’s
   1. GFR is older than 1 year OR his/her GFR<30 in the past year OR
   2. Blood pressure (BP) is out of scope, specifically,

SBP>=220 or DBP>=110

IHD and DBP<60

If BP is out of scope, then we refer the patient to hypertension specialist; and if BP is out of scope AND is older than 1 month, new BP is ordered.

OR

* 1. BP is older than 1 year. In this case, a new BP is ordered.

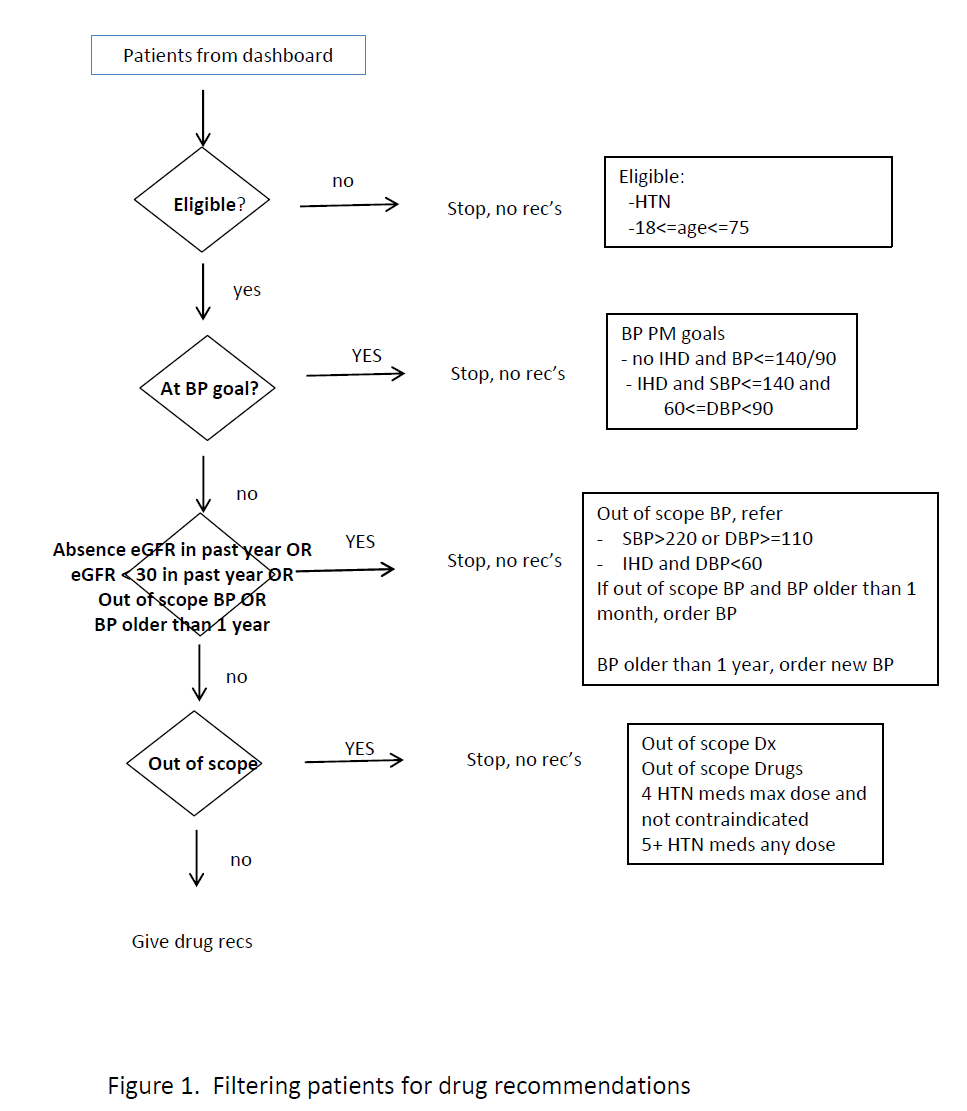
1. Patient has out of scope conditions (described in more detail below), i.e., either
   1. Out of scope diagnosis (Dx) OR
   2. An active prescription (Rx) for an out of scope drug OR
   3. Active prescriptions of 4 drugs that that are either
      1. encoded drugs used in the treatment of HTN OR
      2. non-encoded drugs used in the treatment of HTN OR
      3. drugs with anti-hypertensive affects (i.e. sotalol, aliskiren and any loop diuretic).

In addition, the encoded drugs are at their maximum dose and not contraindicated. If encoded drugs are not at their maximum dose or are contraindicated, patient is *not* out of scope.

* 1. Active prescriptions of 5 or more drugs used in the treatment of HTN, encoded drugs at any dose, or non-encoded, or drugs with anti-hypertensive effects (i.e. sotalol, aliskiren and any loop diuretic). Drugs are not evaluated for absolute contraindications.

See Figure 1.

Patients who are out of scope receive an out of scope message. These messages can be found in the Messages section of this document [5.2 Eligibility, Restrictions and Out of Scope messages](#_Eligibility,_Restrictions_and).



## List of out of scope Rx

Cyclosporine (used by patients with organ transplants, an out of scope Dx)

Tacrolimus (used by patients with organ transplants an out of scope Dx)

Metolazone (used for short periods primary for Heart Failure, an out of scope Dx)

Sacubitril (constituent, with valsartan, of combination drug Entresto, prescribed only for the treatment of Heart Failure, an out of scope Dx)

Bepridil (currently not prescribed in U.S., and no information if has same drug-drug interactions as other drugs in its class)

Amiloride (potassium sparing diuretic that primarily used by nephrologists)

Loop diuretics AND Thiazide Diuretics prescribed at the sane time (generally not used together for treatment of hypertension; indicates more complicated patient)

Loop diuretics AND Potassium Sparing Diuretics prescribed at the same time (generally not used together for treatment of hypertension; indicates more complicated patient)

## List of out of scope Diagnosis

Ascites

Hemodialysis

Idiopathic Subaortic Stenosis (IHSS)

Narcolepsy

Organ Transplant (various organs, as well as peripheral stem cell transplant)

renal artery stenosis

renovascular disease

spinal cord injury

Heart Failure

Secondary Hypertension – this includes Cushing's syndrome (hypercortisolism), Conn's syndrome (primary hyperaldosteronism), Pheochromocytoma, Polycystic kidney disease, Chronic glomerulonephritis, Polyarteritis nodosa, Systemic sclerosis, Aortic coarctation

***In scope Dx:*** There may be diagnoses that can cause Secondary Hypertension, but, only if untreated, or inadequately treated. We give recommendations for these diagnoses, assuming that patients are being treated. We chose to do this because, many of these cases are prevalent, and we did not want to exclude giving recommendations for large segments of the patients, when their elevated BP is likely not due to Secondary Hypertension. Messages are issued in these cases.

Acromegaly, Chronic Reflux Nephropathy, Hyperparathyroidism, Obstructive Sleep Apnea, Polycystic Ovarian Syndrome.

## Limitations

## Issue date of existing prescription vs date of CDS recommendations

For the current CDS, we assumed that the patient had had his HTN medication for a “reasonable” period of time, but was still not at goal. More specifically, we did not consider the issue date of a patient’s HTN prescription relative to the date that we provide recommendations. That means that a patient could have received his/her new prescription (or medications) within the last few days. Any recommendations we provide would be, in such a situation, premature. Inclusion of the an issue date, or a consideration of an appropriate cutoff date of “reasonable” period of time, is a wish list item, and listed in the Wish list section.

## Differences between Performance Measure goals vs VA HTN Guideline goals

In contrast to the Performance Measure/Dashboard goals above, the VA HTN Guideline goals are:

* BP<150/90, for patients without DM
* BP<140/85, for patients with DM (those on HTN medication)

And are summarized in Table 1 below.

|  |  |  |
| --- | --- | --- |
| Dx | Performance Measure (Dashboard) Goals | VA HTN Guideline Goals |
| No DM | SBP<140 | SBP<150 |
| Has DM | DBP<90 | DPB<85 |

Because we are using Performance Measure goals, which differs from the VA HTN GL goals, we will issue the following Primary messages:

If a patient does NOT have DM and has 140<=SBP<150

*“Pt does not have DM and has 140<=SBP<150. This above Performance Measure target, but is within VA GL target.”*

If a patient has DM and has 85<DBP<90,

*“Pt has DM and 85<DBP<=90. This below Performance Measure target, but is above VA GL target.”*

# Drugs Therapies

## Overview

As mentioned previously, the following drug classes are evaluated for recommendations:

* Thiazide Diuretics
* Angiotensin Converting Enzyme inhibitors
* Angiotensin Receptor Blockers
* Long Acting Dihydropyridine Calcium Channel Blockers
* Long Acting Non- Dihydropyridine Calcium Channel Blockers
* Beta blockers (excluding sotalol)
  + Cardioselective Beta Blockers
  + Non-cardioselective Beta Blockers
  + Alpha-beta blockers

For a list of the drugs in these drug classes see [Appendix A](#_Appendix_A:_).

There are other drugs that are used in the treatment of hypertension, per the VA Guidelines, but are not evaluated by the CDS. These are also listed in [Appendix A](#_Appendix_A:_). If a patient has an active prescription of any HTN drugs that we do not evaluate, we will issue a Drug-Related message:

*“Pt has Rx for HTN med ?nonEncodedDrug that we have not evaluated.”*

Where ?nonEncodedDrug is the name of the drug that we did not evaluate.

There are also drugs that have antihypertensive effects, but are not counted here as an antihypertensive agent in part because they were not listed in the VA 2014 GL as recommended agents. These agents are: loop diuretics and direct renin inhibitors (aliskiren) and sotalol.

Drugs can be recommended as first, second or third line therapies. That is, a drug is either

* First line drug
* Second line drug
* Third line dug

depending upon whether they have a diagnosis of

* HTN and no Chronic Kidney Disease (CKD) or
* HTN and CKD and are African American or
* HTN and CKD and are not African American

Drugs are evaluated based upon the presence of conditions (laboratory values, diagnoses, etc.) encoded as one or more of the following conditions:

* Compelling indication
* Relative Indications
* Absolute Contraindications
* Relative Contraindications
* Do not Start Controllable Criteria
* Do not Intensify Controllable Criteria
* Bad Drug Partner (the presence of another drug that interacts with the HTN drug)
* Additional Adverse Reaction (ADR) checks

First, these concepts are defined in general terms. Then, for each of the encoded drug classes, the specific conditions that constitute the concepts (i.e. indications, contraindications, etc.) are listed. Based upon the evaluation of these conditions, drugs are either recommended, not recommended, substituted, or doses are increased.

## Definitions of evaluation criteria

### Compelling indication

A diagnosis or any condition, other than HTN alone or HTN and CKD together, that makes a drug *strongly* advisable (compelling). When there are multiple first line drugs, this indication is used to order the display of drugs. That is, if a patient has such a diagnosis or condition, the first line drug with this relative indication will displayed above other first line drugs. Similarly, when there are multiple second/third line drugs, this indication is used to order the display of drugs “within” that line. Has higher weight for such ordering higher than relative indication (below). Displayed in GUI, but text not constructed in KB.

### Relative indication

A diagnosis or any condition, other than HTN alone or HTN and CKD together, that makes a drug advisable. When there are multiple first line drugs, this indication is used to order the display of drugs. That is, if a patient has such a diagnosis or condition, the first line drug with this relative indication will displayed above other first line drugs. Similarly, when there are multiple second/third line drugs, this indication is used to order the display of drugs “within” that line. Has lower weight than Compelling Indication. Displayed in GUI, but not constructed in KB.

### Absolute contraindication

A drug will not be recommended if patient has this condition; and the drug will be stopped (or a substitution recommended) if the patient has this condition and hasan active prescription for the drug. The drug will not be visible as a therapeutic option. ADRs that are absolute contraindications, e.g. anaphylaxis, are encoded here. Displayed in GUI only when drug is being replaced or stopped; text not constructed in KB.

### Relative contraindication

If a drug is recommended and is listed as a therapeutic option and if the patient has this condition, then the drug will be displayed lower in the list than those without a relative contraindication. If the patient has an active prescription of the drug and this condition exists, the drug will *not* be stopped. Message displayed in GUI and is encoded in KB.

### Do not start controllable criteria

Evaluating a drug for a recommendation often depends upon laboratory values or other measurements. If relevant measurements are missing (e.g. missing sodium in the past month), this constitutes a “Do not start controllable criteria.” In this case, the drug will be visible as a therapeutic option, but the recommendation will be “blocked” (controllable). In the CDS we refer to this as a “blocked controllable” recommendation. The recommendation for adding the drug is visible to the user, but it is presented as a recommendation that would have been made had the missing data been available and normal. Message displayed in GUI and is encoded in KB. Orders for missing labs displayed.

### Do not increase dose controllable criteria

Criteria similar to “Do not start controllable criteria,” but applies when there is an active prescription for the drug. Patient has an active prescription for a drug whose dose needs to be increased, but the change is “blocked” because there are missing data, a “controllable” criteria (e.g. missing sodium in past month). The increase in dose will be visible as a therapeutic option, but it is presented as a recommendation that would have been made had the missing data been available and normal. Message displayed in GUI, and is encoded in KB. Orders for missing laboratory values displayed.

### Bad drug partner

List of drugs that change, interfere with, have a cross-reactivity with, or otherwise negatively affect the action of the listed HTN drug. This may be a drug in the same class, a HTN drug in a different class, or a drug used in a different therapeutic area. In the evaluation of candidate drugs to add, if a patient already has an active prescription of a bad drug partner of that candidate drug, the candidate drug will be ruled out and will not appear as a therapeutic option. In this case, the bad drug partner is not displayed. If a patient already has active prescriptions for the candidate drug as well as the Bad drug partner, both the candidate drug and the Bad drug partner are displayed in GUI in a message. Recommendations are still provided.

### Additional ADR check

ADRs for drug being evaluated are automatically checked. In addition, there may be drugs in other drug classes where a similar adverse reaction would occur with the drug being evaluated. These drugs are listed here. List of drugs is often, but not always, the same as that as Bad drug partner, above. For example, for the drug class Thiazide Diuretics, under Additional ADR check, the sulfonylureas, such as those used in the treatment of diabetes, or sulfa drugs, are listed in this section. Another example: all beta blockers are listed here for the drug class Cardioselective Beta Blockers. ADRs for the drug class being evaluated, and for the drugs listed under Additional ADR check are displayed if they are not Absolute Contraindications. These ADRs are not encoded in the KB, but handled by the GUI. For a more detailed discussion of ADRs, see [Appendix C](#_Appendix_C:_).

## Definition of Chronic Kidney Disease (CKD)

In this KB, we have defined CKD either

* An ICD9 or icd10 code (See [Appendix X](#_Appendix_H:_ICD-9)) or
* GFR<60 in the past year

We have not included proteinuria checks as of 11/2018.

## Definition of race

At the current time (11/2018), we define race as the most recent value of race recorded in the VA records. If the value is “Black or African American”, then he/she is considered to be African American, and the therapeutic recommendations follow this identification. If the value is anything else (this includes “Missing” or “Unknown at this time” or “Declined to answer), then he/she is considered to be not African American.

For the list of possible values for race currently in our database, see [Appendix E](#_Appendix_D:_).

## Active prescriptions

We consider a patient to have an active prescription for a drug if the provider has written a prescription for that drug. More specifically, we call an active prescriptions, those medications that have an RxStatus=”Active”, “Hold”, “Provider Hold” or “Suspended” and the Issue date of the prescription (date prescription was written) is less than a year old, in the SQL data table, cdwwork.rxout.rxoutpatfil. This is consistent with what is done in the PBM Clinical Dashboard. That start date of the prescription used in EON is the release date of the medication (when the patient has possession of the drug, picked up by the patient or mailed to the patient). It is therefore possible that, in EON, a medication is considered active, but does not have a start date, because the patient does not yet have possession of the medication.

## Notes on Drug Dosages

If a patient has two different active prescriptions for the same drug, the dosages are summed and a recommendation is made using this summed dosage. There will be a message that there are two active prescriptions for the same drug (name of drug) and that we have summed the doses.

If the dose of an active prescription is above its maximum dose, the CDS will display a message indicating that the prescription is above maximum dose, but recommendations will be given as if the drug is at its maximum dose. Values of maximum doses are given in [Appendix B](#_Appendix_B:_).

## Medication Possession Ratio (Patient adherence)

A patient’s adherence to a medication is calculated via a Medication Possession Ratio (MPR). This MPR is the total number of days supplied (of drugs received by the patient) divided by the total number of days elapsed between the first and last fill date (of the prescription). For a more detailed description of this ratio, please see reference (5) [References](#_References) section

## Note on Dates & Session Times

The KB and execution engine evaluates patients on a fixed date. All diagnoses recorded before that date are considered and all laboratory values recorded *two years* before that date are used for all laboratory values EXCEPT sodium and potassium. This fixed date is referred to as the “session time.” (All values of sodium and potassium are used.)

Normally, “session time” is the current date. However, for testing and debugging purposes, we need to have patient data that does not change. For this purpose, we extract all relevant patient data and fix the date that that data was extracted. Therefore, the “session time” is the date of the data extraction, and not the current date.

When a time frame is given in the sections below, e.g. “within the past year,” this time frame is relative to this session time and, the most recent laboratory value is always used. For example, the phrase, “GFR < 30 in the past year” should be read as “the most recent value of GFR within the past year, relative to the session time.”

For this Rules Document: 1 year is equal to 365 days and 1 month is 365.0/12 = 30.4 days. This contrasts with the Clinical Dashboard, which uses “1 year is equal to 370 days and 1 month is 30 days.” We are aware of the discrepancy and believe the difference will not affect our recommendations or patient safety.

## Messages associated with drug recommendations

All messages associated with drug recommendations are not given here, but, instead, are included in the Messages “[Section 5 Messages and text in GUI](#_Messages_and_text)”. We have decided to do this because the offline testing does not test these messages, and inclusion here makes this section substantially longer. Unfortunately, in order to give context to all the messages, much of what is described in the Encoded drug section below is duplicated, making the overall document longer.

## Encoded Drugs

First and Second Line Drugs

### Thiazide diuretics

Recommended drugs: chlorthalidone (preferred), indapamide (preferred), hydrochlorothiazide

Is first line drug for:

* HTN and no CKD
* HTN and CKD and African American

Is second line drug for

* HTN and CKD and not African American

Drug Evaluation Criteria

* Compelling indication (none)
* Relative indication
  + Osteoporosis
* Absolute contraindication
  + Na<130 past month
  + K<3 past month and Rx thiazide
  + K<3.5 past month and no Rx thiazide
  + Gout, complicated
  + Lithium
  + ADR of anaphylaxis to thiazide

[[1]](#footnote-1)Anaphylaxis may present (and be recorded) as a reaction other than simply “anaphylaxis”. Therefore, these other “anaphylaxis-equivalent” reactions are also Absolute contraindications, and will be displayed simply as anaphylaxis. “Anaphylaxis-equivalent” reactions are: airway constriction, bronchospasm, hives.

* Relative contraindication
  + Gout, not complicated
  + Allergy to sulfonamide
  + Hypoatremia
  + 130<Na<135 past month
  + Na<=130 any time in the past
  + Presence of thiazide and 3<K<3.5 past month
  + K<3.5 any time in the past
  + Uric Acid > 6.8 past year
  + Hyperuricemia
  + Anuria or Oliguria
* Do not start controllable conditions
  + Absence of SBP in past month
  + Absence of K in past month
  + Absence of Na in past month
  + Absence of uric acid in past year
* Do not intensify controllable conditions
  + Absence of SBP in past month
  + Absence of K in past month
  + Absence of Na in past month
* Bad drug partner
  + Loop Diuretics (e.g. furosemide) [[2]](#footnote-2)
* Additional ADR check
  + Sulfa drugs
  + Sulfonylureas

### Angiotensin Converting Enzyme Inhibitiors (ACE Inhibitor)

Recommended drug: lisinopril

Is first line drug for:

* HTN and CKD and African American (with thiazide)
* HTN and CKD and not African American

Is second line drug for:

* HTN and no CKD

Drug Evaluation Criteria

* Compelling indication
  + Heart Failure
  + CVD
  + DM and CKD
* Relative indication
  + DM without CKD
* Absolute contraindication
  + K>5.5 past month
* ADR of anaphylaxis to ACE

1Anaphylaxis may present (and be recorded) as a reaction other than simply “anaphylaxis”. Therefore, these other “anaphylaxis-equivalent” reactions are also Absolute contraindications, and will be displayed simply as anaphylaxis. “Anaphylaxis-equivalent” reactions are: airway constriction, bronchospasm, hives.

* + ADR of angioedema to[[3]](#footnote-3) ACE
  + ADR of angioedema3 to ARB

3Angioedema, like anaphylaxis, may present (and be recorded) as a reaction other than simply “angioedema”. Therefore, these other “angioedema-equivalent” reactions are also Absolute contraindications, and will be displayed simply as angioedema. “Angioedema-equivalent” reactions are: lip swelling, swelling of throat, swelling-lips, swelling-throat, swelling-tongue, oral swelling, throat spasm, eye swelling, facial swelling, edema of tongue, angioedema of eyelids, angioedema of lips, angioedema of tongue, angioneurotic edema of larynx, laryngeal spasm.

* Relative contraindication
  + K sparing diuretics
  + 5<K<=5.5 past month
* Do not start controllable conditions
  + Absence of SBP in past month
  + Absence of K in past month
  + Absence of GFR in past month
* Do not intensify controllable conditions
  + Absence of SBP in past month
  + Absence of K in past month
  + Absence of GFR in past month
* Bad drug partner
  + ARB
  + Aliskiren
* Additional ADR check
  + ARB

### Angiotensin Receptor Blocker (ARB)

Recommended drug: losartan

Is first line drug for:

* HTN and CKD and African American (with thiazide)
* HTN and CKD and not African American

Is second line drug for:

* HTN and no CKD

Drug Evaluation Criteria

* Compelling indication
  + Heart Failure
  + CVD
  + DM and CKD
  + HTN without CKD and ADR to ACE not angioedema
  + HTN and CKD not African American and ADR to ACE not angioedema
* Relative indication
  + DM without CKD
* Absolute contraindication
  + K>5.5 past month
* ADR of anaphylaxis1 to ARB
  + ADR of angioedema to3 ACE
  + ADR of angioedema3 to ARB
* Relative contraindication
  + K sparing diuretics
  + 5<K<=5.5 past month
* Do not start controllable conditions
  + Absence of SBP in past month
  + Absence of K in past month
  + Absence of GFR in past month
* Do not intensify controllable conditions
  + Absence of SBP in past month
  + Absence of K in past month
  + Absence of GFR in past month
* Bad drug partner
  + ACE
  + Aliskiren
* Additional ADR check
  + ACE

Second and Third Line Drug

### Long Acting Dihydropyridine Calcium Channel Blocker (DHP CCB) [[4]](#footnote-4)

Recommended drug: amlodipine

Is second line drug for:

* HTN and no CKD
* HTN and CKD and African American

Is third line drug for

* HTN and CKD and not African American

Drug Evaluation Criteria

* Compelling indication (none)
* Relative indication
  + Angina
  + Raynaud’s syndrome
  + Migraine
  + DM
* Absolute contraindication
  + ADR of anaphylaxis1 to DHP CCB or NDHP CCB
  + ADR of angioedema3 to DHP CCB or NDHP CCB
* Relative contraindication (none)
* Do not add controllable condition
  + Absence of SBP in past month
* Do not intensify controllable condition
  + Absence of SBP in past month
* Bad drug partners
  + NDHP CCB2
  + Short acting DHP CCB
* Additional ADR check
  + NDHP CCB
  + Short acting DHP CCB

Third line Drugs

### Long Acting Non Dihydropyridine Calcium Channel Blocker (NDPH CCB)[[5]](#footnote-5)

Recommended drug: verapamil SA, diltiazem SA

Is third line drug for:

* HTN and CKD
* HTN and no CKD

Drug Evaluation Criteria

* Compelling indication
  + Presence Dx HTN and ADR to DHP CCB not anaphylaxis not angioedema
* Relative indication
  + Angina
  + Raynaud’s syndrome
  + Myocardial Infarction
  + Atrial Fibrillation
  + Atrial Tachycardia
* Absolute contraindication
  + ADR of anaphylaxis1 to DHP CCB or NDHP CCB
  + ADR of angioedema3 to DHP CCB or NDHP CCB
  + Heart block and no pacemaker
  + Unspecified heart block and no pacemaker
  + Sinoatrial node dysfunction and no pacemaker
* Relative contraindication
  + Heart Failure
  + Amiodarone
  + Bradycardia
* Do not add controllable condition
  + Absence of SBP in past month
* Do not intensify controllable condition
  + Absence of SBP in past month
* Bad drug partners
  + Short acting NDHP CCB
  + DHP CCB2
  + Beta Blockers[[6]](#footnote-6)
  + sotalol6
  + lovastatin
  + simvastatin
  + atorvastatin
* Additional ADR check
  + DHP CCB
  + Short Acting NDHP CCB

### Cardioselective Beta Blocker (Cardioselective BB)

Recommended drug: sustained release metoprolol succinate

Is third line drug for:

* HTN and CKD
* HTN and no CKD

Drug Evaluation Criteria

* Compelling indication
  + Myocardial infarction
  + Heart Failure
* Relative Indication
  + Atrial Fibrillation
  + Atrial Tachycardia
  + Angina
  + Hyperthyroidism
  + Coronary Artery Disease
  + DM
* Absolute contraindication
  + ADR of anaphylaxis1 to Beta Blockers
  + ADR of anaphylaxis1 to Alpha Beta Blockers
  + Heart block and no pacemaker
  + Unspecified heart block and no pacemaker
  + Sinoatrial node dysfunction and no pacemaker
* Relative contraindication
  + Depression
  + Obstructive Pulmonary Disease
  + Bronchospastic disease
  + Amiodarone
* Do not add controllable condition
  + Absence of SBP in past month
* Do not intensify controllable condition
  + Absence of SBP in past month
* Bad drug partners
  + Beta Blockers
  + Alpha-beta blocker
  + Sotaol
  + NDHP CCB
  + Central adrenergic inhibitors
* Additional ADR check
  + Beta blockers
  + Sotalol
  + Alpha-beta blocker

### Non-Cardioselective Beta Blocker (Non-Cardioselective BB)

Recommended drug: propanolol

Is third line drug for:

* HTN and CKD
* HTN and no CKD

Drug Evaluation Criteria

* Compelling indication (none)
* Relative Indication
  + MIgraine
  + Essential\_Tremor
* Absolute contraindication
  + ADR of anaphylaxis1 to Beta Blockers
  + ADR of anaphylaxis1 to Alpha Beta Blockers
  + Heart block and no pacemaker
  + Unspecified heart block and no pacemaker
  + Sinoatrial node dysfunction and no pacemaker
* Relative contraindication
  + Depression
  + Obstructive Pulmonary Disease
  + Bronchospastic disease
  + Amiodarone
* Do not add controllable condition
  + Absence of SBP in past month
* Do not intensify controllable condition
  + Absence of SBP in past month
* Bad drug partners
  + Beta blockers
  + Sotaol
  + Alpha beta blockers
  + NDHP CCB
  + Central adrenergic inhibitors
* Additional ADR check
  + Beta blockers
  + Sotalol
  + Alpha-beta blocker

### Alpha-Beta Blocker

Recommended drug: carvedilol

Is third line drug for:

* HTN and CKD
* HTN and no CKD

Drug Evaluation Criteria

* Compelling indication (none)
* Relative Indication (none)
* Absolute contraindication
  + ADR of anaphylaxis1 to Alpha-Beta Blocker
  + ADR of anaphylaxis1 to Beta Blockers
  + Heart block and no pacemaker
  + Unspecified heart block and no pacemaker
* Relative contraindication
  + Depression
  + Obstructive Pulmonary Disease
  + Bronchospastic disease
  + Myocardial Infarction
* Do not add controllable condition
  + Absence of SBP in past month
* Do not intensify controllable condition
  + Absence of SBP in past month
* Bad drug partners
  + Beta blockers
  + sotaol
  + Central adrenergic inhibitors
  + NDHP CCB
* Additional ADR check
  + Beta blockers
  + Sotalol

# Behavior of the CDS

## **Overview**

Therapeutic options are provided to patients who are eligible to receive recommendations, not at BP goals, have a GFR>=30 in the past year, and who are not out of scope. All these criteria have been described earlier in this document. As mentioned earlier, we *do* provide recommendations for patients who have active prescriptions of bad drug partners (and issue a message that there are active prescriptions of bad drug partners.)

Patients who receive recommendations are separated into “scenarios”, based upon their number of active prescriptions of HTN control medications *and* drugs that have anti-hypertensive effects (sotalol, aliskiren, loop diuretics). There are 4 such possible scenarios:

* Patient is not prescribed any HTN control medication
* Patient has active prescription of one HTN control medication
* Patient has active prescriptions of
  + two or three HTN control medications (any dose) or
* Patients has active prescriptions of four HTN control medications and at least one of which an encoded drug that is not at max dose or has an absolute contraindication.

We wish to emphasize that the CDS and GUI display what it considers to be all possible therapeutic options. For example, the phrase “add a drug” means that *all* drugs that do not have an absolute contraindication and *could* be added will be displayed. Similarly, the phrase, “increase drug dose” means that *all* drugs that *could* have their dosage increased will be displayed. This display of actions for multiple drugs does not mean we are recommending that all drugs be added, or that all drugs have their dosage increased (or both), which is clearly clinically incorrect. Instead, we are simply displaying all therapeutic options from which the provider can select.

Please note that we use the term therapeutic options and therapeutic recommendations synonymously here.

The CDS recommends drugs following a “recommendation cascade”. Roughly speaking, we evaluate and recommend sequentially, first line drugs (only), or second line drugs (only) or third line drugs (only), with the caveat that patients who are African American cannot have an active prescription of ACE or ARB alone. We describe this cascade in more detail below.

## No meds scenario

Recall that the first line and second line drugs differ as a function of Dx

* HTN no CKD
* HTN and CKD and not African American
* HTN and CKD and African American

And, for HTN no CKD,

* First line drug is Thiazide diuretics
* Second line drugs are ACE, ARB, long acting DHP CCB
* Third line encoded drugs are long acting NDHP CCB, Cardioselective Beta Blockers, non-cardioseletive beta blocker, alpha-beta blocker

HTN and CKD and not African American

* First line drugs are ACE and ARB
* Second line drugs are Thiazide diuretics
* Third line encoded drugs are long acting DHP CCB, long acting NDHP CCB, Cardioselective Beta Blockers, non-cardioseletive beta blocker, alpha-beta blocker

HTN and CKD and African American

* First line drugs are Thiazide diuretics and ACE/ARB (together)
* Second line drug is long acting DHP CCB
* Third line encoded drugs are long acting NDHP CCB, Cardioselective Beta Blockers, non-cardioseletive beta blocker, alpha-beta blocker

We start first by describing how we recommend adding HTN drugs (the “recommendation cascade”) to patients with Dx of HTN with CKD who are not African American (Figure 2) and use that as a template for the recommendation cascade for the other Dx. We refer to Figure 2 (and this recommendation cascade) as the “template” cascade. Patients with Dx of HTN with CKD who are African American, and patients with a Dx of HTN without CKD will be described separately (Figure 3 and 4 respectively).

For patients with Dx of HTN with CKD who are not African American, when he/she does not have an active prescription of any HTN meds, we evaluate and recommend first line drugs only (Figure 2 cascade step A). If first line drugs cannot be recommended, then we then evaluate and recommend second line drugs (cascade step B). If second line drugs cannot be recommended, we recommend third line encoded drugs (cascade step C). Finally, if third line encoded drugs cannot be recommended, we provide a link to alternative drugs.

For patients with Dx of HTN and CKD who are African American (Figure 3), Cascade step A differs from the template cascade. In this case, when a patient does not have an active prescription of any HTN medications, we evaluate first line drugs only, thiazide diuretics, ACE and ARB. If only ACE and/or ARBs are recommended, but not thiazides, then we continue to evaluate second line drugs. We continue evaluating second line drugs because VA Guidelines recommend that patients who are African American not have an active prescription of an ACE or ARB alone. On the other hand, if a thiazide is recommended, or thiazide and ACE/ARB, then we stop providing more recommendations. Then behavior of the recommendation cascade proceeds as described previously, flowing through Cascade step B, and C, as needed.

For patient with Dx of HTN and no CKD (Figure 4), we start with Cascade step A in Figure 2, our “template” recommendation cascade. Cascade B differs from the template *for patients who are African American. For patients who are African American,* if only ACE and/or ARBs are recommended, but not DHP CCB (nor Thiazides), then we continue to evaluate third line drugs. We continue evaluating third line drugs because VA Guidelines recommend that patients who are African American not have an active prescription of an ACE or ARB alone. On the other hand *for patients who are not African American,* if ACE and/or ARBs are recommended, then we stop providing more recommendations. That is, *for patients who are not African American*, the behavior is the same as in the template cascade. Then, both for patients who are African American or not African American, the recommendation cascade continues down the same path as the template cascade.

**Table 2. List of possible recommendations No med scenario**

|  |  |
| --- | --- |
| **Case** | **noMeds HTN no CKD recommendations** |
| i | rec 1st line drug (thiazide) |
| ii | Thiazide contraindicated, rec 2nd line drugs (ACE, ARB, DHP CCB) |
| iii | Thiazide, ACE. ARB, DHP CCB contraindicated, rec 3rd line encoded drugs (cardioselective BB, non-cardioselective BB, alpha-beta BB, NDHP CCB) |
| iv | Thiazide contraindicated, rec 2nd and third line drugs (if African American and only rec ACE/ARB) |
|  |  |
|  | **no Meds HTN and CKD and not African American recommendations** |
| v | rec 1st line drug (ACE, ARB) |
| vi | ACE and ARB contraindicated, rec 2nd line drug (thiazide) |
| vii | Thiazide, ACE. ARB contraindicated, rec 3rd line encoded drugs (cardioselective BB, non-cardioselective BB, alpha-beta BB, DHP CCB, DHP CCB, NDHP CCB) |
|  |  |
|  | **no meds HTN and CKD and African American recommendations** |
| viii | rec 1st line drugs (thiazide AND ACE/ARB) |
| ix | Thiazide, ACE, ARB contraindicated, rec 2nd line drug (DHP CCB) |
| x | Thiazide, ACE. ARB, DHP CCB contraindicated, rec 3rd line encoded drugs (cardioselective BB, non-cardioselective BB, alpha-beta BB |
| xi | Thiazide contraindicated, rec 1st and 2nd line drugs (ACE, ARB, DHP CCB |

Table 2 above summaries the figures and the descriptions.

For Table 2, we condensed the total number of recommendations for simplidity. We have

* Collapsed “recommend add” and “recommend blocked add” to simply “rec”

Examples of the cases listed above in Table 2 can be found in [Appendix F](#_Appendix_E:_).

Cascade step A

Evaluate 1st line drug

true

Stop, no more rec’s

false

Rec 1st line drug

Cascade step B

Evaluate 2nd line drugs

true

Stop, no more rec’s

false

Rec 2nd line drug

Cascade step C

Evaluate 3rd line encoded drugs

true

Stop, no more rec’s

false

Rec 3rd line encoded drug

Link to 3rd line non- encoded drug ; Stop

**Figure 2:** **“Template”** **Recommendation cascade of adding a new drug, for patients who Dx of HTN + CKD who are not African American.**

Evaluate thiazide, ACE, ARB

true

Stop, no more rec’s

false

Rec thiazide

Evaluate 2nd line drugs

true

Stop, no more rec’s

false

Rec 2nd line drug

Evaluate 3rd line encoded drugs

true

Stop, no more rec’s

false

Rec 3rd line encoded drug

Link to 3rd line non- encoded drug ; Stop

Figure 3: **Recommendation cascade of adding a new drug for patients who are African American and with Dx of HTN and CKD.** Steps in blue box are the same as that in Figure 2. Difference between Figure 2 and Figure 3 is due to the requirement that, while both thiazide and ACE/ARB are 1st line drugs for this Dx, patient cannot be on ACE or ARB alone—but can be on thiazide alone.

Evaluate 1st line drug

true

Stop, no more rec’s

false

Rec 1st line drug

Evaluate ACE, ARB, DP CCB

Stop, no more rec’s

false

(Non- African American and Rec any 2nd line drug) OR (African American and rec DHP CCB)

true

Evaluate 3rd line encoded drugs

true

Stop, no more rec’s

false

Rec 3rd line encoded drug

Link to 3rd line non- encoded drug ; Stop

Figure 4: **Recommendation cascade of adding a new drug for patients who have Dx of HTN and no CKD.** Steps in blue box are the same as that in Figure 2.

## One med scenario

While we refer to this scenario as the “one med” scenario, in reality, this scenario evaluates patients who

* Have an active prescription of 1 HTN medication OR
* Have active prescriptions of 2 HTN medications in the same drug class

For the latter, we issue a message to “stop one”, giving recommendations for all drugs.

For patients in this scenario, the behavior of the CDS differs, depending upon whether or not there is an active prescription of a first or second line vs third line encoded drug.

We start first with description of the algorithm, then a simplified list of the possible recommendations.

**Algorithm description**

We start this section assuming that the patient’s HTN medications do not have any absolute contraindications. Recommendation cascade is depicted in Figure 5.

No absolute contraindications, active prescription of first or second line drug

When a patient has an active prescription of only first or second line HTN medications, we follow the template recommendation cascade, as described above. In addition, we also recommend

* increasing the dose of all active prescription of the first or second line drugs (if not at max dose) and
* If HCTZ is at max dose, or if a thiazide diuretic other than indapamide or chlorthalidone (referred to as “alternative thiazide”) is prescribed, we substitute with preferred thiazides, chlorthalidone and indapamide (not depicted in Figure)

No absolute contraindications, active prescription of third line encoded drug

When a patient has an active prescription one HTN medication that is a third line encoded drug, we *start* down the path of template recommendation cascade and evaluate adding first and second line drugs. Then, if a first line or second line drug cannot be recommended, the cascade diverges from the template cascade, and we then consider increasing the dose of the third line encoded drug. We then return back to the recommendation cascade graph, and evaluate and recommend a third line encoded drug (Cascade step C). If the dose of the third line drug cannot be increased because it is at its maximum dose, then we also return back to the template recommendation cascade graph, and evaluate and recommend a third line encoded drug (Cascade step C), and continue down the graph.

To be clear: we do not recommend increasing the dose of a third line drug if we can recommend adding a first or second line drug. Only if we cannot recommend adding a first or second line drug, do we consider increasing the dose of a third line encoded drug.

Evaluate 1st line drugs AND incr dose 1st, 2nd line drug

Evaluate 2nd line drugs

Rec 1st line drug

Stop, no more rec’s

true

false

Stop, no more rec’s

true

Rec 2nd line drug

Evaluate 3rd line encoded drugs

Link to 3rd line non- encoded drug ; Stop

true

false

Stop, no more rec’s

false

Evaluate increase dose 3rd line encoded drugs

Rec 3rd line encoded drug

true

Increase dose 3rd line encoded drug

False (max dose)

Figure 5**: One med scenario, no absolute contra:** **Add drug and** **Increase dose.** Increase dose 1st or 2nd line drug, if not at max dose. Also add drug following Recommendation cascade. 3rd line encoded drugs not at max dose are only recommended to have their dose increased if a 1st line and a 2nd line drug can*not* be recommended; i.e. if a 1st or 2nd line drug can be recommended, then the dose of the 3rd line drug will *not* be increased. After a recommendation of increase dose of 3rd line encoded drug, or if the 3rd line encoded drug is at max dose, continue to evaluate drugs to add. Steps in blue boxes are similar to “Recommendation Cascade” Figure 2, with addition of “increase dose 1st, 2nd line drug” at start.

Presence of Rx with absolute contraindication: substitution (Figure 6)

When the prescribed HTN drug has an absolute contraindication, we recommend substituting that drug with another HTN drug (Figure 6). The evaluation and recommendation of drugs has the same nodes as the template cascade in Figure 6. The difference between Figure 2 (Adding new drug) and Figure 6 (Substitution) is

* We are not only adding a drug, but also simultaneously deleting contraindicated drug
* For patients who are African American, we also check that, because of the substitution(s), we would not be recommending only ACE or ARB, resulting in the patient having an Rx only of ACE or ARB.

Evaluate 1st line drugs

Evaluate 2nd line drugs

Non African American SUBSTITUTE any 1st line drug OR African American and NOT on only ACE/ARB

Stop, no more rec’s

true

false

Non African American SUBSTITUTE any 2nd line drug OR African American and NOT on only ACE/ARB

true

Stop, no more rec’s

false

false

Evaluate 3rd line encoded drugs

Link to 3rd line non- encoded drug ; Stop

true

false

Stop, no more rec’s

Non African American SUBSTITUTE any 3rd line encoded drug OR African American and NOT on only ACE/ARB

Figure 6: **Substitution for absolute contraindication.** Graph has same nodes as Figure 2, “Template recommendation cascade”, except that ‘non-African American SUBSTITUTE OR African American and not on only ACE/ARB’ replaces “rec add”.

Table 3 below contains the list of possible recommendations, when a patient has an active prescription of one HTN drug. As mentioned above, the recommendations depend upon whether the HTN drug is a 1st or 2nd line drug vs a 3rd line drug.

**Table 3 List of possible recommendations for One med scenario**

|  |  |
| --- | --- |
| **Case** | **Recommendations** |
|  | **Active prescription one encoded 1st or 2nd line med, drug not contraindicated** |
| A | increase dose 1st or 2nd line, add 1st line drug |
| B | increase dose 1st or 2nd line, add 2nd line drug |
| C | increase dose 1st or 2nd line, add 3rd line drug |
| D | increase dose 1st or 2nd line, link to other 3rd line drugs |
| E | 1st or 2nd line not HCTZ at max dose, only add 1st line drug |
| F | 1st or 2nd line not HCTZ at max dose, only add 2nd line drug |
| G | 1st or 2nd line not HCTZ at max dose, only add 3rd line drug |
| H | 1st or 2nd line not HCTZ at max dose, only link to other 3rd line drugs |
| I | HCTZ at max dose or alternative thiazide, add 1st line drug, sub with preferred thiazide |
| J | HCTZ at max dose or alternative thiazide, add 2nd line drug, sub with preferred thiazide |
| K | HCTZ at max dose or alternative thiazide, add 3rd line drug, sub with preferred thiazide |
| L | HCTZ at max dose or alternative thiazide, link to 3rd line drug, sub with preferred thiazide |
|  |  |
|  | **Active prescription one encoded med, 3rd line encoded drug not contraindicated** |
| a | 3rd line any dose no rec, add 1st line drug |
| b | 3rd line any dose no rec, add 2nd line drug |
| c | increase dose 3rd line drug, add 3rd line drug |
| d | increase dose 3rd line drug, link to other 3rd line drugs |
| e | 3rd line at max dose, only add 3rd line drug |
| f | 3rd line at max dose, only link to other 3rd line drugs |
|  |  |
|  | **Active prescription one encoded med** **contraindicated** |
| s1 | sub with 1st line drug |
| s2 | sub with 2nd line drug |
| s3 | sub with 3rd line drug |
| s4 | sub via link to other 3rd line drugs |

For Table 3, we simplified the total number of recommendations in a similar manner that we simplified recommendations of the No Med scenario in Table 2. We have

* Merged recommendations where there is an active prescription of first line drug with active prescription of second line drug
* Collapsed “recommend add” and “recommend blocked add” to simply “add”
* Similarly have collapsed “recommend increase” and “recommend blocked increase” to simply “increase”.
* Merged the different drug recommendations for the different diagnoses (HTN without CKD, HTN with CKD and not African American, HTN and CKD and African American)

We did this because enumerating all possible recommendations (and ruling out those that are not possible) is prohibitive. There are, in principle, 24 *potential* recommendations to be considered (2x2x2x3) for Cases A through D, inclusive

* Increase dose and blocked increase dose (factor of 2)
* Recommend add drug and blocked recommend add drug (factor of 2)
* 1st line drug and 2nd line drug (factor of 2)
* Three different diagnoses (HTN no CKD; HTN and CKD and African American; HTN and CKD and notAfrican American)

There are, in principle, 12 possible recommendations to be considered (2x2x3) for Cases E through H, inclusive (no increase dose or blocked increase dose). There are 24 possible recommendations (2x2x2x3) for Cases I through L, inclusive, to be considered (no increase or blocked increase dose but a second add and blocked add for the substitution).

As an example, we expand Case A, “increase dose 1st or 2nd line, add 1st line drug”, to:

For patients with HTN and CKD and African American

* If patient has active prescription of 1st line drug not at max dose,
  + Recommend increase dose of 1st line drug and recommend adding another 1st drug (Case A1)
  + Recommend increase dose of 1st line drug and blocked add another 1st line drug (Case A2)
  + Recommend blocked increase dose of 1st line drug and recommend another add 1st line drug (Case A3)
  + Recommend blocked increase dose of 1st line drug and blocked add another 1st line drug (Case A4)
* If patient has active prescription of 2nd line drug not at max dose,
  + Recommend increase dose of 2nd line drug and recommend adding 1st drug (Case A5)
  + Recommend increase dose of 2nd line drug and blocked add 1st line drug (Case A6)
  + Recommend blocked increase dose of 2nd line drug and recommend add 1st line drug (Case A7)
  + Recommend blocked increase dose of 2nd line drug and blocked add 1st line drug (Case A8)

Recommendations for the other diagnoses (HTN and no CKD, HTN and CKD and not African American) are not possible because there is, effectively, only one first line drug that the patient may be taking (patient cannot have active prescriptions of both ACE and ARB for HTN). This leaves only 8 actual recommendations—after examination of all cases.

We also did not incorporate into the table, the checks for whether or not the patient was African American and we were only recommending an ACE or and ARB (and therefore need to recommend another drug). We did, however, incorporate this into the figures of the algorithm.

Examples of the cases listed above in Table 3 can be found in [Appendix G](#_Appendix_G:_).

## Two med scenario

The scenario is more exactly evaluates patients who

* Have active prescriptions of 2 HTN medications that are not in the same drug class

For patients who have active prescriptions two HTN medications, the behavior of the CDS is similar to that described by the One med scenario. When there are no contraindications, the algorithm for adding a drug is the same as depicted as for the One med scenario, depicted in Figure 5.That is, when there are no absolute contraindications,

* We always increase the dose of a 1st or 2nd line drug, if not at max dose, and we have dosage information
* Follow the recommendation cascade of adding a new drug
* Increase the dose of a 3rd line drug only if a 1st or 2nd line drug cannot be added

On the other hand, when there is an absolute contraindication, we follow the algorithm depicted in Figure 6. If there is only one drug that has an absolute contraindication, there is no need to check, when the patient is African American, that we are only recommending an ACE and ARB (and therefore need to recommend another drug). However, if we need to substitute both drugs, then we would need to check if we are recommending only ACE and ARB. For this “double” substitution situation, only one drug can be recommended as a substitution for both drugs.

The possible recommendations are a cross product of the One med scenario outcomes, with that caveat that not all pairs are possible. For example, we would not recommend the pair AB

* Increase dose of 1st or 2nd line drug and
* Add 1st line drug and
* Add 2nd line drug

because our recommendation cascade stops after adding a 1st line drug.

The possible pairs are depicted in Table 4.

Like the One med scenario, Table 3, because we used labels of Cases from the One med scenario, in Table 4 below, we collapsed “recommend add” and “recommend blocked add” to simply “add”, and similarly collapsed “recommend increase” and “recommend blocked increase” to simply “incr”. In addition, if there was a substitution for one drug and an increase dose and add drug for a second drug, this was collapsed into simply substitution and increase dose, because an addition of a drug includes an addition of a drug.

If a patient has active prescriptions of bad drug partners, i.e., two drugs that are normally prescribed together, we issue a message to “stop one”, then give recommendations.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | A | B | C | D | E | F | G | H | I | J | K | L | a | b | c | d | e | f | s1 | s2 | s3 | s4 |
| A | AA |  |  |  | AE |  |  |  | AI |  |  |  | Aa |  |  |  |  |  | As1 |  |  |  |
| B |  | BB |  |  |  | BF |  |  |  | BJ |  |  |  | Bb |  |  |  |  |  | Bs2 |  |  |
| C |  |  | CC |  |  |  | CG |  |  |  | CK |  |  |  | Cc |  | Ce |  |  |  | Cs3 |  |
| D |  |  |  | DD |  |  |  | DH |  |  |  | DL |  |  |  | Dd |  | Df |  |  |  | Ds4 |
| E |  |  |  |  | EE |  |  |  | EI |  |  |  | Ea |  |  |  |  |  | Es1 |  |  |  |
| F |  |  |  |  |  | FF |  |  |  | FJ |  |  |  | Fb |  |  |  |  |  | Fs2 |  |  |
| G |  |  |  |  |  |  | GG |  |  |  | GK |  |  |  | Gc |  | Ge |  |  |  | Gs3 |  |
| H |  |  |  |  |  |  |  | HH |  |  |  | HL |  |  |  | Hd |  | Hf |  |  |  | Hs4 |
| I |  |  |  |  |  |  |  |  |  |  |  |  | Ia |  |  |  |  |  | Is1 |  |  |  |
| J |  |  |  |  |  |  |  |  |  |  |  |  |  | Jb |  |  |  |  |  | Js2 |  |  |
| K |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Kc |  |  |  |  |  | Ks3 |  |
| L |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Ld |  | Lf |  |  |  | Ls4 |
| a |  |  |  |  |  |  |  |  |  |  |  |  | aa |  |  |  |  |  | as1 |  |  |  |
| b |  |  |  |  |  |  |  |  |  |  |  |  |  | bb |  |  |  |  |  | bs2 |  |  |
| c |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | cs3 |  |
| d |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | dd |  |  |  |  |  | ds4 |
| e |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| f |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | ff |  |  |  | fs4 |
| s1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | s1s1 |  |  |  |
| s2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | s2s2 |  |  |
| s3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | s3s3 |  |
| s4 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | s4s4 |

**Table 4. Two med scenario recommendations.** Blue Highlighted letters (Cases) indicate recommendations for 1st or 2nd line drugs.

## Three med scenario

Cases of the three med scenario are cross products of the one med scenario cases with the two med scenario cases. As with the two med scenario, not all cross products are possible. Enumerating these cases is out of scope for this document.

## Four med scenario

Recommendations are provided *only* if there is at least one encoded HTN control medication (that has dosage information) that is not at its maximum dose or one or more of the encoded drugs has an absolute contraindications. If all encoded medications are at their maximum dosage, and do not have an absolute contraindication, the patient is out of scope.

If the encoded medications do not have absolute contraindications, then the we recommend

* increasing the dose of those encoded meds that are not at max dose and
* if HCTZ is at max dose or there is an Rx of a thiazide diuretic that is not chlorthalidone or indapamide, then we recommend substituting that thiazide with chlorthalidone and indapamide

If one of the encoded medications has an absolute contraindication, then

* we substituting that drug with all 1st 2nd and 3rd line encoded drugs that do not have an absolute contraindication or bad drug partners AND
* we recommend increasing the dose of all encoded drugs not at max dose and not contraindicated and
* if HCTZ is at max dose or there is an Rx of a thiazide diuretic that is not chlorthalidone or indapamide, then we recommend substituting that thiazide with chlorthalidone and indapamide

Note that the substitution behavior differs from the One med, Two med and Three med scenario; it does not follow the “recommendation cascade” described for these other scenarios.

## Special note: Presence of Bad drug partners

If a patient has active prescriptions of two medications that are not normally taken together (bad drug partners) recommendations are still provided. This applies to bad drug partners that are in the same drug class or in different drug classes. Messages are triggered, indicating that there are bad drug partners, whether or not the drugs are contraindicated.

# Messages and text displayed in GUI

## Overview

We describe here all messages encoded in the KB. Some of these messages have been described earlier, but are repeated here for completeness. Messages are organized and ordered in the same way as the previous sections.

Messages described below are one of 18 different Message Types:

* Out of scope
* No drug recommendation
* No drug recommendation missing data
* Follow up
* Primary recommendation (aka Primary message)
* Recommendation (*not* Primary message)
* Drug-related
* General info
* bad drug partner
* Messages associated with a particular drug recommendations, referred to as “collateral messages” (“Collateral messages” appear next to the drug recommendation) that are of type
  + do not add controllable condition
  + do not intensify controllable condition
  + Is first line drug
  + Is second line drug
  + Is third line drug
  + Compelling indication
  + Relative indication
  + Relative contraindication
  + General Info

There is also

* Order (lab)

Which is not, per se, a message, but is treated as if it were a message.

The use of different message types is, in part, to determine where the messages are displayed on the GUI (when they are not Collateral messages), as well as determine the order of the messages.

Note that there are Collateral messages associated with a particular drug recommendations that have message type=General info, as well as messages that are not associated with a particular drug recommendations that can be of type=General info. While Collateral messages and the messages described below are of the same Message type, they are displayed in different areas on the GUI.

To help distinguish the messages themselves from the rest of the text, they are in *italics*. In the GUI, they are not italicized.

## Eligibility, Restrictions and Out of Scope messages

## Eligibility and Restriction messages

The following primary recommendation will be issued to women of child bearing ages (18-50):

*Warning: recommendations do not apply to pregnant women.*

If the patient has an active prescription for non-encoded drug that we do not evaluate:

*Pt has Rx for HTN med ?nonEncodedDrug that we have not evaluated.*

Where ?nonEncodedDrug is a 3rd line non-encoded HTN medication OR sotalol OR aliskiren OR a loop diuretic.

And, if the patient has an active prescription of sotalol or aliskiren or a loop diuretic, there will be an additional message:

*?otherDrug is not a drug primarily used for the treatment of HTN.*

Where ?otherDrug is either sotalol or aliskiren or a loop diuretic.

## Messages when there are no drug recommendations

At goal

If a patient is at goal, he/she will receive a “No drug recommendation” message only.

*Patient is at dahsboard goal. Good job! No drug recommendations.*

GFR

If a patient’s GFR is older than 1 year, he/she will receive a “No drug recommendation Missing Labs” message,

*No drug recommendations. No GFR in past year.*

And there is an order for GFR.

BP older than 1 year

If a patient’s BP is older than 1 year, he/she will receive a “no drug recommendations Missing labs” message:

*No drug recommendations. No BP in past year.*

And there is an order for new BP.

Out of scope messages (no drug recommendations)

Low GFR

If a patient’s GFR<30 in the past year, he/ she will receive “Out of scope” message only,

*Out of Scope. GFR<30 past year.*

Out of scope BP

If SBP>=220 or DBP>=110, he/she will receive the following “Out of scope” message

*Out of scope. SBP>=220 or DBP>=110, If MARKED BP ELEVATION is confirmed, then the patient* *needs further TREATMENT and EARLY FOLLOW-UP to MONITOR THERAPEUTIC EFFICACY*.

And there will be a referral to a hypertension specialist.

If the patient has a diagnosis of IHD and most recent DBP<60 and SBP<140 (no time frame), he/she will receive the following “Out of scope” message

*Out of scope: Pt has IHD and most recent DBP < 60. Evaluate benefit/risk of continuing present doses.*

And there will be a referral to a hypertension specialist.

If the patient has a diagnosis of IHD and most recent DBP<60 and SBP>140 (no time frame), he/she will receive the following “Out of scope” message

*Out of scope: Pt has IHD and the most recent DBP<60 and SBP>140. Pt at high risk for cardiovascular events.*

And there will be a referral to a hypertension specialist.

If the patient has Dx of IHD patient’s and most recent DBP<60 and SBP>140 BUT most recent BP is older than one month, he/she will also receive the following “No Drug recommendation” message

*Pt most recent BP is older than 1 month, but indicates possible need for immediate attention. Please enter current BP or obtain new BP*

And a new BP is ordered

Out of scope Rx

If a patient has an active prescription (Rx) of an out of scope drug (listed above), he/she will receive an “out of scope” message only:

*Out of scope. Rx for ?OutOfScopeRx.*

Where ?OutofScopeRx is one of the (cyclosporine, tacrolimus, metalozone, bepridil, amiloride)

If a patient has an active prescription (Rx) of an out of scope drug pair (listed above), he/she will receive an “out of scope” message only:

*Out of scope: Pt has Rx for ?loopDiuretic and ?thiazideDiuretic.*

Or

*Our of Scope: Pt has Rx for ?loopDiuretic and ?KsparingDiuretic.*

Where ?loopDiuretic is a Loop Diuretic nad ?thiazideDiuretic is a thiazide Diuretic and ?KsparingDiuretic is a Potassium sparing diuretic.

Out of scope Dx

If a patient has an out of scope diagnosis (described above), he/she will receive one of two possible “Out of scope” messages.

*Out of scope. Dx of ?OutOfScopeDx that needs special attention.*

Where ?OutOfScopeDx is one of the diagnoses listed previously, excluding Secondary Hypertension.

OR, if the patient has Secondary Hypertension (or a diagnosis that is mapped to Secondary Hypertension), the Out of scope message is:

*Out of scope. Pt has a condition that causes Secondary Hypertension that needs special attention.*

If a patient has an out of scope diagnosis of Heart Failure, he/she will receive the “Out of scope message:

*Out of scope: Dx of CHF. Will address HTN and CHF in HF module*.

In scope Dx

There may be Dx that can cause Secondary Hypertension, but, only if untreated, or inadequately treated. We ***give*** HTN drug recommendations for patients with these Dx, assuming that patients are being treated. In this case, we issue the message,

*Pt has a Dx of ?InScopeDx which may cause secondary hypertension; please insure treatment of ?InScopeDx*

Where ?InscopeDx is the diagnosis where we have assumed that the patient has received adequate treatment. List of diagnoses provided previously.

Out of scope, number of HTN and related medications

Active prescriptions of 4 drugs that are encoded drugs OR non-encoded drugs used in the treatment of HTN OR drugs with anti-hypertensive affects (i.e. sotalol, aliskiren and any loop diuretic). In addition, the encoded drugs at their maximum dose and not contraindicated. If encoded drugs are not at their maximum dose or are contraindicated, patient is *not* out of scope.

*Out of scope. Rx for 4 anti hypertensive meds-related ?HTNmeds ; and encoded meds at max dose*.

Where ?HTNmeds are the HTN medications.

Active prescriptions of 5 or more (encoded and non-encoded) drugs used in the treatment of HTN; encoded drugs at any dose.

*Out of Scope. Rx for 5 or more anti-hypertensive-related meds ?HTNmeds.*

Where ?HTNmeds are the HTN medications.

## Messages related to differences between Performance Measure goals and VA HTN GL goals

(duplicated here for completeness)

Because we are using Performance Measure goals, which differs with the VA HTN GL goals, for the first two cases, where Performance Measure goals are stricter than VAT HTN GL goals, we will issue the following Primary messages:

If a patient does NOT have DM and has 140<=SBP<150

*“Pt does not have DM and has 140<=SBP<150. This above Performance Measure target, but is within VA GL target.”*

If a patient has DM and has 85<DBP<90,

*“Pt has DM and 85<DBP<=90. This below Performance Measure target, but is above VA GL target.”*

## Messages associated with drug recommendations

There are often messages associated with drug recommendations. These messages are referred to as “Collateral messages”. These Collateral messages are also described in the Drug Therapies section. These messages have one of 10 message types:

* + do not add controllable condition
  + do not intensify controllable condition
  + bad drug partner
  + Is first line drug\*
  + Is second line drug\*
  + Is third line drug\*
  + Compelling indication\*
  + Relative indication\*
  + Relative contraindication
  + General Info
  + Order (labs) (not a Message per se)

\*Messages of these types are not included in the KB itself, but, instead are ‘constructed’ after processing by EON. See [Appendix H](#_Appendix_H:_Messages) for more information about such messages. Only messages that are encoded in the KB are included in this section.

All message types, except the last (General info) are associated with the Indications and contraindications described previously. For example, if there is a “do not add controllable” condition resulting in a blocked add recommendations, there is an associated “do not add controllable condition” message.

A “General info” message contains, as the type implies, general information about the drug, including educational information.

Orders are for missing laboratory values. For specific drug recommendations, Orders are associated with “do not add controllable” messages and “do not increase controllable” messages.

When a patient has an active prescription of a DM medication and is not contraindicated, the drug will not be recommended (e.g. it may be at its maximum possible dose), but there can still be messages associated with that DM drug. Such messages are *not* Collateral messages. These non-Collateral messages have one of the following message types:

* “Primary Recommendation”
* “Drug-Related”
* “General info”

These messages are also described here

As before, to help distinguish the messages themselves, they are in *italics*.

## Encoded Drug Messages (includes Orders)

First and Second Line Drugs

### Thiazide diuretics

Thiazide diuretics are

* First line drug for HTN and no CKD
* First line drug for HTN and CKD and African American
* Second line drug for HTN and not African American

Recommended drugs: chlorthalidone (preferred), indapamide (preferred), hydrochlorothiazide

Drug Evaluation criteria

* Compelling indication (none)
* Relative indication
  + Osteoporosis
* Absolute contraindication
  + Na<130 past month
  + K<3 past month and Rx thiazide
  + K<3.5 past month and no Rx thiazide
  + Gout, complicated
  + Lithium
  + ADR of anaphylaxis to thiazide
* Relative contraindication
  + Gout, not complicated

*Relative contraindication.* *Pt has uncomplicated gout.*

* + Allergy to sulfonamide

*Relative contraindication.* *Pt has Pt has Dx Allelrgy to sulfonamide,*

* + Hypoatremia

*Relative contraindication. Pt has Dx of hyperuricemia.*

* + 130<Na<135 past month

When adding thiazide or increasing dose thiazide, if 130<Na<135 past month, there will be a relative contraindication message:

*Relative contraindication. Pt has Na ?value (?date). Hyponatremia may worsen.*

* + Na<=130 any time in the past

When adding thiazide or increasing dose of thiazide, if Na<130 any time in the past, there will be a relative contraindication message:

*Relative contraindication. Pt has Na ?value (?date). Hyponatremia may worsen.*

* + Presence of thiazide and 3<K<3.5 past month

When there is an Rx for thiazide, if 3<K<3.5 past month, there will be a relative contraindication message:

*Relative contraindication. Pt has K ?value (?date). Hypokalemia may worsen.*

* + K<3.5 any time in the past

When adding thiazide or increasing dose of thiazide, if K<3.5 any time in the past older than 1 month, there will be a relative contraindication l message:

*Relative contraindication. Pt has K ?value (?date). Hypokalemia may worsen.”*

* + Uric Acid > 6.8 past year

When adding thiazide or increasing dose of thiazide, if uric acid>6.8 past year, there will be a relative contraindication message

*Relative contraindication. Pt has Uric Acid ?value (?date).*

* + Hyperuricemia

*Relative contraindication. Pt has Dx of hyperuricemia.*

* Do not start controllable conditions
  + Absence of SBP in past month

If SBP is completely missing, patient is ineligible.

If SBP is missing in the past month, and if there are multiple drugs that have a “blocked add” recommendations, rather than displaying multiple messages, there will be, instead, one message. This message also in Section, Messages associated with multiple drugs.

*Would add ?blockedDrug but missing SBP ?value (?date).*

Where ?blockedDrug contains the list of drug classes with the blocked add recomendation, and ?value and ?date are the most recent SBP value and date, respectively.

* + Absence of K in past month

If there is no K, the following collateral “do not start” message will be displayed:

*Would add thiazide diuretics, but missing K.*

If there is no K in the past month, the following collateral “do not start” message will be displayed

*Would add thiazide diuretics, but old K ?value (?date).*

* + Absence of Na in past month

If there is no Na, the following collateral do not start message will be displayed:

*Would add thiazide diuretics, but missing Na.*

If there is no Na in the past month, the following collateral “do not start” message will be displayed:

*Would add thiazide diuretics, but old Na ?value (?date).*

* + Absence of uric acid in past year

If there is no uric acid, the following collateral “do not start” message will be displayed:

*Would add thiazide diuretics, but missing uric acid.*

If there is no uric acid in the past year, the following collateral “do not start” message will be displayed.

*Would add thiazide diuretics, but old uric acid ?value (?date).*

* Do not intensify controllable conditions
  + Absence of SBP in past month

If SBP is completely absent, patient is ineligible.

If SBP is missing in the past month, and if there are multiple drugs that have a “blocked increase” recommendations, rather than displaying multiple messages, there will be, instead, one message:

*Would increase ?blockedDrug but missing SBP ?value (?date).*

Where ?blockedDrug contains the list of drug classes with the blocked increase recommendation, and ?value and ?date are the most recent SBP value and date, respectively.

* + Absence of K in past month

If there is no K, the following collateral “do not intensify” message will be displayed:

*Would increase ?thiazide\_drug, but missing K.*

Where ?thiazide\_drug is the thiazide medication*.*

If there is no K in the past month, the following collateral “do not intensify” message will be displayed

*Would increase ?thiazide\_drug, but old K ?value (?date).*

Where ?thiazide\_drug is the thiazide medication.

In both cases there is an Order for K.

* + Absence of Na in past month

If there is no Na, the following collateral message will be displayed:

*Would increase ?thiazide\_drug, but missing Na.*

If there is no Na in the past month, the following collateral “do not intensify” message will be displayed:

*Would increase ?thiazide\_drug, but old Na ?value (?date).*

In both cases there is an Order for Na.

* + Absence of uric acid in past year

If there is no uric acid, the following collateral “do not intensify” message will be displayed:

*Would increase ?thiazide\_drug, but missing uric acid.*

If there is no uric acid in the past year, the following collateral “do not intensify” message will be displayed.

*Would increase ?thiazide\_drug, but old uric acid ?value (?date).*

In both cases there is an Order for uric acid.

* Bad drug partner
  + Loop Diuretics (e.g. furosemide)

Bad drug partner messages are given in a later section, “Messages Associated with multiple drugs.”

* Other messages, of type= General Info, issued when recommending adding or increasing Thiazide diuretics
  + If Benign Prostrate Hyperplasic and alpha blocker are present:

*“Thiazide diuretics may worsen urinary symptoms of BPH; Monitor for hyponatremia, hypokalemia, and uric acid levels.*

### Angiotensin Converting Enzyme Inhibitiors (ACE Inhibitor)

ACE Inhibitors are

* Second line drug for HTN and no CKD
* First line drug for HTN and CKD and African American
* First line drug for HTN and not African American

Recommended drug: lisinopril, benazepril, captopril, enalapril, fosinopril, ramipril (all formulary)

Drug Evaluation Criteria

* Compelling indication
  + Heart Failure
  + CVD
  + DM and CKD
* Relative indication
  + DM without CKD
* Absolute contraindication
  + ADR of anaphylaxis1 to ACE
  + ADR of angioedema to2 ACE
  + ADR or angioedema2 to ARB
  + K>5.5 past month
* Relative contraindication
  + K sparing diuretics

When adding ACE Inhibitor or or increasing dose of ACE inhibitor, if pt has Rx for K sparing diuretics, there will be a relative contraindication message

*Relative contraindication: Pt has Rx for ?K\_sparing\_diuretic.*

* + 5<K<=5.5 past month

When adding ACE Inhibitor or when there is an Rx for ACE inhibitor, if 5<K<=5.5 past month, there will be a relative contraindication message:

*Caution: Pt has K ?value (?date). Hyperkalemia may worsen.*

* Do not start controllable conditions
  + Absence of SBP in past month

See Messages associated with multiple drugs.

* + Absence of K in past month

If there is no K, the following collateral “do not start” message will be displayed:

*Would add ACE inhibitor, but missing K.*

If there is no K in the past month, but there is a value of K<=5.5, the following collateral “do not start” message will be displayed

*Would add ACE Inhibitor, but old K ?value (?date).*

If there is no K in the past month, but there is a value of K>5.5, the following collateral “do not start” message will be displayed

*Would consider adding ACE Inhibitor, but old and high value of K ?value (?date).*

In all cases there is an Order for K.

* + Absence of GFR in past month

If there is no GFR, the following collateral “do not start” message will be displayed:

*Would add ACE inhibitor, but missing GFR*.

If there is no GFR in the past month, the following collateral “do not start” message will be displayed:

*Would add ACE inhibitor, but old GFR ?value (?date).*

In both cases there is an Order for GFR.

* Do not intensify controllable conditions
  + Absence of SBP in past month

See Messages associated with multiple drugs.

* + Absence of K in past month

If there is no K, the following collateral “do not intensify” message will be displayed:

*Would increase ?ACEInhibitor, but missing K.*

Where ?ACEInhibitor is the name of the ACE Inhibitor.

If there is no K in the past month, but there is a value of K<=5.5, the following collateral “do not intensify” message will be displayed

*Would increase ?ACEInhibitor, but old K ?value (?date).*

If there is no K in the past month, but there is a value of K>5.5, the following collateral “do not intensify” message will be displayed

*Would consider increasing ?ACEInhibitor, but old and high value of K ?value (?date).*

In all cases there is an Order for K.

* + Absence of GFR in past month

If there is no GFR, the following collateral “do not intensify” message will be displayed:

*Would increase ?ACEInhibitor, but missing GFR.*

If there is no GFR in the past month, the following collateral “do not intensify” message will be displayed:

*Would increase ?ACEInhibitor, but old GFR ?value (?date).*

In both cases there is an Order for GFR.

* Bad drug partner
  + ARB
  + Aliskiren

Bad drug partner messages are given in a later section, “Messages Associated with multiple drugs.”

* Other collateral messages, of type=General Info issued when adding ACE inhibitors and/or ARBs or increasing dose of ACE Inhibitors or ARBs
  + *Beware of 20% increase in creatinine (or 15% decrease in GFR) after initiation or change in dose of ACE/ARB.*
* If age>70 and Presence of CKD

*Per JNC8 there is lack of evidence to support use of ACE Inhibitor for patients with CKD and age>70 years. Evaluate clinical benefit.*

* Presence of DM:

*ACE Inhibitors or ARBs in pt with DM and proteinuria significantly reduces risk of MI, stroke, overt nephropathy and cardiovascular death.*

* Other messages, of type=Drug Related, issued when recommending ACE inhibitors and ARB, that are not collateral messages:
  + If patient is African American:

*For African Americans with hypertension, the VA GL recommends against using ACE or ARB as monotherapy.*

* + When recommending an ACE and an ARB:

*VA Guidelines recommends against the use of both an ACE and ARB together.*

### Angiotensin Receptor Blocker (ARB)

ARBs are

* Second line drug for HTN and no CKD
* First line drug for HTN and CKD and African American
* First line drug for HTN and not African American

Recommended drug: losartan

Drug Evaluation Criteria

* Compelling indication
  + Heart Failure
  + CVD
  + DM and CKD
  + HTN without CKD and ADR to ACE not angioedema
  + HTN and CKD not African American and ADR to ACE not angioedema
* Relative indication
  + DM without CKD
* Absolute contraindication
  + ADR of anaphylaxis1 to ARB
  + ADR of angioedema2 to ARB
  + ADR angioedema2 to ACE
  + K>5.5 past month
* Relative contraindication
  + K sparing diuretics

When adding ARB or increasing dose of ARB, if pt has Rx for K sparing diuretics, there will be a relative contraindication message

*Relative contraindication: Pt has Rx for ?K\_sparing\_diuretic.*

* + 5<K<=5.5 past month

When adding ARB or increasing dose of ARB, if 5<K<=5.5 past month, there will be a relative contraindication message:

*Relative contraindication: Pt has K ?value (?date). Hypokalemia may worsen.*

* Do not start controllable conditions
  + Absence of SBP in past month

See Messages associated with multiple drugs

* + Absence of K in past month

If there is no K, the following collateral “do not start” message will be displayed:

*Would add ARB, but missing K.*

If there is no K in the past month, but there is a value of K<=5.5, the following collateral “do not start” message will be displayed

*Would add ARB, but old K ?value (?date).*

If there is no K in the past month, but there is a value of K>5.5, the following collateral “do not start” message will be displayed

*Would consider adding ARB, but old and high value of K ?value (?date).*

In all cases there is an Order for K.

* + Absence of GFR in past month

If there is no GFR, the following collateral “do not start” message will be displayed:

*“Would add ARB, but missing GFR.”*

If there is no GFR in the past month, the following collateral “do not start” message will be displayed:

*“Would add ARB, but old GFR ?value (?date).”*

In all cases, there is an order for GFR.

* Do not intensify controllable conditions
  + Absence of SBP in past month

See Messages associated with multiple drugs

* + Absence of K in past month

If there is no K, the following collateral “do not intensify” message will be displayed:

“Would increase ?ARB, but missing K.”

Where ?ARB is the name of the ARB.

If there is no K in the past month, but there is a value of K<=5.5, the following collateral “do not intensify” message will be displayed

*Would increase? ARB, but old K ?value (?date).*

If there is no K in the past month, but there is a value of K>5.5, the following collateral “do not intensify” message will be displayed

*Would consider adding ?ARB, but old and high value of K ?value (?date).*

In all cases there is an Order for K.

* + Absence of GFR in past month

If there is no GFR, the following collateral “do not intensify” message will be displayed:

“*Would increase ARB, but missing GFR.”*

If there is no GFR in the past month, the following collateral “do not intensify” message will be displayed:

*“Would increase ARB, but old GFR ?value (?date).”*

In all cases there is an order for GFR.

* Bad drug partner
  + ACE
  + Aliskiren

Bad drug partner messages are given in a later section, “Messages Associated with multiple drugs.”

* Other collateral messages, of type=General Info issued when adding ACE inhibitors and/or ARBs or increasing dose of ACE Inhibitors or ARBs
  + *Beware of 20% increase in creatinine (or 15% decrease in GFR) after initiation or change in dose of ACE/ARB.*
* If age>70 and Presence of CKD

*Per JNC8 there is lack of evidence to support use of ACE Inhibitor for patients with CKD and age>70 years. Evaluate clinical benefit.*

* Presence of DM:

*ACE Inhibitors or ARBs in pt with DM and proteinuria significantly reduces risk of MI, stroke, overt nephropathy and cardiovascular death.*

* Other messages, of type=Drug Related, issued when recommending ACE inhibitors and ARB, that are not collateral messages:
  + If patient is African American:

*For African Americans with hypertension, the VA GL recommends against using ACE or ARB as monotherapy.*

* + When recommending an ACE and an ARB:

*VA Guidelines recommends against the use of both an ACE and ARB together.*

### Long Acting Dihydropyridine Calcium Channel Blocker (DHP CCB)

DHP CCBs are the second line drug for

* HTN and no CKD
* HTN and CKD and African American

And third line drug for

* HTN and CKD and not African American

Recommended drug: amlodipine

Drug Evaluation Criteria

* Compelling indication (none)
* Relative indication
  + Angina
  + Raynaud’s syndrome
  + Migraine
  + DM
* Absolute contraindication
  + ADR of anaphylaxis1 to DHP CCB or NDHP CCB
  + ADR of angioedema2 to DHP CCB or NDHP CCB
* Relative contraindication (none)
* Do not add controllable condition
  + Absence of SBP in past month

See Messages associated with multiple drugs

* Do not intensify controllable condition
  + Absence of SBP in past month

See Messages associated with multiple drugs

* Bad drug partners
  + NDHP CCB

Bad drug partner messages are given in a later section, “Messages Associated with multiple drugs.”

* Other collateral messages, of type= General Info, issued when recommending adding DHP CCB
  + *“ Use with caution in patients with hepatic or renal dysfunction*. “
* Other messages, of type= Drug\_Related, that are not collateral messages:
  + If patient has active prescription of short acting DHP CCBs:

*“Pt has Rx for ?ShortActingDHP\_CCB. VA recommends long acting DHP CCBs for treatment of HTN.”*

Where *?ShortActingDHP\_CCB* is the short acting DHP CCB*.*

Third line Drugs

### Long Acting Non Dihydropyridine Calcium Channel Blocker (NDPH CCB)

NDHP CCBs are the third line drug for

* HTN and no CKD
* HTN and CKD and African American
* HTN and CKD and not African American

Recommended drug: verapamil SA, diltiazem SA

Drug evaluation Criteria

* Compelling indication
  + ADR to DHP CCB not anaphylaxis nor angioedema
* Relative indication
  + Angina
  + Raynaud’s syndrome
  + Myocardial Infarction
  + Atrial Fibrillation
  + Atrial Tachycardia
* Absolute contraindication
  + ADR of anaphylaxis1 to DHP CCB or NDHP CCB
  + ADR of angioedema2 to DHP CCB or NDHP CCB
  + Heart block and no pacemaker
  + Unspecified heart block and no pacemaker
  + Sinoatrial node dysfunction and no pacemaker
* Relative contraindication
  + Heart Failure

*Relative contraindication: CHF*

* + Amiodarone

*Relative contraindication: Rx amiodarone*

* + Bradycardia

*Relative contraindication: Bradycardia*

* Do not add controllable condition
  + Absence of SBP in past month

See Messages associated with multiple drugs

* Do not intensify controllable condition
  + Absence of SBP in past month

See Messages associated with multiple drugs

* Bad drug partners
  + DHP CCB
  + Beta Blockers
  + Sotalol

Bad drug partner messages are given in a later section, “Messages Associated with multiple drugs.”

* Other messages, of type=General info, issued when recommending adding NDHP CCBs.
  + *“ Use with caution in patients with Rx for drugs that are CYP3A4/5 inhibitors or substrates. “*
* Other messages, of type=Drug\_Related, that are not collateral messages
  + If patient has active prescription of short acting NDHP CCBs:

*“Pt has Rx for ?ShortActingNDHP\_CCB. VA recommends long acting DHP CCBs for treatment of HTN.”*

Where *?ShortActingNDHP\_CCB* is the short acting NDHP CCB*.*

### Cardioselective BB, non-cardioselective BB and alpha beta blockers

We have combined messages for these drugs because the messages are all essentially the same.

Cardioselective, non-cardioselective BB and alpha-beta blockers are all third line drug for

* HTN and no CKD
* HTN and CKD and African American
* HTN and CKD and not African American

Drug evaluation criteria

* Compelling indication
  + Myocardial infarction
  + Heart Failure
* Relative Indication
  + Atrial Fibrillation
  + Atrial Tachycardia
  + Angina
  + Hyperthyroidism
  + Coronary Artery Disease
  + DM
* Absolute contraindication
  + ADR of anaphylaxis1 to BB
  + Heart block and no pacemaker
  + Unspecified heart block and no pacemaker
  + Sinoatrial node dysfunction and no pacemaker
* Relative contraindication
  + Depression

*Relative contraindication: Depression*

* + Obstructive Pulmonary Disease

*Relative contraindication: Obstructive Pulmonary Disease*

* + Bronchospastic disease

*Relative contraindication: Bronchospastic Disease*

* + Amiodarone

*Relative contraindication: Rx amiodarone*

* Do not add controllable condition
  + Absence of SBP in past month

See Messages associated with multiple drugs

* Do not intensify controllable condition
  + Absence of SBP in past month

See Messages associated with multiple drugs

* Bad drug partners
  + Non cardioseletive beta blockers
  + Alpha beta blockers
  + ISA beta blockers
  + Sotaol
  + Guanabenz
  + clonidine
  + guanfacine
  + NDHP CCB
* There are other messages, of type= General Info, issued when recommend adding or increasing dose of Cardioselective BB or non-Cardioselective BB or apha-beta blocker. However, because all BB are often recommended, rather than duplicate these messages for each type of BB, instead, these messages will be displayed only once. See Messages associated with multiple drugs.

### Messages associated with multiple drugs

Do not start controllable messages

If SBP is missing in the past month, and if there are multiple drugs that have a “blocked add” recommendations, rather than displaying multiple messages, there will be, instead, one message:

*Would add ?blockedDrug but missing SBP ?value (?date).*

Where ?blockedDrug contains the list of drug classes described above, and ?value and ?date are the most recent SBP value and date, respectively.

Do not intensify controllable messages

If SBP is missing in the past month, and if there are multiple drugs that have a “blocked increase dose” recommendations, rather than displaying multiple messages, there will be, instead, one message:

*“Would increase ?blockedDrug but missing SBP ?value (?date).”*

Primary Messages

If patient has Rx for two drugs that are normally not prescribed together (“bad drug partners”):

*“Pt has Rx for ?BadDrugPartnerHTNGL Evaluate clinically.”*

Where ?BadDrugPartnerHTNGL are the bad drug partners.

If patient has Rx for two drugs in the same drug class:

*“Pt has Rx for two drugs ?MultiMedHTNGL from the same drug class. Stop one.”*

Where ?MultiMedHTNGL are the two drugs from the same drug class.

If patient adherence to drug prescription is less than 90%:

*MPR ?mpr% - evaluate adherence to ?drugName. <Br>*

If patient has multiple prescriptions for the same drug:

“*There are multiple Rxs for ?dup\_GL\_drug. Doses summed.”*

Drug-related messages

If no encoded drug can be recommended,

*No thiaide, ACE, ARB, CCB, BB can be recommended. Please consider other drugs “Appendix E, Table E1 of the VA 2014 HTN Guidelines “*

Where ?contraindicatedDrug is the contraindicated drug, and “*Appendix E, Table E1 of the VA 2014 HTN Guidelines “* is a hyperlink.

If there needs to be a substitution, but no encoded drug can be recommended, then the following message is displayed:

*Contraindicated ?contraindicatedDrug but no thiaide, ACE, ARB, CCB, BB can be recommended. Please consider other drugs “Appendix E, Table E1 of the VA 2014 HTN Guidelines “*

If a patient has active prescription(s) for a drug with a dose greater than its maximum dose

*?drugName dose (?dailyDose) greater than max dose.*

Where ?drugName is name of the drug and ?daily dose is dose of the drug.

If patient has benign prostatic hypertrophy (BPH) and has an active prescription of one antihypertensive drug that is an alpha blocker:

*“VA recommends against the use of alpha-adrenergic blockers as monotherapy for HTN, but this drug class may be used as supplemental therapy or if warranted by BPH. “*

If patient does NOT have benign prostatic hypertrophy (BPH) and has an active prescription one hypertensive drug that is an alpha blocker:

*“VA recommends against the use of alpha-adrenergic blockers as monotherapy for HTN.”*

If patient has active prescription of loop diuretic (e.g. furosemide) and does not have heart failure nor egGFR<45:

*“ Pt has Rx for loop diuretic and does not have heart failure or renal insufficiency. Assess risks”*

If patient has active prescription for a drug that belongs to an encoded drug class, but for which we have no included dosage information, if that drug is evaluated:

*Pt has Rx for ?1st2nd3rdLineNoDose. Drug considered to be at max dose because we have not encoded dosage information.*

Where ?1st2nd3rdLineNoDose is the drug in question.

General info messages

When we are recommend adding or increase dose of any BB:

* + If patient has Dx of DM:

*“Beta blockers may diminish symptoms of and recovery from hypoglycemia.*

* + If patient has Rx for diltiazem:

*“Use caution if combining a beta blocker with diltiazem because of the risk of heart block or myocardial depression. “*

* + If patient has Dx of peripheral vascular disease

“*Beta blockers may exacerbate symptoms of peripheral vascular disease.”*

* + If patient has asthma:

“*Pt has asthma. Use with caution.”*

* + If patient’s pulse <65

*“Pt has relatively low heart rate; BB may reduce heart rate.”*

* + All patients, all BB

*“Discontinue BB with slow taper over 1 week.”*

## Other messages

Follow Up message, displayed to all patients:

*Follow up in 1 month.*

Alerts (Primary message)

If most recent K>5.5

*ALERT. K ?value (?date).*

If most recent Na<=130:

*ALERT: Na ?value (?date).*

If patient’s race is “unknown” or “missing”, the following message is displayed (not Primary message)

*Pt’s race is unknown or missing. We have assumed he/she is not African American. Please update race.*

If patient’s race is “declined to answer”, the following message is displayed (not Primary message)

*Pt declined to answer race. We have assumed he/she is not African American.*

Following message (not Primary message) is displayed to all patients who receive recommendations and who are above target goals:

*These recommendations are applicable when BP is above target goals.*

If patient has Dx of CKD via icd9/10 code OR most recent GFR<60 in the past year, the following message (not Primary message) is displayed:

*CKD defined by icd9/10 code OR most recent GFR<60 in the past year.*

If patient’s GFR >=60, the following messages (not Primary message) is displayed

*Changes in GFR when GFR >= 60 are not interpretable.*

# Some final notes.

Recommendations and Knowledge from the VA 2014 GL that were used in the creation of the KB and Rules document can be found in Encoded Knowledge and Recommendations from VA 2014 HTN Guidelines

Wish list/To do items are found in Wish list/To do

# Appendix A: Anti-Hypertensive drugs: encoded, non-encoded, those with antihypertensive effects

### Encoded Drugs, used in the treatment for HTN, organized by Drug Class (not all have dosage info)

**Thiazide Diuretics**

bendroflumethiazide

bendroflumethiazide\_SA

benzthiazide

chlorothiazide

cyclothiazide

hydroflumethiazide

indapamide

methyclothiazide

polythiazide

quinethazone

trichlormethiazide

chlorthalidone

hydrochlorothiazide

**ACE Inhibitors**

captopril

enalapril

fosinopril NA

lisinopril

quinapril

benazepril

moexipril

perindopril

ramipril

trandolapril

**Angiotensin II Receptor Blockers**

candesartan

azilsartan

irbesartan

losartan

telmisartan

valsartan

olmesartan

eprosartan

**Long Acting Dihydropyridines Calcium\_channel\_blockers**

amlodipine

felodipine\_SA

nifedipine\_SA

nisoldipine\_SA

nicardipine\_SA

isradipine\_SA

**Short Acting Dihydropyridines Calcium\_channel\_blockers**

nimodipine

nifedipine

nicardipine

isradipine

**Long Acting Non Dihydropyridines Calcium\_channel\_blockers**

diltiazem\_SA

verapamil\_SA

**Short Acting Non Dihydropyridines Calcium\_channel\_blockers**

Bepridil (out of scope)

diltiazem

verapamil

**Cardioselective beta blockers**

sustained release metoprolol succinate

metoprolol\_tartrate

bisoprolol

acebutolol

betaxolol

atenolol

**Non cardioselective beta blockers**

carteolol

nadolol

penbutolol

propranolol

propranolol\_SA

timolol

**Alpha beta blockers**

carvedilol

carvedilol\_SA

labetalol (tablet, not injectable)

### Non-encoded drugs

**Cardioselective and vasodilatory beta blockers**

nebivolol

**ISA beta blockers**

pindolol

**Alpha blockers**

doxazosin

prazosin

terazosin

**Direct\_vasodilators**

Hydralazine

minoxidil

flosequinan

**Central adrenergic inhibitors**

clonidine

guanabenz

guanfacine

methyldopa

methyldopa\_SA

**Peripheral adrenergic inhibitors**

reserpine

alseroxylon

cryptenamine

deserpidine

guanadrel

guanethidine

rauwolfia serpentina

rauwolfia

rescinnamine

**Aldosterone/mineralocorticoid receptor antagonist**

spironolactone

eplerenone

**Potassium sparing diuretics**

Amiloride (out of scope)

triamterene

spironolactone (also aldosterone antagonist)

eplerenone ((also aldosterone antagonist)

### Other drugs with anti-hypertensive effects

Sotalol

**Direct Renin Inhibitor**

Aliskiren

**Loop\_diuretics**

ethacrynic\_acid

torsemide

bumetanide

furosemide

# Appendix B: Dosage: Medication cut-off doses

The table below contains two different cutoff values used in the KB: the “increase dose ceiling” and the “maximum dose.” If a patient has an active prescription with a dose that is greater than or equal to the “increase dose ceiling,” then we will not recommend increasing the dose of the drug. If a patient has an active prescription with a dose that is greater than the “maximum dose,” then a message will be issued stating that patient has an active prescription for a dose greater than the maximum dose.

The following cutoff area is used, in part, because the daily drug dose is calculated using the (strength of the tablet \* number of tablets)/days of prescription; this may not be an integer. Example: 100 pills at 5mg each for 90 days. Calculation applies to tablets only (encoded drugs are all tablets).

Not all encoded drugs listed in Appendix A are listed here because these cutoff values are not in the KB. Should a patient have a prescription for such a drug, that drug is assumed to be at its maximum dose.

|  |  |  |
| --- | --- | --- |
|  | **Increease dose celing** | **Maximum dose** |
| **Thiazide diuretics** |  |  |
| chlorthalidone | 24.9 | 25.1 |
| hydrochlorothiazide | 49.9 | 50.1 |
| indapamide | 2.4 | 2.6 |
|  |  |  |
| **ACE inhibitors** |  |  |
| benazepril | 39.9 | 40.1 |
| captopril | 449.9 | 450.1 |
| fosinopril NA | 39.9 | 40.1 |
| lisinopril | 39.9 | 40.1 |
| quinapril | 79.9 | 80.1 |
| ramipril | 19.9 | 20.1 |
|  |  |  |
| **ARB** |  |  |
| irbesartan | 299.9 | 300.1 |
| losartan | 99.9 | 100.1 |
| valsartan | 319.9 | 320.1 |
|  |  |  |
| **DHP CCB** |  |  |
| amlodipine\_besylate | 9.9 | 10.1 |
| felodipine\_SA | 9.9 | 10.1 |
| nifedipine SA | 119.9 | 120.1 |
|  |  |  |
| **NDHP CCB** |  |  |
| diltiazem | 359.9 | 360.1 |
| diltiazem\_SA | 539.9 | 540.1 |
| verapamil | 479.9 | 480.1 |
| verapamil\_SA | 479.9 | 480.1 |
|  |  |  |
| **Cardioselective BB** |  |  |
| acebutolol | 599.9 | 600.1 |
| atenolol | 99.9 | 100.1 |
| bisoprolol | 9.9 | 10.1 |
| metoprolol\_tartrate | 299.9 | 300.1 |
| sustained release metoprolol succinate | 199.9 | 200.1 |
|  |  |  |
| **Non-cadioselective BB** |  |  |
| propranolol | 159.9 | 160.1 |
| propranolol\_SA | 159.9 | 160.1 |
|  |  |  |
| **Alpha-beta blocker** |  |  |
| carvedilol | 49.9 | 50.1 |
| labetalol | 799.9 | 800.1 |

# Appendix C: Dealing with Adverse Reactions (ADRs)

An ADR has two components: a reactant and a reaction. For this discussion, the reactant is a drug and the reaction can be a myriad of possibilities, e.g. rash, cough, angioedema, etc.

We have encoded specific, potentially life-threatening reactions to a HTN drug as absolute contraindications. This is for not only the HTN drug that is being evaluated, but also a related drug that has a cross-reactivity, listed under “Additional ADR check”. Thus, for reactant = thiazide duiretics, we have, as an absolute contraindication, the reaction = anaphylaxis, to all the thiazide diuretics, as well as sulfa drugs, and the sulfonylureases such as glipizide, glyburide used in the treatment of DM.

Thiazide diuretics, and these cross-reactive drugs may have reactions other than anaphylaxis or angioedema (that are absolute contraindications) and these other reactions are handled differently. Thiazide diuretics and these cross-reactive drugs, along with their associated reactions, are displayed. Note that, while the encoding in the KB identifies the cross-reactive drugs and associates these ADRs with the recommended drugs, there is no additional KB/EON processing (except for the absolute contraindications, above). The ADRs are a “pass-through” of the patient data.

# Appendix D: Bad drug partners

Footnote #2 The VA GL is silent about these bad drug partners.

We have encoded

* loop diuretics as bad drug partners to thiazide diuretics
* NDHP CCB as bad drug partners to DHP CCB
* DHP CCB as bad drug partners to NDHP

And are aware that this is in contrast to the 2017 ACC/AHA HTN GL that states (***text in boldface, italics***)

***Drug combinations that have similar mechanisms of action or clinical effects should be avoided. For example***, 2 drugs from the same class should not be administered together (e.g., 2 different beta blockers, ACE inhibitors, or nondihydropyridine CCBs). Likewise, 2 drugs from classes that target the same BP control system are less effective and potentially harmful when used together (e.g., ACE inhibitors, ARBs). ***Exceptions to this rule include concomitant use of a thiazide diuretic, K-sparing diuretic, and/or loop diuretic in various combinations. Also, dihydropyridine and nondihydropyridine CCBs can be combined*.** High-quality RCT data demonstrate that simultaneous administration of RAS blockers (i.e., ACE inhibitor with ARB; ACE inhibitor or ARB with renin inhibitor aliskiren) increases cardiovascular and renal risk

The 2014 VA HTN Guidelines are silent about bad drug partners for thiazide diuretics, NDHP CCBs and DHP CCBs, which is the primary basis for our work. We have encoded in a different way, following historic KB encoding precedence, following the input of a domain expert (Dr. Brian Hoffman, head of HTN clinic).

We are unable to include all recommendations from all guidelines.

# Appendix E: Race

The current values of race in the database are

Missing

Unknown at this time

AMERICAN INDIAN OR ALASKA NATIVE

ASIAN

BLACK OR AFRICAN AMERICAN

DECLINED TO ANSWER

NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER

UNKNOWN BY PATIENT

WHITE

WHITE NOT OF HISP ORIG

# Appendix F: Examples of No Med Scenario using simple, sample patient characteristics

session time = 8/15/2017.

**HTN no CKD**

### Case i: rec 1st line drug

Dx: HTN no CKD

all labs ok (K=4.1 past month, Na=140 past month, uric acid=6 past year, GFR=80 past year), no ADR

SBP=160 past month

Therapeutic options:

* Add thiazide diuretics (chlorthalidone (preferred), indapamide (preferred), HCTZ)

### Case ii: rec 2nd line drug

Dx: HTN no CKD

Na=120<130 past month an absolute contraindication to thiazide diuretics, all other labs ok , no ADR, SBP=160 past month

Therapeutic options:

* Add ACE (lisinopril)
* Add ARB (losartan)
* Add DHP CCB (amlodipine)

### Case iii: rec 3rd line drug

Dx: HTN no CKD

Na=120<130 past month an absolute contraindication to thiazide diuretics, K=5.6>5.5 an absolute contraindication to ACE/ARB, ADR anaphylaxis to DHP CCB, all other labs ok , SBP=160 past month

Therapeutic options:

* Add Cardioselective BB (sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

### Case iv: rec 2nd and 3rd line drug (if only rec ACE/ARB and African American)

Dx: HTN no CKD

Race: African American

Na=120<130 past month an absolute contraindication to thiazide diuretics, ADR anaphylaxis to DHP CCB, all other labs ok,SBP=160 past month

Therapeutic options:

* Add ACE (lisinopril)
* Add ARB (losartan)
* Add Cardioselective BB (sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

HTN and CKD and not African American

### Case v: rec 1st line drug

Dx: HTN and CKD and not African American

all labs ok (K=4.1 past month, Na=140 past month, uric acid=6 past year, GFR=80 past year), no ADR

SBP=160 past month

Therapeutic options:

* Add ACE (lisinopril)
* Add ARB (losartan)

### Case vi: rec 2nd line drug

Dx: HTN and CKD and not African American

K=5.6>5.5 an absolute contraindication for ACE/ARB, all other labs ok, no ADR, SBP=160 past month

Therapeutic options:

* Add thiazide diuretics (chlorthalidone (preferred), indapamide (preferred), HCTZ)

### Case vii: rec 3rd line drugs

Dx: HTN and CKD and not African American

Na=120<130 an absolute contraindication for Thiazide diuretics, K=5.6>5.5 an absolute contraindication for ACE/ARB, all other labs ok, no ADR, SBP=160 past month

Therapeutic options:

* Add Cardioselective BB ( sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)
* Add DHP CCB (amlodipine)
* Add NDHP CCB (verapamil SA, diltiazem SA)

HTN and CKD and African American

### Case vii: rec 1st line drug

Dx: HTN and CKD and African American

Race: African American

all labs ok (K=4.1 past month, Na=140 past month, uric acid=6 past year, GFR=80 past year), no ADR, SBP=160 past month

Therapeutic options:

* Add thiazide diuretics (chlorthalidone (preferred), indapamide (preferred), HCTZ)
* Add ACE (lisinopril)
* Add ARB (losartan)

### Case ix: rec 2nd line drug

Dx: HTN and CKD and African American

Race: African American

Na=120<130 an absolute contraindication for Thiazide diuretics, K=5.6>5.5 an absolute contraindication for ACE/ARB, all other labs ok, no ADR, SBP=160 past month

Therapeutic options:

* Add DHP CCB (amlodipine)

### Case x: rec 3rd line drug

Dx: HTN and CKD and African American

Race: African American

Na=120<130 an absolute contraindication for Thiazide diuretics, K=5.6>5.5 an absolute contraindication for ACE/ARB, all other labs ok, ADR anaphylaxis to DHP CCB, SBP=160 past month

Therapeutic options:

* Add Cardioselective BB ( sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

### Case xi: rec 1st and 2nd line drugs

Dx: HTN and CKD and African American

Race: African American

Na=120<130 an absolute contraindication for Thiazide diuretics, all other labs ok, SBP=160 past month

Therapeutic options:

* Add ACE (lisinopril)
* Add ARB (losartan)
* Add DHP CCB (amlodipine)

# Appendix G: Examples of One Med Scenario using simple, sample patient characteristics

All doses given as daily doses; session time = 8/15/2017.

**Active prescription one encoded 1st or 2nd line med, drug not contraindicated**

### Case A: increase dose 1st or 2nd line, add 1st line drug

Dx: HTN and no CKD

Race: not African American

Medication: lisinopril; not contraindicated and dose can be increased; all labs ok; SBP=160 past month, no ADR

Therapeutic options:

* Increase dose lisinopril
* Add thiazide diuretics (chlorthalidone (preferred), indapamide (preferred), HCTZ)

### Case B: increase dose 1st or 2nd line, add 2nd line drug

Dx: HTN and no CKD

Race: not African American

Medication: chlorthalidone, not contraindicated and dose can be increased; all labs ok; SBP=160 past month, no ADR

Therapeutic options:

* Increase dose chlorthalidone
* Add ACE inhibitors (lisinopril)
* Add ARB (losartan)
* Add DHP CCB (amlodipine)

### Case C: increase dose 1st or 2nd line, add 3rd line drug

Dx: HTN and CKD and African American

Race: African American

Medication: chlorthalidone, not contraindicated and dose can be increased; K=5.6>5.5, an absolute contraindication for ACE and ARB, all other labs ok , SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Increase dose chlorthalidone
* Add Cardioselective BB ( sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

### Case D: increase dose 1st or 2nd line, link to other 3rd line drugs

Dx: HTN and CKD and African American

Dx: Unspecified Heart Block and no pacemaker (absolute contraindication all BB)

Race: African American

Medication: chlorthalidone, not contraindicated and dose can be increased; K=5.6>5.5, an absolute contraindication for ACE and ARB, SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Increase dose chlorthalidone
* Link to other 3rd line non-encoded drugs

### Case E: 1st or 2nd line not HCTZ at max dose, only add 1st line drug

Dx: HTN and no CKD

Race: not African American

Medication: lisinopril, not contraindicated and at max dose; all labs ok; SBP=160 past month, no ADR

Therapeutic option:

* Add thiazide diuretics (chlorthalidone (preferred), indapamide (preferred), HCTZ)

### Case F1: 1st or 2nd line not HCTZ at max dose, only add 2nd line drug

Dx: HTN and CKD and not African American

Race: not African American

Medication: lisinopril, not contraindicated and at max dose, all labs ok; SBP=160 past month, no ADR

Therapeutic option:

* Add thiazide diuretics (chlorthalidone (preferred), indapamide (preferred), HCTZ)

### Case F2: 1st or 2nd line not HCTZ at max dose, only add 2nd line drug

Dx: HTN and CKD and African American

Race: African American

Medication: chlorthalidone, not contraindicated and at max dose, K=5.6<5.5 an absolute contraindication for ACE and ARB; all other labs ok; SBP=160 past month, no ADR

Therapeutic option:

* Add DHP CCB (amlodipine)

### Case G: 1st or 2nd line not HCTZ at max dose, only add 3rd line drug

Dx: HTN and CKD and African American

Race: African American

Medication: chlorthalidone, not contraindicated and at max dose; K=5.6>5.5, an absolute contraindication for ACE and ARB, all other labs ok , SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Add Cardioselective BB ( sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

### Case H: 1st or 2nd line not HCTZ at max dose, link to other 3rd line drugs

Dx: HTN and CKD and African American

Race: African American

Dx: Unspecified Heart Block and no pacemaker (absolute contraindication all BB)

Medication: chlorthalidone, not contraindicated at max dose; K=5.6>5.5, an absolute contraindication for ACE and ARB, SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Link to other 3rd line non-encoded drugs

### Case I: 1st or 2nd line (HCTZ) at max dose, add 1st line drug, sub with preferred thiazide

Dx: HTN and CKD and not African American

Race: not African American

Medication: HCTZ max dose, not contraindicated; all labs ok; SBP=160 past month, no ADR

Therapeutic options:

* Susbtitute HCTZ with preferred thiazides (chlorthalidone, indapamide)
* Add ACE inhibitors (lisinopril)
* Add ARB (losartan)

### Case J: 1st or 2nd line (HCTZ) at max dose, add 2nd line drug, sub with preferred thiazide

Dx: HTN no CKD

Race: not African American

Medication: HCTZ max dose, not contraindicated; all labs ok; SBP=160 past month, no ADR

Therapeutic options:

* Substitute HCTZ with preferred thiazides (chlorthalidone, indapamide)
* Add ACE inhibitors (lisinopril)
* Add ARB (losartan)
* Add DHP CCB (amlodipine)

### Case K: 1st or 2nd line (HCTZ) at max dose, add 3rd line drug, sub with preferred thiazide

Dx: HTN and CKD and African American

Race: African American

Medication: HCTZ max dose, not contraindicate; K=5.6>5.5, an absolute contraindication for ACE and ARB, all other labs ok , SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Substitute HCTZ with preferred thiazides (chlorthalidone, indapamide)
* Add Cardioselective BB ( sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

### Case L: 1st or 2nd line (HCTZ) at max dose, link to other 3rd line drugs, sub with preferred thiazide

Dx: HTN and CKD and African American

Race: African American

Dx: Unspecified Heart Block and no pacemaker (absolute contraindication all BB)

Medication: HCTZ, not contraindicated at max dose; K=5.6>5.5, an absolute contraindication for ACE and ARB, SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Substitute HCTZ with preferred thiazides (chlorthalidone, indapamide
* Link to other 3rd line non-encoded drugs

### Case a: 3rd line drug any dose, add 1st line drug

Dx: HTN and no CKD

Race: not African American

Medication: propranolol not contraindicated, not at max dose, all labs ok

Therapeutic options:

* Add chlorthalidone (preferred), indapamide (preferred), HCTZ

### Case b: 3rd line drug any dose, add 2nd line drug

Dx: HTN and no CKD

Race: not African American

Medication: propranolol not contraindicated, not at max dose, Na=120<130 an absolute contraindication for thiazide diuretics, all other labs ok, SBP=160 past month

Therapeutic options:

* Add ACE inhibitors (lisinopril)
* Add ARB (losartan)
* Add DHP CCB (amlodipine)

### Case c: 3rd line drug not at max dose, incr dose 3rd line drug, add 3rd line drug

Dx: HTN and CKD and not African American

Race: not African American

Medication: amlodipine not contraindicated, no at max dose, Na=120<130 an absolute contraindication for thiazide diuretics, K=5.6>5.5 an absolute contraindication for ACE and ARB, all other labs ok, SBP=160 past month

Therapeutic options:

* Increase dose amlodipine
* Add Cardioselective BB ( sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

### Case d: 3rd line drug not at max dose, incr dose 3rd line drug, link to other 3rd line drugs

Dx: HTN and no CKD

Race: not African American

Medication: metoprolol tartrate, not contraindicated not at max dose; Na=120<130, an absolute contraindication for thiazide diuretics, K=5.6>5.5, an absolute contraindication for ACE and ARB, SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Increase dose metoprolol tartrate
* Link to other 3rd line non-encoded drugs

### Case e: 3rd line drug at max dose, add 3rd line drug

Dx: HTN and CKD and not African American

Race: not African American

Medication: amlodipine not contraindicated, at max dose, Na=120<130 an absolute contraindication for thiazide diuretics, K=5.6>5.5 an absolute contraindication for ACE and ARB, all other labs ok, SBP=160 past month

Therapeutic options:

* Add Cardioselective BB ( sustained release metoprolol succinate)
* Add Non-cardioselective BB (propranolol)
* Add Alpha-beta blocker (carvedilol)

### Case f: 3rd line drug at max dose, link to other 3rd line drugs

Dx: HTN and no CKD

Race: not African American

Medication: metoprolol tartrate, not contraindicated at max dose; Na=120<130, an absolute contraindication for thiazide diuretics, K=5.6>5.5, an absolute contraindication for ACE and ARB, SBP=160 past month, ADR anaphylaxis to amlodipine, an absolute contraindication to CCB

Therapeutic options:

* Link to other 3rd line non-encoded drugs

**Active prescription one encoded 1st or 2nd or 3rd line med, drug has absolute contraindication**

### Case s1: 1st or 2nd or 3rd line drug contraindicated, substitute with 1st line drug

Dx: HTN and CKD and not African American

Race: not African American

Medication: HCTZ any dose contraindicated; Na=120<130, an absolute contraindication for thiazide diuretics, all other labs ok

Therapeutic options:

* Substitute HCTZ with
  + ACE inhibitors (lisinopril)
  + ARB (losartan)

### Case s2: 1st or 2nd or 3rd line drug contraindicated, substitute with 2nd line drug

Dx: HTN and no CKD

Race: not African American

Medication: Chlorthalidone any dose contraindicated; Na=120<130, an absolute contraindication for thiazide diuretics, all other labs ok

Therapeutic options:

* Substitute chlorthalidone with
  + ACE inhibitors (lisinopril)
  + ARB (losartan)
  + DHP CCB (amlodipine)

### Case s3: 1st or 2nd or 3rd line drug contraindicated, substitute with 3rd line drug

Dx: HTN and no CKD

Race: not African American

Medication: Chlorthalidone any dose contraindicated; Na=120<130, an absolute contraindication for thiazide diuretics, K=5.6>5.5 an absolute contraindication for ACE/ARB, ADR anaphylaxis to DHP CCB, all other labs ok

Therapeutic options:

* Substitute chlorthalidone with
  + Add Cardioselective BB ( sustained release metoprolol succinate)
  + Add Non-cardioselective BB (propranolol)
  + Add Alpha-beta blocker (carvedilol)

### Case s4: 1st or 2nd or 3rd line drug contraindicated, substitute with link to other 3rd line drug

Dx: HTN and no CKD

Dx: Unspecified Heart Block and no pacemaker (absolute contraindication all BB)

Race: not African American

Medication: Chlorthalidone any dose contraindicated; Na=120<130, an absolute contraindication for thiazide diuretics, K=5.6>5.5 an absolute contraindication for ACE/ARB, ADR anaphylaxis to DHP CCB, all other labs ok

Therapeutic options:

* Substitute chlorthalidone with link to other 3rd line drugs

# Appendix H: Messages composed outside of KB

There are Collateral messages that are displayed in the GUI Drug Therapies section that are not encoded in the KB, but are, instead, constructed after EON processing. These messages are of message types:

* + Is first line drug
  + Is second line drug
  + Is third line drug
  + Compelling indication
  + Relative indication

These messages are constructed by joining the message types above with their respective ‘values’; for indications, the compelling indications and relative indications listed under the different Drug Therapies, will be displayed in the GUI, concatenated with the text ‘Compelling Indication’ or ‘Relative indication’, as appropriate.

This is best described by example.

If we are recommending a thiazide, then

If the patient has Dx for: HTN and no CKD, we will display the first line drug message

*First line drug for HTN and no CKD*

OR If the patient has Dx for: HTN and CKD and African American, we will display the first line message:

*First line drug for HTN and CKD and African American*

OR If the patient has Dx for: HTN and CKD and not African American, we will display the second line message:

*Second line drug for HTN and not African American*

Where the underlined text is the message type, and the second part of the message is the Dx. Note that the formatting of the underline and italics are NOT displayed in the GUI.

Similarly, again, if we are recommending a thiazide, and if the patient has a Dx of Osteoporosis, a relative indication, we will display

*Relative indication: Osteoporosis*

# Appendix X: ICD-9 and ICD-10 Codes for Hypertension and CKD

# Encoded Knowledge and Recommendations from VA 2014 HTN Guidelines

***Lifestyle Modification Therapies***

8. We recommend offering lifestyle modification interventions for patients with prehypertensionor hypertension based on patient indications and preferences as well as assessment of available local resources *(recommended via link)*

***A physical exam should include an evaluation for signs of secondary hypertension or hypertensive organ damage***

Most common causes of secondary hypertension [21]

•Renal

Renal artery stenosis

Polycystic kidney disease

Chronic reflux nephropathy

Chronic glomerulonephritis

Polyarteritis nodosa

Systemic sclerosis

•Endocrine

Cushing's syndrome

Conn's syndrome

Pheochromocytoma

Acromegaly

Hyperparathyroidism

Polycystic ovarian syndrome

•Other

Obstructive sleep apnea

Aortic coarctation

Pre-eclampsia

Drugs (cmbined ral cntraceptive pill, cyclsprin, steroids)

***Systolic Blood Pressure Goals***

*(messages displayed when differs from Performance Measures)*

26. For patients 60 years and over, we recommend treating to a systolic blood pressure goal of<150 mmHg.

27. For patients below 60 years of age, we suggest treating to a systolic blood pressure goal of<150 mmHg.

28. We recommend treating to a diastolic blood pressure goal <90 mmHg in patients 30 years and older.

29. We suggest treating to a diastolic blood pressure goal <90 mmHg in patients age 18 to 29.

30. For patients with diabetes (all age groups), we recommend treating to a systolic blood pressure goal of <150 mmHg.

31. For patients with diabetes (all age groups) who tolerate antihypertensive drugs, we suggest treating to a systolic blood pressure goal of <140 mmHg.

32. For patients with diabetes, we recommend treating to a diastolic blood pressure goal <85mmHg.

*Follow up time*

33. We suggest that patients be seen within one month of initiation of lifestyle or pharmacological therapy to determine adequacy of hypertension control, degree of patient adherence, and presence of adverse effects.

***Drug recommendations***

37. We recommend the use of thiazide-type diuretics for the treatment of hypertension.

38.We suggest the use of thiazide-type diuretics at recommended treatment doses as first-line therapy for drug treatment of hypertension either as monotherapy or in combination with other agents.

39. To initiate treatment of hypertension with a thiazide-type diuretic, we suggest the use ofchlorthalidone or indapamide over hydrochlorothiazide.

40. We do not suggest switching from hydrochlorothiazide to chlorthalidone or indapamide if the patient is adequately controlled on and tolerating hydrochlorothiazide.

41. We suggest considering a switch from hydrochlorothiazide to chlorthalidone for patients whosehypertension is inadequately controlled on 50mg/day of hydrochlorothiazide.

42. We recommend a dosage of 12.5-25mg/day of chlorthalidone, 25-50mg/day of hydrochlorothiazide, or a dosage of 2.5mg/day immediate-release or 1.5-2.5mg/day sustained-release (not currently available in the US) of indapamide.

43. We recommend using the following as alternative therapies for patients who cannot tolerate thiazide-type diuretics, as supplementary therapies for patients who do not reach their hypertensive goals, or for those starting on combination therapy:

1. Angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers (but not together)
2. Long-acting dihydropyridine calcium channel blockers

44. We recommend against the use of more than one of the following three drug classes together in the same patient: angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, or direct renin inhibitors.

45. We recommend additional therapy in refractory hypertension (for those who do not tolerate or are not adequately controlled with triple therapy [i.e., thiazide-type diuretics, ACEI or ARB, and LA DHP CCBs] described in **Recommendation 43**) or as supplementary therapy in some clinical indications. Drug classes for consideration can include (not in priority order):

1. Aldosterone/mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone)
2. Other potassium-sparing diuretic (i.e., amiloride)
3. Alpha adrenergic blockers
4. Beta adrenergic blockers
5. Non-dihydropyridine calcium channel blockers
6. Combined alpha-beta adrenergic blockers
7. Peripherally acting antiadrenergic agents (reserpine, pending availability)
8. Direct acting vasodilators (e.g., hydralazine, minoxidil)
9. Centrally acting antiadrenergic drugs (e.g., clonidine, methyldopa)

46. We recommend against the use of alpha-adrenergic blockers as monotherapy, but this class of agents may be used as supplemental therapy or if warranted by comorbid conditions (e.g.,symptomatic prostatic hypertrophy).

***Patients with Chronic Kidney Disease***

47. In patients with hypertension and chronic kidney ~~disease (reduced kidney function with albuminuria),~~ we recommend treatment with an angiotensin-converting-enzyme inhibitor, or angiotensin II receptor blocker for improving kidney outcomes.

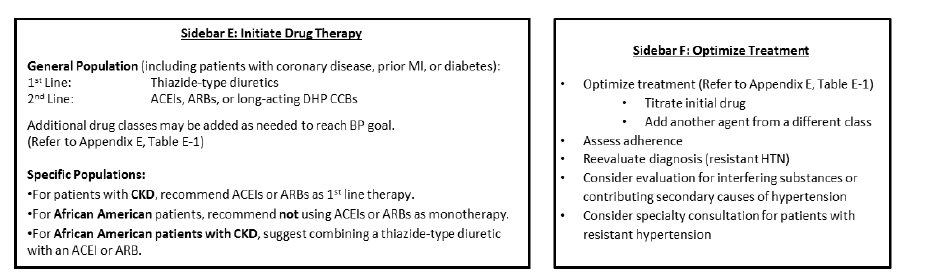
Most patients with CKD and hypertension will require more than one medication to achieve the recommended blood pressure target. In the trials reviewed, the most frequently used add-on therapy to an ACEI or ARB was a diuretic, followed by a LA DHP CCB or beta blocker. A diuretic should be considered as add-on or concomitant initial therapy with an ACEI or ARB in patients with CKD, as a general recommendation to improve cardiovascular outcomes in patients with hypertension.

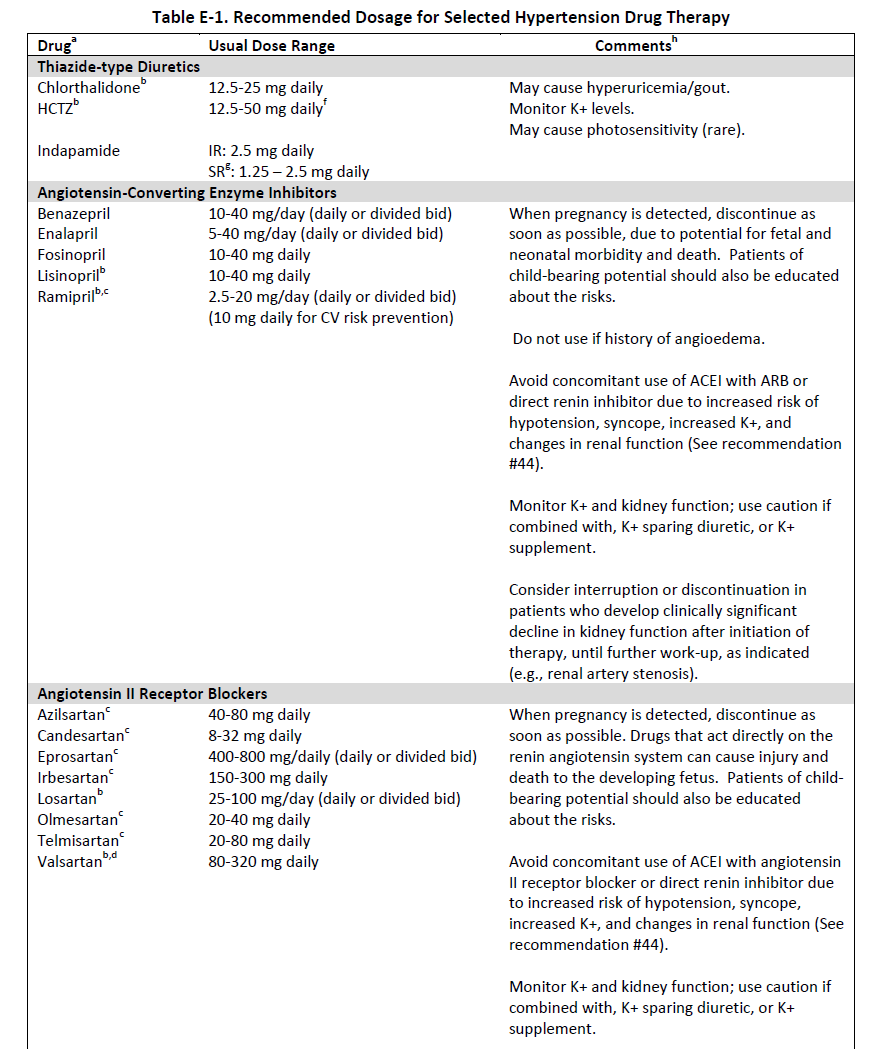
***African American Population***

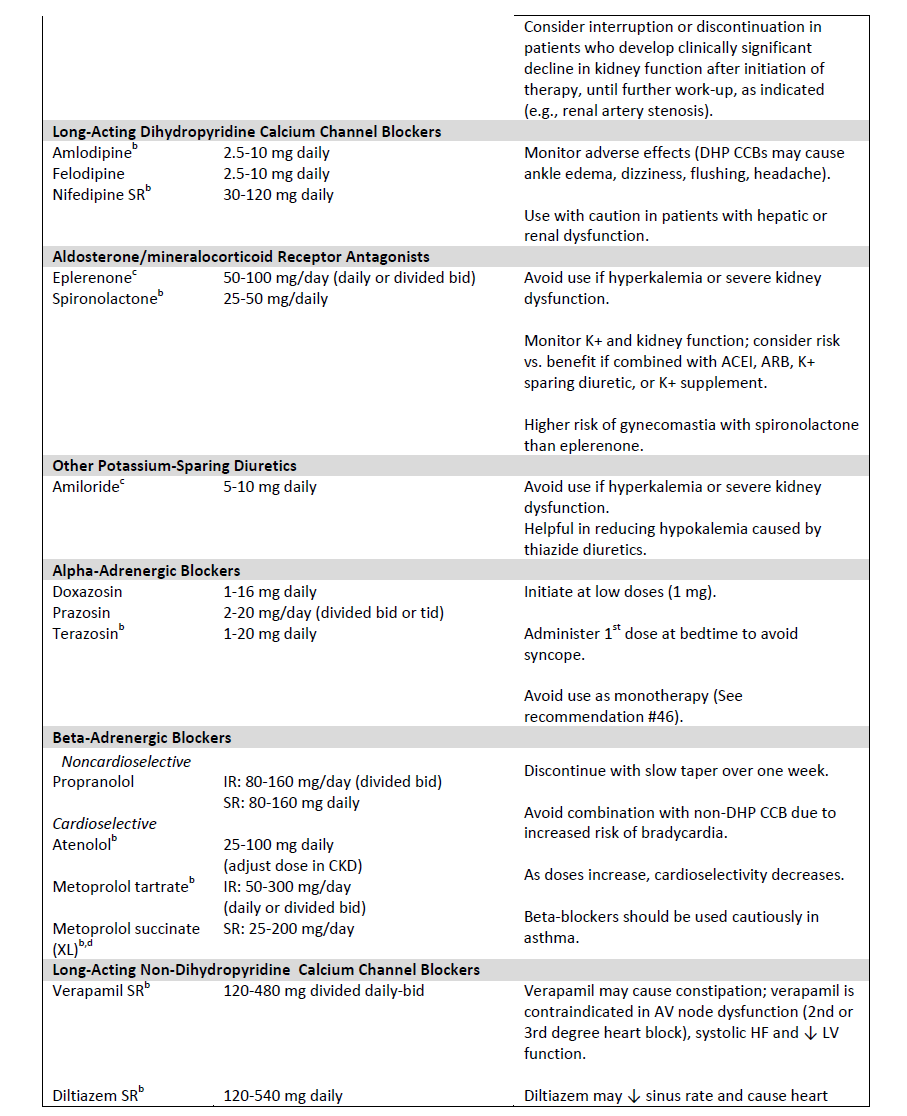
48. In African American patients with hypertension, we recommend against using an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker as monotherapy.

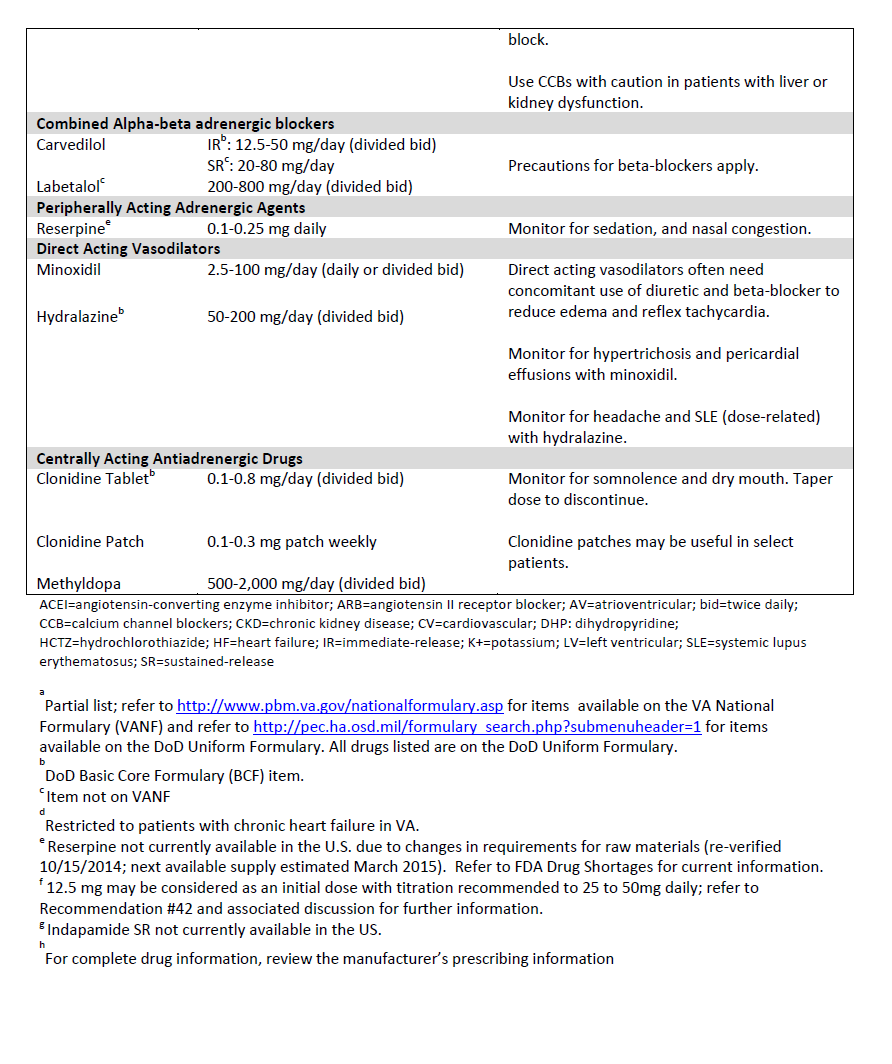
49. In African American patients with hypertension and stage 1-3 chronic kidney disease, we suggest a combination of a thiazide-type diuretic (for cardiovascular protection) with either an angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker (for renal protection).

***Management Module B***









# Wish list/To do

In random order

1. 10/9/18 In the future, include in this KB or in HF KB, Dx of HTN and HF. Considerations:
   * patients with HF and be on both ACE and ARB
   * patients on HF can be on combo drug Entresto (valsartan + sacubitril); sacubitril is anti-hypertensive but not prescribed except as combo for HF; consider as complication factor?
   * For alpha-beta blocker, removed HF as complication factor
2. Related to DM, but applies to HTN. From clinical and medsafe meeting 6/26/2028) Consider date of prescription of DM med relative to session date or date recommendations are provided. Currently we do not do this, so patient could have received new med a few days ago, and CDS rec’s are pre-mature. Need to consider:

What date should be used as date of med? Date of prescription? Date patient received his/her med?

What is ‘reasonable’ length of time between date of med and current date/session time for CDS rec’s to be ok?

# List of Footnotes

This description of ADR of anaphylaxis contained under Thiazide diuretics applies to other drug classes as well.

2 The VA GL is silent about these bad drug partners. See [Appendix D](#Appendix D:  Bad drug partners) for more discussion

3 This description of ADR of anaphylaxis contained under ACE Inhibitors applies to other drug classes as well..

4 Only long acting, and not short acting, DHP CCBs are recommended by VA.

5 Only long acting, and not short acting, NDHP CCBs are recommended by VA.

6 See Reference 6 about use of negative inotropic agents.

# References

1. *VA/DoD Clinical Practice Guideline for the Diagnosis and Management of Hypertension in the Primary Care*. *VA/DoD Clinical Practice Guidelines Version 3 2014 .* **Departnemtn of Veterans Affairs and Department of Defense** [Online] [Cited: August 28, 2017.] <https://www.healthquality.va.gov/guidelines/CD/htn/VADoDCPGHTN2014.pdf>
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1. This description of ADR of anaphylaxis contained under Thiazide diuretics applies to other drug classes as well. [↑](#footnote-ref-1)
2. The VA GL is silent about these bad drug partners. See [Appendix D](#Appendix D:  Bad drug partners) for more discussion. [↑](#footnote-ref-2)
3. This description of ADR of angioedema contained under ACE Inhibitors applies to other drug classes as well. [↑](#footnote-ref-3)
4. Only long acting, and not short acting, DHP CCBs are recommended by VA. [↑](#footnote-ref-4)
5. Only long acting, and not short acting, NDHP CCBs are recommended by VA. [↑](#footnote-ref-5)
6. See Reference 6 about use of negative inotropic agents. [↑](#footnote-ref-6)