**Evidence Review for NCQA HEDIS Quality Measure: Annual Monitoring for Patients on Persistent Medications**

Leigh Efird, PharmD

Yulin Huang, BSPharm

Stephanie Southard, PharmD

Ken Shermock, PharmD, PhD

Johns Hopkins Hospital Center for Medication Quality and Outcomes

**Project Goals**

* To provide a comprehensive review of the evidence for annual monitoring of patients using specific persistent medications

|  |
| --- |
| HEDIS Medications:  Angiotensin Converting Enzyme Inhibitors  Angiotensin Receptor Blockers  Aldosterone Antagonists  Diuretics  Digoxin |

**Research Strategies**

A drug database and literature review was conducted to explore the evidence level of monitoring parameters for HEDIS and non-HEDIS medications as outlined below.

1. Drug Databases
   1. Access Pharmacy

Medication specific class and name were used as search terms within Dipiro’s Pharmacotherapy and the Drugs & Supplements Monograph text.

* 1. MicroMedex

Medication specific class and name were used as search terms within MicroMedex. Information was gathered from the Drug Information Summary “Administration/Monitoring” section. In most cases, the monitoring parameters were cited from the FDA-approved medication label/package insert.

* 1. SafeMedication.com

Medication specific class and name were used as search terms within the American Society of Health-Systems Pharmacists drug information resource. In most cases, the monitoring parameters were extremely vague and stated as “certain lab tests may be ordered.”

* 1. Drugs@FDA

Medication specific brand name was used as a search term within the FDA drug information resource. Results included the FDA-approved medication label/package insert. Searches using the medication class or generic name did not often return FDA-approved medication label/package insert (i.e., Luminal (phenobarbital)).

1. Literature Databases

The following resources were explored using the drug class/name and the search terms persistent medications, monitoring parameters, and therapeutic monitoring. No language restrictions were used in the literature review. The reference lists of selected articles were reviewed for relevant studies.

* 1. MEDLINE (Ovid)

The MEDLINE (Ovid) literature search was restricted to guideline, meta-analysis, practice guideline, and systematic review.

* 1. PubMed

In addition to the above search strategy, PubMed was used to find the relevant studies listed in the reference section of selected articles.

* 1. Google Scholar

General search strategy used to refine search terms, guidelines, and disease state societies.

* 1. National/International Society Guidelines

Societies that provide disease state, based on the HEDIS and non-HEDIS medication approved indications, guidelines were reviewed.

* 1. Cochrane Collaboration

Systematic reviews on the monitoring parameters of HEDIS and non-HEDIS medications were evaluated.

* 1. National Guideline Clearinghouse

Limited guidance was obtained from the search results because, in many cases, irrelevant studies were provided.

1. Review Approach

The initial search strategy included evidence-based and consensus-based guidelines, meta-analyses, and systematic reviews. Upon review, the search strategy was broadened to include randomized, controlled trials and cohort studies. It also included relevant studies listed in the selected articles. Two independent reviewers evaluated all selected articles to ensure quality.

**Table of HEDIS Medication Monitoring Parameters with Strength of Evidence**

**Rate 1: Annual Monitoring for Members on ACE Inhibitors or ARBs**

**Numerator.** At least one serum potassium and either a serum creatinine or a blood urea nitrogen therapeutic monitoring test in the measurement year.

**Interpretation:** We believe the evidence supports monitoring of serum potassium and serum creatinine at least once during the measurement year. There is sufficient evidence that ACE inhibitors or ARBs can alter serum potassium concentrations via several mechanisms. Additionally, ACE inhibitors and ARBs can alter renal function, for which serum creatinine is a commonly used clinical marker. We believe that there is less evidence of the utility of using blood urea nitrogen (BUN) to monitor renal function for patients taking ACE inhibitors or ARBs.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference (No.)** | **Medication** | **Monitoring Parameter** | **Population** | **Frequency** | **Rationale** | **Score** |
| FDA1 | ACE Inhibitors-  Lotensin ®  (benazepril) | Renal function: serum creatinine or blood urea nitrogen | Hypertensive patients | Within first few weeks of therapy | Treatment associated with increases in blood urea nitrogen and serum creatinine | FDA Label |
| Serum potassium | Patients using an ACE Inhibitor and potassium supplements or potassium-sparing diuretics | Periodic monitoring | Hyperkalemia occurred in approximately 1% of hypertensive patients |
| FDA2 | ARB-  Cozaar ®  (losartan potassium) | Serum creatinine  Serum potassium | Patients with Type II Diabetes with nephropathy | Endpoint: doubling of serum creatinine | Based on the RENAAL study, treatment associated with reduction in the occurrence of sustained doubling of serum creatinine3  Incidence of hyperkalemia was higher in active treatment group than placebo but few patients discontinued treatment | FDA Label |
| Serum creatinine  Blood urea nitrogen | Patients with unilateral or bilateral renal artery stenosis |  | Treatment associated with increases in serum creatinine or blood urea nitrogen |
| Brenner, B.M.; Cooper, M.E.; et. al.3  (RENAAL) | ARB  (losartan) | Serum creatinine  Serum potassium | Patients over 30 years old with Type II Diabetes with nephropathy | Baseline, 1 week, 1 month, 3 months, and then 3 month intervals for 3.5 years | Elevated serum creatinine level adversely impacts renal outcomes | RCT [1b] |
| Miao, Y.; Dobre, D.; et. al.4 (RENAAL) | ARB  (losartan) | Serum creatinine  Estimated glomerular filtration rate (eGFR)  Serum potassium | Patients with Type II Diabetes with nephropathy | Baseline, 1 week, 1 month, 3 months, and then 3 month intervals for 3.5 years | High risk of increased serum creatinine levels (increased risk of renal outcomes) | Retrospective Cohort [2b] |
| Chobanian, A.V.; et. al.5 (JNC7) | ACE Inhibitor  ARB | Serum potassium | Patients with heart failure and using an aldosterone antagonist | 1 – 2 weeks following initiation or escalation in therapy | Risk of hyperkalemia | Consensus [5] |
| Serum creatinine  Serum potassium | Patients with renal disease or renal transplantation | 1 – 2 weeks following initiation or escalation in therapy |  |
| Hunt, S.A.; Abraham, W.T.; et. al.6 (ACC/AHA) | ACE Inhibitor  ARB | Serum potassium | Patients with heart failure | Serial monitoring | Hyperkalemia may complicate therapy and cause cardiac conduction disturbances | Consensus [5] |
| Renal function  Serum potassium | Patients using an ACE Inhibitor and potassium-sparing diuretic (aldosterone antagonist) | Renal Function: monthly for first 3 months and then every 3 months  Potassium: within 3 days and again at 1 week | Increases risk for hyperkalemia |
| ACE Inhibitor | Renal function  Serum creatinine | Patients with bilateral renal artery stenosis or using an nonsteroid anti-inflammatory drug | Renal Function: monthly for first 3 months and then every 3 months | Increases serum creatinine level7-9 |
| Pinkerman, C,; Sander, P.; et. al.10  (ICSI) | ACE Inhibitor  ARB | Serum creatinine  Blood urea nitrogen  Serum potassium | Patients age 18 years or older with heart failure | 1- to 4-weeks after initiation/dose increase then 1- to 2-times per year  IF elderly: 1- to 2-weeks after initiation/dose increase then 1- to 2-times per year |  | Consensus [5] |
| McDowell, S.E.; Thomas, S.K.; et al.11 | ACE Inhibitor  ARB | Serum creatinine  Serum potassium | Hypertensive patients  (19 published guidelines included) | Practical guidelines: baseline, first 2 weeks of therapy, then every 12 months  (three studies described them as routine, one every 3-6 months, two every 6-12 months, five annually) | Monitoring recommendations varied between guidelines; Practical guidelines allow for monitoring parameters at the same time | Systematic Review [2b] |
| McDowell, S.E.; Ferner R.E.12 | ACE Inhibitor  ARB | Serum creatinine  Serum potassium | Hypertensive patients treated with antihypertensive therapy | Monitoring at 2 weeks, 4 weeks, 3 months, 6 months, 1 year, and 2 years | Limited research on monitoring  Publication included: 16 | Systematic Review [2b] |
| Hurley, J.S.; Roberts, M.; et. al.13 | ACE Inhibitor | Serum creatinine  Serum potassium | Patients age 19 or older and taking at least 1 chronic medication | Monitoring at 1 year after initiation | Objective: to evaluate laboratory safety monitoring in patients taking selected chronic prescription drugs | Retrospective Cohort [2b] |
| Smellie, W.S.; Forth J.; et. al.14 | ACE Inhibitor  ARB | Serum creatinine  Serum electrolytes | Low-risk patients with heart failure using ACE Inhibitors, ARBs, and diuretics | 1 – 2 weeks after each dose increase/relevant drug addition | To assess deterioration in kidney function associated with use of  ACEIs or ARBs (patients with kidney disease and/or heart failure)15 | Consensus [5] |
| High-risk patients with heart failure using potassium-sparing diuretics or combination therapy or with existing renal dysfunction | 5 – 7 days after each dose increase/relevant drug addition | Based on the European  Taskforce guideline16 |
| Coleman, J.J.; McDowell, S.E.; et. al.17 | ACE Inhibitor  ARB | Renal function  Serum potassium | Patients, 18 and older, with newly diagnosed hypertension and newly treated with a single anti-hypertensive drug | Monitoring at 3 days and at 6 months after initiation |  | Retrospective Cohort [2b] |
| Raebel, M.A.; McClure D.L.; et. al.18 | ACE Inhibitor  ARB | Serum creatinine  Serum potassium | Patients prescribed an ACE Inhibitor or ARB in published studies | Monitoring at 1 year after initiation | The purpose of the study was to assess creatinine and potassium monitoring and characteristics associated with monitoring among patients dispensed ACEi or ARB | Retrospective Cohort [2b] |
| Wright J.M.; Musini V.M.19 (Cochrane) | ACE Inhibitor  ARB |  | 1-year RCTs of first-line anti-hypertensive drug classes | No monitoring parameters were mentioned |  | Cochrane Review [1a] |
| Yusuf, S.; Phil, D.; et. al.20 (HOPE) | ACE Inhibitor  (ramipril) | Serum potassium  Serum creatinine | Patients 55 years and older with hypertension | Monitored at 7 – 10 day run-in phase to rule out patients with abnormal levels |  | RCT [1b] |

**Additional Monitoring Parameters for Members on ACE Inhibitors or ARBS**

**Interpretation:** We do not believe there is sufficient evidence to justify using serum sodium or serum urea as a monitoring parameter for patients taking ACE inhibitors or ARBs.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference (No.)** | **Medication** | **Monitoring Parameter** | **Population** | **Frequency** | **Rationale** | **Score** |
| McDowell, S.E.; Thomas, S.K.; et. al.11 | ACE Inhibitor  ARB | Serum sodium | Hypertensive patients  (19 published guidelines included) | Monitoring after first 2 weeks and every 12 months of therapy |  | Systematic Review [2b] |
| McDowell, S.E.; Ferner R.E.21 | ACE Inhibitor  ARB | Serum urea | Hypertensive patients treated with antihypertensive therapy | Monitoring at 6 months and 1 year after initiation |  | Systematic Review [2b] |
| McDowell, S.E.; Ferner R.E.21 | ACE Inhibitor  ARB | Serum sodium | Hypertensive patients treated with antihypertensive therapy | Monitoring at 6 months, 1 year, and 2 years after initiation |  | Systematic Review [2b] |
| Coleman, J.J.; McDowell, S.E.; et. al.17 | ACE Inhibitor  ARB | Serum sodium | Patients, 18 and older, with newly diagnosed hypertension and newly treated with a single anti-hypertensive drug | Monitoring at 3 days and 6 months after initiation | Study examined the extent of laboratory monitoring in patients with newly diagnosed hypertension and newly treated with antihypertensive drugs | Retrospective Cohort [2b] |
| Brenner, B.M.; Cooper, M.E.; et. al.3  (RENAAL) | ARB  (losartan) | Serum uric acid  Serum cholesterol | Patients over 30 years old with Type II Diabetes with nephropathy | Baseline, 1 week, 1 month, 3 months, and then 3 month intervals for 3.5 years | Elevated LDL cholesterol level adversely impacts renal outcomes | RCT [1b] |

**Rate 2: Annual Monitoring for Members on Digoxin**

**Numerator.** At least one serum potassium and either a serum creatinine of a blood urea nitrogen therapeutic monitoring test in the measurement year.

**Interpretation:** While we acknowledge that strong clinical evidence is lacking for these parameters, we would still recommend that serum potassium and serum creatinine be considered as an annual monitoring parameter for patients taking digoxin. It is generally accepted and agreed upon that hypokalemia poses a serious and potentially fatal risk to patients taking digoxin. Additionally, digoxin is renally excreted and, therefore, the potential for digoxin toxicity increases for patients with decreasing renal function. The utility of blood urea nitrogen is less clear, given the lack of evaluation of this monitoring parameter (not to mention that a serum creatinine will be available in virtually all cases where a BUN is reported).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference (No.)** | **Medication** | **Monitoring Parameter** | **Population** | **Frequency** | **Rationale** | **Score** |
| Hunt, S.A.; Abraham, W.T.; et. al.6 (ACC/AHA) | Digoxin | Serum potassium | Patients with heart failure and using a diuretic | Serial monitoring | Hypokalemia may cause fatal arrhythmias and increase the risk of digoxin toxicity | Consensus [5] |
| Pinkerman, C,; Sander, P.; et. al.10  (ICSI) | Digoxin | Serum creatinine  Electrolytes | Patients age 18 years or older with heart failure | Baseline and periodically thereafter |  | Consensus [5] |
| Hurley, J.S.; Roberts, M.; et. al.13 | Digoxin | Serum creatinine  Serum potassium | Patients age 19 or older and taking at least 1 chronic medication | Monitoring at 1 year after initiation |  | Retrospective Cohort [2b] |

**Additional Monitoring Parameters for Members on Digoxin**

**Interpretation:** The evidence supports using an annual serum digoxin concentration measurement as a monitoring parameter. Digoxin toxicity is known to be a serious (potentially fatal) safety concern and there are a number of factors that may precipitate toxicity, even in the setting of a stable dose over time.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference (No.)** | **Medication** | **Monitoring Parameter** | **Population** | **Frequency** | **Rationale** | **Score** |
| Lindenfield, J.; et. al.22  (HFSA) | Digoxin | Serum digoxin  (0.7 – 0.9 ng/mL) | Majority of patients except the elderly or those with impaired renal function | Monitoring in specific situations (see rationale) | Serum digoxin concentration < 1.0 ng/mL were associated with favorable outcomes whereas those > 1.2 ng/mL were associated with harm (B)  Monitoring considered when:  - a significant change in renal function occurs  - a potentially interacting drug is added or discontinued  - confirmation of suspected digoxin toxicity23-25 | Evidence-based guideline [1b] |
| Garg, R.; Gorlin, R.; et. al.25  (DIG Trial) | Digoxin | Serum digoxin | Patients with heart failure, a left ventricular ejection fraction of 0.45 or less, and normal sinus rhythm | 1 month and 12 months | Patients with heart failure, a left ventricular ejection fraction of 0.45 or less, and normal sinus rhythm | RCT [1b] |
| Young, J.B.; Gheorghiade, M.; et. al.26 | Digoxin | Serum digoxin | PROVED & RADIANCE Trial Patient Databases | Varied with study | Serum digoxin levels did not predict likeliness of patients to experience worsening symptoms | Review [1b] |
| Uretsky, B.F.; Young, J.B.; et. al.23 (PROVED) | Digoxin  Diuretic | Serum digoxin | Patients with chronic, stable mild to moderate heart failure secondary to left ventricular systolic dysfunction with normal sinus rhythm and receiving long-term treatment with diuretic drugs and digoxin | 2, 8, 12, and 20 weeks |  | RCT [1b] |
| Packer, M.; Gheorghiade, M.; et. al.24  (RADIANCE) | Digoxin  Diuretic  ACE Inhibitor | Serum digoxin | Patients with New York Heart Association class II or III heart failure and left ventricular ejection fraction of 35 percent or less in normal sinus rhythm who were clinically stable and receiving digoxin, diuretics, and ACEi | Baseline & End of Study (0 and 12 weeks) |  | RCT [1b] |
| Krum, H.; Bigger, J.T.; et. al.27 | Digoxin | Serum digoxin | Patients with mild to moderate chronic heart failure | Baseline & End of Study (4 or 8 weeks) |  | RCT [2b] |
| FDA 28 | Digoxin  (Lanoxin) | Serum digoxin | Adults with mild to moderate heart failure and for the control of resting ventricular rate in patients with chronic atrial fibrillation | Sample just before next scheduled dose of drug | Blood tests will be necessary to ensure digoxin dose is appropriate (therapeutic and toxic effect)  Dose of digoxin should be based on clinical grounds but serum digoxin concentration can be helpful to the clinician in determining the adequacy of digoxin therapy and in assigning certain probabilities to the likelihood of digoxin intoxication. | FDA Label |
| Pinkerman, C,; Sander, P.; et. al.10  (ICSI) | Digoxin | Serum digoxin | Elderly or renal-impaired patient with heart failure | Monitor at 1 – 2 weeks after initiation | Monitor to avoid digoxin toxicity: serum digoxin levels do not always correlate to symptoms of toxicity | Consensus [5] |
| Serum digoxin | Patients age 18 years or older with heart failure | 5- to 7-days after initiation/dose change | Monitoring also recommended for: suspected toxicity, suspected non-adherence, new or existing renal dysfunction, determination of therapeutic range |
| Hurley, J.S.; Roberts, M.; et. al.13 | Digoxin | Serum digoxin | Patients age 19 or older and taking at least one chronic medication | Monitoring at 1 year after initiation |  | Retrospective Cohort [2b] |

**Rate 3: Annual Monitoring for Members on Diuretics**

**Numerator**. At least one serum potassium and either a serum creatinine or a blood urea nitrogen therapeutic monitoring test in the measurement year.

**Interpretation**: We believe the evidence supports using serum creatinine and serum potassium as annual monitoring parameters for patients taking diuretics. There is less evidence of the utility of using blood urea nitrogen (BUN) to monitor renal function for patients taking diuretics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference (No.)** | **Medication** | **Monitoring Parameter** | **Population** | **Frequency** | **Rationale** | **Score** |
| Chobanian AV et al.29 | Potassium-Sparing Diuretic | Serum potassium | Patients with heart failure |  |  | Consensus-Based Guideline [5] |
| Lindenfeld J et al. 22 | Aldosterone Antagonist (Potassium-Sparing Diuretic) | Serum potassium | Patients with heart failure | Varied with RCT | RALES Trial: Serum potassium was monitored every 4 weeks for 12 weeks, every 3 months up to a year, and every 6 months after the first year during Potassium-Sparing Diuretic therapy in patients with diabetes or renal insufficiency or in those taking ACE Inhibitors or ARBs30  EPHESUS Trial: Serum potassium was monitored at 48 hours, at 4 – 5 weeks, and then every 3 months during Potassium-Sparing Diuretic therapy in patients taking a large number of concomitant medications31 | Evidence-Based Guideline [1b] |
| Lindenfeld J et al. 22 | Spironolactone | Serum potassium Serum creatinine | Patients with heart failure | Within first few weeks of the treatment | See above rationale. | Evidence-Based Guideline [1b] |
| Lindenfeld J et al. 22 | Eplerenone | Electrolytes, especially serum potassium | Patients with heart failure and with eGFR <60 ml/min, baseline serum potassium  >4.3 mEq/L, diabetes mellitus, and prior use of antiarrhythmic drugs. | Not specified | See above rationale | Evidence-Based Guideline [1b] |
| Hunt SA et al. 32 | Diuretics | Serum potassium | Patients with heart failure | Not specified | Hypokalemia is a common adverse effect of treatment with Diuretics and may cause fatal arrhythmias and increase the risk of digitalis (digoxin) toxicity, whereas hyperkalemia may complicate therapy with ACE Inhibitors, ARBs, and Potassium-Sparing Diuretics (Aldosterone Antagonists) | Consensus-Based Guideline [5] |
| Hunt SA et al. 32 | Potassium-Sparing Diuretic (Aldosterone Antagonist) | Serum potassium  Renal function | Patients with heart failure | 3 days, 1 week, 3 months, and then 3 month intervals | Subsequent monitoring should be dictated by the general clinical stability of renal function and fluid status  The addition or an increase in dosage of ACE Inhibitors or ARBs should trigger a new cycle of monitoring | Consensus-Based Guideline [5] |
| Hunt SA et al. 32 | Potassium-Sparing Diuretic (Aldosterone Antagonists) | Serum potassium Renal function | Patients with heart failure | Not recommended | Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of the therapy in patients with current or prior symptoms of heart failure33-35 | Evidence-Based Guideline [3b] |
| Institute for Clinical Systems Improvement (ICSI)36 | ACE Inhibitor  ARB  Diuretic  Potassium-Sparing Diuretic  (Aldosterone Antagonist) | Serum potassium  Electrolytes  Renal function | Patients with heart failure and hypotension | Not specified | NA | Consensus-Based Guideline [5] |
| McDowell SE et al.11 | ACE Inhibitor  ARB  Diuretic | Serum potassium  Serum creatinine | Patients with hypertension | 2 weeks and then every 12 months of therapy | NA | Systematic Review [2b] |
| McDowell SE et al.12 | Diuretic | Serum potassium  Serum creatinine | Ambulatory patients with hypertension | 6 months, 1 year, and 2 years after initiation of therapy | Renal function (serum creatinine and serum electrolytes) should be monitored at 1 – 2 weeks after each dose increase/relevant drug addiction in low-risk patients (e.g., those receiving ACE Inhibitors, ARBs, and Diuretics) and at 5 – 7 days in higher-risk patients [e.g., those receiving spironolactone (Potassium-Sparing Diuretic), those with existing renal dysfunction, those receiving combination therapy] with heart failure.14  Serum potassium and renal function were monitored at 3 days and at 6 months after initiation of ACE Inhibitors, ARBs, and Diuretics in patients, 18 and older, with newly diagnosed hypertension and newly treated with a single antihypertensive drug.17 | Systematic Review [2b] |
| LASIX ®  (furosemide)37 | Furosemide | Serum electrolytes (particularly potassium)  Serum creatinine  Blood urea nitrogen | Not specified | frequently during the first few months of therapy and periodically thereafter | NA | FDA label |
| Aldactone ® (spironolactone)38 | Spironolactone | Serum electrolytes | elderly patients and those with significant renal or hepatic impairments | Not specified | NA | FDA Label |
| Hydrochlorothiazide39 | Hydrochlorothiazide | Serum electrolytes | Not specified | Not specified | NA | FDA Label |

**Additional Monitoring Parameters for Members on Diuretics**

**Interpretation**: We do not believe the evidence supports using volume status as an annual monitoring parameter for patients taking diuretics.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Reference (No.)** | **Medication** | **Monitoring Parameter** | **Population** | **Frequency** | **Rationale** | **Score** |
| Lindenfeld J et al. 22 | Diuretics | Volume status | Patients with heart failure using multiple diuretics | Close monitoring |  | Consensus-Based Guideline [5] |

**References**

1 . Novartis Pharmaceutical Corporation; 2012.

2 . Merck & Company, Inc.; 2013.

3 Brenner BM, Cooper ME, de Zeeuw D et al. The losartan renal protection study--rationale, study design and baseline characteristics of renaal (reduction of endpoints in niddm with the angiotensin ii antagonist losartan). *Journal of the renin-angiotensin-aldosterone system : JRAAS.* 2000; 1(4): 328-35.

4 Miao Y, Dobre D, Heerspink HJ et al. Increased serum potassium affects renal outcomes: A post hoc analysis of the reduction of endpoints in niddm with the angiotensin ii antagonist losartan (renaal) trial. *Diabetologia.* 2011; 54(1): 44-50.

5 Chobanian A, Bakris G and Black H. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension.* 2003; 42(6): 1206-52.

6 Hunt SA AW, Chin MH et al. . 2009 focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults: A report of the american college of cardiology foundation/american heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. *Circulation.* 2009; 119(14): e391-479.

7 Gottlieb SS, Robinson S, Krichten CM et al. Renal response to indomethacin in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1992; 70(9): 890-3.

8 Packer M. Adaptive and maladaptive actions of angiotensin ii in patients with severe congestive heart failure. *Am J Kidney Dis.* 1987; 10(1 Suppl 1): 66-73.

9 Burnier M, Waeber B, Nussberger J et al. Effect of angiotensin converting enzyme inhibition in renovascular hypertension. *J Hypertens Suppl.* 1989; 7(7): S27-31.

10 Pinkerman C, Sander P, Breeding JE et al. Heart failure in adults. *Institute for Clinical Systems Improvement (ICSI).* 2013.

11 McDowell SE, Thomas SK, Coleman JJ et al. A practical guide to monitoring for adverse drug reactions during antihypertensive drug therapy. *Journal of the Royal Society of Medicine.* 2013; 106(3): 87-95.

12 McDowell SE and Ferner RE. Biochemical monitoring of patients treated with antihypertensive therapy for adverse drug reactions: A systematic review. *Drug Saf.* 2011.

13 Hurley JS, Roberts M, Solberg LI et al. Laboratory safety monitoring of chronic medications in ambulatory care settings. *Journal of general internal medicine.* 2005; 20(4): 331-3.

14 Smellie WS, Forth J, Coleman JJ et al. Best practice in primary care pathology: Review 6. *Journal of clinical pathology.* 2007; 60(3): 225-34.

15 Burden R and Tomson C. Identification, management and referral of adults with chronic kidney disease: Concise guidelines. *Clin Med.* 2005; 5(6): 635-42.

16 Swedberg K, Cleland J, Dargie H et al. Guidelines for the diagnosis and treatment of chronic heart failure: Executive summary (update 2005): The task force for the diagnosis and treatment of chronic heart failure of the european society of cardiology. *Eur Heart J.* 2005; 26(11): 1115-40.

17 Coleman JJ, McDowell SE, Evans SJ et al. Oversight: A retrospective study of biochemical monitoring in patients beginning antihypertensive drug treatment in primary care. *British journal of clinical pharmacology.* 2010; 70(1): 109-17.

18 Raebel MA, McClure DL, Simon SR et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf.* 2007; 16(1): 55-64.

19 Wright J and Musini V. First-line drugs for hypertension (review). *Cochrane Database of Systematic Reviews.* 2009; (3).

20 Yusuf S and Phil D. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *The New England Journal of Medicine.* 2000; 342(3): 145-53.

21 McDowell S and Ferner R. Biochemical monitoring of patients treated with antihypertensive therapy for adverse drug reactions a systematic review. *Drug Safety.* 2011; 34(11): 1049 - 59.

22 Lindenfeld J, Albert NM, Boehmer JP et al. Hfsa 2010 comprehensive heart failure practice guideline. *Journal of cardiac failure.* 2010; 16(6): e1-194.

23 Uretsky B, Young J, Shahidi F et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: Results of the proved trial. *Journal of American College of Cardiology.* 1993; 22(4): 955-62.

24 Packer M, Gheorghiade M, Young J et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. *The New England Journal of Medicine.* 1993; 329(1): 1-7.

25 Garg R and Gorlin R. The effect of digoxin on mortality and morbidity i patients with heart failure. *The New England Journal of Medicine.* 1997; 336(8): 525-33.

26 Young J, Gheorghiade M, Uretsky B et al. Superiority of "triple" drug therapy in heart failure: Insights from the proved and radiance trials. *Journal of American College of Cardiology.* 1998; 32: 686-92.

27 Krum H, Bigger J, Goldsmith R et al. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. *Journal of American College of Cardiology.* 1995; 25(2): 289-94.

28 . Roxane Laboratories, Inc.; 2012.

29 Chobanian AV, Bakris GL, Black HR et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension.* 2003; 42(6): 1206-52.

30 Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldactone evaluation study investigators. *N Engl J Med.* 1999; 341(10): 709-17.

31 Pitt B, Remme W, Zannad F et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med.* 2003; 348(14): 1309-21.

32 Hunt SA, Abraham WT, Chin MH et al. 2009 focused update incorporated into the acc/aha 2005 guidelines for the diagnosis and management of heart failure in adults: A report of the american college of cardiology foundation/american heart association task force on practice guidelines: Developed in collaboration with the international society for heart and lung transplantation. *Circulation.* 2009; 119(14): e391-479.

33 Juurlink DN, Mamdani M, Kopp A et al. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA.* 2003; 289(13): 1652-8.

34 Juurlink DN, Mamdani MM, Lee DS et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. *N Engl J Med.* 2004; 351(6): 543-51.

35 Svensson M, Gustafsson F, Galatius S et al. How prevalent is hyperkalemia and renal dysfunction during treatment with spironolactone in patients with congestive heart failure? *J Card Fail.* 2004; 10(4): 297-303.

36 . Heart failure in adults. *Institute for Clinical Systems Improvement (ICSI).* 2011.

37 . Lasix (furosemide) prescribing information. Bridgewater, nj: Sanofi-aventis. 2011 Aug.

38 . Aldactone (spironolactone) prescribing information. New york, ny; pfizer. 2013 Jun.

39 . Hydrochlorothiazide prescribing information.Morgantown, wv; mylan pharmaceuticals. 2011 May.

40 Tomson T, Dahl ML and Kimland E. Therapeutic monitoring of antiepileptic drugs for epilepsy. *Cochrane Database Syst Rev.* 2007; (1): CD002216.

41 Jannuzzi G, Cian P, Fattore C et al. A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. *Epilepsia.* 2000; 41(2): 222-30.

42 Patsalos PN, Berry DJ, Bourgeois BFD et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: A position paper by the subcommission on therapeutic drug monitoring, ilae commission on therapeutic strategies. *Epilepsia.* 2008; 49(7): 1239-76.

43 Johannessen SI and Landmark CJ. Antiepileptic drug interactions - principles and clinical implications. *Curr Neuropharmacol.* 2010; 8(3): 254-67.

44 Johannessen Landmark C and Patsalos PN. Drug interactions involving the new second- and third-generation antiepileptic drugs. *Expert Rev Neurother.* 2010; 10(1): 119-40.

45 Eadie MJ. Therapeutic drug monitoring--antiepileptic drugs. *Br J Clin Pharmacol.* 2001; 52 Suppl 1: 11S-20S.

46 Johannessen SI, Battino D, Berry DJ et al. Therapeutic drug monitoring of the newer antiepileptic drugs. *Ther Drug Monit.* 2003; 25(3): 347-63.

47 . Dilantin (phenytoin) prescribing information. New york, ny; pfizer. . 2012 Jan.

48 . Depakene (valproic acid) prescribing information. North chicago, il; abbvie inc. 2013 Jun.

49 . Tegretol ® (carbamazepine) prescribing information. East hanover, nj; novartis. 2013 Feb.