NATIONAL PBM BULLETIN

September 30, 2014

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), VISN PHARMACIST EXECUTIVES (VPES), OFFICE OF NATIONAL PROGRAM DIRECTOR FOR CARDIOLOGY, AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

DIGOXIN IN PATIENTS WITH ATRIAL FIBRILLATION: POTENTIAL HARMS

I. ISSUE

Results from TREAT-AF (The Retrospective Evaluation and Assessment Therapies in Atrial Fibrillation), evaluating data in veteran patients, were recently published. Results of this analysis, along with additional retrospective evaluations, may have implications for clinical practice, especially in patients prescribed digoxin for rate control in atrial fibrillation (AF), and where other effective therapies are available.

II. BACKGROUND

FDA Approved Indications: Digoxin is indicated for the control of ventricular response in chronic atrial fibrillation and for patients with mild to moderate heart failure.[1]

Clinical Practice Guideline Recommendations:

- ***Atrial Fibrillation [2014 AHA/ACC/HRS]:*** [2] Digoxin is not usually considered first-line therapy for AF. Control ventricular rate using a beta blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) [Class I Recommendation; Level of Evidence B]. Digoxin reduces resting heart rate but is not effective for management of the ventricular response in patients with AF during exercise. Digoxin may be considered in combination with a beta blocker or non-DHP CCB for rate control and has been used in patients with concomitant HF.[2]
- ***Heart Failure with reduced Ejection Fraction (HFrEF) [2013 ACCF/AHA]:*** [3] Digoxin can be beneficial in patients with HF*r*EF, unless contraindicated, to decrease hospitalizations for HF [Class IIa Recommendation; Level of Evidence B]; the addition of digoxin may be considered in patients with persistent symptoms despite treatment with guideline directed medical therapy (i.e., Class I recommended therapies: diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, mineralocorticoid receptor antagonists, hydralazine/isosorbide dinitrate, as indicated). [3]

III. DISCUSSION

After the on-treatment analysis of the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) Study reported an increased mortality in the subgroup of patients receiving digoxin (HR 1.42, 95% CI 1.09 to 1.86; p=0.0007),[4] several subgroup and retrospective analyses have been conducted to evaluate the potential association between treatment with digoxin and all-cause mortality.[5-9] Two separate evaluations of the AFFIRM data, using different methods to evaluate the data based on propensity scores, reported conflicting results;[5,6] the first finding an increased risk of mortality associated with digoxin[5] whereas the second did not find a significant increase in mortality with digoxin treatment.[6] More recently, TREAT-AF retrospectively studied 122,465 VA patients, 28,679 (23.4%) of whom received digoxin, and reported a 21% increased risk of all-cause mortality in newly diagnosed patients with AF who received treatment with digoxin compared to those who did not.[7] The respective results were not modified by concomitant HF.[5-7]

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Analysis	All-Cause Mortality HR (95% CI)	p value
TREAT-AF[7]		
Digoxin vs. No Digoxin	1.21 (1.17 to 1.25)	<0.001
HF diagnosis	1.28 (1.21 to 1.36)	NS for interaction
AFFIRM (Whitbeck et al)[5]		
Digoxin vs. No Digoxin	1.41 (1.19 to 1.67)	<0.001
HF diagnosis	1.41 (1.09 to 1.84)	0.010
No HF diagnosis	1.37 (1.05 to 1.79)	0.019
AFFIRM (Gheorghiade et al)[6]		
Digoxin vs. No Digoxin	1.06 (0.83 to 1.37)	0.640
HF diagnosis	1.08 (0.80 to 1.47)	0.609
No HF diagnosis	1.08 (0.69 to 1.69)	0.743

NS=not statistically significant

As a prospective comparison trial is not available, definitive data on the risk of mortality with digoxin use in patients with AF, with or without concomitant HF*r*EF, has yet to be determined. However, given the potential association, and as recommended by clinical practice guidelines, digoxin should not be used as initial therapy for rate control in patients with AF, and should only be considered after a trial of a beta blocker (in patients with AF, alone or with concomitant HF*) or non-DHP CCB (in patients with AF without concomitant HF). In addition, providers are encouraged to reevaluate the treatment regimen of their patients receiving digoxin to ensure they are receiving the most appropriate therapy for AF.

***Note that according to an individual-patient data meta-analysis, treatment with a beta blocker in patients with HF*r*EF did not demonstrate a significant reduction in death or major cardiovascular outcomes in patients with concomitant AF; treatment with a beta blocker would still be appropriate for patients requiring rate control of rapid AF with symptoms.[10]

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

Prior to initiating therapy with digoxin, patients requiring rate control in AF should be evaluated for and preferentially treated with other recommended therapies (i.e., beta blocker, non-DHP CCB) as outlined under Clinical Practice Guideline Recommendations.

For patients already receiving digoxin for rate control in **atrial fibrillation**, providers are encouraged to review treatment at the next routine (non-urgent) visit at which the following is recommended:

- Control the ventricular rate using a beta blocker or non-DHP CCB, as indicated. Consider additional therapy with digoxin after consideration of the potential risk vs. benefit. Digoxin should not be used as monotherapy in patients for exercise-induced rate control in AF.
- If digoxin is prescribed, conservative dosing should be used and the patient's kidney function assessed and dose adjusted accordingly to avoid potential digoxin toxicity.*

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For patients with **concomitant HF*r*EF and requiring rate control of AF**, the following is recommended regarding the use of digoxin:

- In addition to the above recommendation for management of AF, patients with HF*r*EF and AF should preferentially receive treatment with guideline directed medical therapy for their HF*r*EF (i.e., diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, mineralocorticoid receptor antagonists, hydralazine/isosorbide dinitrate, as indicated); the addition of digoxin may be considered in patients with persistent HF symptoms despite the recommended therapy, as indicated.[3,11]
- If digoxin is prescribed, conservative dosing should be used and the patient's kidney function assessed and dose adjusted accordingly to avoid potential digoxin toxicity.*

* In general, trough (or a minimum of 6 hours post dose) serum digoxin levels should be monitored if any of the following occurs: renal function deteriorates; signs of toxicity develop; dose adjustments are made; medications are added that affect serum digoxin concentration, or the sensitivity to digoxin by altering potassium levels. In addition, the lowest effective dose should be used (per post hoc analyses, as a linear association was seen with increasing digoxin levels and mortality in patients with HF;[12] with the risk vs. benefit questioned in women with HF due to the lack of benefit compared to men, and trend toward increased mortality in women with HF treated with digoxin[13-15]).

Although the use of digoxin for atrial fibrillation has decreased substantially in VA (by > 50% from 2002 to 2011), with an increase in the use of certain beta blockers,[16] it is estimated that approximately 51,500 patients in VA are currently receiving an active prescription for digoxin, with roughly 62% of these patients having a diagnosis of AF (and approximately 24% with both a diagnosis of AF and heart failure). Approximately 39% of patients prescribed digoxin have a diagnosis of AF without concomitant heart failure. It is also noted that of the patients in VA with a diagnosis of AF, less than 15% are receiving an active prescription for digoxin.

V. REFERENCES

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DIGOXIN IN PATIENTS WITH ATRIAL FIBRILLATION: POTENTIAL HARMS *(continued from page 3)*

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ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers and health care staff (e.g.,* ***primary care providers, and cardiologists , including contract providers, etc****.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*