Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Clinical Guidance Document: Digoxin Use
-February 2016-

Background:
Digoxin has been routinely used in the treatment of various cardiac conditions including atrial fibrillation (AF) and congestive heart failure (CHF). There remains controversy however surrounding the benefit of digoxin use in these patient populations. Recent published findings of patient outcomes with digoxin use question its role in contemporary practice, creating an opportunity for IHS clinicians to evaluate their current digoxin usage as well as identify alternative treatment approaches, when warranted.

Discussion:
Digoxin, an important cardiac glycoside with cardiotonic and rate control properties, remains widely used in clinical practice despite recent publicized concern of its disputed efficacy and safety in AF[1-4]. Originally derived from the Foxglove plant (*digitalis purpurea*) over 200 years ago, digoxin's narrow therapeutic window requires routine serum drug monitoring to both avoid toxicity and derive optimal therapeutic benefit. A *post-hoc* analysis from the famed DIG trial found that elevated serum digoxin levels (defined as $\geq$1.2 ng/ml) were significantly associated with increased mortality whereas lower serum digoxin levels appeared to impart benefit[5]. Current national and international guidelines recommend digoxin use in certain AF and CHF populations despite the scarcity of randomized, controlled trials (RCTs) demonstrating net benefit[6-9]. To date, there are no randomized, placebo-controlled trials yielding supportive data for digoxin use (rate control) in AF patients and only one large, randomized placebo-controlled study of digoxin in CHF patients demonstrating positive outcomes. Recent observational studies have presented compelling data that associate digoxin with increased all-cause mortality, in some populations by more than 2-fold[10].

Literature review:
Vamos et al. published a 2015 meta-analysis on digoxin-associated mortality which included 19 trials (AF=9, CHF=7, AF+CHF=3) comprising 326,426 patients[11]. Only 1 RCT was included in the analysis, all others were either retrospective or prospective, observational studies. Compared to patients not receiving digoxin, the authors found that digoxin use overall, regardless of indication, was associated with a 21% increased risk of all-cause mortality (HR=1.21; 95% CI: 1.07-1.38, p<0.01). Specifically, its use in AF patients resulted in 29% higher mortality risk (HR=1.29; 95% CI: 1.21-1.38) whereas patients receiving digoxin for CHF had a 14% increased risk of mortality (HR=1.14; 95% CI: 1.06-1.22). The authors stated that only a few studies in their analysis provided data on digoxin dose or plasma levels and that no association of mortality and digoxin dose/plasma level was reported.

Ziff et al. also published a meta-analysis in 2015 of 42 observational and experimental studies on digoxin safety and efficacy (n=621,845) in patients receiving digoxin for AF or CHF[12]. Overall, data from observational studies showed an increased risk in all-cause mortality however, interestingly, in the 7 RCTs (all CHF) included in the study, digoxin use was associated with a neutral effect on mortality (RR=0.99; 95% CI: 0.93-1.05, p=0.75). No evidence of heterogeneity was observed across these 7 studies (I^2=0%, p=0.97). The authors concluded that the observational studies showing increased mortality with digoxin had higher risk for bias and were unable to adjust for differences in digoxin patient types. Subsequently, they recommended that clinical decisions be based on methodologically superior data from RCTs.

Lastly, limited data from their analysis provided that serum digoxin levels of 0.5-0.9 ng/ml were associated with improved prognosis while elevated levels correlated with higher mortality.

Lastly, a third meta-analysis published in 2015 analyzed 302,738 patients receiving digoxin for AF[13]. None of the 8 studies included were RCTs but rather prospective or retrospective cohort studies. It found that digoxin use was associated with 37.5% increased risk of all-cause mortality overall (HR=1.38; 95% CI: 1.20-1.57, p=0.0001). Furthermore, subgroup analyses showed all-cause mortality was increased in both AF patients with CHF (HR=1.20; 95% CI: 1.07-1.34, p=0.001) and in those without CHF (HR=1.17; 95% CI: 1.15-1.20, p=0.0001). The authors concluded that digoxin use was associated with increased all-cause mortality in AF patients regardless of concomitant CHF and suggested that digoxin be non-preferred to other rate control medications. Several other published analyses of observational data have shown similar results, concluding that digoxin use in AF patients is associated with increased mortality, often regardless of concurrent CHF status[2,10,14].

Clinical guidance:
Given the new analyses and compelling data, the NPTC offers the following strategies to help mitigate, provide alternatives for or improve safety in digoxin use:

1) Review current AF and CHF practice guidelines to ensure a thorough, contemporary understanding of select patients where digoxin is both encouraged and contraindicated.
2) Use caution if selecting digoxin for use in AF patients (with or without HF); consider other pharmacotherapeutic options where possible.
3) In CHF patients, consider reserving digoxin for those who remain symptomatic despite optimization of treatments with proven mortality benefit (ACEi/ARBs, B-blockers) and diuretics.
4) If digoxin is selected as adjunctive therapy in CHF patients, regular serum drug level monitoring is highly encouraged to target a serum digoxin level of 0.5-0.9 ng/ml.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

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