Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Antiarrythmic Drugs***
-November 2020-

Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed atrial fibrillation during the Fall 2020 NPTC meeting. Atrial fibrillation is a common and challenging cardiac tachyarrhythmia to treat. Antiarrhythmic drugs (AADs) have long been the primary treatment for atrial fibrillation. Recent changes in treatment strategies resulted in the review of this drug class. As a result of this review, no changes were made to the IHS National Core Formulary.

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting over 33 million people worldwide and over 3 million in the United States[1]. In 2001, high costs were associated with non-valvular AF for inpatients ($6.65 billion), outpatients ($1.53 billion) and for medications alone ($235 million)[1]. AF is defined as a rapid, irregular heart rhythm diagnosed typically by electrocardiogram and physical exam. Severity can range from asymptomatic to life-threatening. AF with rapid ventricular rate (AF with RVR) may be complicated by hemodynamic instability requiring emergent management. AF can also be a risk factor for new onset heart failure, stroke and dementia[1]. An evaluation of the PINNACLE-AF registry found considerable disparities in the treatment of American Indian/Alaskan Native populations with AF including both oral anticoagulants and rhythm control strategies[2].

Treatment of asymptomatic and chronic AF is typically managed in the outpatient setting using behavioral changes, pharmacologic therapies, and consideration of procedural therapies. This review considered the following questions; (1) is a rate control or rhythm control strategy preferable, (2) is there a singular preferred medication for optimal control, and (3) are procedural interventions preferable to AADs?

Discussion:

Rate control versus rhythm control: Rate-control strategies are therapies that aim to control heart rate only (without a goal of returning to sinus rhythm) while rhythm-control strategies attempt to return the heart to sinus rhythm. Prior to 2000, rhythm-control was the primary goal for AF therapy. However, in the early 2000's two large studies, the RACE and AFFIRM trials, demonstrated that a rate control strategy had a trend towards lower mortality believed in large part due to the safer and easier use the medications for rate control. These studies concluded that rate control was superior[3]. The AFFIRM trial demonstrated a significant reduction in mortality for two pre-specified subgroups: those without a history of heart failure (adjusted HR 0.69) and those aged 65 years or older (HR 0.76)[4]. Similarly, the number of patients requiring hospitalization during the follow-up period was significantly lower in the rate control group (73% vs 80%)[4]. No significant differences were found with any of the other pre-specified subgroups including the composite secondary end point of death, stroke, bleeding, cardiac arrest, death due to stroke, or quality of life[4].

In 2004, a subgroup analysis of the mortality benefit of achieving sinus rhythm found that the presence of sinus rhythm was associated with a lower incidence of death, that AADs were associated with increased mortality only after adjustment for the presence of sinus rhythm, and that AADs were not associated with increased mortality when sinus rhythm was removed from the model[5]. In 2013, Chaterjee et al. performed a comprehensive meta-analysis of rate vs. rhythm control studies. Using pooled data, they confirmed that rate-control strategies had improved outcomes in most measures with the exception of people less than 65 years old where a rhythm-control strategy was superior in the prevention of all-cause mortality (RR 3.03, 95% CI: 1.59-5.75, p=0.0007)[6]. This led to guidelines favoring a rate-control strategy in most patients[7]. A study published in October 2020, the EAST-AFNET 4 trial, showed that a rhythm-control strategy is superior to usual care in improving cardiovascular (CV) outcomes at 5 years among patients with recent diagnosis of AF and concomitant CV conditions[8]. This study was stopped early because the primary outcome (composite of CV death, stroke, hospitalization for HF, or acute coronary syndrome) for rhythm-control vs usual care was 3.9 vs. 5.0/100 person-years (HR 0.79, 95% CI: 0.66-0.94, p=0.005). It should be noted that in the EAST-AFNET trial rhythm-control therapies included both AAD and catheter ablation. The EAST-AFNET trial is likely influenced by both improved procedures for rhythm control as well as increased experience with narrowly therapeutic AADs.

Preferred AAD for rhythm control: The selection of AAD for long term AF treatment is based on the underlying heart disease of the patient, specific drug profile for specific patient characteristics, and the presence or absence of structural heart disease. For example, amiodarone and dofetilide are the only AADs that have not been shown

to increase mortality in patients with heart failure[1]. A 2019 Cochrane review compared the safety and efficacy of all available AADs in the United States[9]. This study found that sotalol was associated with higher all-cause mortality (RR 2.23, 95% CI: 1.03-4.81) with NNH=102, amiodarone (RR 1.66, 95% CI: 0.55-4.99) showed increased RR for mortality with wide confidence intervals, dofetilide and dronedarone had little to no difference in mortality compared to placebo/no treatment, and too few data existed to determine mortality effect for disopyramide, flecanide, and propafenone. All of the AADs examined had an increased study withdrawal rate due to adverse effects and all AADs were proarrhythmic, with dofetilide and flecanide being the highest with relative risks of 5.50 and 4.80, respectively. Conclusions from this study continued to support the use of these medications with careful consideration of drug and patient characteristics.

Procedural Interventions for treatment of long term AF: In 2019 two large trials, the CABANA (Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation) and CAPTAF (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation) compared catheter ablation outcomes to AAD outcomes. The CABANA trial demonstrated no difference in a primary composite endpoint of death, disabling stroke, serious bleeding or cardiac arrest and no difference in the secondary endpoints of all-cause mortality, total mortality or CV hospitalization, and AF recurrence, although this may have been biased by the high rates of post-randomization crossover from the AAD arm to ablation[10]. The CAPTAF trial demonstrated that improvement in quality of life at 12 months was greater in those treated with catheter ablation compared with AADs[11]. This included a reduction in AF burden from 24.9% to 5.5% in the ablation group versus 23.3% to 11.5% in the medication group. Thus, catheter ablation has similar rates of mortality and AF recurrence reduction to AADs and may be preferred due to absence of life-threatening side effects of AADs.

Clinical society guidelines: The 2014 ACC/AHA guidelines, with regard to AADs for maintenance of sinus rhythm, state that “the risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug” (IC) and “antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent, including dronedarone” (IIIC/B for harm). The 2020 European Society of Cardiology does recommend rhythm control strategies for improvement of symptoms and quality of life in symptomatic patients with AF (IA).

Findings:

Atrial fibrillation is common and treatment is worthwhile to mitigate risks of more serious disease. While recent data supports early rhythm-control as a means to treat AF and its complications, rate-control is preferred in most clinical scenarios. Catheter-ablation has similar rates of mortality and AF recurrence reduction and may be preferred due to absence of life-threatening side effects of AADs, however limitations exist with regard to access to specialty care. No singular AAD is preferred by clinical societies and many have strict contraindications. Thus, given the need for specialty consult in use of AADs which have narrow therapeutic windows and even narrower therapeutic indications, no additions were made to the IHS National Core Formulary.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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