# Indian Health Service
# National Pharmacy and Therapeutics Committee
# Formulary Brief: Direct Oral Anticoagulants (DOACs)
*-November 2017-*

**Background:**
The direct oral anticoagulants (DOACs) were reviewed at the November 2017 National Pharmacy & Therapeutics Committee (NPTC) meeting for use in patients with atrial fibrillation and venous thromboembolism. Randomized controlled trials (RCTs), observational "real world" effectiveness studies, clinical practice guidelines and meta-analyses were scrutinized to distinguish individual DOAC safety and efficacy, as well as their potential role(s) for inclusion on the National Core Formulary (NCF). Following a clinical and pharmacoeconomic review of this drug class, the NPTC voted to **ADD apixaban** to the NCF**.**

**Discussion:**
The first DOAC (dabigatran) was FDA-approved in 2010, giving clinicians the first oral anticoagulant alternative to warfarin in over 60 years[1]. Since then, 4 more agents (rivaroxaban, apixaban, edoxaban, betrixaban) have received FDA approval for various indications including stroke prophylaxis in nonvalvular atrial fibrillation and/or thromboembolic conditions[2-5]. Despite the majority of DOACs sharing a similar mechanism of action (Factor Xa inhibition), these medications have differing pharmacokinetic and pharmacodynamic profiles that contribute to subtle yet meaningful patient outcomes.

*DOACs in Atrial Fibrillation (stroke and systemic embolism prevention):*
Patients diagnosed with atrial fibrillation (AF) are at increased risk of cardioembolic stroke (3 to 5 fold), mortality (24%) and hospitalization (10-40%)[6-8]. Warfarin has long been recognized as the standard of care by reducing stoke incidence by up to two-thirds in patients with AF[9]. Challenges exist however to broad utilization of warfarin, leading to suboptimal prescribing and management of warfarin (i.e., INR time-in-range) in eligible patients[10-12]. When compared to warfarin in randomized trials, DOACs have demonstrated comparable or improved patient outcomes and offer greater opportunity for widespread use by virtue of improved drug characteristics (e.g., standard dosing, less monitoring, fewer drug/food interactions)[13-16]. Clinical practice guidelines from major national and international organizations published in 2014 suggest that DOACs be considered for initial selection in patients starting an anticoagulant[17,18]. More recently, the 2016 European Society of Cardiology AF guidelines strongly recommended DOACs in preference to warfarin (Level 1A recommendation) in eligible patients initiating anticoagulant therapy.

Although no head-to-head studies of DOACs exist, clinicians can glean clinically meaningful differences in outcomes derived from RCTs, meta-analyses and observational, "real-world" effectiveness studies of DOACs. Through indirect comparison of the DOAC-approving RCTs, statistically significant reductions were shown with dabigatran and apixaban (prevention of stroke/systemic embolism) while only apixaban and edoxaban demonstrated statistically significant reductions in major bleeding. Only apixaban produced a significant reduction in all-cause mortality[13-16]. Several meta-analyses support and agree that the DOACs' reductions in bleeding events (major bleeding, hemorrhagic stroke and intracranial bleeding) contribute primarily to their overall net benefit (reduced mortality) over conventional warfarin therapy[19-21].

Analysis of observational data can offer valuable insight by enabling clinicians to compare outcomes from the larger, post-marketing "real world" effectiveness studies to those outcomes reported in methodically-superior RCTs. Effectiveness studies are also useful by allowing for direct comparison of individual DOAC outcomes. Inherent limitations exist (i.e., biases) when utilizing observational data however but can be mitigated through applied statistical methodologies such as propensity score matching. Appreciating this, multiple real world effectiveness studies have universally concluded that DOACs appear to be similarly effective in stroke/systemic embolism reduction but that apixaban is routinely associated with lower overall rates of bleeding events (i.e., major, hemorrhagic, gastrointestinal)[22-25].

*DOACs in Venous Thromboembolism (prevention and treatment):*

The annual incidence of venous thromboembolism (VTE) in adults is approximately 1 in 1000. Unprovoked VTE has a 10% risk of recurrence within the first year after ending treatment and a 30% risk of reoccurrence within 5 to 10 years[26]. Hospitalizations for VTE compared to controls are 1.5 to 2.5 fold higher for acute medical illness, major surgery, and active cancer[27]. Vitamin K antagonists (VKA) have historically been preferentially recommended for the treatment and prevention of recurrence of VTE in the outpatient setting. In 2014, the European Society of Cardiology Guidelines for acute pulmonary embolism (PE) stated that DOACs were non-inferior in efficacy and possibly safer than standard heparin/VKA regimens for the treatment of PE and recommended DOACs as alternatives to standard therapy[28]. More recently, the 2017 American College of Chest Physicians antithrombotic guidelines recommended DOACs over VKAs in the treatment of VTE episodes (both deep venous thrombosis and PE) in patients without cancer. Low molecular weight heparin (LMWH) remains recommended (first line) therapy for patients with cancer and VTE. DOACs are listed as alternative to LMWH in total hip and total knee arthroplasty for VTE prophylaxis[29].

As with AF, there are no head-to-head comparisons of DOACs in VTE treatment and/or prevention. Systematic reviews and meta-analyses of phase III trials for each of the DOACs, excluding betrixaban, show DOACs as effective as and generally safer than standard therapy for acute VTE. There is a statistically significantly lower risk of all bleeding events, except major GI bleeding, with all DOACs[30,31]. For both acute treatment and prevention of VTE, DOACs reported a similar reduction in VTE or VTE-related death in all-cause mortality compared with each other and with conventional therapy. Apixaban has a significantly improved bleeding profile compared with other DOACs[32]. An observational, comparative safety study concluded that DOACs (when compared to warfarin) were not associated with increased risk of major bleeding or all-cause mortality in the first 90 days of treatment. These results were consistent across all age and gender groups and in those with or without chronic kidney disease[33].

In 2014, Geldhof et al. performed a meta-analysis of phase III trials evaluating DOACs (except betrixaban) with VKAs in the elderly and in those with impaired renal function. VKAs were favored only over dabigatran for overall efficacy, according to age and renal function, as well as for major bleeding in the subgroup with CrCl $\leq$50 ml/min. Although this analysis suggested that the DOACs (minus dabigatran) were preferable to VKA in these patients, appropriately powered studies are needed to confirm[34].

As mentioned previously, LMWHs remain first line for treating patients with cancer and VTE. Both a network meta-analysis (using VKA as a common comparator for LMWH and DOACs) as well as a meta-analysis reviewing both DOACs and VKA versus LMWH suggested that DOACs are as safe and effective as LMWH for preventing recurrent VTE; head-to-head comparison is however recommended[35,36].

Betrixaban was approved in June 2017 for the prophylaxis of VTE in adult patients hospitalized with acute medical illness but remains unavailable in the United States. The Acute Medically Ill VTE Prevention with Extended Duration Betrixaban trial concluded that no differences in outcomes were found between betrixaban and enoxaparin in asymptomatic proximal DVT (between days 32 and 47), symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE (between day 1 and 42)[37]. At this time, betrixaban has not been compared with other DOACs.

**Findings:**

The availability of DOACs provide clinicians with (perhaps superior) alternatives to warfarin therapy in addressing current gaps in treatment/prophylaxis of thromboembolic events. Though DOACs offer clear pharmacotherapeutic advantages over warfarin, in the IHS their use can be complementary to existing treatment approaches. Warfarin remains a viable option in select patients given its history of use, array of clinical indications, low acquisition cost and widespread management services available across the IHS. Evolving practice guidelines, prescribing trends (both in IHS and nationally) and health care delivery challenges inherent to IHS provide support for the addition of a DOAC to the National Core Formulary. Following critical literature appraisal of outcomes data and analyses, the NPTC felt apixaban offered safety advantages beyond other DOACs and voted to ADD apixaban to the National Core Formulary.

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