Direct Oral Anticoagulants (DOACs): Current Status Among Distinct Patient Subgroups

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ABSTRACT

The landscape of anticoagulant therapy for atrial fibrillation and deep-vein thrombosis has evolved considerably in the last decade with the advent of Novel or Direct-Acting Oral Antiocoagulants (DOACs). The initial phase III randomized controlled trials established the individual DOACs as viable alternatives to warfarin for thromboprophylaxis but generalizations to the larger population were limited by the small number of protocol subjects with renal insufficiency, congestive heart failure, advanced age and other comorbidities. All the DOACs have some degree of renal excretion and while safe and effective in patients with mild to moderate renal insufficiency, dose adjustment is necessary based on creatinine clearance. Subsequent data registries and real-world experience with DOACs have continued to refine their role in these particular patient subgroups. Off-label use with both under- and overdosing is not uncommon in renal failure and carries increased risk. Their increasing use among the elderly, in patients with heart failure, hepatic and renal insufficiency and among the Asian population has been shown to be relatively safe and effective compared to warfarin. Gaps in our current understanding of this new class of anticoagulants will continue to narrow as additional data becomes available through ongoing registries and real-world experience.

KEYWORDS: DOACs, NOACs, thromboprophylaxis

INTRODUCTION

For almost six decades following its discovery and commercialization in the 1950s, warfarin has been the mainstay of anticoagulant therapy for the prevention of thromboembolic phenomena. Starting in 2009, a new group of potent oral anticoagulants called DOACs (Direct Oral Anti-Coagulants) or NOACs (Non-vitamin K antagonist Oral Anti-Coagulants née Novel Oral Anti-Coagulants) were approved as alternatives to warfarin.

Warfarin's anticoagulant effect is indirect; inhibition of Vitamin K oxide reductase results in decreased levels of pro-coagulant clotting factors in the direct, indirect, and common pathways. By contrast, the DOACs all act on the "Final Common Pathway" of the coagulation cascade.[1-4] Since FDA approval,[1-5] prescribing has rapidly expanded as DOACs replace warfarin, occasionally beyond approved indications. Growing evidence from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) suggests that off-label use carries increased risk.[6] Current guidelines are limited by the paucity of real-world data with DOACs, and providers often fill gaps in trial data with therapeutic strategies derived from years of experience with warfarin. While meta-analysis of large randomized controlled trial data has shown consistently favorable results with DOACs, it must be applied with caution given the limited real-world data available.[6, 7]

DOACS IN RENAL IMPAIRMENT

Chronic Kidney Disease (CKD) is a frequent comorbidity in patients requiring anticoagulation.[8,9] CKD may potentiate renally cleared pharmaceuticals without appropriate dose adjustment, and all current DOACs undergo some renal excretion (See **Table 1**).[4,10-12] Concern about worsening renal function, lack of readily available anticoagulation reversal agents, and limited real-world experience with DOACs may lead to premature dose-reduction and inadequate thromboprophylaxis. Recent studies of real-world prescription practice suggest significant rates of under-dosing (10%) or over-dosing (3%).[6] Current safety data and renal dosing guidelines were derived from large RCTs that excluded patients with creatinine clearance (CrCl) of <25 mL/min or hemodialysis.[3,13,14] Recently, two large meta-analyses of data from patients with mild-moderate stable CKD suggested that all DOACS may provide a modest reduction of systemic embolization, stroke, and bleeding compared to warfarin, and furthermore, apixaban and edoxaban have significantly lower rates of major bleeding than dabigatran or rivaroxaban.[1-4,15,16] Anticoagulant use in subjects with declining renal function was evaluated in a sub-group of 3,000 patients in the ROCKET-AF trial who had a 20% reduction in CrCl from baseline. In this population, the risk of vascular death was significantly higher than in patients with stable renal function, and rivaroxaban significantly decreased embolization without increasing rates of major bleeding as compared to warfarin.[3,13]

Patients with end-stage renal disease (ESRD) were excluded from the Phase III trials for all current DOACs [14]. Apixaban was approved in ESRD-based on pharmacokinetic data;

but no RCT data exists to evaluate its safety, and all other DOACs are contraindicated in ESRD.[17, 18] Despite this, rivaroxaban and dabigatran were prescribed for 6% of patients in a large hemodialysis database, frequently without dose reduction. This was associated with increased rates of bleeding requiring hospitalization and fatal bleeding compared to warfarin.[14] Current guidelines recommend warfarin as first-line for thromboprophylaxis in ESRD patients; if warfarin is contraindicated, apixaban may be an acceptable alternative.[18] Of note, edoxaban is contraindicated in patients with Cr Cl>95mL/min due to ineffective thromboprophylaxis.

Current DOAC maintenance dosing guidelines for thromboprophylaxis are summarized in **Table 1**. The maintenance dose for most DOACs is reduced in renal insufficiency to mitigate the effects of reduced excretion and half-life prolongation. Prolonged half-life requires earlier discontinuation of DOACs prior to procedures and current recommendations suggest discontinuation of DOACs 2–3 days prior to surgery and other invasive procedures.

DOACS IN HEPATIC IMPAIRMENT

Hepatic impairment and cirrhosis impose unique challenges in patients requiring anticoagulation. Standard laboratory assays for anticoagulant monitoring are rendered unreliable by altered production of pro- and anticoagulant factors, and variation in metabolic kinetics can lead to unpredictable serum drug levels.[20,21] DOACs are attractive candidates for patients with liver disease who require anticoagulation due to their independence from laboratory monitoring and lack of pro-coagulant effect seen with initiation of warfarin.[21-23] Initial DOAC phase III trials excluded chronic liver disease. Current use is guided by small trials and pharmacokinetic studies suggesting apixaban and dabigatran may be used in CTP class A or B, and rivaroxaban in CTP class A. All DOACs are contraindicated in patients with CTP Class C.[20,24] Small retrospective studies of anticoagulants in moderate hepatic impairment have shown DOACs to have non-inferior rates of embolization and reduced rates of bleeding compared to warfarin,[22,24] and surveillance data on DOAC

Table 1. Dosing Guidelines for DOACs

	DABIGATRAN	RIVAROXABAN	APIXABAN	ENDOXABAN
RENAL ELIMINATION	80%	36%	27%	50%
DOSING	Standard Dose: 150mg BID For eGFR >30 mL/min AND Age >80 years: 110mg BID For eGFR 15-30 ml/min: 75mg BID	Standard Dose: 20mg Daily For eGFR 15-49 ml/min: 15 mg Daily	Standard Dose: 5 mg BID IF 2 of following present: -Age > 80 yrs -Cr> 1.5 mg/dL -Weight < 60Kg THEN: 2.5mg BID For CrCl 15-29 ml/min: 2.5 mg BID For ESRD when warfarin is contraindicated: 2.5mg BID	Standard Dose: 60 mg Daily For eGFR 15 to 49 ml/min: 30mg Daily
CONTRA-INDICATIONS	eGFR <30 ml/min AND use of pGP inhibitor, ESRD-HD, CTP Class C	eGFR <15 ml/min, ESRD-HD, CTP Class B, C	eGFR <15 ml/min, CTP Class C	eGFR >95 ml/min, eGFR< 15 ml/min, ESRD-HD, CTP Class B,C
Cleared by Hemodialysis?	Yes	No	No	Minimally
HALF-LIFE (HOURS) BASED ON RENAL FUNCTION				
CrCl > 80mL/min	14-17	5-9	8-15	9-11
CrCl 50-79 mL/min	16.6 (12-18)	8.7	14.6	No data
CrCl 30-49 mL/min	18.7 (18-24)	9	17.6	No data
CrCl <30 mL/min	27.5	9.5	17.3	No data
When to discontinue before surgery:	2-3 days; if CrCl <50 mL/min 2-4 days	2-3 days	2-3 days	2-3 days

eGFR – estimated glomerular filtration rate;
CrCl – creatinine clearance;
ESRD-HD end-stage renal disease- hemodialysis; bid-twice daily;
pGP- p Glycoprotein inhibitor (ketoconazole oral or dronedarone);
CTP- Child-Turcotte-Pugh Hepatic Impairment Class

use for splanchnic vein thrombosis found no significant difference in adverse event rates in cirrhotic versus non-cirrhotic patients.[25] Of note, early concerns of DOAC-induced hepatitis[26, 27] were evaluated in large prospective studies, which found that compared to warfarin, dabigatran, apixaban, or rivaroxaban did not increase risk of liver injury and dabigatran carried the lowest risk.[28]

DOACS IN CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a common comorbidity in the atrial fibrillation population, and significantly increases the risk of stroke in these patients.[29-31] There is evidence that CHF constitutes a pro-thrombotic syndrome with low-flow states, biomarker evidence of endothelial dysfunction, and elevated pro-thrombotic biomarkers.[29,32] Risk of thrombosis appears to increase correspondingly with clinical and echocardiographic worsening of CHF and can contribute to the development of left ventricular thrombi.[32,33] Anticoagulation with warfarin has been traditionally used to treat apical thrombi, as well as cardiac structural abnormalities including noncompaction cardiomyopathy.[34,35] The phase III trials evaluating DOACs in nonvalvular AF included many patients with CHF.[1-4] Pooled analysis of data from CHF patients in these trials showed a significant reduction in intra-cranial hemorrhage (ICH) and major bleeding events with dabigatran and apixaban as compared to warfarin. Edoxaban was not included as detailed subgroup data from the ENGAGE-AF trial was not available.[36,37] These findings may be driven by low time in therapeutic range for warfarin in CHF patients. There is evidence that CHF predisposes patients on warfarin to low time in therapeutic range as compared to other comorbidities, and CHF has been associated with higher rates of bleeding in subgroup analyses from large trials of AF patients.[38-40] Together, these results suggest that DOACs are at least as efficacious as warfarin for thromboprohpylaxis in patients with nonvalvular AF and CHF, and may confer a reduction in bleeding as compared to warfarin.

There are no large RCT data available to guide the use of DOACs in treatment of left ventricular thrombi or in cardiomyopathies conferring additional thromboembolic risk; and current evidence is limited to case reports of ventricular thrombi treated successfully with apixaban or rivaroxaban.[41,42] The pathophysiology conferring additional stroke risk in these conditions is mechanistically similar to that of atrial fibrillation and heart failure.[43] There may be a similar role for DOACs in this patient population; however, further study is needed.

The role of prophylactic anticoagulation in CHF patients in sinus rhythm without known thrombus has been extensively studied in large trials.[44] Data from these studies demonstrated a reduction in thromboembolic events with prophylactic anticoagulation with warfarin; however, no survival benefit was seen due to a concomitant increase in bleeding risk. Current guidelines do not recommend prophylactic anticoagulation in patients with heart failure without another primary indication.[44,45] Emerging evidence supports an advantageous bleeding profile of DOACs as compared to warfarin in the CHF population, and CHF as a primary indication for anticoagulation is undergoing re-evaluation in the COMMANDER-HF trial designed to evaluate the efficacy and safety of rivaroxaban in reducing death, MI, or stroke in CHF patients with CAD.[46, 47]

DOACS IN THE ASIAN AND AFRICAN-AMERICAN POPULATIONS

There is growing evidence that optimal management of atrial fibrillation may differ in the Asian patient population compared to Western patients. Data from large global registries indicates that the incidence and mortality of stroke, especially hemorrhagic, is significantly greater in Asian countries as compared to the West,[48-50] and is highest in patients of Japanese ancestry.[51-53] The mechanisms behind this difference are unclear, but differential risk has been shown repeatedly in large international studies, including the phase III trials for dabigatran, apixaban and rivaroxaban.[1,2,54] Subgroup analyses found that a composite clinical outcome of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding occurs at significantly higher rates in Asian patients on warfarin as compared to non-Asian patients, raising the question of whether anticoagulation with warfarin has a reduced net clinical benefit in the Asian population.[1,2,48] Prescription practice analysis of large international registries suggests that warfarin is prescribed in Asian countries at approximately half the rate of Western countries, and antiplatelet therapy alone is more common for stroke prevention.[55] Meta-analysis of the phase III RCTs for DOACs has demonstrated similar efficacy of embolic prevention in Asian patients treated with DOACs compared to warfarin, but with an overall mortality benefit largely driven by reduced rates of hemorrhagic stroke.[56,57] Furthermore, a recent retrospective cohort study of Taiwanese patients anticoagulated with dabigatran, rivaroxaban, or warfarin found a significant reduction in rates of embolism, ICH, and all-cause mortality in patients anticoagulated with a DOAC compared to warfarin.[58]

African-Americans (AA) have a lower incidence of AF compared to Caucasians but a higher risk of stroke. This may be related to a higher prevalence of other stroke risk factors and limited access to health care among AAs. Warfarin is utilized less frequently among AAs who have a lower time in the therapeutic range and require higher warfarin dosage to maintain therapeutic INRs. Racial subgroups were underrepresented in Phase III RTCs of DOACs and limited subgroup analyses have been published. However, the DOACs compared to warfarin were similar for outcomes of stroke, systemic embolization and bleeding and may be preferable agents in the AA population.[63]

DOACS IN THE GERIATRIC POPULATION

Advanced age increases risk of stroke and also increases risk of ICH due to increased fragility of cerebral bridging veins, increased frailty and falls. Thus, the risk/benefit ratio of anticoagulation for thromboprophylaxis is less clear in the elderly population. Sub-group analysis of patients over age 75 in the Phase III RCTs suggested that DOACs were noninferior to warfarin for thromboembolism prophylaxis. Rivaroxaban carried equivalent hemorrhagic risk compared to warfarin, and dabigatran, apixaban, and edoxaban were all found to have lower risk of ICH or major bleeding, despite an increased risk of GI bleed with dabigatran.[59,60] Emerging evidence from subsequent RCTs and real-world practice observational studies supports these findings. A sub-group analysis of approximately 2,000 patients over age 75 from a trial comparing aspirin to apixaban found significantly improved thromboprophylaxis with apixaban, without significant difference in bleeding rates.[61] A cohort study drawn from Medicare data of 118,000 patients over ager 65, on dabigatran or rivaroxaban found that rivaroxaban usage had higher rates of ICH and major bleeding compared to dabigatran; however, renal function data was not available and dose-reduced regimens were not studied.[62]

CONCLUSIONS

The landscape of anticoagulation has evolved considerably in the last decade. The initial phase III RCTs established the DOACs as viable alternatives to warfarin. Subsequent data registries and real-world experience have shed light on potential differences in outcomes in certain subpopulations. In patients with renal impairment, there is mounting evidence that DOACs are safe, and may reduce ischemia and major bleeding in patients with stable mild-moderate CKD as compared to warfarin. Apixaban undergoes the least renal excretion of DOACs and may have lower bleeding risks than other DOACs in CKD. There is also limited evidence that apixaban may be useful in ESRD when warfarin is specifically contraindicated, while edoxaban, rivaroxaban, and dabigatran are contraindicated in ESRD, and may increase bleeding risk as compared to warfarin in this population. Current guidance for the use of DOACs in patients with hepatic impairment is driven by pharmacokinetic data and small studies suggesting that most DOACs are safe in mild-moderate hepatic impairment, though rivaroxaban should not be used in Class B impairment and all DOACs are contra-indicated in CTP Class C.

In patients with CHF, meta-analysis of pooled RCT data demonstrates that apixaban, dabigatran, and rivaroxaban are non-inferior to warfarin for thromboprophylaxis and may carry reduced risk of bleeding; therefore DOACs may be preferable first-line agents. Current guidelines do not recommend prophylactic anticoagulation for patients with heart failure; however, this concept is undergoing re-evaluation in the COMMANDER-HF trial. The Asian population is known to have elevated rates of stroke and hemorrhage with warfarin thromboprophylaxis and a growing body of evidence suggests that use of DOACs in place of warfarin carries reduced rates of hemorrhage and overall clinical benefit in this subgroup. Among the elderly, DOACs are non-inferior to warfarin for thromboprophylaxis, and dabigatran, apixaban, and edoxaban may confer reduced rates of major bleeding and ICH. Emerging evidence suggests rivaroxaban may carry a higher bleeding risk. However, until robust real-world outcomes data is available, caution must be exercised in extrapolating from RCTS, as even now available registry data suggests inappropriate dosing occurs at not-insignificant rates and is associated with adverse outcomes. Still, this emerging signal suggests an opportunity to improve outcomes in certain subpopulations and the picture will undoubtedly become clearer as data from ongoing registries and newer trials fill gaps in our knowledge.

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