CHAPTER 120

Recent Advances for Stroke Prevention in Patients With Atrial Fibrillation and Advanced Kidney Disease

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OBJECTIVES

This chapter will:

1. Describe the efficacy/safety of oral anticoagulant therapy in chronic kidney disease patients with atrial fibrillation.
2. Identify novel oral anticoagulants in chronic kidney disease patients with atrial fibrillation.
3. Discuss percutaneous left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation, with and without chronic kidney disease.

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population with estimated prevalence of 1% to 2% and is associated with an increased risk of thromboembolic complications, in particular stroke.[1–4] Patients with chronic kidney disease (CKD), regardless of severity, have a higher prevalence of AF compared with patients with preserved renal function[5,6]; CKD is an independent risk factor for increased mortality[7] and stroke in patients with AF.[8] The overall prevalence of AF is approximately 12% among dialysis patients.[9] In patients with AF, but preserved renal function, anticoagulation therapy markedly reduces the risk of thromboembolism but is associated with an increased risk of bleeding. Patients with end-stage CKD undergoing hemodialysis represent a particular subgroup of patients in whom anticoagulation therapy with warfarin seems to have an unfavorable risk/benefit ratio because it is less effective at preventing strokes and carries an increased risk of major bleeding.[10,11] Recently, novel anticoagulant agents (NOACs) have proven effective in preventing strokes in patients with AF and have demonstrated an improved safety profile. These drugs are contraindicated in patients with advanced renal disease because they are not cleared effectively in patients with renal failure. Moreover, patients with CKD stages 4 and 5 were excluded from clinical trials on anticoagulation therapy for stroke prevention in AF. Left atrial appendage (LAA) occlusion represents a nonpharmacologic alternative for stroke prevention in patients with AF who are difficult to manage medically.

NOVEL ORAL ANTICOAGULANTS AND CHRONIC KIDNEY DISEASE

Novel oral anticoagulant agents (NOACs), have been adopted in the last few years as alternative therapy to warfarin for thromboembolism risk reduction in patients with AF. These drugs have been shown to be equal or more effective than vitamin K–dependent oral anticoagulant agents (VKA), have an improved safety profile, and do not require continuous level monitoring. An important limitation of NOACs, besides their increased cost and our limited experience with their antidotes, is the fact that they all depend on renal elimination to a varying degree. There is a risk of drug accumulation in the presence of renal disease, particularly in patients with advanced CKD. The presence of an estimated glomerular filtration rate (eGFR) of less than 30 mL/min was an exclusion criterion for patient enrollment in all four randomized trials comparing NOACs with warfarin,[12–15] contributing to the lack of evidence regarding their use in patients with advanced and end-stage renal disease (ESRD). In fact, current cardiology guidelines for the management of patients with AF suggest not using NOACs in the setting of severe CKD.[16–17] Despite this, data from the Fresenius Medical Care records show there is a considerable proportion of patients with AF and eGFR below 30 mL or on hemodialysis taking NOACs (23.5% and 11.6%, respectively).[18] The kidney, primarily through renal filtration, eliminates these drugs, so in patients with CKD the pharmacokinetics are altered and their half-life is increased. Dosage and frequency of administration must be corrected to avoid problems with accumulation and toxicity.

Renal function is estimated by a variety of equations. Traditionally, these calculations are based on the value of plasma creatinine. Currently, however, the most validated equations to estimate GFR are the Modification of Diet in Renal Disease (MDRD)[19] and Chronic Kidney Disease Epidemiology (CKD-EPI).[20] Patients enrolled in the trials that compared NOACs with warfarin were included or excluded from the studies based on eGFR values calculated by the older Cockroft-Gault formula instead of the more current equations.[21] Furthermore, these formulas can be used only in patients with stable creatinine values. They lose reliability in patients with a fluctuating creatinine as in the case acute renal failure. In contrast to warfarin, which is exclusively hepatically metabolized, all NOACs have some level of renal elimination. For example, renal elimination accounts for 80% of the drug elimination for dabigatran, 36% for rivaroxaban, 27% for apixaban, and 50% for edoxaban. Furthermore, the binding of different NOACs with plasma proteins varies greatly. High protein binding makes some of these drugs virtually nondialyzable. Levels of protein binding range from 35% for dabigatran, 55% for edoxaban, 87% for apixaban, and up to 95% for rivaroxaban. In the absence of reversal agents (the only one currently available is the idarucizumab, a reversal agent of dabigatran) or the ability to dialyze, accumulation of these drugs can cause severe bleeding. Currently four NOACs have been approved by the European Medicines Agency (EMA)

and the Food and Drug Administration (FDA): dabigatran, rivaroxaban, apixaban, and edoxaban. The only direct thrombin inhibitor is dabigatran, whereas the other three act by inhibiting factor Xa activation. Randomized trials have been performed using these four agents, comparing their safety and efficacy to warfarin.[12–15] Posthoc analyses also were performed, analyzing the subgroup of patients with eGFR of less than 50 mL/min. The RE-LY study,[12] which excluded patients with an eGFR less than 30 mL/min, demonstrated the superiority of dabigatran (150 mg twice daily) compared with warfarin in terms of protection from thromboembolism, with an equal risk of hemorrhage. Using a lower dose of dabigatran (110 mg twice a day) provided the same level of protection from thromboembolism when compared with warfarin with a decreased risk of bleeding. A subgroup analysis comparing warfarin with dabigatran in relation to baseline renal function showed that the efficacy of dabigatran was maintained irrespective of eGFR, but both dabigatran dosages displayed significantly lower rates of major bleeding in patients with eGFR of at least 80 mL/min.[22] However, in this study, although the eGFR decreased gradually over time in patients treated with warfarin or dabigatran, the decline in eGFR was significantly lower in the high- and low-dose dabigatran group,[23] suggesting a possible nephroprotective effect of this NOAC.

The ROCKET-AF[13] study demonstrated a noninferiority of rivaroxaban against warfarin in the prevention of thromboembolic events, with no difference in bleeding. This study excluded patients with an eGFR less than 30 mL/min and adjusted doses based on eGFR. Patients with eGFR exceeding 50 mL/min took 20 mg/day of rivaroxaban, whereas those with eGFR between 30 to 50 mL/min took 15 mg/day. There was no significant difference in rivaroxaban's efficacy and risk of hemorrhage in both groups.[24]

The ARISTOTLE study[14] compared the use of apixaban with warfarin and included patients with a plasma creatinine up to 2.5 mg/dL. Patients were randomized to a low-dose (2.5 mg twice daily) and high-dose (5 mg twice daily) apixaban group. Patients who had at least two risk factors: creatinine between 1.25 and 2.5 mg/dL, age over 80 years old or body weight below 60 kg were placed in the low-dose group, whereas the rest of the patients were placed in the higher-dose group. The study demonstrated a superiority of apixaban in the protection of thromboembolism, compared with warfarin, with a lower incidence of bleeding events. A subgroup analysis, performed in patients with an eGFR below 50 mL/min, showed a similar trend with a nonsignificant reduction of thromboembolic events and a significant decrease in bleeding risk.[25] When the efficacy and safety as a function of the deterioration of renal function over time were investigated, apixaban maintained its advantage compared with warfarin, in terms of protection from thromboembolic events and of reduction of bleeding.[26]

The ENGAGE-AF study[15] included patients with eGFR above 30 mL/min and included a different dosing regimen of the drug edoxaban for patients with a eGFR between 30 and 50 mL/min versus eGFR exceeding 50 mL/min. Subjects with eGFR between 30 and 50 mL/min took 30 mg of edoxaban twice a day versus 60 mg twice a day for patients with an eGFR exceeding 50 mL/min. The study showed no evidence of inferiority of edoxaban compared with warfarin in the prevention of stroke and systemic thromboembolism, with a simultaneous reduction of bleeding events. Similar results were obtained in the subgroup analysis of patients with an eGFR between 30 and 50 mL/min.[27]

The information about the use of NOACs in ESRD patients is very scarce. Chan et al. recently published data from Fresenius Medical Care records regarding the use of dabigatran and rivaroxaban in hemodialysis patients. They identified an increased risk of hospitalization or death from bleeding in patients receiving NOACs compared with those taking warfarin.[28] Another study showed similar drug levels in 18 hemodialysis patients taking 10 mg/day of rivaroxaban compared with healthy volunteers taking 20 mg/day. There was, however, accumulation of the drug after a few days despite receiving hemodialysis, which had no effect on plasma concentrations of the drug.[29] Given its high rate of renal elimination, dabigatran accumulates when administered to patients with end-stage renal disease[30]; however, it is the only of the four NOACs that is eliminated quickly by hemodialysis because of its low rate of binding to plasma proteins.

Although EMA has not approved the use of any of the four NOACs in ESRD patients, the FDA approved only apixaban. This controversial decision was made on the results of two small studies suggesting that a dose adjustment of apixaban is not required on the basis of renal function alone.[31–33] In 2014 the FDA approved a labeling change for apixaban, indicating that the full dosage of 10 mg/day can be prescribed to ESRD/dialysis patients. A reduced dose of 5 mg/day is indicated only with the presence of one of the following clinical characteristics: age ≥ 80 years or weight ≤ 60 kg.

In conclusion, there are limited data to suggest the safe and effective use of NOACs in patients with moderate renal impairment (i.e., eGFR between 30 and 50 mL/min). The question still remains whether NOACs can be used in patients with an eGFR below 30 mL/min because there are no published studies addressing this subject. Patients on hemodialysis with a high thromboembolic risk and demonstrated intolerance to vitamin K inhibitors conceivably could use apixaban (2.5 mg or 5 mg twice daily). Other options include using rivaroxaban or edoxaban at a reduced dose. There is a paucity of data to support the use of these agents in this patient population, so alternative, non–drug-related therapies, such as LAA closure, should be taken into consideration.[34]

Percutaneous Left Atrial Appendage Occlusion

Rationale and Clinical Evidence

Anticoagulation therapy represents the standard of care to prevent thrombus formation and cardioembolic events in patients with AF. Unfortunately, about 13% to 20% of patients have an absolute or relative contraindication to oral anticoagulation therapy because of an increased risk of bleeding.[35–37] The majority of these patients are often those that are also at high risk for thromboembolic events. In fact, some clinical parameters assessed in the thromboembolic risk scores (arterial hypertension, advanced age, and previous stroke) are also predictors of risk of hemorrhagic events (Tables 120.1 and 120.2). A balance between risks and benefits must be assessed before starting patients on anticoagulation. LAA is the site of thrombus formation in at least 90% of cases of cardioembolic events (stroke and acute embolic arterial ischemia), in patients with nonrheumatic AF.[40] Pathophysiology of thrombus formation in the LAA during AF includes endothelial dysfunction, decreased blood flow, and activation of inflammatory/hemostatic cascade, a mechanism described by Virchow about 150 years ago known as "Virchow's triad."[41,42] The hypothesis that anatomic exclusion of the most common site of thrombus formation in patients with AF could prevent a large proportion of cardiac embolism is the rationale for considering the LAA occlusion

TABLE 120.1

Thromboembolic Risk Score

European Society of Cardiology (ESC), American Heart Association (AHA) and American College of Cardiology (ACC) Guidelines recommend to use CHA2DS2-VASc Score to assess the risk of stroke in patients with atrial fibrillation. ESC Guidelines[38] recommend patients with risk factor(s) ≥ 1 to receive effective stroke prevention therapy. Antithrombotic therapy is not recommended in patients with AF (irrespective of gender) who are aged <65 and with lone AF as they have very low absolute event rates. AHA/ACC Guidelines[39] recommend oral anticoagulation for patients with CHA2DS2-VASc ≥2; for patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered.

CHA_2DS_2-VASc RISK FACTORS	SCORE
Congestive heart failure	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Previous stroke, TIA, or thromboembolism	2
Vascular disease	1
Age 65–75	1
Female	1

TABLE 120.2

Bleeding Risk Score

HAS-BLED is the most validated bleeding score for patients with AF in whom antithrombotic therapy is indicated. When HAS-BLED score ≥3, caution and regular review are appropriate, as well as efforts to correct the potentially reversible risk factors for bleeding.

HAS-BLED RISK FACTORS	SCORE
Hypertension	1
Abnormal liver function	1
Abnormal renal function	1
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65)	1
Drugs	1
Alcohol	1

INRs, International normalized ratio.

as an alternative to anticoagulation therapy. Surgical resection of the LAA was performed in patients with AF for the first time in the 1940s.[43] Multiple studies over the years have evaluated the safety and efficacy of LAA exclusion during cardiac surgery with equivocal results. One meta-analysis, which included 3653 patients from 7 relevant studies, suggested LAA occlusion effectively reduced the risk of stroke peri- and postoperatively, without a significant increase in complications.[44] Nevertheless, surgical removal of the LAA was never widely adopted because of a lack of consistent clinical evidence from large clinical randomized trials. Technical issues, such as bleeding during the procedure as a result of fragility of the LAA wall or incomplete closure of the LAA, contributed to the premature abandonment of the first randomized surgical trial to evaluate the effectiveness and safety of surgical exclusion of the LAA.[45] A randomized control trial currently underway consisting of 4700 patients

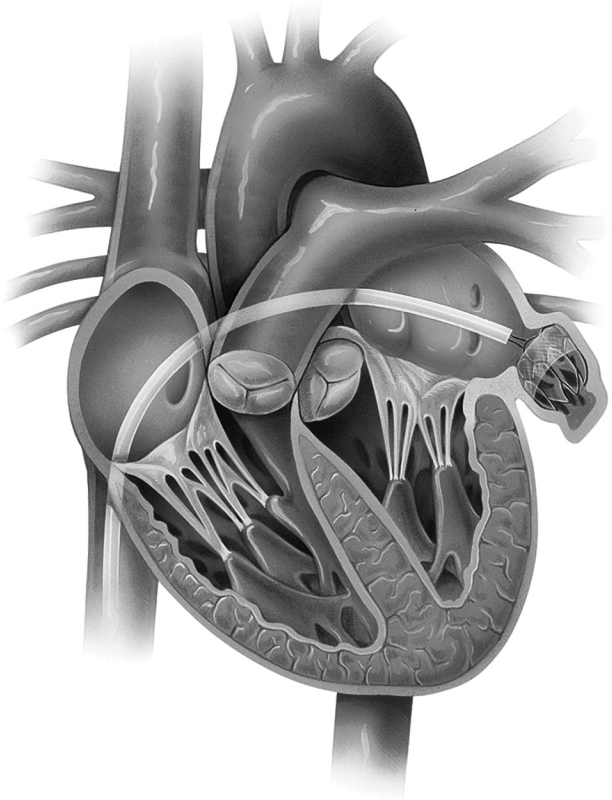

FIGURE 120.1 The Watchman device. Image provided courtesy of Boston Scientific. © 2017 Boston Scientific Corporation or its affiliates. All rights reserved.

with AF undergoing heart surgery (for other reasons) to have the LAA removed or not to establish the safety and efficacy of LAA exclusion.[46] A variety of devices were designed recently to percutaneously occlude the LAA. The PLAATO (percutaneous left atrial appendage transcatheter occlusion) was the first percutaneous LAA occlusion device and demonstrated an approximately 61% risk reduction for strokes when studied in 210 consecutive patients.[47] This device, however, is no longer being developed.

The Watchman (Boston Scientific, Maple Grove, MN [Fig. 120.1]), a self-expanding nitinol cage with fixation barbs, covered with porous polyethylene membrane on the proximal face, received CE mark in 2005 and is the only FDA-approved device for transcatheter LAA occlusion. The PROTECT-AF[48–50] is a multicenter, prospective randomized clinical trial comparing the Watchman device with long-term warfarin therapy. It demonstrated the noninferiority of the Watchman device to traditional medical therapy using stroke, cardiovascular or unexplained death, and systemic embolism as the primary end point at 1-year follow-up. The PROTEC-AF trial achieved statistical superiority for the composite primary efficacy end point at 4 years of follow-up. In this trial, the rate of procedure-related serious cardiovascular complications was 8.7%, mainly because of periprocedural pericardial effusion. The number of procedural adverse events was higher in the early period of device implantation. In the PREVAIL[51] study, implant success rate increased to 95% (from 90% of PROTECT) and procedural adverse events at 7 days decreased to 4.4%. A meta-analysis by Holmes et al. included 2406 patients with 5931 patient-years of follow-up from the PROTECT-AF and the PREVAIL trials (and their respective continued access registries). They concluded that in patients with

nonvalvular AF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAA occlusion with the Watchman device resulted in decreased rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared with warfarin.[52]

The Amulet device (AGA, St Jude Medical, Minneapolis, MN, Fig. 120.2), newer model of the Amplatzer Cardiac Plug (ACP) device, is a self-expanding nitinol occluder for the LAA consisting of a lobe with fixation barbs (that anchors the prosthesis inside the appendage), a disk that seals the ostium of the appendage, and a waist (that connects the lobe to the disk). Most of the clinical evidence for ACP and Amulet devices is from pooled multicenter registry data outside the United States. A pooled analysis of 1047 consecutive patients from 22 centers reports a procedural success of 97.3% with 5% of periprocedural major adverse events.[53] Santoro et al. reported an ischemic stroke rate of 0.8/100 person-years, embolic event rate of 2.5/100 person-years, and all-cause mortality of 2.5% over the follow-up period in a population of 134 patients implanted with ACP devices.[54]

A number of other different devices are currently under development or clinical investigation (Occlutech, LAmbre, WaveCrest, Cardia, Lariat).

Patient Selection and Preprocedural Screening

The most commonly accepted indication for LAA occlusion is the prevention of stroke in patients with AF at high risk for thromboembolic events and contraindications to oral anticoagulants.[55] Interestingly, most of the data on safety and efficacy were obtained in patients without contraindications to anticoagulants, but the indication of LAA occlusion as an alternative to oral anticoagulation when medical therapy is possible remains a point of discussion. Dual antiplatelet therapy generally is indicated after the procedure for at least 1 to 6 months followed by the lifelong use of a single antiplatelet agent. Antiplatelet agents have comparable hemorrhagic risk to that of warfarin, which is why the duration of dual antiplatelet therapy is kept to a minimum after the LAA is excluded. Often the antiplatelet therapy is tailored according to the patient, balancing the risk of stroke and hemorrhagic events. Patients with advanced renal failure represent a particular population in which the best strategy for stroke prevention in case of AF remains uncertain. All NOACs are in fact contraindicated if the creatinine clearance is less than 15 mL/min. The use of warfarin may increase tissue calcification and atherosclerosis and at the same time exposes patients to an increased risk of bleeding. Moreover, patients with severe renal failure usually have been excluded from most important clinical trials. LAA occlusion seems to have a similar safety profile in patients with CKD compared with patients with normal renal function and offers an important reduction of stroke and bleeding rates in all stages of CKD as compared with expected annual risk.[56] The indication for LAA closure for stroke prevention in patients with AF and renal disease should be discussed with a multidisciplinary team as well as with the patient, determining on a case-by-case basis the risks and benefits of anticoagulation versus LAA closure. Transesophageal echocardiogram (TEE) is the best imaging modality to assess LAA anatomy and rule out the presence of thrombus. Presence of thrombus is a contraindication to proceed with percutaneous LAA occlusion because of the risk of thrombus dislodgement. CT angiography can be useful to evaluate the shape and size of the appendage before the procedure.

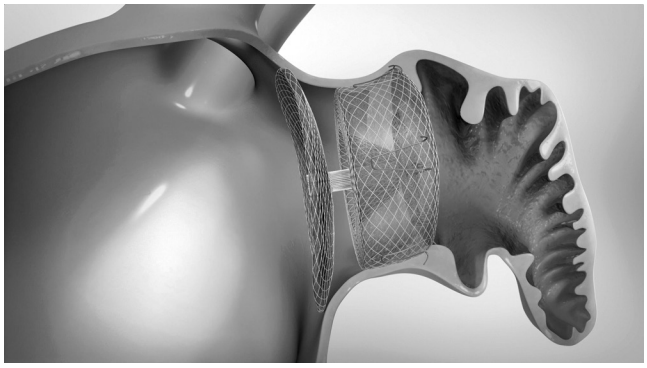

FIGURE 120.2 The Amulet device. (Courtesy St Jude Medical.)

Procedure Overview

Usually the procedure is performed under general anesthesia with TEE and angiographic guidance. Some operators have developed an expertise with intracardiac echocardiography (ICE).[57,58] The advantage of this technique is that the procedure can be accomplished without sedation, with the patient awake. The theoretical disadvantage is the need an additional venous access and images that may be limited compared with TEE. Once the femoral venous access is obtained with Seldinger technique, a transseptal kit consisting of a sheath and a needle is advanced into the right atrium at the level of the septum. The transseptal puncture is performed under TEE or ICE guidance to facilitate left atrial catheterization and avoid complications such as cardiac tamponade. A bolus of unfractionated heparin is administered usually once the catheter is advanced into the left atrium. Angiographic images of the LAA (Fig. 120.3A) typically can be obtained in the right caudal and right cranial views. Angiographic measurements of the LAA can be compared with ones

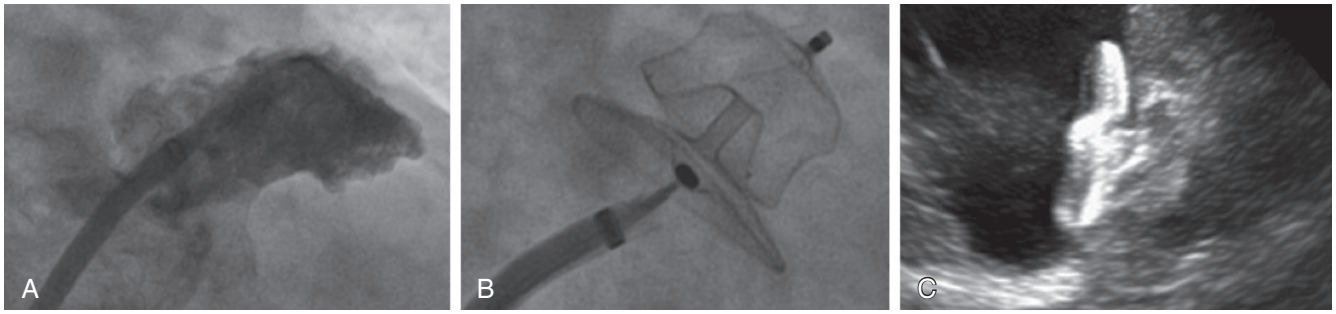

FIGURE 120.3 Angiographic view of the left atrial appendage (LAA) (A). Amulet device deployed, angiographic view (B) and ICE view (C).

obtained by ICE or TEE to decide the correct device size. A delivery catheter then is advanced in the LAA, and the device is positioned under echocardiographic and fluoroscopic guidance with the aim to obtain a complete sealing and exclusion of the appendage (Figs. 120.3B and 120.3C). After safety, stability, and efficacy assessments, the device is released and the delivery catheter is withdrawn. Hemostasis of the venous access site generally is obtained by mechanical compression.

CONCLUSION

Patients with AF and severe renal failure are at high risk not only for stroke and thromboembolism but also for serious bleeding events. This population has not been studied adequately because they have been excluded from most important clinical trials. This complicates the assessment of the risk/benefit balance of thromboprophylaxis in patients with renal disease. Warfarin has been for many years the only option for oral anticoagulation therapy, but data on patients with advanced renal failure show a high rate of bleeding events, with uncertain protection against thromboembolic events. Among patients with normal renal function, NOACs demonstrate a better safety profile and similar efficacy compared with warfarin. However, these drugs are not recommended in patients with eGFR less than 30 mL/min or ESRD because they are dependent, to some extent, on renal elimination.

A promising therapeutic option is the anatomic exclusion of the site of thrombus formation with the percutaneous occlusion of the LAA, and preliminary data indicate that it seems to have a similar efficacy and safety profile in patients with CKD compared with patients with normal renal function. Further investigations are indicated to evaluate the best strategy for thromboprophylaxis in patients with AF and severe renal disease.

Key Points

1. Chronic kidney disease is associated with a high prevalence of atrial fibrillation, but in this population the risk/benefit ratio of anticoagulant therapy with warfarin for stroke prevention is uncertain.
2. Data suggest the safe and effective use of novel oral anticoagulants in patients with moderate renal impairment, but the question still remains whether novel oral anticoagulants can be used in patients with an eGFR below 30 mL/min.
3. Percutaneous left atrial appendage occlusion has been demonstrated to be an alternative to oral anticoagulant therapy to prevent thromboembolic events in atrial fibrillation patients. Preliminary data indicate that it seems to have a similar efficacy and safety profile in patients with chronic kidney disease compared with patients with normal renal function, but further investigations are needed to evaluate the best strategy for stroke prevention in patients with atrial fibrillation and severe renal disease.

Key References

16. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am CollCardiol*. 2014;64:2246-2280.
17. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non valvular atrial fibrillation. *Europace*. 2015;17:1467-1507.
18. Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With Atrial Fibrillation. *J Am Coll Cardiol*. 2016;67:2888-2899.
34. Holmes DR, Doshi SK, Kar S, et al. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol*. 2015;65:2614-2623.
50. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312:1988-1998.

A complete reference list can be found online at ExpertConsult.com.

References

1. Go A, Hylek E, Phillips K, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-2375.
2. Miyasaka Y, Barnes M, Gersh B, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-125.
3. Heeringa J, Van Der Kulp D, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart L*. 2006;27:949-953.
4. Lloyd-Jones D, Wang T, Leip E, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042-1046.
5. Soliman EZ, Prineas RJ, Go AS, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J*. 2010;159:1102-1107.
6. Baber U, Howard VJ, Halperin JL, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm Electrophysiol*. 2011;4:26-32.
7. Genovesi S, Vincenti A, Rossi E, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysispatients. *Am J Kidney Dis*. 2008;2:255-262.
8. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Circulation*. 2009;199:1363-1369.
9. Zimmerman D, Sood MM, Rigatto C, et al. Systematic review and meta-analysis of incidence, prevalence and outcomes of atrial fibrillation in patients on dialysis. *Nephrol Dial Transplant*. 2012;27:3816-3822.
10. Genovesi S, Rossi E, Gallieni M, et al. Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation. *Nephrol Dial Transplant*. 2015;30:491-498.
11. Dahal K, Kunwar S, Rijal J, et al. Stroke, major bleeding and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest*. 2016;149:951-959.
12. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-1151.
13. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365:883-891.
14. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981-992.
15. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013; 369:2093-2104.
16. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *J Am CollCardiol*. 2014;64:2246-2280.
17. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non valvular atrial fibrillation. *Europace*. 2015;17:1467-1507.
18. Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With Atrial Fibrillation. *J Am Coll Cardiol*. 2016;67:2888-2899.
19. Levey AS, Bosch JP, Lewis JB, et al; for the Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med*. 1999;130:461-470.
20. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150:604-612.
21. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
22. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation*. 2014;129(9):961-970.
23. Böhm M, Ezekowitz MD, Connolly SJ, et al. Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial. *J Am CollCardiol*. 2015;65(23):2481-2493.
24. Fox KAA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32:2387-2394.
25. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33:2821-2830.
26. Hijazi Z, Hohnloser SH, Andersson U, et al. Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation in Relation to Renal Function Over Time Insights From the ARISTOTLE Randomized Clinical Trial. *JAMA Cardiol*. 2016;1(4):451-460.
27. Bohula EA, Giugliano RP, Ruff CT, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. *Circulation*. 2016;134:24-36.
28. Chan KE, Edelman ER, Wenger JB, et al. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. *Circulation*. 2015;131(11):972-979.
29. De Vriese AS, Caluwé R, Bailleul E, et al. Dose finding study of rivaroxaban in hemodialysis patients. *Am J Kidney Dis*. 2015;66:91-98.
30. Stangier J, Rathgen K, Stähle H, et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49:259-268.
31. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol*. 2016;56:628-636.
32. Chang M, Yu Z, Shenker A, et al. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. *J ClinPharmacol*. 2016;56:637-645.
33. Deal EN, Pope H, Ross W. Apixaban use among patients with severe renal impairment. *Ann Pharmacother*. 2014;48: 1667.
34. Holmes DR, Doshi SK, Kar S, et al. Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol*. 2015;65:2614-2623.
35. O'Brien EC, Homes DJN, Ansell JE, et al. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J*. 2014;167:601-609.
36. Go AS, Hylek EM, Borowsky LH, et al. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131:927-934.
37. Stafford RS, Singer DE. Recent national patterns of warfarin use in atrial fibrillation. *Circulation*. 1998;97:1231-1233.
38. Kirchhof P, Benussi S, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
39. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *J Am CollCardiol*. 2014;64:e1-e76.
40. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. *Heart*. 1999; 82:547-554.
41. Virchow R. Thrombose und embolie. Gefässentzündung und septische infektion. *Gesammelte Abhandlungen zurwissenschaftlichen MedicinThrombosis and embolism. Vascularinflammation and septicinfection. Collected Essays on Scientific Medicine*. Frankfurt amMain: Von Meidinger & Sohn; 1856:219-732.

42. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrialfibrillation: Virchow'striadrevisited. *Lancet*. 2009;373:155-166.
43. Madden JL. Resection of the left auricular appendix. *JAMA*. 1948;140:769-772.
44. Tsaia YC, Phan K, Munkholm-Larsenc S, et al. Surgical left atrial appendage occlusion during cardiac surgery for patients with atrialfibrillation: a meta-analysis. *Eur J Cardiothorac Surg*. 2015;47:847-854.
45. Crystal E, Lamy A, Connolly SJ, et al. Left Atrial Appendage Occlusion Study (LAAOS): a randomized clinical trial of left atrial appendage occlusion during routine coronary artery bypass graft surgery for long-term stroke prevention. *Am Heart J*. 2003;145:174-178.
46. Whitlock R, Healey J, Vincent J, et al. Rationale and design of the Left Atrial Appendage Occlusion Study (LAAOS) III. *Ann Cardiothorac Surg*. 2014;3:45-54.
47. Bayard Y, Omran H, Kramer P, et al. Worldwide experience of percutaneous left atrial appendage transcatheter occlusion (PLAATO). *J Neurol Sci*. 2005;238:S70.
48. Holmes DR, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. *Lancet*. 2009;374:534-542.
49. Reddy VY, Doshi SK, Holmes DR, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3 year follow-up of the PROTECT-AF Trial. *Circulation*. 2013;127:720-729.
50. Reddy VY, Sievert H, Halperin J, et al. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. *JAMA*. 2014;312:1988-1998.
51. Holmes DR, Saibal K, Reddy VY, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy. *J Am CollCardiol*. 2014;64(1):1-12.
52. Holmes DR, Doshi SK, Kar S, et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation. *J Am CollCardiol*. 2015;65:2614-2623.
53. Tzikas A, Shaker S, Gafoor SA, et al. Left atrial appendage occlusion for stroke prevention in atrial fibrillation: multicentre experience with the AMPLATZER Cardiac Plug. *Eurointervention*. 2016;11:1170-1179.
54. Santoro G, Meucci F, Stolcova M, et al. Percutaneous left atrial appendage occlusion in patients with non-valvular atrial fibrillation: implantation and up to four years follow-up of the AMPLATZER Cardiac Plug. *Eurointervention*. 2016;11:1188-1194.
55. Pison L, Potpara TS, Chen J, et al. Left atrial appendage closure–indications, techniques, and outcomes: results of the European Heart Rhythm Association Survey. *Europace*. 2015;17:642-646.
56. Kefer J, Tzikas A, Freixa X, et al. Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation. *Int J Cardiol*. 2016;207:335-340.
57. Berti S, Paradossi U, Meucci F, et al. Periprocedural Intracardiac Echocardiography for left atrial appendage closure a dual-center experience. *JAAC Cardiovasc Interv*. 2014;7:1036-1044.
58. Ronco F, Pascotto A, Barbierato M, et al. Percutaneous left atrial appendage closure in awake non intubated patient: multimodality intraprocedural imaging. *Cardiovasc Revasc Med*. 2012;13:360-361.