Louisiana Medicaid | Provider UPDATE

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Re-Shaping Medicaid and Louisiana's Behavioral Health Services: The Louisiana Behavioral Health Partnership (LBHP)

All Providers

The Louisiana Behavioral Health Partnership (LBHP), an initiative of Governor Bobby Jindal, will reshape the way that behavioral healthcare will be delivered in Louisiana. The LBHP will reinvent the behavioral health delivery system through improved leveraging of funding, expanding the number of services and behavioral health providers, and placing an emphasis on early intervention and preventive care that will discourage "deep involvement" in healthcare, judicial, and other social services. A wide array of tailored interventions will target those who are most at risk in order to prevent worsening of conditions that inevitably lead to costlier care.

In order to change the way that behavioral healthcare is delivered in Louisiana, change had to first occur with how the state's neediest populations receive care. Therefore, Medicaid is being restructured to maximize federal match dollars through the use of Medicaid waivers and changes to traditional Medicaid State Plan services.

Perhaps most significant of all the waiver changes is the use of a managed care entity, known as the State Management Organization (SMO), to manage the care of all Medicaid eligible behavioral health recipients. Managed care has shown to improve health outcomes as well as decrease total expenditures through careful management of care delivery. The management of care has been shown to reduce unnecessary care, prevent duplicative services, and to ensure advantage is made of the totality of available services.

Due to the complexity of Medicaid and the expansion of services available in the new waiver system, the SMO will be vital to the transformation of the care network. Basic services offered by the SMO will include: 24 hour access for members, care coordination and utilization management, quality management and outcome monitoring, protections for members and providers (grievance and appeals process, credentialing of qualified providers, member input, etc.), and improved reporting. In addition, the SMO will provide value added functions to ensure preventive care and early interventions are maximized. These functions will reduce the utilization of costly hospital bed/emergency room visits as well as prevent "deeper involvement" into the multiple systems in which recipients of behavioral health services may interact (e.g., judicial, social, medical, etc.). Magellan Behavioral Health has been chosen as the SMO and will soon begin implementation for a March 1, 2012 start date.

As part of this effort, focused resources have been allocated to youth who are most at risk. The Coordinated System of Care (CSoC) was formed as a specialized component of the LBHP to address the needs of up to 2,400 youth who utilize services from multiple agencies and are at the greatest risk for out of home placement. The CSoC initiative brings together the Department of Children and Family Services, the Department of Education, the Department of Health and Hospitals, and the Office of Juvenile Justice, as well as a representative from the Governor's Office and advocate representatives for the family. Goals for the CSoC include reducing the number of youth in residential/detention settings, leveraging Medicaid and other funding sources to lower the state's cost of providing services, and improving the overall outcomes for these youth and their caregivers.

The CSoC is scheduled to begin enrollment in five regions, Shreveport, Monroe, Alexandria, Jefferson Parish and the Capital area, beginning March 2012. Youth enrolled in the CSoC will receive individualized care planning using an innovative practice known as "wraparound" from regionally-based agencies and additional support services from Family Support Organizations. Youth with intensive needs will also receive parent support and training, youth support and training, crisis stabilization, respite, and independent living/skill building.

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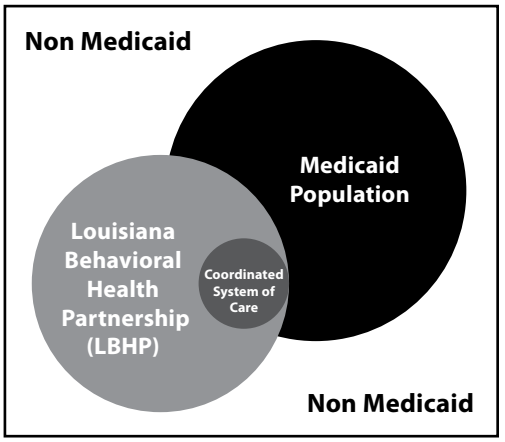

It is estimated that 155,000 people will receive services under the LBHP. Services will include addictions services, community psychiatric support and treatment, psychosocial rehabilitation services, evidence-based practices, crisis intervention, and psychiatric care, as well as numerous other treatments over various settings.

The move toward coordinated care is a big step for Louisiana – one which will inevitably provide better access to a more complete array of quality services, improve overall outcomes, and provide costs savings through the reduction of unnecessary care.

Change of Ownership for Home and Community-Based Providers

HCBS Providers

The Louisiana licensing regulations for Home and Community-Based Service (HCBS) providers found in Section 5013 (D) of the emergency rule states that a change of ownership (CHOW) of the HCBS provider shall be reported in writing to the Department of Health and Hospitals within five days of the change. The license of an HCBS provider is not transferable or assignable and cannot be sold.

Prospective new HCBS providers of personal care attendant supervised independent living or respite services who wish to undergo a CHOW must submit the legal CHOW document, all documents required for a new license and the applicable licensing fee. The following must be done **simultaneously:**

- Submit a new Facility Need Review (FNR) application, a letter of intent to purchase the HCBS agency and the required $150 application fee to the Health Standards' FNR program manager. The HCBS agency must be identified on the FNR application and in the letter of intent that shows the seller's or transferor's intent to relinquish their current FNR approval.
- Submit the following documents to the Health Standards HCBS Program Manager:
- A letter of intent to purchase the agency,
- The legal transaction between the buyer and seller,
- All documents required for a new license (i.e., license application and non-refundable fee, disclosure of ownership, proof of financial viability including Workman's Compensation insurance, $50,000 line of credit issued from a federally insured licensed lending institution and general and professional liability insurance of at least $300,000.

If center based services such as Adult Day Care or Center Based Respite are also being acquired in the change of ownership, then the prospective new owner will be required to submit floor plans along with the Office of Public Health and the Office of the State Fire Marshall approvals for occupancy. Such approvals from these agencies shall contain the new name of the center based service provider.

If the CHOW results in a change of geographic address, an on-site survey may be required prior to issuance of the new license.

An HCBS provider that is under license revocation may not undergo a CHOW or an agency that has ceased to operate and does not meet operational requirements to hold a license as defined by Section 5031, Business Location, of the emergency rule may not be sold or purchased.

Due diligence on the part of all prospective buyers is expected prior to signing an act of sale. A buyer's failure to assure the following may result in denial of the CHOW:

- The current owner is not under license revocation,
- The current owner is not under investigation by the Office of the State Attorney General,
- The current owner is not excluded from participation in the Medicaid Program or under vendor hold, and
- The current owner is not under penalties imposed by the Internal Revenue Service or any other federal or state agency.

Once all applications requirements are completed and approved by Health Standards, a new license shall be issued to the new owner.

The following information is available on the web:

- The FNR instructions, application and rule can be found at http://new.dhh.louisiana.gov/index.cfm/newsroom/detail/1687,
- The "Home and Community Based Services License Application" can be found at http://new.dhh.louisiana.gov/index.cfm/page/427, and
- A copy of the "Disclosure of Ownership and Control Interest Statement" can be found at http://new.dhh.louisiana.gov/index.cfm/page/788.

Remittance Advice Corner

All Providers

The following is a compilation of messages that were recently transmitted to providers through Remittance Advices (RA):

Attention Hospital Providers

Effective with date of processing on or after November 1, 2011, claims processing will be changed to reflect the use of the new guidelines on Point of Origin (form locator 15) according to the National Uniform Billing Committee (NUBC). This was formally called Source of Admission. This change affects inpatient claims billed on the electronic 837I claims and the paper claims on the UB 04.

Any questions should be directed to Provider Relations.

Attention Professional Services Providers Radiopharmaceutical Diagnostic Imaging Agents

Louisiana Medicaid has recently made the following radiopharmaceutical diagnostic imaging agents payable on the procedure code file effective January 1, 2010:

- A9503 (Technetium Tc-99m, Medronate, diagnostic, per study dose, up to 30 millicuries)
- A9507 (Indium IN-111 Capromab Pendetide, diagnostic, per study dose, up to 10 millicuries)
- A9512 (Technetium Tc-99m-Pertechnetate, diagnostic, per millicurie)
- A9560 (Technetium Tc-99m Labeled Red Blood Cells, diagnostic, per study dose, up to 30 millicuries)
- A9562 (Technetium Tc-99m Mertiatide, diagnostic, per study dose, up to 15 millicuries)
- A9572 (Indium IN-111 Pentetreotide, diagnostic, per study dose, up to 6 millicuries)

The system has been updated to reflect this change. Claims for these imaging agents with dates of service January 1, 2010 through April 6, 2011 that were adjudicated prior to April 7, 2011 were systematically adjusted on October 12, 2011.

Effective with date of processing August 16, 2011, claims for radiopharmaceutical diagnostic imaging agents will only be reimbursed when billed with the appropriate medically necessary radiological procedure. The imaging agent is not to be paid unless the appropriate radiological procedure is also paid on the same date of service. Providers are encouraged to contact the Provider Relations unit at (800) 473-2783 or (225) 924-5040 with questions concerning this issue.

Attention Professional Services Providers Influenza Immunizations for Adults – New Vaccine Available

A new influenza virus vaccine for intradermal use will be available for the 2011-2012 influenza season. This vaccine is currently licensed and indicated for use in patients 18 years through 64 years of age. Louisiana Medicaid has added this new vaccine as a covered service for recipients 18 through 64 years of age only. This intradermal influenza vaccine will be in addition to the currently covered influenza, pneumococcal and human papillomavirus vaccines. At this time, this vaccine will not be available from the Louisiana Vaccines for Children (VFC) program.

Professional Services providers may be reimbursed for seasonal influenza vaccines and the administration of the vaccines for adult recipients. As the new intradermal vaccine will not be available from the VFC program for the 2011-2012 flu season, Louisiana Medicaid will reimburse providers for the new intradermal influenza vaccine as well as for the administration of the vaccine for recipients aged 18 through 64 years. If at a later date this vaccine is included in the VFC program, Louisiana Medicaid will no longer reimburse providers for the vaccine for recipients 18 years of age but only for the administration of the vaccine.

For detailed information, see www.lamedicaid.com following the link for Billing Information/Immunizations/Adult Immunization Policy. For the current Immunization Fee Schedule, follow the link for Fee Schedules/Immunization Fee Schedules and choose the Immunization Fee Schedule appropriate for the recipient's age.

Contact Molina Medicaid Solutions Provider Relations at (800) 473-2783 or (225) 924-5040 if you should have any questions.

Attention Professional Service Providers: Update and Clarification of Obstetrical Services and Postpartum Care Policy

It has come to the attention of DHH that some providers are continuing to submit claims for CPT code 59430 (Postpartum care only

[separate procedure]) when they have also submitted and been paid for one of the delivery codes that include postpartum care. It has been the intent of DHH that when the delivery codes that include postpartum care were made payable, separate reimbursement for postpartum care was no longer valid if those inclusive codes were used. Providers who perform both the OB delivery service and the postpartum care should use the code that describes these services and not unbundle the services by use of individual procedure codes. As with all claim submissions, providers are to use the most inclusive code available. Only when a more appropriate code is not available should providers use the separate code for the postpartum service. At no time does Louisiana Medicaid intend to reimburse more than once for postpartum care. Providers should refer to the Current Procedural Terminology manual for additional coding guidance related to these services. Providers are urged to review their billing practices and take action as needed to be in compliance with Medicaid policy. Overpayments and abusive billing are subject to recoupment and/or sanction.

Attention Professional Service Providers

Effective December 1, 2011, Louisiana Medicaid will provide coverage for fluoride varnish. For coverage details and policy information, please refer to www.lamedicaid.com. Providers should contact the Provider Relations unit at (800) 473-2783 or (225) 924-5040 with billing or policy questions.

Online Medicaid Provider Manual Chapters

All Providers

The following Medicaid Provider Manual Chapters are available on the Louisiana Medicaid website at www.lamedicaid.com under the "Provider Manual" link.

- Administrative Claiming
- Adult Day Health Care Waiver
- Ambulatory Surgical Centers
- American Indian 638 Clinics
- Children's Choice Waiver
- Dental
- Durable Medical Equipment
- Elderly and Disabled Adult Waiver
- Family Planning Clinics
- Family Planning Waiver (Take Charge)
- Federally Qualified Health Centers
- General Information and Administration
- Greater New Orleans Community Health Connection (GNOCHC)
- Home Health
- Hospitals
- ICF/DD
- Medical Transportation
- Mental Health Clinics
- Mental Health Rehabilitation
- Multi-Systemic Therapy
- New Opportunities Waiver (NOW)
- Personal Care Services
- Pharmacy
- Psychological Behavioral Services
- Residential Options Waiver
- Rural Health Clinics
- Supports Waiver
- Vision (Eye Wear)

This list will be updated periodically as other Medicaid program chapters become available online.

Direct Service Worker Registry

All Providers

Effective April 20, 2011, the direct service worker registry became a "negative" registry maintaining only the names of direct service workers who have substantiated findings of abuse, neglect, or misappropriation of an individual's property or funds placed against them. Providers are required to access the registry prior to hiring an individual to assure there is no finding against the prospective employee. If there is such a finding, the individual shall not be hired.

Providers are also required to check the registry every six months to assure the names of their current employees have not been placed on the registry since the date of hire. It is imperative that providers maintain printed confirmation from the registry web site to verify compliance with this requirement.

Programming changes have also been made to the registry to make searching for an individual's name easier. Instead of having to scroll through all the names on the registry, providers are now able to search the registry by the individual's social security number.

The direct service worker registry can be accessed at www.labenfa.com.

Document to Aid in End-of-Life Care Planning

All Providers

The Louisiana Physician Order for Scope of Treatment (LaPOST) document, which was approved by the Louisiana Legislature in June 2011, is now available as a physician resource to help terminally ill patients plan their end-of-life treatment preferences and care in the event they are unable to communicate. LaPOST was created as a best-practice model for advance-care planning through efforts of the LaPOST Coalition, recommended by the End of Life Work Group of the Louisiana Health Care Redesign Collaborative and endorsed by the Louisiana State Medical Society.

The document is completely voluntary and neither for nor against life-sustaining treatment. LaPOST is a medical order that transfers with patients across health care settings from hospitals to nursing homes to hospice. The document is free and can be downloaded from the LaPOST website at www.la-post.org. In order for the form to be valid, it must be completed by a physician. The official form is printed on gold-colored paper and includes a LaPOST watermark, making it easily recognizable.

In addition to information about the document, the website includes information about implementing LaPOST in a variety of medical settings, suggestions for discussing the issue with patients, recommendations for ensuring information in the document is accessible to all health care professionals treating the patient and explanations about advance directives and health care power-of-attorney documents.

New Possibilities for Stroke Prevention in Atrial Fibrillation: A Review of Dabigatran, Rivaroxaban and Apixaban

Louisiana Drug Utilization Review (LADUR) Education

Elizabeth C. Perry, Pharm, BCPS
Assistant Professor
College of Pharmacy
University of Louisiana at Monroe

Since the time of submission of this article, rivaroxaban (Xarelto®) has received FDA approval for the prevention of thromboembolism in patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is a common supraventricular tachyarrhythmia associated with increased mortality due to cardiovascular causes and stroke.[1] Patients with AF are up to 5 times more likely to have a stroke than the general population and the risk increases with age.[2] It is predicted that by the year 2050, 5-6 million Americans will be diagnosed with atrial fibrillation (AF), which would be a 2.5-fold increase since 2001.[3]

For the past two decades warfarin has remained relatively unchallenged when used for prevention of thromboembolism in patients with AF. Warfarin reduces the incidence of stroke by 69% in nonvalvular AF.[4] Despite the significant benefit, warfarin therapy is often difficult to manage due to drug-drug, drug-disease and drug-food interactions, genetic considerations, and the need for consistent monitoring.[5] In a study by Glazer et al, it was found that 73% of newly diagnosed AF patients were prescribed either warfarin or aspirin and, among those in the high-risk group, 59% were prescribed warfarin .[6] Another study reported that 19% of physicians feel that the risk of warfarin outweighs the benefits in elderly patients residing in long-term care facilities.[7]

Atrial fibrillation guidelines utilize risk stratification schemes, like $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke [doubled]), to determine appropriate candidates for warfarin therapy (Table 1).[8,9] Based on the $CHADS_2$ scheme, patients receive points for stroke risk factors and cumulative scores determine treatment recommendations (Table 2). Guidelines stratify the risk factors for thromboembolism into moderate and high risk factors. High risk factors include previous stroke, transient ischemic attack (TIA) or embolism, mitral stenosis, or prosthetic heart valve. Moderate risk factors include age ≥ 75 years, hypertension, heart failure, left ventricle ejection fraction ≤ 35%, or diabetes. Patients with a high-risk factor or more than one moderate risk factor should receive warfarin dosed to achieve a target INR between 2 and 3 as it has proven more efficacious than aspirin (Table 2).[8-10] Warfarin or aspirin may be used for patients with only one moderate risk factor. The decision whether to use aspirin or warfarin is based on patient preferences and individual bleeding risk.[8] In patients with no risk factors for stroke, only aspirin is recommended. [8,9]

New Anticoagulants

On October 19, 2010, the Food and Drug Administration (FDA) announced the approval of a new oral anticoagulant for use in stroke prevention in patients with AF, the direct thrombin inhibitor, dabigatran etexilate (Pradaxa®).[11] This approval was based on the results of a Phase III clinical trial, Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) which compared dabigatran to warfarin in patients with nonvalvular AF.[12] Two additional agents, both oral direct factor Xa inhibitors, are also being investigated for use in AF, rivaroxaban and apixaban. Rivaroxaban has been approved for venous thromboembolism (VTE) prevention in patients undergoing hip or knee replacement and the FDA Advisory Committee has recently submitted its recommendation to the FDA for use in AF.[13,14] Apixaban may be further down the line to approval as new data has just been published on its use in AF. The remainder of this article will serve as a review of the pharmacology, pharmacokinetics, and clinical trial data for these new oral anticoagulants.

Dabigatran etexilate

Dabigatran etexilate is a prodrug which is rapidly absorbed after oral administration and hydrolyzed by serum esterases to the active metabolite, dabigatran.[15] Once converted into its active metabolite, dabigatran competitively and reversibly binds to the active site of thrombin, preventing the conversion of fibrinogen to fibrin and clot formation.[16] As a direct inhibitor, dabigatran can inhibit both free and clot-bound thrombin, independent of the antithrombin III complex, unlike heparin and low molecular weight heparins (LMWH).[16] Dabigatran is not a substrate, inhibitor, or inducer of any CYP450 enzymes which limits the potential for drug-drug interactions involving these enzyme systems.[15] However, a few notable drug-drug interactions have been identified with medications affecting the p-glycoprotein complex (P-GP).[15] P-GP inducers like rifampin reduce exposure to dabigatran and should generally be avoided.[15] P-GP inhibitors including, amiodarone, verapamil, ketoconazole, and quinidine all increase dabigatran concentrations and should be used with caution or avoided (quinidine).[15,16] Dabigatran exhibits predictable, linear pharmacokinetics with a rapid onset of action and a terminal half-life of 12-17 hours after multiple doses (Table 3). Dabigatran is primarily renally eliminated and concentrations increase up to 6-fold for patients

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with CrCl 10-30 ml/min.[15-17] The utility of coagulation monitoring while on dabigatran is low due to the low interpatient variability and lack of correlation between thrombosis and bleeding risk with these tests.[16,18]

The results from the RE-LY trial were published in 2009.[12] This multicenter trial randomized patients with nonvalvular AF to one of 3 treatment groups: dabigatran 110 mg BID, dabigatran 150 mg BID, or warfarin.[12] Patients were included in the trial if they were diagnosed with AF and were ≥ 75 years of age with a previous stroke, TIA or heart failure, or if they were 65-74 years of age with at least one of the following risk factors: diabetes mellitus, hypertension or coronary artery disease (CAD). The primary efficacy outcome was the incidence of stroke or systemic embolism and the primary safety outcome was the incidence of major hemorrhages.[12] The net clinical benefit outcome, which is a measure of the overall benefit and risk, was a composite outcome including the incidence of stroke, systemic embolism, pulmonary embolism (PE), myocardial infarction (MI), death, or major hemorrhage.

RE-LY enrolled 18,113 patients with an average age of 71 years and an average $CHADS_2$ score of 2.1.[12] For the primary efficacy outcome, both dabigatran doses demonstrated noninferiority compared to warfarin and the dabigatran 150 mg dose was superior to warfarin ($p<0.001$) and to the 110 mg dabigatran dose ($p=0.005$).[12,19] There was a 74% reduction in the risk of hemorrhagic strokes in the dabigatran 150 mg treatment group and a 60% reduction in the risk of intracranial bleeding relative to warfarin ($p<0.001$).[12] Major bleeding, defined as a reduction in hemoglobin by 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ, occurred less frequently in the dabigatran 110 mg group compared to warfarin ($p=0.003$), but similar bleeding rates were seen between the dabigatran 150 mg group and warfarin ($p=0.32$). There was a higher rate of major gastrointestinal bleeding with dabigatran 150 mg compared to warfarin ($p<0.001$).[12] The composite outcome demonstrating net clinical benefit revealed a significant advantage of the dabigatran 150 mg dose over warfarin ($p=0.04$), while the benefit was not significant with the 110 mg dose ($p=0.1$).[12] Apart from serious adverse events like gastrointestinal bleeding, the only adverse effect that was reported significantly more with dabigatran than with warfarin was dyspepsia.[12]

Two strengths of dabigatran were approved by the FDA in October for patients with AF.[11] The approved dose for patients with a creatinine clearance (CrCl) >30 ml/min is 150 mg twice daily. Patients with a CrCl 15-30 ml/min should receive a reduced dose of 75 mg twice daily and dosing recommendations cannot be provided for patients with a CrCl <15 ml/min or those on dialysis.[15] The 75 mg twice daily regimen came as a shock to many since it was not studied in clinical trials and patients with CrCl <30 mL/min were excluded from the trials. The FDA felt that, based on pharmacokinetic analyses, this dose would provide equivalent concentrations to the higher dose in patients with reduced renal function.[20] The FDA failed to approve the 110 mg BID dose of dabigatran due to the RE-LY results proving superiority of the 150 mg dose over the lower dose.

While the approval of dabigatran is a milestone in oral anticoagulation, there are still a few looming concerns. One concern is the lack of an antidote. In the event of a hemorrhage, the recommendations are to stop the medication and maintain adequate diuresis as the drug is primarily renally eliminated.[15] The short half-life of the drug should lend itself to relatively fast elimination in patients with normal renal function. Other supportive measures including administration of fresh frozen plasma may be indicated for severe bleeding. Dabigatran is about 60% dialyzable and can be removed over a few hours by dialysis, but there is little evidence behind this approach.[15] Another concern is hepatotoxicity, which was seen with earlier agents in this class of medications. The risk of long term hepatic damage with dabigatran cannot be ruled out due to the short duration of the clinical trials.[21] Also, the borderline increased risk of myocardial infarction seen in the RE-LY trial will be an issue that receives attention as dabigatran has been studied in a Phase II trial, RE-DEEM, for the treatment of acute coronary syndromes.[22]

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Dabigatran may be a preferred option for patients who are compliant but hard to maintain in the therapeutic range with warfarin, those at a high risk of intracranial bleeding, those who are on multiple medications with potential to interact with warfarin, or those who are unable to take warfarin due to inability to meet the stringent monitoring schedules. Current guidelines have been updated to recommend dabigatran as an alternative to warfarin in patients with nonvalvular AF and at least one risk factor for stroke who do not have renal failure (CrCl <15 ml/min) or advanced liver disease (Table 2).[23] If a practitioner desires to switch a warfarin patient to dabigatran it is recommended to wait until the patients INR is <2.0 before beginning dabigatran.[15] No additional bridge therapy is required.

Rivaroxaban

At the time of writing, rivaroxaban has not been approved for stroke prevention in AF. Rivaroxaban is a potent and selective inhibitor of factor Xa in the coagulation cascade.[24] Factor Xa acts at the convergence of the intrinsic and extrinsic pathway and catalyzes the reaction to convert prothrombin to thrombin.[25] As a direct factor Xa inhibitor, rivaroxaban does not require cofactors, such as antithrombin III for its action.[25] Rivaroxaban exhibits predictable dose-dependent, linear pharmacokinetics, with low interpatient variability (Table 3).[25] Rivaroxaban is highly bioavailable after oral administration and peak concentrations are quickly achieved.[24] Rivaroxaban displays dual elimination, with a half-life from 5-9 hours after multiple dosing.[26] Patients with CrCl <50 ml/min may exhibit extended effects. Therefore, patients with CrCl 30 to 50 ml/min should be closely observed, while use in patients with CrCl <30ml/min should be avoided.[26] Rivaroxaban is a substrate of CYP3A4 and P-GP and administration with strong CYP3A4 and P-GP inhibitors, including ketoconazole, itraconazole, ritonavir and conivaptan should be avoided due to increased concentrations of rivaroxaban and potential for increased bleeding risk.[26] Likewise, strong P-GP and CYP3A4 inducers should be avoided including phenytoin, rifampin, and carbamazepine due to decreased concentrations of rivaroxaban.[26] The prothrombin time (PT) and plasma concentrations of rivaroxaban exhibited a direct, linear relationship. Therefore, PT may be an option for monitoring the anticoagulant effect of rivaroxaban if needed, but it is not recommended at this time.[25,28]

The Rivaroxaban-Once Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial was a randomized, double-blind, multicenter trial which compared rivaroxaban 20 mg daily to dose-adjusted warfarin in patients with moderate to high risk of stroke.[27] Patients were included in the trial if they had documented AF and a risk of stroke, including history of stroke or TIA or a $CHADS_2$ score of ≥2. Patients with CrCl 30-49 mL/min were given a reduced dose of rivaroxaban, 15 mg daily.[27] The primary efficacy endpoint studied was the incidence of stroke (ischemic or hemorrhagic) and non-CNS embolism and the primary safety endpoint was the incidence of major and/or clinically relevant bleeding.

ROCKET-AF enrolled 14,264 patients with an average age of 73 years and an average $CHADS_2$ score of 3.5.[27] For patients in the warfarin treatment group, the average time spent at a therapeutic INR was only 58%, which is lower than most clinical trials using warfarin as a comparator.[27] In the intention-to-treat and per-protocol analyses, rivaroxaban was found noninferior to warfarin for prevention of stroke and systemic embolism ($p<0.001$ for both) with a greater than 30% decrease in the risk of intracranial bleeding ($p=0.02$).[27] There was no significant difference in major or non-major clinically relevant bleeding between the two agents ($p=0.576$), although bleeding from gastrointestinal sites was more common with rivaroxaban ($p<0.001$).[27]

Common adverse effects seen with rivaroxaban include bleeding, nausea, increased transaminases, and anemia.[28] Similar to dabigatran, there is no specific antidote for rivaroxaban, and due to high protein binding, it is not expected to be dialyzable.[26] Discontinuation of the drug with symptomatic treatment of the bleeding is all that is recommended at this point, although recombinant factor VIIa may be considered in those with life-threatening bleeding non-responsive to supportive measures.[28] The FDA Advisory Committee recently voted to recommend to the FDA that rivaroxaban be approved for the prevention of stroke in patients with atrial fibrillation. If approved by the FDA for AF, the committee hopes that rivaroxaban will be considered a third line agent after warfarin and dabigatran.[14]

Apixaban

A recently published study may lead to the approval of another oral anticoagulant for AF, apixaban. Apixaban is a direct factor Xa inhibitor, similar to rivaroxaban (Table 3).[29] The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE) was a randomized, double-blind trial that compared apixaban 5 mg BID to warfarin in 18,201 patients with AF and at least one additional risk factor for stroke.[30] The median age of enrolled patients was 70 years with a mean $CHADS_2$ score of 2.1. Patients treated with warfarin maintained a therapeutic INR 62.2% of the time. Apixaban proved to be noninferior and superior to warfarin for prevention of stroke or systemic embolism ($p<0.001$ and $p<0.01$), including a 49% reduction in hemorrhagic strokes ($p<0.001$).[30] Safety outcomes showed that apixaban significantly reduced the risk of major and non-major bleeding compared to warfarin ($p<0.001$) with no increased risk of gastrointestinal bleeding.[30] In summary, apixaban demonstrated superiority over warfarin in stroke prevention while reducing the risk of bleeding.[30]

Conclusion

The lack of monitoring, low interpatient variability and relatively few drug-drug interactions make these new oral agents an attractive option. Each agent has been shown to have similar, if not better, efficacy than warfarin for stroke prevention with similar or lower risks of bleeding. There are still concerns with each agent and more long-term surveillance will be needed. Cost analyses are also needed to determine whether the decreased necessity for monitoring justifies the increased cost of the medication. There seems to be a niche for these agents among patients who are difficult to control on warfarin therapy due to extraneous factors or patients who have a high risk for intracranial bleeding with warfarin. With nearly two decades of unrivaled use, warfarin may have finally met its match with dabigatran, rivaroxaban and apixaban. Currently, only dabigatran has received FDA approval for the indication of stroke prevention in atrial fibrillation, but keep a close eye for updates on rivaroxaban and apixaban in the future.

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Table 1. $CHADS_2$ Risk Stratification Scheme for Stroke Risk in Atrial Fibrillation.

CHADS2 Risk Factor	Score	Relative Risk
Heart Failure	1	1.4
Hypertension	1	1.6
Advanced age	1	1.4
Diabetes	1	1.7
Previous stroke or TIA	2	2.5

Adapted from Fuster et al[8]
TIA, transient ischemic attack

Table 2. Antithrombotic Therapy for Patients with Atrial Fibrillation.[8,23]

Risk Category	Recommended Therapy
No risk factors ($CHADS_2$ = 0)	aspirin 81-325 mg daily
One moderate risk factor ($CHADS_2$ = 1)	aspirin 81-325 mg daily ***or*** warfarin (INR target 2.5) ***or*** dabigatran 150 mg BID ***or*** 75 mg BID (CrCl 15-30 ml/min)[21]
Any high-risk factor or >1 moderate-risk factor ($CHADS_2$ ≥ 2)	warfarin (INR target 2.5) ***or*** dabigatran 150 mg BID ***or*** 75 mg BID (CrCl 15-30 ml/min)

CrCl, creatinine clearance; BID, twice daily; INR, international normalized ratio

Table 3. Pharmacokinetic and pharmacodynamic properties of dabigatran, rivaroxaban, and apixaban.

	Dabigatran etexilate	Rivaroxaban	Apixaban
Mechanism of action	Direct thrombin inhibitor, competitive and reversible16	Direct factor Xa inhibitor, selective[26]	Direct factor Xa inhibitor, selective[29]
Bioavailability, %	3-7[15]	80-100[26]	66[29]
t_{max}, h	1-2[15]	2-4[26]	3[29]
Half-life, h	12-17[15]	5-9[26]	8-15[29]
Elimination	Renal – 80%[15]	Renal – 66% (36% unchanged drug) Fecal – 28% (7% unchanged drug)[26]	~75% fecal 25% renal[29]
Metabolism	Esterases[15] Conjugation [15] No CYP450[15]	CYP3A4/5, CYP2J2[26]	CYP3A4[29]
Drug-Drug interactions	P-GP inducers/ inhibitors (rifampin, amiodarone, quinidine, ketoconazole, verapamil)[15]	P-GP and CYP3A4 inhibitors/inducers[26]	Minor[29]
Monitoring parameters	None supported[15]	None supported[26]	None supported[30]
Dosing	150 mg BID CrCl 15-30ml/min: 75 mg BID CrCl <15 ml/min: dosing information cannot be provided[5]	*20 mg daily27 *CrCl 30-49 ml/min: 15 mg daily27 <30 ml/min: not recommended[26]	*5 mg BID[30]

P-GP indicates p-glycoprotein; tmax , time to maximum concentration; PT, prothrombin time; BID, twice daily; CrCL, creatinine clearance

*Not currently approved by FDA, doses used in clinical trials

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1. Krahn AD, Manfreda J, Tate RB, Mathewson FAL, Cuddy TE. The Natural History of Atrial Fibrillation: Incidence, Risk Factors, and Prognosis in the Manitoba Follow-up Study. Am J Med. 1995; 98: 476-84
2. Wolf PA, Abbott RD, Kannel WB. Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study. Stroke. 1991; 22:983-8.
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault, LE, Selby JV, Singer DE. 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: 2370-5.
4. Albers GW, Sherman DG, Gress DR, Paulseth JE, Petersen P. Stroke Prevention in Nonvalvular Atrial Fibrillation: A Review of Prospective Randomized Trials. Ann Neurol. 1991; 30: 311-8.
5. Hirsh J, Dale JE, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D. Oral Anticoagulants: Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. Chest. 2001; 119: 8S-21S.
6. Glazer NL, Dublin S, Smith NL, French B, Jackson LA, Hrachovec JB, Siscovick DS, Psaty BM, Heckbert SR. Newly Detected Atrial Fibrillation and Compliance with Antithrombotic Guidelines. Arch Intern Med. 2007; 167: 246-52.
7. Monette J, Gurwitz JH, Rochon PA, Avorn J. Physician attitudes concerning warfarin for stroke prevention in atrial fibrillation: results of a survey of long-term care practitioners. J Am Geriatr Soc. 1997; 45: 1060-5.
8. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 114; 7: e257-354.
9. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ. Antithrombotic Therapy in Atrial Fibrillation: American College of Chest Physicians Guidelines (8th Edition). Chest. 2008; 133: 546S-92S.
10. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic Therapy to Prevent Stroke in Patients with Atrial Fibrillation: A Meta-Analysis. Ann Intern Med. 1999; 131: 492-501.
11. Food and Drug Administration. FDA News Release: FDA Approves Pradaxa to prevent stroke in people with atrial fibrillation. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm (Accessed 2010 November 15).
12. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients the Atrial Fibrillation (RELY Trial). NEJM. 2009; 361: 1139-51.
13. Food and Drug Administration. FDA News Release: FDA approves Xarelto to reduce the risk of blood clots after hip, knee replacements. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm261839.htm (Accessed 2011 October 25).
14. O'Riordan M. Rivaroxaban should be approved for stroke prevention in AF, panel tells FDA. http://www.theheart.org/article/1276073.do. (Accessed 2011 October 25).
15. Pradaxa [package insert]. Ridgefield, CT: Boehringer Inelheim Pharmaceuticals Inc; 2010.
16. Ma TKW, Yan BP, Lam Y. Dabigatran etexilate versus warfarin as the oral anticoagulant of choice? A review of clinical data. Pharamcol Ther. 2011; 129: 185-94.
17. Escobar C, Barrios V, Jimenez D. Atrial Fibrillation and Dabigatran: Has the Time Come to Use New Anticoagulants? Cardiovasc Ther. 2010; 28: 295-301.
18. Stangier J, Rathgen K, Stahle H, Ganseer D, Roth W. The pharmacokinetics, pharmacodynamics, and tolerability of Dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol. 2007; 64: 292-303.
19. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly Identified events in the RE-LY trial. NEJM. 2010; 363: 1875-6.
20. Wood S, O'Riordan M. FDA approves Dabigatran for stroke prevention, embolism, in AF patients. http://www.theheart.org/article/1138703.do (Accessed 2010 November 15).
21. Gage BF. Can we rely on RE-LY? NEJM. 2009; 361: 1200-03.
22. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind phase II trial. Presented at the American Heart Association, O rlando, Florida, US A, 18 November 2009.
23. Wann LS, Curtis AB, Ellenhogen KA, et al. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation (Update on Dabigatran). Heart Rhythm. 2011; 8: e1-e8.
24. Perzborn E, Kubitza D, Misselwitz F. Rivaroxaban: A novel, oral, direct factor Xa inhibitor in clinical development for the prevention and treatment of thromboembolic disorders. Hamostaseologie. 2007; 27: 282-9.
25. Kubitza D, Becka M, Wensing G, Voith B, Zuehlsdorf M. Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939 – an oral, direct Factor Xa inhibitor – after multiple dosing in healthy male subjects. Eur J Clin Pharmacol. 2005; 61: 873-80.
26. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2011.
27. 27. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. NEJM. 2011; 365: 883-91.
28. Xarelto [Summary of Product Characteristics – EU]. Berlin, Germany: Bayer Schering Pharma; 2009.
29. Davis EM, Packard KA, Knezevich JT, et al. New and emerging anticoagulant therapy for atrial fibrillation and acute coronary syndrome. Pharmacotherapy. 2011; 31: 975-1016.
30. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with Atrial Fibrillation. NEJM. 2011; 365; 981-92.

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