CLINICAL ALERT

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April 2012

Antithrombotic and Thrombolytic Therapy Clinical Practice Guidelines

The American College of Chest Physicians (ACCP) has published the 9th edition of *Evidence-based Clinical Practice Guidelines for Antithrombotic and Thrombolytic Therapy*. These 2012 guidelines update the 2008 guidelines. Select major changes with the most impact on outpatient pharmacologic therapy are summarized:

For prevention of venous thromboembolism (VTE) in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA), ACCP recommends use of low molecular weight heparins (LMWH), fondaparinux, unfractionated heparin (UFH), vitamin K antagonist (VKA) e.g., warfarin, or aspirin (ASA) and also includes the newer agents dabigatran, rivaroxaban, and the investigational agent apixaban (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C). LMWH is recommended over the other agents (Grade 2B-2C). Limitations of alternative agents include the possibility of increased bleeding (which may occur with fondaparinux, rivaroxaban, and VKA), possible decreased efficacy (UFH, VKA, aspirin, and IPCD alone), and lack of long-term safety data (dabigatran, rivaroxaban, and apixaban). In patients undergoing hip fracture surgery, ACCP recommends use of one of the following for VTE prophylaxis: LMWH, fondaparinux, low dose unfractionated heparin, adjusted-dose VKA, aspirin (all Grade 1B), or an IPCD (Grade 1C).

For the treatment of acute DVT of the leg, acute pulmonary embolism (PE), or acute upper extremity DVT (UEDVT) of the axillary or more proximal veins, LMWH or fondaparinux is suggested over UFH (Grades 2B and 2C); and once-daily LMWH dosing is suggested over twice-daily dosing as long as the total daily dosing is the same for both regimens (Grade 2C). In patients with DVT of the leg, or PE and no cancer, ACCP suggests VKA therapy over LMWH for long-term therapy (Grade 2C); for patients with cancer, ACCP suggests LMWH over VKA therapy (Grade 2B). Both VKA and LMWH are preferred over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

For patients with atrial fibrillation (AF), including those with paroxysmal AF, with intermediate or high risk of stroke, ACCP recommends oral anticoagulation over ASA (75-325 mg once daily) or ASA/clopidogrel (Grade 2B, 1B); dabigatran is preferred over VKA (Grade 2B). ACCP suggests no therapy for patients at low risk of stroke.

In patients with acute ischemic stroke or acute primary intracerebral hemorrhage (ICH) and restricted mobility, ACCP suggests LMWH over UFH (Grade 2B).

In patients with a history of noncardioembolic ischemic stroke or TIA, for the prevention of secondary noncardioembolic ischemic stroke, ACCP recommends long-term treatment with low-dose ASA, clopidogrel, ASA/dipyridamole ER, or cilostazol; with preference to clopidogrel or ASA/dipyridamole ER (Grade 2B).

ASA slightly reduces total mortality regardless of cardiovascular risk profile if taken over 10 years. For primary prevention in persons aged 50 years or older without symptomatic CVD, ACCP suggests aspirin low-dose (75–100 mg daily) (Grade 2B). For secondary prevention in patients with established CAD, defined as one-year post-ACS, with prior revascularization, coronary stenoses > 50 percent, and/or evidence for cardiac ischemia, ACCP recommends long-term low-dose aspirin or clopidogrel (Grade 1A); for patients undergoing elective PCI but no stenting, ACCP suggests aspirin 75 to 325 mg daily and clopidogrel for the first month; for patients in the first year after an ACS with stent placement, ACCP recommends low-dose aspirin plus ticagrelor, clopidogrel, or prasugrel (Grade 1B), with a preference of aspirin plus ticagrelor over aspirin plus clopidogrel (Grade 2B). The new guidelines do not include ticlopidine.

In patients with symptomatic carotid stenosis, including recent carotid endarterectomy, ACCP recommends long-term antiplatelet therapy with clopidogrel, ASA/dipyridamole ER, or ASA (Grade 1A); with preference to either clopidogrel or ASA/dipyridamole ER over ASA (Grade 2B).

It should be noted that the method for grading research studies was more stringent, using experts in methodology and interpretation of the evidence rather than world experts in the field of antithrombotics. This resulted in 2012 guidelines that recommend antithrombotic treatment less often and less strongly than before.

Infectious Diseases Society of America (IDSA) Acute Bacterial Rhinosinusitis (ABRS) Practice Guidelines

One in seven US adults suffers from rhinosinusitis annually. IDSA has released clinical practice guidelines for diagnosis and management of ABRS. Only 2 to 10 percent of acute rhinosinusitis is bacterial; the rest are viral. Patients presenting with persistent, severe, or worsening symptoms typically have ABRS rather than viral rhinosinusitis. Once a clinical diagnosis of bacterial rhinosinusitis is established, a β-lactam rather than a respiratory fluoroquinolone is recommended for initial therapy. Amoxicillin-clavulanate is recommended instead of amoxicillin monotherapy in adults for 5–7 days. Prior guidelines suggested 10–14 days.

Drug Information Highlights

- The FDA has announced a drug interaction label change for certain statins with HCV and HIV protease inhibitors, due to increased risk of myopathy/rhabdomyolysis. Concomitant administration of lovastatin and simvastatin with HIV protease inhibitors or HCV protease inhibitors (boceprevir and telaprevir) is contraindicated. Atorvastatin is contraindicated with tipranavir plus ritonavir, and telaprevir. Atorvastatin should be used with caution (at the lowest effective dose) in patients taking lopinavir plus ritonavir. The labels have also been updated to include dosing recommendations for those statins that may safely be co-administered with HIV or HCV protease inhibitors.
- Genentech has announced a temporary supply constraint for peginterferon alfa-2a (Pegasys®) 180 mcg/0.5 mL prefilled syringe (PFS). This shortage is expected to resolve by September 2012. Peginterferon alfa-2a (Pegasys) ProClick™ and vials are not affected by the PFS shortage.
- The FDA has revised recommendations for citalopram (Celexa®) dose-dependent QT interval prolongation, which can cause torsades de pointes, ventricular tachycardia, and sudden death. It is not recommended at doses > 40 mg per/day, or in congenital long QT syndrome, bradycardia, hypokalemia, or hypomagnesemia, recent acute myocardial infarction, or uncompensated heart failure, or with other drugs that prolong the QT interval. The maximum recommended dose is 20 mg per/day for hepatic impairment, age > 60 years, CYP 2C19 poor metabolizers, concomitant cimetidine (Tagamet®) or another CYP2C19 inhibitor.

Sources:
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FDA Approved New Molecular Entities (NMEs), Biologic Products (BLAs)/Orphan Drugs, and New Indications/New Formulations for Existing Products				
Generic Name	***Trade Name***	***Description***	***Applicant***	***FDA Status***
pancrelipase	Ultresa™	The FDA approved pancrelipase delayed-release capsule (Ultresa) for the treatment of exocrine pancreatic insufficiency due to cystic fibrosis (CF) or other conditions. Exercise caution when prescribing Ultresa to patients with gout, renal impairment, hyperuricemia, or known porcine allergy. Ultresa is not interchangeable with other pancrelipase products and its use in pediatric patients is limited by the ability of the available dosage strengths to provide the recommended dose based on age and weight. Ultresa capsules should be swallowed whole, but for children or patients unable to swallow intact capsules, the contents may be sprinkled on applesauce, yogurt, and other acidic soft food with pH ≤ 4.5. The delayed-release capsules are available as 13,800/27,600/27,600 and 20,700/41,400/41,400 USP units of lipase/protease/amylase.	Aptalis	FDA NDA Approval 03/01/2012
pancrelipase	Viokace™	The FDA also approved pancrelipase tablets (Viokace) indicated for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy. Viokace is not interchangeable with other pancrelipase products and its use in pediatric patients has not been established. Viokace should be used with caution in patients with gout, renal impairment, hyperuricemia, or known porcine allergy. Viokace tablets are available in two strengths providing 10,440/39,150/39,150 and 20,880/78,300/78,300 of lipase/protease/amylase.	Aptalis	FDA NDA Approval 03/01/2012
ziprasidone hydrochloride	ziprasidone hydrochloride	The FDA approved ziprasidone hydrochloride, the generic for Geodon®, indicated for the treatment of schizophrenia and the acute and maintenance treatment of bipolar I disorder.	Apotex, Dr. Reddy's, Lupin	FDA ANDA Approval 03/02/2012
alendronate sodium	Binosto™	The FDA approved alendronate sodium effervescent tablets (Binosto) for the treatment of osteoporosis in postmenopausal women, and as a treatment to increase bone mass in men with osteoporosis. Binosto 70 mg tablet rapidly dissolves in 4 ounces of room temperature water to produce a buffered solution. It is dosed once weekly and is available in packs of 4 and 12 tablets. It is expected to be commercially available in the United States in the third quarter of 2012.	EffRx Pharmaceuticals	FDA NDA Approval 03/14/2012
escitalopram oxalate	escitalopram oxalate	The FDA approved escitalopram oxalate tablets, the generic for Lexapro® tablets, indicated for the treatment of acute and maintenance treatment of major depressive disorder (MDD) in adults and adolescents aged 12–17 years and acute treatment of generalized anxiety disorder (GAD) in adults.	IVAX	FDA ANDA Approval 03/14/2012
escitalopram oxalate	escitalopram oxalate	The FDA approved escitalopram oxalate oral solution, the generic for Lexapro® oral solution, indicated for the treatment of acute and maintenance treatment of major depressive disorder (MDD) in adults and adolescents aged 12–17 years and acute treatment of generalized anxiety disorder (GAD) in adults.	Amneal	FDA ANDA Approval 03/14/2012
ibandronate sodium	ibandronate sodium	The FDA approved ibandronate sodium 150 mg tablets, generic for Boniva® 150 mg, a once-monthly tablet indicated for the treatment and prevention of osteoporosis in postmenopausal women.	Apotex, Mylan, Orchid, and Watson	FDA ANDA Approval 3/19/2012, 3/20/2012
beclomethasone dipropionate	QNASL™	The FDA approved beclomethasone dipropionate (QNASL), a nonaqueous ("dry") nasal aerosol for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. The safety and efficacy of the recommended dose of 320 mcg once-daily administered as two sprays in each nostril was demonstrated in four Phase III randomized, double-blind, parallel-group, placebo-controlled clinical trials.	TEVA	FDA NDA Approval 03/23/2012
peginesatide	Omontys®	An erythropoiesis-stimulating agent (ESA) approved to treat anemia, in adult dialysis patients who have chronic kidney disease. Initiate when the hemoglobin level is < 10 g/dL. The recommended starting dose in patients who are not currently on an ESA is 0.04 mg/kg body weight as a once-monthly IV or SC injection.	Affymax	FDA NDA Approval 03/27/2012