In patients with atrial fibrillation (AF), halving the standard dose of edoxaban, a new anticoagulant, does not reduce its efficacy for preventing strokes or systemic embolism. This finding, said Dr. Ruff, emerged from analysis of data from the approximately one-third of ENGAGE AF-TIMI trial patients with clinical features that put them at high risk for major bleeding. The initial randomization among 21,105 patients with AF and CHADS2 scores of 2 or more was to low-dose edoxaban (30 mg daily), high-dose edoxaban (60 mg daily), or warfarin (international normalized ratio [INR] 2.0–3.0). Edoxaban doses among high-risk patients were reduced by 50% (15 mg or 30 mg daily).

The clinical features defining high risk, which the data suggest can now be used as a basis for edoxaban dose reduction, were creatinine clearance of 30 to 50 mL/minute; weight of 60 kg or less; and current regular administration of strong P-glycoprotein inhibitors such as verapamil, quinidine, or amiodarone.

In ENGAGE AF-TIMI 48, reducing the edoxaban dose lowered the mean edoxaban exposure by 29% to 39% and reduced factor Xa activity by 20% to 25% compared with the full-dose population. That suggests, Dr. Ruff explained in a Hot Line session, that “the therapeutic window and dose–response curve of edoxaban differ between safety and efficacy, and are steeper for major bleeding but more forgiving for stroke or systemic embolism—and reassuringly very wide for intracranial hemorrhage.”

ENGAGE AF-TIMI 48 researchers evaluated trough concentrations in 6,780 patients randomized to edoxaban and anticoagulation in a subset of 2,865 of those patients, looking for correlations between safety and efficacy outcomes compared with warfarin. Compared with warfarin, hazard ratios (HRs) for stroke or systemic embolism among patients receiving edoxaban at full (0.81) or half dose were almost the same (interaction, \( P = 0.85 \)). “So, by lowering the dose by 50% we did not sacrifice overall efficacy,” Dr. Ruff said.

Despite a 60% higher bleeding risk among patients with the listed clinical features, use of edoxaban at 30 mg produced a 45% relative risk (RR) decrease in bleeding versus warfarin (12% absolute reduction), and a 69% RR decrease (\( P = 0.0002 \)) among those with edoxaban dose reductions (37% absolute reduction, \( P = 0.02 \)).

Annual percent stroke or systemic embolic event rates for warfarin, high-dose edoxaban, and low-dose edoxaban were 1.29, 1.00, and 1.38. For those with reduced edoxaban doses, they were 1.79 and 2.36.

Dr. Ruff concluded that tailoring the edoxaban dose based on clinical features, with no measuring of drug levels or anticoagulation activity, prevented excess edoxaban levels and helped optimize the balance between ischemic and bleeding events.

**Colchicine for Prevention of Post-Pericardiotomy Syndrome and Post-Operative Atrial Fibrillation: The COPPS-2 Randomized Clinical Trial**

- Massimo Imazio, MD, University of Torino, Torino, Italy

The original COPPS trial showed colchicine administered starting at the third postoperative day significantly reduced postpericardiotomy syndrome incidence (8.9% versus 21.1%) compared with placebo. However, results from the COPPS-2 trial of colchicine given preoperatively were far less compelling.

Postpericardiotomy syndrome (PPS) is a febrile immune phenomenon that may appear days to months after surgical incision of the pericardium. It may be accompanied by pleuritis (with possible pleural effusion) and pericarditis (with possible pericardial effusion).

Given that most PPS occurs in the first 60 days postoperatively and AF in the first three days, the “very impressive” PPS relative-risk reduction in COPPS led investigators to hypothesize that giving colchicine before surgery could improve efficacy.

In COPPS-2, 360 consecutive candidates for cardiac surgery at 11 Italian centers were randomized 1:1 to colchicine or placebo for one month (as in COPPS), with treatment initiated 48 to 72 hours before surgery. Dosing was weight-based (0.5 mg twice daily in patients weighing at least 70 kg or 0.5 mg once daily in those less than 70 kg). The primary outcome was PPS within three months of surgery.
The PPS rate, Dr. Imazio reported, was 19.4% for patients assigned to colchicine and 29.4% for those receiving placebo, an absolute difference of 10.1% (95% confidence interval [CI], 1.1 to 18.7). No significant differences were observed, however, for postoperative AF (colchicine, 33.9%; placebo, 41.7%) or postoperative pericardial/pleural effusions (colchicine, 57.2%; placebo, 58.9%). Among patients who tolerated treatment, the AF reduction was significant.

Safety, with adverse events at 11.7% for placebo but 20.0% for colchicine, was the main concern. Gastrointestinal intolerance (diarrhea, nausea, cramping, abdominal pain, or vomiting) was reported in 14.4% of colchicine patients compared with 6.7% for placebo.

Dr. Imazio commented, “You have to consider that in the perioperative period, patients usually take other drugs such as proton pump inhibitors and antibiotics that may also be responsible for GI intolerance. … That’s probably why the drug was not efficacious for preventing AF.”

In their concurrently published online article in the Journal of the American Medical Association, the researchers concluded that the higher rate of adverse events among patients assigned to colchicine “is a reason for concern and suggests that colchicine should be considered only in well-selected patients.” They suggested, as well, that regarding PPS, it may be “better to treat than to prevent.”

Lower doses of colchicine may be explored in future studies.

Harris Poll: Global Survey of Cardiologists On Non-Valvular Atrial Fibrillation (NVAF)

Management

• Hugh Calkins, MD, Professor of Medicine, Johns Hopkins University, Baltimore, Maryland

A Harris Poll of 1,100 cardiologists in the U.S., Japan, United Kingdom, Germany, France, Brazil, and Spain confirmed the diversity of the nonvalvular atrial fibrillation (NVAF) population and affirmed that the complexity of NVAF management requires an integrated approach. The poll was jointly sponsored by Daiichi Sankyo and was conducted in a partnership with the Heart Rhythm Society. Dr. Calkins presented survey findings at a Daiichi Sankyo press conference at the ESC meeting.

The survey questions were designed to further understanding of cardiologists’ perspectives on NVAF populations and their disease management.

NVAF Population

More than half of cardiologists (58%) agreed that there is no such thing as a “typical” NVAF patient. Many cardiologists (77%) reported an increase in the number of NVAF patients in their practices in the last five years.

Nearly all cardiologists (98%) believed that NVAF patients may experience a delay in diagnosis, primarily because they are asymptomatic, but also because of low NVAF awareness among health care professionals and the public.

NVAF Management

A large majority of cardiologists (88%) agreed that the diversity of NVAF patients requires that patient management be guided by individual comorbidities and other patient characteristics. On average, the survey found that NVAF patients have about three comorbid conditions.

Consistent among cardiologists’ NVAF stroke-prevention treatment concerns were product efficacy and bleeding risk. High bleeding risk was noted as an impediment to oral anticoagulant therapy. However, cardiologists indicated that only 83.7% of NVAF patients receive oral anticoagulation therapy for stroke prevention. The most important factors for management of anticoagulant therapy included patients’ bleeding risk, histories of hemorrhagic stroke, and patient compliance with medication. Renal dysfunction and age were noted as concerns by 54% and 53% of cardiologists, respectively. The most important factor guiding medication choice was the agent’s overall efficacy profile.

The top three reasons why some NVAF patients do not receive oral anticoagulant therapy for stroke prevention were patient refusal, high bleeding risk, and other contraindications. About a third of these patients, cardiologists reported in the survey, have stroke risk warranting oral anticoagulant therapy based on current guidelines.

Dr. Calkins noted that in other disease areas, coordinated care among health care professionals has been shown to improve patient outcomes. Most of the cardiologists polled (84%) believe that such coordinated care is important for NVAF management—however, two-thirds of them feel that current care is not sufficiently coordinated. The U.S. cardiologists were seventh-lowest in their belief in the adequacy of coordinated care (27%; range, 26%–60%).

The Role of Caregivers

Most cardiologists (73%) believe that caregivers play important roles for NVAF patients, with 43% stressing assistance with taking medications as prescribed and 84% emphasizing support for communication with all health care professionals involved in the patient’s care. “The majority of cardiologists agree that there is an opportunity for caregivers to play a more prominent role in helping patients manage nonvalvular AF,” Dr. Calkins said.

AF increases stroke risk threefold to fivefold, and AF-induced strokes are nearly twice as likely to be fatal as strokes in patients without AF at 30 days.

PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial). A Comparison of Angiotensin Receptor-Nephrilysin Inhibition (ARNI) With ACE Inhibition in the Long-Term Treatment of Chronic Heart Failure With a Reduced Ejection Fraction

• Milton Packer, MD, Professor, University of Texas Southwestern Medical Center, Dallas, Texas

“PARADIGM-HF may well represent a new threshold of hope for patients with heart failure. … The beneficial results seen in PARADIGM-HF may apply to a wide spectrum of patients, even those who are currently receiving the best possible therapy.”
Mariel Jessup, MD, wrote in a *New England Journal of Medicine* editorial\(^2\) appearing concurrently with the PARADIGM-HF presentation by Dr. Packer at ESC. PARADIGM-HF, which was conducted by more than 1,000 investigators in 47 countries, included 4,187 patients randomized to LCZ696 and 4,212 randomized to enalapril.

Inhibition of the renin-angiotensin system has been the cornerstone of heart failure (HF) treatment for the last 25 years. While enalapril was one of the first agents to show a survival benefit, that benefit was modest compared with other drugs now added to angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), such as beta blockers or mineralocorticoid receptor antagonists.

Neprilysin inhibition potentiates actions of endogenous vasoactive peptides that counter maladaptive mechanisms in HF that result in neurohormonal activation, poor vascular tone, cardiac fibrosis/hypertrophy, and sodium retention.

“The neprilysin inhibitor LCZ696 was specifically designed to replace current use of ACE inhibitors and angiotensin-receptor blockers as the cornerstone of treatment of heart failure,” Dr. Packer said. PARADIGM-HF, he underscored, was designed as a cardiovascular mortality trial. The primary endpoint was cardiovascular death or hospitalization for HF.

Patients included in PARADIGM-HF had New York Heart Association class II–IV HF with left ventricular ejection fractions (LVEFs) of 35%–40% or less with at least mild increases in BNP (brain natriuretic peptide) or N-terminal proBNP. The patient population, Dr. Packer said, was “pretty representative of those with heart failure.”

The study was terminated early, after a median follow-up of 27 months, because LCZ696 was found to be superior to enalapril. With LCZ696, compared with enalapril, the primary endpoint was reduced by 20% (HR, 0.80 [0.73–0.87]; \(P = 0.000002\)), with a number needed to treat (NNT) of 21. Cardiovascular death alone with LCZ696 was reduced by 20% as well (HR, 0.80 [0.71–0.89]; \(P = 0.00004\)), with a NNT of 32. All-cause mortality with LCZ696 was reduced by 16% (\(P < 0.0001\)).

Furthermore, HF hospitalization was reduced by an incremental 21% over enalapril, with improved HF symptoms and physical limitations. LCZ696 was better tolerated than enalapril, with less cough, hyperkalemia, and renal impairment. While there was more hypotension, there was no increase in discontinuation of therapy. Serious angioedema was not increased.

The findings of PARADIGM-HF, given the 20% greater effect of LCZ696 than enalapril, extend enalapril’s ethical mandate for treatment of all patients with chronic HF who can tolerate the drug. “It strongly supports the conclusion that LCZ696 should replace current use of ACE inhibitors and angiotensin-receptor blockers in the management of chronic heart failure,” Dr. Packer said.

Dr. Jessup suggested, during a question-and-answer session, that the drug, once approved, might not be used among patients with mild HF who are already doing well on standard therapy because of cost. However, Dr. Packer pointed out that the drug’s major advantage in patients with mild class II HF is that it reduces HF progression, hospitalization, and mortality. “It changes the natural course of the disease,” he said.

### TRANSLATE-ACS (Treatment With ADP Receptor Inhibitors: Longitudinal Assessment Of Treatment Patterns and Events After Acute Coronary Syndrome)

- Tracy Y. Wang, MD, Associate Professor of Medicine, Duke University, Durham, North Carolina

While randomized clinical trials of postmyocardial infarction use of adenosine diphosphate (ADP) receptor inhibitors have established prasugrel’s efficacy, data on the comparative effectiveness and safety of prasugrel versus the older standard agent clopidogrel in routine U.S. clinical practice are limited. To assess those, investigators for TRANSLATE-ACS, a multicenter, prospective observational study, enrolled 12,227 ST-segment-elevation and non–ST-segment-elevation myocardial infarction (MI) patients treated with percutaneous coronary intervention (PCI) at 235 U.S. hospitals.

Prasugrel was used in 25.5% of patients and clopidogrel in 72.3%. Patients receiving prasugrel were significantly (\(P < 0.0001\)) more likely to be younger, male, and have ST-segment-elevation MI and to receive drug-eluting stents. Prior MI, prior bypass surgery, prior stroke, and multivessel disease were more common (\(P < 0.0001\)) among patients receiving clopidogrel, as was diabetes (\(P = 0.003\)).

Unadjusted composite major adverse clinical events (MACE) were higher for clopidogrel (intention-to-treat) at 17.3% versus 13.5% for prasugrel (\(P = 0.0001\)). After adjustment for baseline risk, however, an as-treated analysis of MACE showed the HR for clopidogrel treatment to be 1.03 (\(P = 0.59\)).

Stent thrombosis rates were lower with prasugrel (0.98% versus 1.33%; adjusted HR, 0.63 [0.42–0.97]; \(P = 0.04\)), while unadjusted bleeding was higher for clopidogrel (2.7% versus 3.9%, \(P = 0.007\)). After adjustment among all comers, however, bleeding was higher with prasugrel (adjusted HR, 1.30; 95% CI, 1.04–1.63; \(P = 0.02\)). “When you focus on those who in routine practice are more likely to be treated with prasugrel, then that difference is no longer significant,” Dr. Wang noted. She called the results “somewhat reassuring” in that they show that interventionists are actually paying attention to the data and are using prasugrel in patients who are younger, male, and have ST-elevation MI and who are likely to benefit the most from more potent antiplatelet therapy—and are less likely to bleed.

“One of the things that clinicians are most afraid of in the U.S.,” said the TCT moderator of the session, Roxana Mehran, MD, Professor of Medicine at Mount Sinai Hospital, New York, New York, “is that because of cost, patients will not fill the prescription for the more potent agent or they will discontinue it early.”
TRANSLATE-ACS, Dr. Wang commented, is the largest prospective longitudinal study of acute MI patients undergoing PCI in contemporary community practice.

The TRANSLATE-ACS trial was funded by Lilly USA and Daiichi Sankyo.

Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation

- Katrin A. Fiedler, MD, Deutsches Herzcentrum, Munich, Germany

When patients who already have an indication for oral anticoagulation therapy—such as those with AF, pulmonary embolism, deep vein thrombosis, or mechanical valves—undergo coronary stenting, coronary interventionalists generally add dual antiplatelet therapy (usually consisting of clopidogrel and aspirin). The resulting “triple therapy,” however, entails elevated bleeding risk. The dilemma is that leaving out oral anticoagulation therapy risks stroke and thromboembolism, and leaving out dual antiplatelet therapy risks stent thrombosis and ischemic events.

The ISAR TRIPLE trial tested whether shortening the duration of triple therapy after stenting would reduce major bleeding events or increase ischemic events. It is the largest randomized trial to date investigating triple therapy and the first to examine duration of therapy. It included 614 patients at three European centers undergoing drug-eluting stent implantation. They were randomized, after aspirin and a vitamin K antagonist, to six weeks of clopidogrel (n = 307) or six months of clopidogrel (n = 307), with clinical follow-up at nine months.

Combined MI, stent thrombosis, stroke, or TIMI major bleeding at nine months, the primary endpoint, was reported at 8.8% for the six-month triple therapy group and 9.8% for the six-week group (HR, 1.14; 95% CI, 0.68–1.91; P = 0.63). The secondary endpoint analysis, separating out major bleeding, revealed no differences for the combined ischemic components (4.0% versus 4.3%, respectively, for the six-month and six-week groups; P = 0.87) or for major bleeding (4.0% and 5.3%, respectively; P = 0.44).

“The main finding is that six-week triple therapy is not superior to six-month triple therapy with regard to net clinical outcomes,” Dr. Fiedler said, “and that shortening the duration of triple therapy neither reduced the incidence of major bleeding nor increased the incidence of ischemic events.” When choosing the shorter or longer duration of triple therapy, the physician should weigh the trade-off between ischemic risk and bleeding risk, Dr. Fiedler concluded.

Predictors of Stent Thrombosis After Primary PCI And Risk for 30-Day Mortality: Analysis From the Pooled Patient-Level Data From the HORIZONS-AMI and EUROMAX Trials

- George D. Dangas, MD, PhD, Professor of Medicine, Mount Sinai Medical Center, New York, New York

The risk of early (30 days or less) stent thrombosis is consider able after primary PCI for non–ST-segment MI. The impetus for the current analysis arose out of the observation that patients in the HORIZONS-AMI, EUROMAX, and HEAT-PPCI trials treated with bivalirudin compared with unfractionated heparin ± GP2b/2a inhibitors uniformly showed an increased risk of acute (less than 24 hours) stent thrombosis, but did not show any significant stent thrombosis risk thereafter.

The current analysis covered 5,800 ST-segment MI patients; 100 of them (1.7%) developed early stent thrombosis, and within that group, 20 (20%) died within 30 days. Sixty of the stent thromboses occurred in patients receiving bivalirudin and 40 occurred in those receiving heparin ± GP2b/2a inhibitor.

The predominant stent thrombosis risk in the bivalirudin group, a one-day landmark analysis showed, was in the first day (bivalirudin, 1.3%; heparin ± GP2b/2a inhibitor, 0.2%; P < 0.0001). From day 2 to day 30, risk was similar (bivalirudin, 0.9%; heparin ± GP2b/2a inhibitor, 1.2%; P = 0.271) for both agents. Closer analysis showed the higher risk with bivalirudin to be limited to the first four hours post-procedure.

A further observation was that subacute stent thrombosis (occurring from day 2 to day 30) has higher subsequent mortality than acute stent thrombosis. Mortality at 30 days among patients with acute stent thrombosis was 16.7% with heparin ± GP2b/2a inhibitors and 2.8% with bivalirudin (P = 0.125). For subacute stent thrombosis patients, mortality rates were 44.1% for heparin ± GP2b/2a inhibitor and 12.0% for bivalirudin (P = 0.01). Combined 30-day mortality for all stent thrombosis patients was 6.7% for bivalirudin and 40% for heparin ± GP2b/2a inhibitor (RR, 0.19; 95% CI, 0.7–0.52; P = 0.0002).

The significant predictors of acute stent thrombosis were randomization to bivalirudin (odds ratio [OR], 6.94 [2.71–17.75]; P < 0.0001) and pre-procedure TIMI flow of 0 or 1 (OR, 2.35 [1.04–5.55]; P = 0.041). At 30 days after stent thrombosis, however, bivalirudin was an inverse predictor of mortality (OR, 0.17 [0.04–0.63]; P = 0.008). Age greater than 65 years also predicted mortality (OR, 5.13 [1.48–17.73], P = 0.010).

“Thirty-day mortality after early stent thrombosis is substantially less common in patients randomized to bivalirudin compared to heparin ± GP2b/2a inhibitor. This finding is consistent for both acute and subacute stent thrombosis,” Dr. Dangas concluded.

“The explanation for this finding is not yet clear,” coinvestigator Professor Philippe Gabriel Steg, MD, Hôtel Bichat, Paris, France, said in an interview, “and more data and analyses are required—but it is quite striking.” He speculated, “A possibility among others is that very early stent thrombosis occurring while patients are still in the cath lab or close proximity to it may be less dangerous than later stent thrombosis.

“With approximately a 1% absolute excess incidence and no increased reinfarction or mortality, I think the acute stent thrombosis issue in bivalirudin-treated ST-elevation myocardial infarction patients is important, but has been to some extent overblown,” Dr. Steg added. “It can be addressed by prolonged bivalirudin infusion.”
Conflicting findings from clinical trials have fueled recent controversy over strategies for optimal anticoagulation in patients undergoing PCIs. While a recent trial demonstrated superiority for heparin monotherapy over bivalirudin alone, with a disturbing increased rate of stent thrombosis among bivalirudin-treated patients, prior multicenter trials have demonstrated bivalirudin superiority over heparin plus GP2b/2a inhibition.

The BRIGHT trial included acute MI patients at 82 Chinese sites, 735 randomized to bivalirudin, 729 to heparin monotherapy, and 730 to heparin plus tirofiban, a GP2b/2a inhibitor, said Dr. Han. Most (about 78%) PCI procedures were performed transradially, and 99% of patients received drug-eluting stents. The primary endpoint, 30-day net adverse clinical events (NACE), was a composite of major adverse cardiac and cerebral events (MACCE) or BARC (Bleeding Academic Research Consortium bleeding).

In the bivalirudin group, NACE incidence was lower compared with the heparin and heparin plus tirofiban groups (8.8%, 13.2%, and 17.0%, respectively; P < 0.001). The bivalirudin group also had fewer NACE events at one year (12.8%, 16.5%, and 20.5%, respectively; P < 0.001). Bivalirudin reduced major bleeding (P = 0.04) and minor bleeding (P < 0.001), with similar rates of adverse ischemic events compared with the heparin and heparin plus tirofiban groups. Importantly, overall and acute (less than 24 hours) stent thrombosis rates were similarly low in both groups. The overall rate was 0.6% with bivalirudin, 0.6% with heparin, and 0.3% with heparin plus tirofiban (P < 0.77). Acute stent thrombosis incidence was 0.3% in each group.

Dr. Han suggested that the mandated routine after a PCI bivalirudin infusion in BRIGHT might account for the similar rate of stent thrombosis with bivalirudin in BRIGHT, unlike earlier trials in which bivalirudin had a higher stent thrombosis rate.

At the TCT press conference where Dr. Han presented her data, Rod Stables, MD, Liverpool Heart and Chest Hospital, United Kingdom, whose HEAT-PCI trial had shown higher rates of stent thrombosis with bivalirudin and no bleeding advantage, commented: “I’m very impressed by the emerging data on the use of prolonged infusion, which I think would solve the problem really well, as suggested in this trial.” He added, “Bivalirudin has many theoretical and practical advantages. One is that it has a well-established dose ratio with predictable pharmacodynamics … you certainly can’t say that about heparin.”

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