Lowering Blood Pressure Reduces Vascular Events in Patients with Atrial Fibrillation

Speaker: Hisatomi Arima, MD, PhD, Clinical Research Scientist, George Institute for International Health, and Lecturer, University of Sydney, Sydney, New South Wales, Australia.

For most patients with atrial fibrillation (AF), routine lowering of blood pressure (BP) with an antihypertensive agent such as perindopril (Aceon®, Solvay) appears to provide protection against major vascular events such as stroke, non-fatal myocardial infarction (MI), or vascular death even if they are taking anticoagulants to prevent stroke.

A subsidiary analysis of data from the Perindopril Protection against Recurrent Stroke Study (PROGRESS) showed the benefits of reducing BP in 6,105 patients with cerebrovascular disease. All patients were randomly selected to receive either (1) active treatment with perindopril 2 to 4 mg plus the thiazide diuretic indapamide (Mylan/Parr) for those without an indication for, or a contraindication to, a diuretic or (2) a matching placebo. In this earlier study, treatment with the angiotensin-converting enzyme (ACE)–inhibitor and the diuretic resulted in a 25% reduction in stroke risk.

The analysis focused on 476 patients with AF at baseline, of whom 51% were taking anticoagulants. Over 3.9 years of follow-up, the presence of AF increased the risk of major vascular events by 25% and stroke by 29%.

Active treatment with perindopril and the diuretic reduced systolic BP by 7.3 mm Hg and diastolic BP by 3.4 mm Hg in patients with AF and reduced systolic BP by 9 mm Hg and diastolic BP by 4 mm Hg in patients without AF.

The corresponding reductions in the relative risk of major vascular events were 38% in patients with AF and 25% in patients without AF. Active treatment also reduced the relative risk of stroke by 34% in patients with AF and by 28% in those without AF.

It was estimated that one vascular event was avoided for every 11 patients with AF treated for five years, compared with one vascular event avoided among every 23 patients without AF. The benefits of BP lowering in patients with AF were achieved whether or not anticoagulant therapy was used and whether or not the patients had hypertension.

Early Frovatriptan Treatment for Migraine

Speaker: Arthur H. Elkind, MD, Director, Elkind Headache Center, Mount Vernon, New York, and Clinical Assistant Professor of Medicine, New York Medical College, Valhalla, New York.

The use of frovatriptan (Frova®, Elan) during the initial mild phase of a migraine attack promotes more rapid pain relief while preventing the progression of migraine pain intensity from mild to severe, thus offering a beneficial option.

In a randomized, controlled trial, 241 patients with acute migraine treated two migraine headaches with frovatriptan 2.5 mg or placebo when the headache pain was mild. If the pain progressed to moderate or severe, the patients took an alternative medication as the second dose. The order of treatment was revised for the second attack.

Treating mild pain with frovatriptan improved two-hour and four-hour pain-free responses, compared with placebo, and patients achieved pain-free responses more quickly with frovatriptan. Fifty-one percent of these patients achieved this goal in 3.1 hours, compared with 4.5 hours in the placebo group. Furthermore, 69% to 78% of patients reported mild or no headache two to four hours after taking frovatriptan in the early phase of headache compared with 51% to 64% of patients using placebo early on.

Mean pain scores during the first four hours were lower in
patients taking frovatriptan during the mild headache phase, whereas patients receiving placebo experienced increases in pain scores. From two to four hours after the dose was given, a statistical difference was observed between the treatment and placebo groups, indicating that the early use of frovatriptan impeded the progression of migraine pain intensity.

Finally, among patients who obtained a pain-free response after four hours, the rate of headache recurrence was low in all patients receiving frovatriptan. In patients treated with frovatriptan for the early headache phase, the recurrence rate was 4%. For patients who used frovatriptan for the later headache phase, the recurrence rate was 6%.

A related open-label trial was also reported in conjunction with the randomized study. Early intervention with frovatriptan appeared to be effective and well tolerated during long-term use in more than 13,000 migraine attacks treated. The likelihood of achieving meaningful relief was greatest when treatment was begun while the migraine was still mild.

The use of frovatriptan provided a consistent effect for 12 months. Only 10% of treated attacks required rescue medication within 24 hours of dosing with frovatriptan, and 57% of patients rated the drug’s effectiveness as “good” or “excellent.”

**Intravenous Tramadol for Intractable Migraine**

**Speaker:** John Claud Krusz, MD, PhD, Medical Director, Anodyne Headache and Pain Center, Dallas, Texas.

An open-label study using intravenous (IV) tramadol (Ultram®, Ortho-McNeil) demonstrates a new pharmacological approach to the clinical treatment of intractable migraine.

IV treatment of acute intractable migraine, especially in the headache clinic, can be very gratifying, because patients like their physicians to be able to short-circuit an ongoing migraine attack. Oral tramadol has been available in the U.S. and Europe for years, but the IV form has been available only in Europe.

To test the efficacy and safety of this approach for acute intractable headaches, the investigators prepared an injectable, 50-mg/ml formulation of tramadol in a sterile neutral pH solution. The IV formulation was given to clinic patients with severe migrainous or migraine attacks refractory to their usual medications (e.g., triptans, opiates, and even oral tramadol). In this open-label series, 12 patients were treated 17 times with IV tramadol; one patient was treated three times, and four patients were treated twice. Nine of these 12 patients had already tried oral tramadol.

The average percentage of decrease in headache severity was 75.6% after administration of IV tramadol, as rated by the patients on a numeric rating scale from 0 to 10. This represents a headache severity rating of 8.1 at the start of treatment in contrast to 1.54 after IV tramadol. Seven of 17 headaches (41%) were rated as totally eliminated after tramadol treatment.

Adverse effects during treatment included transient nausea in two patients and drowsiness in two other patients.

**Rasagiline Appears Promising in Parkinson’s Disease**

**Speaker:** Lawrence W. Elmer, MD, PhD, Assistant Professor, Department of Neurology, and Director of the Center for Neurologic Disorders, Medical College of Ohio, Toledo, Ohio.

Once-daily rasagiline mesylate (Agilect™, Azilect®, Teva Neuroscience), a selective reversible monoamine oxidase-B (MAO-B)–inhibitor, is effective and well tolerated by patients with Parkinson’s disease (PD). Patients with levodopa-related motor fluctuations who were already receiving concomitant dopamine agonist (DA) therapy experienced additional symptomatic relief.

Initially, in the Parkinson’s Rasagiline Efficacy and Safety in the Treatment of “Off” (PRESTO) study, rasagiline was effective for PD patients with motor fluctuations. (“Off” refers to when the effects of medication wear off and symptoms return; “on” refers to when the medication is working.)

All of the patients were taking an optimal levodopa–decarboxylase inhibitor (LD–DDI); many were also receiving DA therapy. The study enrolled 472 PD patients who were randomly assigned to rasagiline 1 mg or 0.5 mg once daily or to placebo for 26 weeks. In this analysis of PRESTO data, the efficacy and tolerability of adjunctive rasagiline were compared in PD patients with or without concomitant DA therapy.

A total of 106 patients (71%) receiving rasagiline 1 mg/day and 111 patients (70%) receiving placebo had concomitant treatment with DA therapy. Consequently, 43 patients (29%) receiving rasagiline 1 mg/day and 48 patients (30%) receiving placebo formed the “without DA” subgroup. Baseline characteristics (e.g., age, sex, disease duration, daily levodopa dosage, mean daily “off” time) were comparable in both patient groups with and without DA therapy.

As shown previously, rasagiline 1 mg/day produced additional significant symptomatic benefits, compared with placebo, when administered to patients already receiving optimized and stable therapy with LD–DDIs. The clinical benefits of rasagiline are in addition to and unaffected by concomitant treatment with DAs, as determined by the current subgroup analysis.

This study showed that rasagiline reduced daily “off” time, and produced improvements in Clinical Global Impression (CGI) scores, as measured by the examiner; in the Unified Parkinson’s Disease Rating Scale–Activities of Daily Living (UPDRS–ADL) scores while “off”; and in UPDRS–ADL scores while “on.” Similar magnitudes were observed in patients treated both with and without DAs.

**Sustained-Release Fampridine Improves Impressions in Multiple Sclerosis**

**Speaker:** Andrew Goodman, MD, Associate Professor of Neurology, Chief, Neuroimmunology Unit, and Director, Multiple Sclerosis Unit, Department of Neurology, University of Rochester Medical Center, Rochester, New York.

Response to fampridine-SR (Acorda Therapeutics), an investigational, oral sustained-release formulation of 4-aminopyridine (4-AP), in patients with multiple sclerosis (MS), as measured by consistent improvement of walking speed on the Timed 25-Foot Walk (T25-FW) test, identifies a meaningful change that positively affects patients’ impressions of their ambulatory disability.

A 24-center, double blind, placebo-controlled trial enrolled 206 patients with MS. The patients were randomly assigned to receive either fampridine-SR (10 mg, 15 mg, or 20 mg twice
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daily) or placebo, over a 14-week treatment period.

Among the 205 intent-to-treat patients, 62 patients experienced consistent improvements in walking speed during at least three of four visits during treatment that was faster than the maximum speed during the five “off-drug” visits. Response rates were higher in all fampridine-SR groups: 35% with 10 mg, 36% with 15 mg, 39% with 20 mg, and 9% with placebo. Consistent improvement in walking speed was significantly associated with improved Subjects’ Global Impression Questionnaire scores and 12-item Multiple Sclerosis Walking Scale (MSW5-12) scores. This indicates that consistent improvement in walking speed on the Timed Walk associated with this treatment is clinically meaningful to the patient.

Six Months of Memantine Helps Alzheimer’s Disease
Speaker: Rachel S. Doody, MD, PhD, Professor in Alzheimer’s Disease Research, Department of Neurology, and Director, Alzheimer’s Disease Research Center, Baylor College of Medicine, Houston, Texas.

Six months of treatment with memantine (Namenda®, Forest Laboratories, Inc.) offers a valuable therapeutic approach for patients with mild-to-severe Alzheimer’s disease (AD).

Evidence of this efficacy was reached from a meta-analysis of data from six large-scale, placebo-controlled trials (five American, one European). These encompassed 2,312 outpatients with either mild-to-moderate AD or moderate-to-severe AD who received memantine for six months. A meta-analysis such as this applies procedures to the treatment effects from individual trials to allow a quantitative evaluation of the treatment effect across trials. Unlike a pooled analysis, a meta-analysis recognizes that the subjects come from different trials and considers the heterogeneity between trials.

The investigators concluded that memantine over a six-month period resulted in a statistically significant benefit over placebo in cognition, function, and global status in patients with mild-to-severe AD.

Trials of patients with moderate-to-severe AD revealed statistically significant benefits over placebo on cognition, function, behavior, and global status.

Trials of patients with mild-to-moderate AD showed positive effects on cognition and global status. Rates of discontinuation and adverse effects from memantine treatment were similar to those reported for placebo.

Methylphenidate Alone Still Best for Attention-Deficit/Hyperactivity Disorder
Speaker: Donna Palumbo, PhD, Association Professor of Neurology and Pediatrics, University of Rochester Medical Center, and Director, Strong Neurology ADHD Program, Strong Memorial Hospital, Rochester, NY.

Results from the Clonidine in ADHD Treatment (CAT) trial indicated that methylphenidate (Ritalin®, Novartis)—but not clonidine (Datapres®, Boehringer-Ingelheim)—offered the best combination of benefits and the fewest adverse effects in patients with attention-deficit/hyperactivity disorder (ADHD), whether the medications were administered separately or together.

The use of clonidine alone or together with methylphenidate is becoming more common in the treatment of ADHD, but few safety and efficacy data are available. To better guide physicians and parents in making more informed treatment choices, the CAT trial was designed.

The multicenter, double-blind, placebo-controlled study involved 122 children (98 boys and 24 girls, 7 to 12 years of age) with ADHD. The children were randomly assigned to receive clonidine, methylphenidate, a combination of the two drugs, or placebo, according to a 2 × 2 factorial design, over a 16-week study period.

The primary outcome measure was the change from baseline to 16 weeks in scores from the Conner’s Abbreviated Symptom Questionnaire for Teachers (ASQ-T) for ADHD. The researchers used a number of other outcome measures for ADHD, including the ASQ–Parent, Conner’s Continuous Performance Test, and direct classroom observations. Adverse effects were carefully monitored.

On the ASQ-T, children receiving methylphenidate, whether alone or in combination with clonidine, performed better than those not taking methylphenidate and better than those taking clonidine alone or placebo. Overall, they experienced the greatest benefits, the smallest number of side effects, and the most improvement in ADHD symptoms.

Children receiving clonidine, either alone or in combination with methylphenidate, performed better than those not receiving clonidine and better than those taking methylphenidate or placebo, although this effect was small and not statistically significant. Thus, clonidine alone did not improve ASQ-T scores.

The combination of the two active drugs demonstrated only marginal improvement in ASQ-T scores but with significantly more sedation. SEDation was reported more frequently among children receiving clonidine (38%) than among those not receiving it (7%). The medications were otherwise well tolerated. In general, sedation did not result in any child being withdrawn from the study.

Intramuscular Olanzapine Relieves Agitation in Schizophrenia or Bipolar Mania
Speaker: Leslie S. Zun, MD, MBA, Chairman and Professor, Department of Emergency Medicine, Chicago Medical School at Rosaline Franklin University of Medicine and Science, and Mount Sinai Hospital, Chicago, Illinois.

An intramuscular (IM) injection of olanzapine (Zyprexa®, Eli Lilly), an atypical (second-generation) antipsychotic agent indicated for patients with schizophrenia, significantly reduced moderate-to-severe symptoms of agitation in schizophrenia and bipolar mania within 30 minutes of injection, when compared with placebo.

Initially, two randomized trials were conducted to compare treatments for resolution of severe agitation symptoms in mentally disturbed patients. In one study, 311 agitated patients with schizophrenia were randomly assigned to receive, in a 2:2:1 fashion, IM olanzapine, IM haloperidol (Haldol®, Ortho-McNeil), or IM placebo.

In the second study, 3,201 agitated patients with bipolar mania were randomly selected to receive, also in a 2:1:1
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fashion, IM olanzapine, IM lorazepam (Ativa®, Wyeth), or IM placebo. In a post hoc analysis, the investigators examined data on the frequency of patients experiencing a reduction of agitation from baseline moderate-to-extreme ratings on Corrigan Agitated Behavior Scale items and Positive and Negative Symptom Scale—Excitement Component (PANSS–EC) measurement scale items within 30 minutes after the IM injection.

In the patients with bipolar mania, “violence” that was rated as moderate to severe at the baseline was significantly reduced in 11 of 12 patients (90.9%) treated with olanzapine, versus four of 16 patients (25%) taking placebo. However, violence was not significantly reduced with lorazepam compared with placebo.

In agitated schizophrenic patients, “explosive anger” that was rated as moderate to severe at the baseline was significantly reduced in 31 of 40 olanzapine-treated patients (77.4%) versus 15 of 38 placebo patients (40%) and in 20 of 22 haloperidol-treated patients (90.9%) versus six of 15 placebo patients (40%). No significant difference was observed between the two active treatments.

Duloxetine for Rapid Pain Relief in Diabetic Peripheral Neuropathy

Speaker: Joel Raskin, MD, Medical Advisor, Eli Lilly, Indianapolis, Indiana.

Three randomized studies indicate that oral duloxetine (Cymbalta®, Eli Lilly), a selective serotonin and noradrenaline reuptake inhibitor (SSNRI), may have significant value in relieving diabetic peripheral neuropathic pain (DPNP).

Patients with DPNP of six months or more in duration, but who were not depressed, were enrolled in three 12-week studies.

- In study 1, 457 patients received duloxetine 20 mg once daily, 60 mg once daily, 60 mg twice daily, or placebo.
- In study 2, 334 patients were given duloxetine 60 mg once daily, duloxetine 60 mg twice daily, or placebo.
- In study 3, 348 patients were given duloxetine 60 mg once daily, duloxetine 60 mg twice daily, or placebo.

The primary outcome measure in all three studies was the weekly mean score for 24-hour average pain severity. Results from the three studies were comparable.

Duloxetine 60 mg once daily and 60 mg twice daily demonstrated a significant treatment effect on DPNP and a rapid onset of action. Within the first week of treatment, there was a significant difference shown with placebo on 24-hour average pain severity scores. Most secondary pain measurements confirmed these findings.

Whereas duloxetine 60 mg once daily and 60 mg twice daily demonstrated similar efficacy in most measures, the 60-mg, twice-daily dose demonstrated significantly more improvements on some McGill Pain Questionnaire items. A variety of health outcome measures, including the Clinical Global Impression–Severity Scale and the Patients’ Global Impression–Improvement Scale showed the superiority of both 60-mg, once-daily and 60-mg, twice-daily doses of duloxetine over placebo. The active drug was safely administered and well tolerated and showed no adverse effects on diabetic control.