News & Views

Trial Watch

Interview

New combination pill shows efficacy in multiethnic hypertensive populations

A combined pill containing amlodipine and atorvastatin has been well-tolerated in treating hypertension and dyslipidemia. Research has also indicated that the new treatment is effective at reducing blood pressure (BP) and lipid levels in multiethnic populations.

These results were collected from the Gemini–Australia, Asia, Latin America, Africa/Middle East (AALA) study, lead by Serdar Erdine, form the Istanbul University, Turkey.

"Single-pill combination therapy, aimed at lowering both BP and lipids simultaneously, may be an effective strategy for managing patients' overall cardiovascular risk through concomitant treatment with antihypertensive and lipid-lowering therapies," Erdine commented.

The combination therapy strategy may have additional benefits; these could include improved patient adherence and convenience of dosing.

The Gemini–AALA study, a 14-week, open-label study including patients from 27 countries across the Middle East, Asia-Pacific, Africa and Latin America primarily designed to complement previous studies from populations in Europe, the USA and Canada, was designed to evaluate the tolerability and efficacy of combined amlodipine/atorvastatin in varying strengths and over a diverse range of ethnic populations for a period of 14 weeks.

A total of 1649 patients were recruited and allocated one of eight different strengths of the two drugs. The strengths of amlodipine/atorvastatin ranged from 5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80 and 10/80 mg/day, and were adjusted for each patient according to the response elicited.

There target levels for low-density lipoprotein (LDL) cholesterol and BP were 4.1–2.6 mmol/l (160–100 mg/dl) and from 140/90 to 130/80 mmHg, respectively. BP and lipid goals were determined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and the Treatment of High Blood Pressure (JNC 7) and National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) guidelines, respectively.

Results indicated that that 55.2% of participants had reached both their lipid and BP targets at 14 weeks. Additionally, 87.1% had reached their LDL cholesterol target, with 34% reaching the target baseline. A total of 61.3% of patients reached their target for BP reduction.

The treatment was well-tolerated, with only 3.6% patients unable to continue with medication-related adverse events. These adverse events included peripheral edema as the most frequently reported adverse event, and Latin American patients reported a higher incidence of adverse events than those from other regions included in the study.

"Longer-term studies should be conducted to evaluate whether the observed increases in goal attainment, and decreases in predicted coronary heart disease risk, are translated into reductions in cardiovascular events", cautioned Erdine.

However, the study authors concluded that "a combination tablet of amlodipine/atorvastatin is an effective treatment with broad clinical utility in a real-world, multinational setting to help patients from diverse ethnic backgrounds with concomitant hypertension and dyslipidemia achieve recommended BP and lipid targets, and reduce their overall coronary heart disease risk."

Source: Erdine S, Ro YM, Tse H-F et al.*: Single-pill amlodipine/atorvastatin helps patients of diverse ethnicity attain recommended goals for blood pressure and lipids (the Gemini-AALA study).* J. Hum. Hypertens. *(2008) [Epub ahead of Print].*

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Toxin could offer insight into new hypertension treatments

Potassium channels can be studied with a specific inhibitor derived from honeybee venom toxin in the hope to find potential new ways to treat hypertension.

Researchers have successfully modified a honeybee toxin in the hope that it can be used as a tool to study the physiological mechanisms of hypertension. The study was published in the *Proceedings of the National Academy of Sciences,* from the laboratory of Zhe Lu and a Howard Hughes Medical Institute Investigator. The researchers studied the mechanism of action of the natural toxin on inward-rectifier potassium (Kir) channels, in the hope that they will gain insight into new ways to treat cardiovascular disease and hypertension.

The toxin, called tertipan (TPN), interferes with the flow of potassium ions across the cell membrane by inhibiting the Kir channels on the outside of cells; in general, ion channels selectively allow the passage of small ions such as sodium, potassium or calcium into and out of the cell.

Researchers envisage that the Kir channels present in kidneys could be potential targets in the treatment of hypertension.

"The clue comes from patients with genetic defects in these channels who lose a lot of sodium because it cannot be effectively reabsorbed, and thus have low blood pressure," comments Lu. He adds, "An inhibitor specifically against these kidney channels will allow this idea to be tested."

> *"This variant can now be used as a tool in animal studies to prove the hypothesis that reducing salt reabsorption by inhibiting renal Kir type 1 potassium channels is a potential new way to treat hypertension."*

The task has been far from easy; developing specific inhibitors for a single type of Kir channel is made difficult by the fact that the target site is very similar among different types of Kir channels. Originally TPN was not specific for kidney Kir channels and also inhibited Kir channels in the heart, which led to unwanted side effects. Over the past decade the team has successfully bioengineered TPN to selectively inhibit kidney Kir channels responsible for salt recycling.

TPNLQ was achieved by introducing two mutations to produce a variant that is capable of stopping the flow of potassium ions in renal Kir type 1 channels. The TPNLQ variant has a sensitivity 250-fold over six other types of Kir channels.

This variant can now be used as a tool in animal studies to prove the hypothesis that reducing salt reabsorption by inhibiting renal Kir type 1 potassium channels is a potential new way to treat hypertension.

Source: University of Pennsylvania School of Medicine [Press release]: www.uphs.upenn.edu/news/News_Releases/2008/09/honeybee-kir-channels.html

Hyperacute BP lowering linked to improved intracerebral hemorrhage outcomes

Data from a large retrospective study have indicated that lowering high blood pressure (BP) in patients with intracerebral hemorrhage (ICH) could improve the early clinical outcomes.

A total of 688 patients with ICH and with a BP of at least 180/105 mmHg were studied and intense BP-lowering therapy was administrated. After 3 weeks it was reported that 27% had regained complete functional independence. The researchers also discovered that patients in the lowest quartile of systolic BP during the first 24 h after onset, less that 138 mmHg, were the more likely to regain complete independence by week 3 than patients in the highest quartile, with a BP of higher than or equal to 158 mmHg.

Patients in the intermediate quartiles of systolic BP had outcomes similar to those in the highest quartile, and this association was independent of confounders including blood glucose level, onset-to-arrival time, symptom severity and hematoma volume.

The BP during the first 24 h did not appear to predict mortality, and in this study it was not related to hematoma enlargement.

> *"The authors concluded that lowering the systolic BP to less than 138 mmHg during the initial 24 h appears to be predictive of favorable early outcome in ICH."*

Although there is a firmly established link between high BP and poor outcomes in ICH patients, BP reduction is not routinely used, owing to concerns regarding the possibility that global cerebral blood flow (CBF) may be reduced and this may exacerbate perihematomal ischemia.

"Most ICH patients have chronic hypertension, which increases the lower limit of CBF autoregulation," notes Kazunori Toyoda, from the National Cardiovascular Center, Suita, Japan, who led the study.

The authors concluded that lowering the systolic BP to less than 138 mmHg during the initial 24 h appears to be predictive of favorable early outcome in ICH patients. Randomized, controlled trials to answer this question are needed.

Source: Itabashi Ryo, Toyoda K, Yasaka M et al.*: The impact of hyperacute blood pressure lowering on the early clinical outcome following intracerebral hemorrhage.* J. Hypertension *26(10), 2016–2021 (2008).*

Study reveals that early detection and intervention is key to delaying disease progression in pulmonary arterial hypertension

Data presented at the recent European Cardiology Society meeting has demonstrated that mild symptomatic pulmonary arterial hypertension (PAH) patients can progress very rapidly to more serious function classes of the disease.

The randomized, placebo-controlled trial, Endothelin Antagonist tRial in miLdlY symptomatic PAH patients (EARLY), is the first clinical trial to be conducted exclusively in the WHO Functional class (FC) II PAH patient population.

The study aimed to investigate the efficacy of bosentan in WHO FC II PAH patients, as well as gaining a better insight into the early stages of the disease. End points were changes in pulmonary vascular resistance (PVR) and exercise capacity (6-min walk distance [6MWD]). The time to clinical worsening and WHO functional class as used to assess disease progression.

Findings indicated that treatment with the drug appears to be beneficial and prevented clinical deterioration by showing a significant delay in the time taken to clinical worsening to FC III or IV. A significant reduction in pulmonary vascular resistance and a positive trend in increasing the 6MWD were also observed.

The findings of EARLY indicate that treatment with bosentan may be beneficial for WHO FC II PAH patients. In EARLY, bosentan (Tracleer®) prevented clinical deterioration by significantly delaying time to clinical worsening and reduced the number of patients worsening to WHO FC III/IV. A significant reduction in PVR and a positive trend in increasing the 6MWD were also observed.

"The results from EARLY highlight/emphasize the relentlessly progressive nature of PAH, even in its early stages. It is of paramount importance to screen high-risk patients to diagnose PAH in a timely fashion. It is also crucial that all PAH patients, regardless of functional class, be closely monitored for the earliest signs and symptoms of PAH progression and that treatment of all symptomatic PAH patients be considered to prevent PAH progression and worsening", commented Sanjay Mehta, an author from the study and Associate Professor of Medicine at the University of Western Ontario, Canada.

After 6 months of treatment, a 22.6% reduction was seen in PVR, and a 77% risk reduction in delaying time to clinical worsening was also observed, compared with placebo. Time to clinical worsening, defined by death, hospitalization for PAH and symptomatic progression of PAH, showed that more patients remained stable without signs of deterioration in the bosentan-treated group compared with placebo, although the improvement in 6WMD did not reach clinical significance. The authors state that this could be due to the fact that patients in EARLY had a relatively well-preserved exercise capacity, which would be difficult to further improve.

"The EARLY trial clearly demonstrates that without treatment, even mildly symptomatic patients experience PAH progression within a short period of time. In order to properly delay the progression of PAH and increase patients' chances of survival, it is imperative to diagnose patients in the early stages of their disease cycle, ideally WHO functional class II, and treat them with an evidence-based approach as soon as possible", added Mehta.

An open-label extension of EARLY is ongoing to establish the impact of early intervention on long-term patient outcome.

Source: Forfia PR, McLaughlin VV: Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension: The EARLY Study. Lancet *(2008) (Epub ahead of print).*

> *"It is of paramount importance to screen high-risk patients to diagnose pulmonary arterial hypertension in a timely fashion"*

> *"The EARLY trial clearly demonstrates that without treatment, even mildly symptomatic patients experience PAH progression within a short period of time"*

Trial Watch

Company: *Bayer Healthcare*
Drug: *Nifedipine*
Indication: *Stable, symptomatic coronary disease*
Trial: *Phase III Double-blind, placebo-controlled ACTION trial*

The A Coronary Disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION) study was designed as a consequence of ongoing debate regarding the safety of calcium antagonists used in the treatment of cardiovascular disease.

ACTION was used to investigate the effects of the long-acting calcium antagonist nifedipine gastrointestinal therapeutic system on clinical outcomes in patients with stable, symptomatic coronary disease, 52% of whom had hypertension.

Nifedipine appears well-tolerated for use in the treatment of angina and cardiovascular events, and safe in patients with symptomatic coronary disease, but when data from the study were stratified for hypertension, analysis showed that the addition of nifedipine gastrointestinal therapeutic system in patients with symptomatic coronary disease resulted in a significant reduction in cardiovascular morbidity. The authors demonstrated that the stroke and heart failure risk reduction by nifedipine gastrointestinal therapeutic system in patients with coronary artery disease can be attributed partly to its BP-lowering effect.

Source: Sierra C, Coca A: The ACTION study: nifedipine in patients with symptomatic stable angina and hypertension. Expert Rev. Cardiovasc. Ther. *6(8), 1055–1062 (2008).*

Institute: *Duke University Medical Center*
Drug: *Clevidipine*
Indication: *Acute hypertension*
Trial: *Phase III randomized, open-label, parallel comparison study – ECLIPSE*

Clevidipine (CLV), a novel, rapidly acting dihydropyridine L-type calcium channel blocker with an ultrashort half-life can decrease arterial BP. The Evaluation of CLevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events trial (ECLIPSE) compared the safety and efficacy of CLV with nitroglycerin (NTG), sodium nitroprusside (SNP), and nicardipine (NIC) in the treatment of perioperative acute hypertension in patients undergoing cardiac surgery.

Efficacy was asses by a reduction in the incidence of death, myocardial infarction, stroke or renal dysfunction at 30 days.

Overall, there was no difference in the incidence of myocardial infarction, stroke or renal dysfunction in CLV patients and no reduction in mortality rates in CLV, NTP and NIC groups.

Mortality was significantly higher in SNP-treated patients compared with CLV-treated patients. Overall, CVL appeared more effective in controlling and maintaining BP. The authors concluded that CLV is a safe and effective treatment for acute hypertension in patients undergoing cardiac surgery.

Aronson S, Dyke CM, Stierer KA et al.*: The ECLIPSE trials: comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients.* Anesth. Analg. *107(4), 1110–1121 (2008).*