急性MIにおける早期アルドステロンブロック (ESC2015 Presentation # 1167)

ALBATROSS：アルドステロン拮抗薬は心不全のない急性MIにおいて有意な有益性を示さない

ALBATROSS: Aldosterone antagonists show no significant benefits in acute MI without heart failure

ST上昇型心筋梗塞（STEMI）患者のアルドステロンカスケードをブロックすることにより予後改善を試みたが、コントロール患者との有意差を示すことはできなかった、との研究結果が2015年ESC Congressホットラインセッションで示された。1,622人の患者が、標準治療のみ（801人）またはアルドステロン拮抗薬（MRAとしても知られる）を追加する治療（802人）にランダムに割り付けられた。救急を含む早期のランダム化を行うことで、早期の治療開始が可能であった。MRA療法は、カンレノ酸カリウム（20mg）の静脈内ボーラス投与後にスピロノラクトン25mgの初回経口投与を12～24時間以内に行い、その後6か月間毎日投与した。追跡期間中央値118日後の主要評価項目－6か月以内の死亡、蘇生された心停止、有意な心室性不整脈、植込み型除細動器適応、または心不全の新規発症か悪化の複合エンドポイントは、治療群およびコントロール群で同等であった（p=0.81）。死亡率のみの転帰に関しては、MRAはSTEMI群のサブグループにおいて死亡率を低下させた（1,229人、HR 0.20、95% CI 0.06-0.70）が、NSTEMI患者においては低下させなかった。このスタディはSTEMI患者を特異的に評価する目的でデザインされていなかったため、結果を解釈する際には注意が必要である。

Full Text

An attempt to improve outcomes in patients suffering an ST-segment elevation myocardial infarction (STEMI) by blocking the aldosterone cascade failed to show a significant difference when compared to control patients, researchers reported here.

After a median follow-up of 118 days, 11.8% of patients treated with aldosterone inhibition experienced the primary composite outcome of death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for an implantable defibrillator or new or worsening heart failure at 6-months compared with 12.2% of patients in the control group [HR 0.97 (95%CI 0.73-1.28) p=0.81], said Gilles Montalescot, M.D., Ph.D., professor of cardiology at Institut de Cardiologie, Centre Hospitalier Universitaire Pitie Salpetriere, Paris.

The Hot Line findings, reported at ESC Congress 2015, "do not warrant the extension of MRA use" to such patients, said the study's principal investigator Gilles Montalescot, M.D., Ph.D..

MRAs, also known as aldosterone antagonists, inhibit sodium retention and excretion of potassium and magnesium, and therefore "there is an indication for MRA therapy in MI patients with heart failure," explained Professor Montalescot, from the Institut de Cardiologie, Centre Hospitalier Universitaire Pitié-Salpêtri?re, in Paris, France.

"Our results suggest that heart failure is the main factor for the favorable effect of MRAs previously observed in MI patients. In MI patients without heart failure we observed no benefit. We suggest to respect the current indication driven by heart failure." But there is a silver lining to the ALBATROSS findings, which do suggest "a potential mortality benefit" of MRA treatment among a specific group of patients who have ST-segment elevation myocardial infarction (STEMI), although this result "must be interpreted with great caution," warned Professor Montalescot.
"It is an intriguing, hypothesis-generating finding which needs to be examined further in adequately-sized trials specifically dedicated to STEMI patients," he said.

While the MRAs spironolactone and eplerenone have both been shown to reduce mortality in heart attack patients with congestive heart failure, very little is known about this treatment in the absence of heart failure - the more common scenario among patients who are hospitalized for myocardial infarction (MI).

Therefore, ALBATROSS (which stands for Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up) investigated the effects of prolonged MRA therapy initiated early after the onset of MI in a broad population, 92% of whom presented without heart failure.

The study included 1622 patients randomly assigned to standard therapy alone (n=801) or with the addition of MRA therapy (n=802).

The randomization took place as early as possible, including in ambulances, to allow for early treatment.

Standard therapy included in-hospital medications as well as procedures such as coronary angiography, percutaneous coronary intervention and coronary bypass grafting.

The MRA regimen consisted of an intravenous bolus of potassium canrenoate (200 mg) followed by an initial 25mg of oral spironolactone within 12 to 24 hours, and then daily for 6 months. Spironolactone was not given if either potassium or creatinine concentrations were uncontrolled (> 5.5 mmol.L-1 and >220 µmol.L-1 respectively).

After a median follow-up of 118 days, the primary outcome - a composite of death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for an implantable defibrillator or new or worsening heart failure at 6-months - occurred at a similar rate in the treatment and control groups (11.8% and 12.2% respectively, hazard ratio [HR] 0.97).However, for the outcome of mortality alone, MRA reduced the odds of death in the subgroup of STEMI (n=1229, HR 0.20, 95% CI, 0.06 to 0.70), but not NSTEMI patients.

Caution in interpreting this finding is warranted since the study was not designed to specifically assess STEMI patients, said Professor Montalescot, but he added that a potential benefit of early MR therapy is plausible in STEMI patients, who are "a more homogeneous patient population with more acute and severe myocardial ischemia than NSTEMI".

The ALBATROSS study, which is the largest study of MRA therapy in MI patients without heart failure, also highlights the relative safety of the MRA regimen used. Adverse events were equally distributed between the two study groups and although rates of hyperkalemia were more common in the MRA group than in the control group, they were lower than what has been previously reported.

The study was funded by the French Ministry of Health and the Institute of Cardiometabolism And Nutrition (ICAN). Dr. Montalescot reports receiving consulting fees from Acuitude, Amgen, AstraZeneca, Bayer, Berlin Chimie AG, Boehringer Ingelheim, Bristol-Myers Squibb, Brigham Women's Hospital, Cardiovascular Research Foundation, CME resources, Conway, Daiichi-Sankyo, Eli-Lilly, Europa, Evidera, GLG, Hopitaux Universitaires Genève, Lead-Up, McKinsey & Company, Medcon International, Menarini, Medtronic, MSD, Pfizer, Sanofi-Aventis, Stentys, The Medicines Company, TIMI Study Group, Universitat Basel, WebMD, Williams & Connolly, Zoll Medical and grant support from ADIR, Amgen, AstraZeneca, Bristol-Myers Squibb, Celladon, Daiichi-Sankyo, Eli-Lilly, Fédération Française de Cardiologie, Gilead, ICAN, Janssen-Cilag, Pfizer, Recor, Sanofi-Aventis, Stentys.

Conference News