治療抵抗性高血圧にはスピロノラクトンが最適である (ESC2015 Presentation # 4137)

PATHWAY-2：利尿薬スピロノラクトンは治療抵抗性高血圧患者の血圧を有効に低下させる

PATHWAY-2: Diuretic spironolactone effectively lowers blood pressure in resistant hypertension

治療抵抗性高血圧患者において、利尿薬スピロノラクトン追加は他の降圧薬を追加するより効果的であるとのPATHWAY-2トライアルの結果が、2015年ESC Congressホットラインセッションで発表された。3剤（ACE阻害薬またはアンジオテンシン受容体拮抗薬；カルシウム拮抗薬；およびサイアザイド系利尿薬）の最大耐用量をすでに併用投与されている治療抵抗性高血圧患者を対象とした。ベースライン時の治療に加え、患者らはスピロノラクトン（25～50mg）、ビソプロロール（5～10mg）、ドキサゾシン（4～8mg徐放剤）およびプラセボのいずれかを引き続き12週間投与される群にランダムに割り付けられた。314人の患者において、スピロノラクトンはプラセボ（8.70mmHg低下、p<0.001）；ドキサゾシン（4.03mmHg低下、p<0.001）；およびビソプロロール（4.48mmHg低下、p<0.001）、さらにドキサゾシンとビソプロロールの平均（4.26mmHg低下、p<0.001）に比べ、血圧コントロールに優れていた。全体で、スピロノラクトンを追加された患者のほぼ4分の3で血圧が大きく改善し、ほぼ60%の患者においては厳格な血圧コントロールに合致した（p<0.001）。60% の患者においてスピロノラクトンが最良の降圧薬であったが、ビソプロロールやドキサゾシンが最良であったのはそれぞれ17%および18%のみであった。

Full Text

In patients with resistant hypertension, addition of the diuretic spironolactone was significantly more effective than adding other blood pressure lowering drugs according to results of the PATHWAY-2 trial presented during a Hot Line session at ESC Congress 2015.

The study's findings suggest spironolactone "was a clear winner and should be first choice for the additional treatment of resistant hypertension," said investigator Bryan Williams, M.D..

"These results have broad international relevance and applicability," noted Professor Williams, who is from University College London, and the British Hypertension Society Research Network.

"The PATHWAY-2 study showed that spironolactone was overwhelmingly the most effective blood pressure-lowering therapy compared to bisoprolol or doxazosin and suggest that the predominant underlying cause of resistant hypertension is sodium retention - even among patients with baseline diuretic therapy. This establishes, for the first time, a clear hierarchy for drug treatment of resistant hypertension which should influence future treatment guidelines and clinical practice globally."

Resistant hypertension is defined as uncontrolled blood pressure (BP) despite treatment with at least 3 BP-lowering medications. Prior to PATHWAY-2 there was no strong evidence supporting recommendations for the most appropriate additional drug to control blood pressure, and "there has been a growing perception that controlling BP in resistant hypertension is beyond the reach of existing drug therapies," explained Professor Williams. "But PATHWAY-2 shows that control is possible in the majority of patients, using a drug that has been available for many decades."

While the pathogenesis of resistant hypertension is poorly understood, one hypothesis is that it could be related to sodium retention – a result of reduced diuretic doses in recent years, he said.

PATHWAY 2 examined whether additional diuretic therapy with spironolactone would be the most effective at reducing BP compared to treatment with two other antihypertensives that have different mechanisms of action: doxazosin which acts to reduce arterial resistance, and bisoprolol which acts to reduce cardiac output.

The study included patients with resistant hypertension who were already treated with maximally tolerated doses of a combination of three drugs: an ACE-inhibitor or angiotensin receptor blocker (ARB); a calcium channel blocker (CCB); and a thiazide type diuretic. "The key question was, which drug should be added to get blood pressure controlled," said Professor Williams.

Uncontrolled BP was defined as seated clinic systolic BP of 140 mmHg or more for non-diabetic patients, or 135 mmHg or more for patients with diabetes, and a home systolic BP (HSBP) 130mmHg for all patients. In addition to their baseline BP therapy, patients were randomized to sequentially receive 12 weeks of spironolactone (25-50mg), bisoprolol (5-10mg), doxazosin (4-8mg modified release) and placebo in random order.

Blood pressure was measured with an automated BP monitor and recorded both in the clinic as well as at home over 4 consecutive days at baseline as well as at 6 and 12 weeks of each treatment cycle.

The primary end-point was average home systolic blood pressure (HSBP) for each of the treatments, with clinic systolic BP being a secondary endpoint.

In 314 patients, spironolactone had superior HSBP control compared to placebo (a reduction of 8.70 mmHg, p<.001); doxazosin (a reduction of 4.03 mmHg, p<0.001), and bisoprolol (a reduction of 4.48 mmHg, p<0.001); as well as the mean of doxazosin and bisoprolol (a reduction of 4.26 mmHg, p<0.001).

Overall, almost three quarters of patients with uncontrolled blood pressure saw a major improvement in their blood pressure on spironolactone, with almost 60% meeting a stringent measure of blood pressure control (p<0.001). Spironolactone was the best drug at lowering blood pressure in 60%, whereas bisoprolol and doxazosin where the best drug in only 17% and 18% respectively.

Clinic measurements mirrored the HSBP measurements except there was a large placebo effect in the clinic that was not seen at home.

"This is the first study to use home BP rather than clinic BP as a primary outcome in these patients," noted Professor Williams. "Not only did this reduce the placebo effect but it also eliminated patients with 'white coat hypertension' whose BP may have been spuriously elevated due to clinic anxiety."

The findings "challenge the concept that that resistant hypertension cannot be treated adequately with drug therapies, and suggest that treatments which have a natriuretic action, in that they promote sodium excretion, are likely to be the most effective," he concluded.

This trial and PATHWAY-3 are part of the PATHWAY program of trials in Hypertension undertaken by academic investigators within the British Hypertension Society, led by Professor Morris Brown of the University of Cambridge, Professor Williams, and Professor Tom MacDonald of the University of Dundee.

The study was funded by a special project grant from the British Heart Foundation. Further funding was provided by the National Institute for Health Research Comprehensive Local Research Networks. Professor Williams has received honoraria for lectures on hypertension from Novartis, Boehringer Ingelheim, Servier, Daiichi Sankyo and Pfizer.

Conference News

持続性心房細動を止める (ESC2015 Presentation # 2188)

BELIEF：左心耳切除により持続性心房細動を長期にわたり止められる可能性がある

BELIEF: Isolating left atrial appendage could halt long standing persistent atrial fibrillation

標準的な治療を行っているにもかかわらず長期の持続性心房細動（AF）を有する患者において、追加で左心耳（LAA）の電気的切除をすることで合併症を増加させることなくAFから解放される率が改善し得る、とのBELIEFスタディの結果が2015年ESC Congressホットラインセッションで発表された。研究者らは173人の患者を標準的な治療のみ（肺静脈隔離術および肺静脈外トリガーのアブレーション、88人）、または標準治療に加えLAAアブレーションを行う群（85人）にランダムに割り付けた。1年後の無再発率は標準治療群の28%に対し、LAAアブレーション追加群では56%であった（p=0.001）。両群とも再発した患者は次の施術としてLAAアブレーションを施行された。24か月後の平均施術件数は1.3件であり、累積成功率はLAAアブレーション群で76%、標準治療群では56%であった（p=0.003）。追跡期間中の、一過性脳虚血発作や脳卒中などの合併症率は両群間で差はなかったが、平均ラジオ波曝露時間はLAA群で長かった（93分対77分；p<0.001）。多変量解析では、LAAアブレーションを施行しないことはAF再発率が有意に高いことと関連があった（p=0.004）。

Full Text

In patients with long-standing persistent atrial fibrillation (AF) despite standard treatment, additional electrical isolation of the left atrial appendage (LAA) can improve freedom from AF without increasing complications, results of the BELIEF study show.

The findings were presented in a Hot Line session at ESC Congress 2015.
"Empirical left atrial appendage isolation, along with the standard approach of pulmonary vein isolation (PVI) and ablation of extra-pulmonary triggers is superior to the standard approach alone in enhancing the long-term success rate of catheter ablation," reported investigator Luigi Di Biase, M.D., Ph.D., from Montefiore-Albert Einstein Center for Heart & Vascular Care, New York, USA and Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, Texas, USA.

"We first proposed in 2010 that the left atrial appendage was a relevant, under-reported trigger for AF, and now this trial confirms our findings," he added.
The study included 173 patents with "long-standing persistent" AF - defined as extending beyond one year.

Patients were randomly assigned to undergo standard treatment alone (PVI and ablation of extra-pulmonary triggers, n=88), or standard treatment plus the addition of LAA ablation (n=85).

For the primary endpoint of recurrence of AF at one year, 28% of standard treatment patients were recurrence-free compared to 56% of patients who had the additional LAA ablation (hazard ratio [HR] 1.92; p=0.001).

For patients who were not recurrence-free in either group, LAA isolation was performed in a second procedure.

At 24 months, after an average of 1.3 procedures, the cumulative success rate was 76% in the LAA ablation group and 56% in the standard treatment group. (HR 2.24; p= 0.003).

There was no difference in complication rates between groups at follow up, including transient ischemic attacks or strokes, however the mean radiofrequency time was longer in the LAA group (93 versus 77 minutes; p<0.001).

In multivariate analysis, no LAA ablation was associated with significantly higher recurrence of AF (HR 2.2; p = 0.004).

"It is logical to suggest that the LAA may initiate AF like the pulmonary veins because embryologically, the LAA grows out of the primordial LA, which is formed mainly by the adsorption of the primordial pulmonary veins and their branches," explained Dr. Di Biase.

"In fact, an earlier study conducted by our group showed that LAA firing was the source of AF in 27% of patients and, after LAA ablation, 93% of those patients were AF free at long term follow up."

The study was sponsored by Texas Cardiac Arrhythmia Research Foundation. Dr. Di Biase is a consultant for Biosense Webster, Stereotaxis and St Jude Medical and has received speaker honoraria/travel from Medtronic, Atricure, EPiEP, Boston Scientific and Biotronik.

Conference News

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

迅速でより感度の高い検査は胸痛患者のトリアージを迅速にする (ESC2015 Presentation # 1161)

BACC:救急外来において高感度トロポニンI検査はMIトリアージを加速化する

BACC: High-sensitivity troponin I test accelerates MI triage in the emergency department

急性心筋梗塞（AMI）を示唆する胸痛で救急外来を受診した患者は、精密化されたカットオフ値を用いた新たな迅速アッセイを用いることで、より速やかに安全にトリアージできる。2015年ESC Congressホットラインセッションで発表されたBACC（Biomarkers in Acute Cardiovascular Care）スタディでは、AMIを示唆する急性の胸痛で受診した患者1,045人（平均年齢65歳）を対象とし、標準的な3時間のアッセイおよび1時間のアッセイの両者を用いて評価した。標準的な方法に基づき、184人の患者はAMIと診断され入院した。その他は帰宅した。全ての患者が6か月間追跡された。研究者らが2つのアッセイの結果を比較し、AMIを除外する最良のトロポニンIカットオフ値は、現在の推奨値である27ng/Lよりはるかに低い値である6ng/Lであると算出した。その後、心血管イベントを予知するこの新たなカットオフ値の臨床的妥当性をBiomarCaREスタディのデータを用いて確かめた。その結果、トロポニン値が6ng/Lより高いことは死亡または心血管疾患の高リスクを示唆することが確認された。研究者らは次にこの新たなカットオフ値をBAACコホートに適用したところ、この新たなアルゴリズムでトリアージした方がこれまでの3時間の方法で行うよりも死亡率が低くなるであろうことが明らかにされた。

Full Text

Patients arriving at the emergency department with chest pain suggestive of acute myocardial infarction (AMI) can be triaged more quickly and more safely using a new rapid assay with refined cut-offs. The Biomarkers in Acute Cardiovascular Care (BACC) study, presented as a Hot Line at ESC Congress 2015, suggests this new algorithm can reduce mortality and cut triage times to one hour, compared to the standard three-hour approach.

"There is an urgent need for fast decision-making for this growing patient population," said principal investigator of the study Dirk Westermann, M.D., Ph.D., from the University Heart Centre Hamburg, and the German Centre for Cardiovascular Research.

"Use of this algorithm in patients with suspected AMI allows for highly accurate and rapid rule-out as well as rule-in, enabling safe discharge or rapid treatment initiation. This rapid algorithm might be applicable to clinical practice without a loss of diagnostic safety."

For patients with suspected AMI, current guidelines recommend analyzing cardiac troponin I – a marker of myocyte necrosis - directly at admission and then 3 hours later, to determine if the level warrants admission or discharge.

This means patients must remain in the hospital for at least 3 hours before receiving a diagnosis, using resources that are increasingly scarce.

In addition, troponin I levels are currently considered abnormal if they are above the 99th percentile from a healthy reference population - in this case 27 ng/L, said Dr. Westermann.

But new, highly sensitive troponin I assays can give results more quickly and detect more subtle troponin I elevations that may be important for assessing cardiovascular risk, he explained.

The BACC (Biomarkers in Acute Cardiovascular Care) study included 1,045 patients (mean age 65 years) with acute chest pain suggestive of AMI presenting at the emergency room of the university hospital in Eppendorf, Hamburg, Germany.
Patients were assessed using both the standard 3-hour assay as well as a highly-sensitive 1-hour one.

Based on the standard approach, 184 patients were diagnosed with AMI and kept in the hospital, while the rest were discharged home. All patients were then followed for 6 months.

Comparing the results of both assays in the cohort, the researchers calculated the best troponin I cut-off value to rule out AMI was 6 ng/L – "far lower than the currently recommended 27 ng/L," noted Dr. Westermann.

They then tested the clinical relevance of this new cut-off for predicting cardiovascular events using data from the BiomarCaRE study - one of the largest studies to include troponin I measurement in more than 75,000 individuals from the general population.

The BiomarCaRE data confirmed that when individuals from the general population had troponin I values higher than 6 ng/L, they were at increased risk of death or cardiovascular disease, whereas patients with levels below this cut-off could be safely discharged home.

"This documents that even slightly elevated troponin I values are important predictors of cardiovascular disease," said Professor Westermann. "At the same time, utilizing a very low cut-off for discharge of patients with suggestive AMI is safe, since these patients are at the lowest possible risk for future events.

The researchers then applied the new cut-offs to the BAAC cohort and found that mortality would have been lower if patients had been triaged with the new algorithm compared to the routine 3-hour approach.

"The standard approach underestimated risk for many patients and resulted in high mortality," said Dr. Westermann. "In addition, using the rapid, sensitive assay would have reduced usage of the emergency room and scarce medical resources, enabling a faster diagnosis and better treatment."

The algorithm had negative predictive values of 99.7% after 1 hour and 100% after 3 hours.

"Therefore, our algorithm identified all patients at risk, but was not un-necessarily unspecific," said Dr. Westermann.

"This suggests that using more sensitive cut-offs than suggested by the guidelines can improve the safety for patients discharged home."

The algorithm was then validated in two independent cohorts (ADAPT and APACE trials) that included 4,009 patients with acute chest pain suggestive of AMI.

The research was supported by the German Center of Cardiovascular Research (DZHK), the European Union Seventh Framework Programme, and an unrestricted grant by Abbott Diagnostics. Abbott Diagnostics provided test reagents for high-sensitive troponin I measurements. Dr. Westermann and his colleagues declared no conflicts of interest regarding this study.

Conference News

驚くべき心臓の所見が将来のリスクを予測する (ESC2015 Presentation # 1164)

DOPPLER-CIP：左室拡張末期容積の減少および左室心筋重量は将来の心不全を予測する可能性がある

DOPPLER-CIP: Small left ventricular end-diastolic volume and left ventricular mass may predict future heart failure

慢性虚血性心疾患の患者において、壁肥厚を伴い左室容積が小さいことは、一般的に心不全への最初の段階であると考えられている形態学的リモデリングの最強の予測因子であるとの予期せぬDOPPLER-CIPトライアルの結果が、2015年ESC Congressホットラインセッションで発表された。このトライアルは異なる非侵襲的方法を比較し、ベースラインにおいて2年後の心臓リモデリングのリスクを予測する最も有用な方法を検討した。研究者らは慢性虚血性心疾患が疑われる患者676人を対象とした。ベースライン時の評価後、全ての患者が医師らの裁量で血行再建術、部分的血行再建術、または薬物治療などの最良の、ガイドラインに基づく治療を受けた。2年後、対象の約20%がMRIまたは心エコー検査の結果、心リモデリングの所見を示した。ベースライン時におけるリモデリングの最善の予測因子は、左室拡張末期容積（LVEDV）およびLV重量（LVM）などで計測される左室サイズであった。ベースライン時にLVEDVが小さい（<145mL）とリモデリングの確率が25～40%であり、それよりLVEDVが大きい場合の確率の方が低かった（20%；p<0.001）。リモデリングリスクはまた壁厚が厚い場合にも高かった（p=0.003)。これらの結果は、安定冠動脈疾患患者のリスク層別化を完全に変化させ得る、と筆者らは述べている。

Full Text

In patients with chronic ischemic heart disease, a small left ventricle with thick walls, is the strongest predictor of morphologic remodeling, which is generally considered a first step towards heart failure, according to unexpected findings presented at ESC Congress 2015.

Results of the DOPPLER-CIP (which stands for "Determining Optimal non-invasive Parameters for the Prediction of Left vEntricular morphologic and functional Remodeling in Chronic Ischemic Patients") study were not expected and, if confirmed by other studies, "could completely change risk stratification among patients with stable coronary artery disease," according to the study coordinators Frank Rademakers, MD and Jan D'Hooge, Ph.D..

"We were indeed surprised by these findings," said the investigators, who are from the University of Leuven, Belgium. "The general belief is that larger ventricles with thin walls (a typical 'infarct ventricle') would be at higher risk of remodeling, with a possible explanation for this being that there is increased wall stress in such hearts. But out findings show that it is actually small hearts with thick walls that are more at risk. As this goes against general belief, we have checked and re-checked our data, and analysis, and have run several consistency tests, but they all led to this same conclusion."

There are currently no guidelines for assessing a patient's risk for this type of deterioration, they noted.

DOPPLER-CIP compared different non-invasive methods to determine the most useful tool at baseline for predicting risk of cardiac remodeling two years later.
The study included 676 patients, from 6 European countries, with suspicion of chronic ischemic heart disease.

The patients underwent standard diagnostic tests at baseline including: electrocardiogram (ECG), exercise testing with continuous ECG monitoring, and measurement of maximal oxygen uptake (VO2max), as well as blood sampling and quality of life assessments. In addition to these standard tests, patients also underwent at least two stress imaging tests including echocardiography (ECHO), magnetic resonance imaging (MRI) and/or single positron emission computed tomography (SPECT) stress test, stress ECHO and stress MRI.

After these baseline evaluations all patients received optimal, guideline-based treatment including revascularization, partial revascularization, or pharmacologic treatment at their physician's discretion.

At the end of the study period, about 20% of the subjects had evidence of cardiac remodeling based on MRI or ECHO results, with the best baseline predictors of this remodeling being left ventricular size measured as the "left ventricular end-diastolic volume" (LV EDV) and left ventricular mass (LVM).

Specifically, a small LV end-diastolic volume (< 145 ml) at baseline had a 25-40% chance of remodeling, compared to a larger EDV, which had a decreased risk (20%; p<0.001) with risk also increasing with increasing wall thickness. (p=0.003).

"By identifying baseline LV EDV and LVM – measurements that can easily be assessed with standard imaging – as the best predictors of future remodeling and potentially heart failure risk, our study could guide clinicians away from more expensive tests for risk assessment," they said.

The study was funded by the EU (FP7) framework program (DOPPLER-CIP; grant number 223615). Logistical support (software tools for data analysis) was provided by Philips Healthcare, GE Healthcare, TomTec Imaging Systems, MedViso and Bracco Imaging. Dr. D'Hooge disclosed research funding from Philips, research contracts with GE, and a collaboration with MedViso. Professor Rademakers had no disclosures.

Conference News

抗血小板薬2剤併用療法継続期間に関する論議 (ESC2015 Presentation # 3159)

OPTIDUAL：ステント留置後1年を超えて抗血小板薬2剤併用療法を延長することによる恩恵は少ない

OPTIDUAL: Little benefit to extending dual antiplatelet therapy beyond one year after stenting

OPTIDUALトライアルの結果、冠動脈内ステント留置後抗血小板薬2剤併用療法（DAPT）の推奨期間とされている12か月を超えて延長することにより、主要な心有害イベントおよび脳血管イベント（MACCE）は減少しないことが示された。抗血小板薬2剤併用療法の延長により過度の出血がなく虚血性イベントが減少するかもしれない、との兆候が見られていたと研究者らは2015年ESC Congressホットラインセッションで述べた。スタディには、経皮的冠動脈形成術が施行され、安定冠動脈疾患または急性冠症候群のいずれかに対し少なくとも1個の薬剤溶出ステントが留置された1,385人の患者が含まれた。全ての患者が1年間のDAPTを施行され、その後36か月間これを継続する群またはアスピリン単剤に変更し継続する群にランダムに割り付けられた。その結果、主要MACCEエンドポイントに関して有意な群間差は認められなかった（DAPT延長群5.8%対アスピリン単剤群7.5%、p=0.17）。死亡率はDAPT延長群で2.3%であり、アスピリン群では3.5%であった（p=0.18）。しかし、DAPTを延長することにより、ボーダーラインではあるが統計学的に有意でない虚血性イベント（死亡、心筋梗塞、または脳卒中の合計からなるpost-hoc解析）の減少が認められ（DAPT延長群4.2%対アスピリン群6.4% [p=0.006]）、出血が増加したり全死亡率が上昇することはなかった。

Full Text

An investigator-initiated study showed that extending dual antiplatelet therapy (DAPT, a combination of aspirin and the P2Y12-receptor blocker clopidogrel) beyond the recommended 12 months after coronary stenting does not decrease the rate of major adverse cardiovascular and cerebrovascular events (MACCE). There was, nevertheless, a hint that it might reduce ischemic outcomes without excess bleeding. Results of the trial were presented at a Hot Line session at ESC congress 2015.

"Given the lack of harm and the signal for benefit of prolonged DAPT in the OPTIDUAL trial, and the results from prior randomized trials testing long durations of DAPT, prolongation of DAPT beyond 12 months should be considered in patients without high-risk bleeding, who have received a drug-eluting coronary stent and are event-free at 12 months," said principal investigator Gérard Helft, M.D., Ph.D. from the Institut de Cardiologie, Hôpital Pitié-Salpétrière, in Paris, France.

The OPTIDUAL trial included 1,385 patients from 58 French sites who had undergone percutaneous coronary intervention (PCI) with placement of at least one drug-eluting stent (DES) for either stable coronary artery disease or acute coronary syndrome.

All patients had been on DAPT for one year and were randomly assigned to continue or to remain on aspirin alone for an additional 36 months. The study found no statistical difference between the groups for the primary MACCE endpoint, a composite of all-cause death, myocardial infarction, stroke, and major bleeding (5.8% in the extended-DAPT group and 7.5% in the aspirin only group, p=0.17).

Rates of death were 2.3% in the extended-DAPT group and 3.5% in the aspirin group (p=0.18).

However, there was a borderline but non-statistically significant reduction in ischemic outcomes (a post-hoc outcome composite rate of death, myocardial infarction, or stroke) with extended DAPT (4.2% in the extended-DAPT group and 6.4% in the aspirin group (hazard ratio [HR] 0.64, 95% CI 0.40–1.02, p=0.06) without increased bleeding (2.0% in both groups, p=0.95) or increased all-cause mortality.

The OPTIDUAL trial was designed as a superiority trial, and while it failed to show superiority for extended DAPT, "the results are consistent with the recent findings on ischemic outcomes from the DAPT trial regarding the value of prolonging DAPT after DES placement," said Professor Helft.

"There was no apparent harm, and the post hoc efficacy signal on MACE is consistent with the benefit seen in the DAPT trial. Thus, OPTIDUAL adds to the evidence suggesting benefit to extended DAPT after DES in patients who are event free at 12 months."

Professor Helft commented that the optimal duration of dual antiplatelet therapy after PCI with drug-eluting stent (DES) "is one of the hottest topics in interventional cardiology. The use of DAPT is critically important for the prevention of coronary stent thrombosis, but the optimal duration remains highly debated. This is a major clinical issue, given the large number of patients treated with DES, the costs and risks of antiplatelet therapy, the potentially life-threatening consequences of stent thrombosis and the potential benefits of antiplatelet therapy in preventing ischemic outcomes beyond stent thrombosis."

The study was funded by Assistance Publique - Hôpitaux de Paris and the Fédération Française de Cardiologie, with unrestricted grants from Cordis, Boston, Medtronic, Terumo and Biotronik. Professor Helft reports grants from the French Ministry of Health, the Fédération Française de Cardiologie, Cordis, grants from Boston Scientific, Medtronic, Terumo, and Biotronik. During the conduct of the study he received personal fees from Astra Zeneca, Abbott, Pfizer, Boehringer-Ingelheim, and Bayer, outside of the submitted work.

Conference News

中枢性睡眠時無呼吸症用デバイスは心不全の死亡率を上昇させる(ESC2015 Presentation＃5063)

慢性心不全患者における中枢性睡眠時無呼吸症の治療に関して、実際の診療を変化させるガイダンスがスタディにより提供された

Study provides practice-changing guidance for the treatment of central sleep apnea in patients with chronic heart failure

適応補助換気（ASV）は死亡率を増加させるため、心駆出率の低下した心不全患者の中枢性睡眠時無呼吸症の治療には使用すべきでない、との研究結果が2015年ESC Congressで発表され同時に*New England Journal of Medicine*に掲載された。SERVE-HFトライアルにおいて、心駆出率の低下した慢性心不全患者1325人が、ガイドラインベースの薬物管理のみ（コントロール群）または推奨されている夜間5時間週7回のASVを加える群にランダムに割り付けられた。追跡期間中央値31か月後、ASVは中枢性睡眠時無呼吸症の治療には有効であったが、一次エンドポイントである総死亡、救命のための心血管インターベンション、または心不全悪化による予定外入院の合計である一次エンドポイントにおいて効果がなかった。一次エンドポイントのイベント率はASV群の54.1%に対し、コントロール群では50.8%であった（ハザード比[HR]1.13；p=0.10）。さらに、ASVを標準治療に追加しても、QOL、6分間歩行距離、または症状などの機能的計測値において有益な効果が認められなかった。しかし、総死亡率および心血管系死亡率はASV群でコントロール群よりも高かった（34.8% 対29.3%；HR 1.28；p=0.01および29.9%対24.0% HR 1.34；p=0.006）。

Full Text

Adaptive servo-ventilation (ASV) therapy increases mortality and should not be used to treat central sleep apnea in heart failure patients with reduced ejection fraction, the SERVE-HF trial shows.

The Hot Line study, presented at ESC Congress 2015, and published simultaneously in the New England Journal of Medicine, "provides practice-changing guidance for the treatment of chronic heart failure (CHF)," said Martin Cowie, MD, co-principal investigator of the study, from Imperial College London, in London, UK.

"This study has changed our understanding of sleep-disordered breathing in systolic heart failure – the text books will have to be rewritten," he commented. "Doctors now know that treatment of central sleep-disordered breathing by mask therapy is not helpful for these patients and might be harmful. Lives will be saved by the findings of this new study."

Professor Cowie emphasized that patients in the study had reduced ejection fraction and predominantly central sleep apnea, and therefore the results cannot be generalized to patients with preserved ejection fraction or obstructive sleep apnea.
Unlike obstructive sleep apnea, central sleep apnea (CSA) is caused by the brain failing to trigger breathing during sleep.

ASV is designed to detect significant variation in breathing and deliver pressure through a facemask in order to maintain a normal breathing pattern.

In SERVE-HF (which stands for The Treatment of Sleep-Disordered Breathing With Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure) 1,325 chronic heart failure patients with a reduced ejection fraction who were randomized to receive either guideline-based medical management alone (control group), or with the addition ASV for a recommended 5 hours per night, 7 days a week.

After a median follow-up of 31 months ASV effectively treated central sleep apnea but had no effect on the primary end point, which was a combination of all-cause death, life-saving cardiovascular intervention, or unplanned hospitalization for worsening heart failure.

The event rate for the primary outcome was 54.1% in the ASV group compared to 50.8% in the control group (hazard ratio [HR] 1.13; P=0.10). Moreover, the addition of ASV to standard care had no beneficial effect on functional measures, including quality-of-life, six-minute walk distance, or symptoms.

However, all-cause mortality and cardiovascular mortality were higher in the ASV group than in the control group (34.8% versus 29.3%; HR 1.28; P=0.01 and 29.9% versus 24.0%; HR 1.34; P=0.006).

"The early and sustained increase in cardiovascular mortality seen with ASV was unexpected, and the reasons for this effect remain unclear," said Professor Cowie, noting that the SERVE-HF results are contrary to findings from some previous studies.

One possible explanation for this is that central sleep apnea may actually be a compensatory mechanism in some heart failure patients, he suggested.

"Potentially beneficial consequences of central sleep apnea in these patients could be that it rests respiratory muscles, and modulates excessive sympathetic nervous system activity, and by diminishing this effect ASV may be detrimental for patients with heart failure."

Although SERVE-HF did not meet its primary endpoint, "it was a well-designed and executed study," concluded Professor Cowie, "and because of it we now know that ASV therapy is contraindicated in this subset of chronic heart failure patients."

The SERVE-HF study was funded by ResMed Ltd.Professor Cowie receives research funding and consultancy fees from ResMed Ltd.

Conference News

実臨床においてリバーロキサバンは安全性および有効性試験をパスした (ESC2015 Presentation # 5072)

XANTUS：脳卒中予防目的でリバーロキサバンを投与された心房細動患者において出血および脳卒中発現率が低い

XANTUS: Low bleeding and stroke rates in patients with atrial fibrillation given rivaroxaban for stroke prevention

脳卒中予防目的でリバーロキサバンを投与されている心房細動（AF）患者は、出血や脳卒中の発現率が低いとのXANTUSスタディの実臨床におけるデータが2015年ESC Congressで発表された。この単一群観察研究では、日常臨床における非弁膜症性AF患者6,784人の脳卒中予防に対するリバーロキサバンの安全性および有効性を評価した。全ての治療および用量決定は治療担当医の裁量に委ねられ、患者は1年間または早期中止例ではその30日後まで追跡された。観察期間終了までに、大多数の患者（96.1%）は治療中の大出血、全死亡、脳卒中または全身性塞栓症を認めなかった。治療中の全死亡は1.9%／年であった。全体で、治療中の大出血は2.1%／年に認められ、これらの症例の多くが標準的な臨床的尺度を用いて治療された。致死的出血は0.2%／年であり、脳卒中は0.7%／年に発現した。この結果からROCKET AFの第III相試験データが確証され、直接第Xa因子阻害薬リバーロキサバンを用いた抗凝固療法は、AF患者における脳卒中予防において血栓塞栓イベントの高および低リスクの両方に対して安全で有効であることが示された。

Full Text

Atrial fibrillation (AF) patients treated with rivaroxaban for stroke prevention have low rates of bleeding and stroke, reveals real-world data from the XANTUS study presented at ESC Congress 2015. The findings confirm clinical trial data and demonstrate that oral anticoagulation with rivaroxaban, a direct Factor Xa inhibitor, is safe and effective for stroke prevention in patients with AF at both high- and low-risk of thromboembolic events.

"With 10 million people in Europe alone affected by AF, a number that is only expected to increase, real-world insights on routine anticoagulation management in everyday clinical practice is increasingly important for physicians and patients with AF," said XANTUS principal investigator Professor A. John Camm, professor of clinical cardiology in the Cardiovascular and Cell Sciences Research Institute at St George's University of London, UK.

XANTUS is the first international, prospective real-world non-vitamin K antagonist oral anticoagulant (NOAC) study in patients with AF. These patients are five times more likely than the general population to have a stroke. However, oral anticoagulation therapy can prevent many cases of AF-related stroke.

This single-arm, observational study evaluated the safety and effectiveness of rivaroxaban for stroke prevention in 6 784 patients with non-valvular AF from 311 centers across Europe and Canada in routine clinical practice. All treatment and dosing decisions were at the discretion of the treating physicians and patients were followed up for one year or until 30 days after premature discontinuation. Bleeding events and major thromboembolic events were centrally adjudicated by an independent committee.

By the end of the observation period the majority (96.1%) of patients had not experienced treatment-emergent major bleeding, all-cause death or stroke / systemic embolism. The rate of on-treatment all-cause mortality was 1.9% per year. Overall, 2.1% of patients per year experienced treatment-emergent major bleeding and most of these cases were treated using standard clinical measures. The rate of fatal bleeding was 0.2% per year, while stroke occurred in 0.7% patients per year, and critical organ bleeding occurred at a rate of 0.7% per year with 0.4% per year of patients experiencing an intracranial hemorrhage.

"These results demonstrate low rates of both major bleeding and stroke in patients taking rivaroxaban in routine clinical practice," said Professor Camm. "The findings reaffirm the positive benefit-risk profile of rivaroxaban established in the phase III clinical trial ROCKET AF, in which rivaroxaban was shown to provide effective stroke prevention with a similar overall bleeding profile and significantly lower rates of the most feared intracranial and fatal bleeds compared with vitamin K antagonists (VKAs)."

He continued: "The patients included in ROCKET AF were at moderate to high risk of stroke with a mean CHADS2 score of 3.5, and the incidence of major bleeding in those taking rivaroxaban was 3.6 per 100 person-years. In XANTUS, patients seen in daily clinical practice had a lower risk of stroke with a mean CHADS2 score of 2.0 and the incidence rate of major bleeding was lower at 2.1 per 100 person-years."

Furthermore, XANTUS showed that the majority of patients (80%) persisted on their treatment with rivaroxaban throughout the one-year study period, whereas other recent data on VKAs has shown a persistence rate of 62% after one year. "Treatment persistence is especially important as discontinuation of anticoagulation leaves patients with AF unprotected from the risk of stroke," said Professor Camm.

He concluded: "These real-world insights from XANTUS complement and expand on what we already know from clinical trials, and provide physicians with reassurance to prescribe rivaroxaban as an effective and well-tolerated treatment option for the broad range of patients with AF seen in their everyday clinical practice."

The study was supported by Bayer HealthCare Pharmaceuticals and Janssen Research & Development, LLC.

Professor Camm has acted as a consultant for AstraZeneca, Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Sanofi, Aryx, and Johnson & Johnson. Other co-authors report the following: Pierre Amarenco has acted as a consultant for Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi Sankyo, AstraZeneca, Sanofi, Boston Scientific, Edwards, Lundbeck, Merck, and Kowa Pharmaceutical. Sylvia Haas has acted as a consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and Sanofi. Paulus Kirchhof has received consulting fees and honoraria from 3M Medica, MEDA Pharma, AstraZeneca, Bayer HealthCare, Biosense Webster, Boehringer Ingelheim, Daiichi Sankyo, German Cardiac Society, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer/Bristol-Myers Squibb, Sanofi, Servier, Siemens, and Takeda. Alexander G.G. Turpie has been a consultant for Bayer HealthCare, Janssen Pharmaceutical Research & Development, Astellas, Portola, and Takeda. Susanne Hess, Silvia Kuhls and Martin van Eickels are employees of Bayer HealthCare Pharmaceuticals.

Conference News

発作性心房細動におけるカテーテルアブレーションの優位性(ESC2015 Presentation＃5777)

MANTRA-PAF：心房細動軽減においてファーストラインとしてのカテーテルアブレーションは薬物療法より優れる

MANTRA-PAF: First-line catheter ablation superior to drug therapy for reducing atrial fibrillation

心房細動軽減においてカテーテルアブレーションを用いたファーストライン治療が薬物療法よりも優れているとの5年間のMANTRA-PAFトライアルの結果が2015年ESC Congressで発表された。国際多施設共同のこのトライアルでは、重度の症状を有する発作性心房細動患者294人を対象に、ファーストライン治療としてカテーテルアブレーションまたは抗不整脈薬治療群にランダムに割り付けた。以前に示された2年間のトライアル結果によると、両治療群ともに心房細動を有効に減少させたが、どちらの治療が優れているかについては示されなかった。5年間の追跡調査は294人中245人（83%）において完遂され、うち125人はファーストライン治療としてカテーテルアブレーション、120人は抗不整脈薬群に割り付けられた。ホルター心電図検査は227人に施行された。心房細動の回避は、あらゆる心房細動（126/146対105/148、p=0.02）および症候性心房細動（137/146対126/148、p=0.015）いずれにおいても、抗不整脈薬群よりもカテーテルアブレーション群で高かった。心房細動負荷はカテーテルアブレーション群の方が抗不整脈薬群よりも有意に少なかった（あらゆるAF：p=0.003、症候性AF：p=0.02）。この結果は、ホルター心電図検査を実施しなかったことで補正しない場合でも同等であった。

Full Text

First-line treatment with catheter ablation is superior to drug therapy for reducing atrial fibrillation, according to five year results from the MANTRA-PAF trial presented for the first time at ESC Congress 2015.

Atrial fibrillation (AF) is the most common heart rhythm problem that requires medical treatment. Atrial fibrillation reduces quality of life and is associated with increased risk of stroke and disability. Atrial fibrillation is more common with higher age, and is observed in 2% of people aged 60 years and at least 5% of the population older than 70 years.

"In clinical practice most doctors choose antiarrhythmic drug therapy for initial treatment of symptomatic atrial fibrillation and catheter ablation is used for patients who fail drug therapy," said principal investigator Professor Jens Cosedis Nielsen, consultant cardiologist at Aarhus University Hospital in Denmark. "We asked the question: is catheter ablation superior to antiarrhythmic drug therapy as first-line treatment?"

MANTRA-PAF (Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) was an international multicenter trial conducted by heart rhythm specialists. A total of 294 patients with highly symptomatic paroxysmal atrial fibrillation were randomized to receive either catheter ablation or antiarrhythmic drug therapy as first-line treatment. The two-year results of the trial showed that both treatments reduced atrial fibrillation effectively, but none of the two treatment strategies were superior.

The five-year outcomes were presented at ESC 2015. The primary endpoint was the burden of atrial fibrillation assessed by seven day Holter recording. Secondary endpoints were burden of symptomatic atrial fibrillation, quality of life (using physical and mental component scores of the SF-36 questionnaire), and need for additional catheter ablation procedures since the two-year follow up. Analysis was by intention-to-treat and imputation was used to compensate for missing Holter data.

Five year follow up was achieved in 245 out of 294 patients (83%), of which 125 had been randomized to catheter ablation and 120 to antiarrhythmic drug therapy as first-line treatment. Holter recording was available for 227 patients. More patients in the catheter ablation group were free from any atrial fibrillation (126/146 versus 105/148, p=0.001) and symptomatic atrial fibrillation (137/146 versus 126/148, p=0.015) than those in the antiarrhythmic drug therapy group.3 Atrial fibrillation burden was significantly lower in the catheter ablation group (any AF: p=0.003, symptomatic AF: p=0.02) compared to the antiarrhythmic drug therapy group. The results were similar when not compensating for missing Holter recordings.

"At five-year follow-up less atrial fibrillation was observed with catheter ablation as first line treatment," said Professor Nielsen. "The findings indicate that first-line treatment with catheter ablation is superior to drug therapy for reducing atrial fibrillation. The different outcomes observed at two and five years may be because the two treatments have different modes of action."

There was no difference between the two groups in the number of additional catheter ablation procedures since the two-year follow up. Quality of life scores at five years did not differ between groups (physical component score p=0.88, mental component score p=0.94) but remained improved from baseline (both components p<0.001) and did not differ from the two year scores.

"Quality of life scores remained improved from before treatment initiation with either of the two treatments," said Professor Nielsen. "This indicates that quality of life can be improved long-term by treatment aiming to withhold normal heart rhythm, either by antiarrhythmic drug therapy or catheter ablation."

He concluded: "The results indicate that first-line catheter ablation is superior to drug therapy for suppressing atrial fibrillation in patients with paroxysmal AF. The choice of first-line treatment strategy still needs to be discussed with individual patients taking into account their disease burden and risks associated with the different treatment strategies."

The study was funded by the Danish Heart Foundation and Biosense Webster. Biosense-Webster supported the MANTRA-PAF trial with an unrestricted grant. Jens Cosedis Nielsen has received speaker's fees from Biosense-Webster and Biotronik and consultant's fees from Boston Scientific.

Conference News

ARBはCVDバイオマーカーによい影響を及ぼす可能性がある (ESC2015 Presentation # 4134)

ATTEMPT-CVD：心血管系バイオマーカーはARB以外の降圧薬に比べテルミサルタンに対し反応が良好である

ATTEMPT-CVD: Cardiovascular biomarkers respond better to telmisartan than non-ARB blood pressure medications

ATTEMPT-CVDトライアルの結果から、アンジオテンシンII受容体拮抗薬（ARB）テルミサルタンはARB以外の降圧薬よりも有益である可能性のあることが示唆された。2015年ESC Congressで発表され同時に*European Journal of Preventive Cardiology*に掲載されたこの結果は、ARBがARB以外の薬剤よりも2つの心血管系疾患（CVD）バイオマーカーに対しより良い影響を与える可能性があることを示した初めてのエビデンスである。日本の168施設の高血圧患者が、テルミサルタン（615人）またはARB以外の降圧薬（613人）を投与される群にランダムに割り付けられ、3年間追跡された。血圧コントロールは同等であったにもかかわらず、36か月後の時点で尿中アルブミン／クレアチニン比（UACR）の低下はテルミサルタン群でARB以外の降圧薬群よりも大であった（ARB群で12.2mg/gCr低下に対し、非ARB群では4.1mg/gCr、p<0.001）。血漿BNP上昇はテルミサルタン群で非ARB群よりも小であった（血漿BNPはARB群で0.5pg/mL上昇に対し、非ARB群では3.8pg/mL上昇、p=0.044）。他のバイオマーカーに関しては、ARB群でアディポネクチンの増加が大であり（p=0.041）CVD健康状態が良好であることが示され、またeGFR低下が大でありこれから腎機能が低いことが示唆された（p<0.001）ことを

Full Text

When it comes to treating high blood pressure, not all anti-hypertensive medications are equal, and results of the ATTEMPT-CVD trial suggest that telmisartan, an angiotensin II receptor blocker (ARB) might have benefits over non-ARB treatment.

The Hot Line results, presented at ESC Congress 2015, and published simultaneously in the European Journal of Preventive Cardiology, are the first evidence that ARBs may have a better impact on two biomarkers of cardiovascular disease (CVD) compared to non-ARBs, said lead investigator Hisao Ogawa, MD, from Kumamoto University, in Kumamoto City, Japan.

However, the trial did not show a significant difference between the treatments in either cardiovascular or renal events.

ATTEMPT-CVD measured the impact of both telmisartan and non-ARBs on urinary albumin creatinine ratio (UACR) and plasma brain natriuretic peptide (BNP).

Patients with hypertension from 168 institutions in Japan were randomized to receive telmisartan (n=615) or a non-ARB antihypertensive drug (n=613) and followed for three years.

The primary efficacy endpoints were changes from baseline in UACR and plasma BNP levels. Elevations in either of these biomarkers are considered risk factors for CVD. Secondary endpoints were changes in other biomarkers, including serum high-sensitivity C-reactive protein (hsCRP) levels, urinary 8-hydroxy-deoxy-guanosine (8-OHdG), serum adiponectin, estimated glomerular filtration rate (eGFR), and high-molecular weight adiponectin levels.

Another secondary endpoint was time until occurrence of a composite of cardiovascular events consisting of cerebral events, coronary events, cardiac events, aortic/peripheral arterial events, complication of diabetes, and aggravation of renal function.

The study found that, despite similar blood pressure control in both arms, patients treated with the ARB had a smaller increase in plasma BNP and a greater decrease in UACR than non-ARB treated patients.

By 36 months, UACR had decreased by12.2 mg/gCr in the ARB group compared to a decrease of 4.1 mg/gCr in the non-ARB group (P < 0.001).

Similarly, plasma BNP had increased by 0.5 pg/ml in the ARB group and by 3.8 pg/ml in the non-ARB group (P = 0.044).

Fewer cardiovascular events occurred in the ARB group, but the difference was not statistically significant (hazard ratio 0.71, P = 0.14).

Other biomarkers were not different between the two groups except for serum adiponectin, which showed a larger increase (P = 0.041), indicating better CVD health, and eGFR which showed a larger decrease (P < 0.001) indicating poorer renal function in the ARB group compared to the non-ARB group.

"It is well known that a slight but significant decrease in eGFR is not associated with poor outcome and may not be clinically relevant," noted Dr. Ogawa. In fact, the study showed that baseline levels of UACR and plasma BNP levels were associated with cardiovascular risk, but adiponectin and eGFR levels were not.

"Further study is needed to determine the significance of follow-up of BNP and UACR for cardiovascular and renal risk in hypertensive patients," he concluded.
This study was supported by the Japan Foundation for Aging and Health, which has received unrestricted funding from individuals and companies including Boehringer Ingelheim.

Dr. Ogawa has received grants from Astellas Pharma Inc., Bayer Yakuhin Ltd., Bristol Myers Squibb, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Dainippon Sumitimo Pharma Co. Ltd., Mochida Pharmaceutical Co. Ltd., MSD. K.K., Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Pfizer Japan Inc., Sanofi K.K., Shionogi & Co., Ltd., Takeda Pharmaceutical Co., Ltd., and personal fees from Actelion Pharmaceuticals Japan Ltd., Astra Zeneca K.K., Bayer Yakuhin Ltd., Boehringer Ingelheim Japan, Daiichi Sankyo LCo. Ltd., Eisai Co. Ltd., Kowa Co. Ltd., Kyowa Hakko Kirin Co. Ltd., Mitsubishi Tanabe Pharma, MSD K.K., Otsuka Pharmaceutical Co. Ltd., Pfizer Japan Inc., Sanofi K.K., Takeda Pharmaceutical Co. Ltd., and Teijin Pharma Co. Ltd.

Conference News

生体吸収性ステントはメタルステントと同等に好ましい (ESC2015 Presentation # 6001)

ABSORB Japan：薬剤溶出冠動脈ステントの有効性および安全性はメタルステントと同等であることが示された

ABSORB Japan: Dissolving drug-eluting coronary stent shows similar efficacy and safety as metal stent

経皮的冠動脈インターベンション（PCI）を施行される患者において、生体吸収性素材で作られた薬剤溶出ステントの有効性および安全性の結果はメタルステントと同等である、とのABSORB Japanスタディの結果が示された。2015年ESC Congressホットラインセッションで報告されたこの結果は、同時に*European Heart Journal*に掲載された。スタディは400人の患者（平均年齢67.2歳）を対象に、生体吸収性ステント（266人）またはメタルステント（134人）を用いてPCIを施行される群にランダムに割り付けられた。いずれのタイプのステントもエベロリムスでコーティングされていた。スタディの一次エンドポイントは1年後の標的病変不全であった。エンドポイントに達したのは生体吸収性ステント群で4.2%であり、メタルステント群で3.8%（相対リスク[RR]1.10、95%信頼区間 0.39-3.11）であり、生体吸収性スキャフォールドの非劣性が示された（p<0.0001）。13か月後に計測された二次エンドポイントは、造影上のセグメント内遠隔期損失径であった。このエンドポイントは両群で同等であり、これにおいても生体吸収性ステント群の非劣性が認められた（p<0.0001）。筆者らは、これらの結果は生体吸収性ステント使用がPCIを施行される患者の長期予後を改善する可能性が現実的であることを支持した先行研究と一致

Full Text

A drug-eluting coronary stent made from bioresorbable material showed similar efficacy and safety results compared to a metal stent in patients undergoing percutaneous coronary intervention (PCI), according to results of the ABSORB Japan study. The findings, reported in a Hot Line session at ESC congress 2015, were published simultaneously in the European Heart Journal.

"These results support the feasibility of bioresorbable vascular scaffolds (BVS) to potentially improve the long-term outcomes of patients," said principal investigator Takeshi Kimura MD, PhD, from Kyoto University Hospital, Kyoto, Japan.

However, to date there has been little long-term clinical and angiographic follow-up of BVS compared to metal stents, said Dr. Kimura. ABSORB Japan, a prospective, 38-centre trial comparing BVS with metal stents was designed to show non-inferiority of BVS to support regulatory approval in Japan.

The study included 400 patients (mean age 67.2 years) randomized to PCI using either a bioresorbable (266 patients) or metal stent (134 patients) – both types coated with everolimus – a medication to help prevent re-blockage of the artery.
The primary endpoint of the study was target lesion failure (TLF) - a composite of cardiac death, myocardial infarction attributable to target vessel, or ischemia-driven target lesion revascularization at one year.

This endpoint occurred in 4.2% of BVS patients and 3.8% of patients with metal stents (relative risk [RR] 1.10, 95% confidence interval 0.39-3.11), demonstrating non-inferiority of BVS (P <0.0001), reported Dr. Kimura.

The major secondary endpoint, measured at 13 months, was angiographic in-segment late lumen loss (LLL) – which is the amount of re-blockage that occurs in the stented vessel.

This endpoint was comparable in both arms, again demonstrating non-inferiority of BVS (P <0.0001).

"BVS demonstrated a similar 12-month clinical safety and efficacy profile as the metal stent, with comparable 13-month angiographic outcomes," concluded Dr. Kimura. "These results are consistent with a few previous studies reporting either 12-month clinical outcome or 9-month angiographic outcome, supporting the feasibility of BVS use to potentially improve the long-term outcomes of patients undergoing PCI."

The study was sponsored by Abbott Vascular, Santa Clara, California. Dr. Kimura and some of his co-investigators are members of the Advisory Board of Abbott Vascular, Santa Clara, California and Abbott Vascular Japan. Other co-investigators for this study are employees of Abbott Vascular. Dr. Gregg Stone, senior author, is a consultant to Reva Corp.

Conference News

胸痛とうつ病は共通の神経化学的経路を有する可能性がある (ESC2015 Presentation # 4301)

冠動脈疾患の有無にかかわらず、うつ病の重症度は胸痛の頻度と独立して相関がある

Severity of depression was independently associated with the frequency of chest pain in patients with and without underlying coronary artery disease

うつ病患者は冠動脈疾患がなくても胸痛頻度が高いとのEmory Cardiovascular Biobankの結果が2015年ESC Congressで発表された。スタディは成人5,825人を対象とし、平均年齢63歳、男性は65%であった。その結果、うつ病の重症度は胸痛頻度と独立して相関があり、より重度のうつ病患者はより頻回の胸痛を有することが示された。軽度のうつ病であっても、うつ症状のない患者に比べ胸痛頻度が高かった。この結果は、冠動脈疾患重症度、年齢、性別、人種および喫煙の有無、ボディーマスインデックス、血圧、血中脂質レベルなどの従来の心血管リスクファクターで補正してもなお認められた。うつ病患者はうつ病のない患者に比べ胸痛を有する頻度が3倍高かった。これは冠動脈狭窄の有無に関わらず当てはまった。追跡調査で、うつ症状の軽減が胸痛頻度の低下に関連していた。しかし1年後の追跡調査で、血行再建術を施行されたうつ病患者は胸痛頻度の減少が認められなかった。これらの結果から、疼痛とうつ病は共通の神経化学的経路を有している可能性が示唆された。

Full Text

Depressed patients have more frequent chest pain even in the absence of coronary artery disease, according to results from the Emory Cardiovascular Biobank presented at ESC Congress by Dr. Salim Hayek, a cardiologist at Emory University School of Medicine in Atlanta, Georgia, US. The findings suggest that pain and depression may share a common neurochemical pathway.

"Depression is a common and well recognized risk factor for the development of heart disease," said Dr. Hayek. "Patients with known heart disease and depression tend to experience chest pain more frequently. However until now, it was not known whether that association was dependent on underlying coronary artery disease."

The current study assessed whether depression was associated with chest pain independently of underlying coronary artery disease. The study included 5 825 adults enrolled in the Emory Cardiovascular Biobank between 2004 and 2013. The biobank is a prospective registry of patients undergoing cardiac catheterization at three Emory Healthcare sites in Atlanta.

Patients had an average age of 63 years, 65% were male and 22% were African Americans. Prior to cardiac catheterization patients completed the Patient Health Questionnaire-9 (PHQ-9) to assess depressive symptoms and the Seattle Angina Questionnaire to assess chest pain frequency in the past month. The presence and severity of coronary artery disease was determined by angiogram. Patients completed the same questionnaires at one and five years post-procedure.

The researchers found that depression severity as measured by the PHQ-9 was independently associated with the frequency of chest pain, indicating that patients with more severe depression had more frequent chest pain. Even patients with mild depression had more frequent chest pain than patients with no depressive symptoms. The findings remained after adjusting for coronary artery disease severity, age, gender, race and traditional cardiovascular risk factors including smoking status, body mass index, blood pressure and blood lipid levels.

Patients with depression, whether women or men, were three times more likely to experience more frequent chest pain than those without depression. This was found to be true in patients with and without obstructive coronary artery disease.

A reduction in the severity of depression symptoms was associated with a decrease in the frequency of chest pain at follow-up. Most importantly, patients with depression who underwent revascularization did not have an improvement in chest pain frequency at 1-year follow-up.

"We found that depression is strongly associated with the frequency of chest pain in adults with and without underlying coronary artery disease, and that patients with depression and heart disease did not have an improvement in their chest pain frequency even after coronary intervention" said Dr. Hayek.

"One possible explanation for our findings is that pain and depression share a common neurochemical pathway." He added: "Although depression is established as a risk factor for heart disease, there are no clear recommendations in the US for depression screening in patients with cardiovascular disease. ESC prevention guidelines recommend assessing patients for depression to prevent cardiovascular disease.

Although our findings do not establish causality, they do suggest that depression is an important confounder of the relationship between chest pain and heart disease. Screening for depression in patients presenting with chest pain should be considered, and studies examining the effect of appropriate anti-depressive therapy on chest pain are needed."

Dr. Hayek concluded: "The fact that chest pain frequency at follow-up was decreased in patients whose depressive symptoms improved indicates that treating depression may help alleviate chest pain, after obstructive coronary artery disease as a cause of chest pain has been ruled out. This needs to be confirmed in randomized controlled trials."

Dr. Hayek is supported by the Katz Family Foundation Preventive Cardiology Grant (Atlanta, GA).

Conference News

心疾患に対するうつ病と血圧の相乗効果 (ESC2015 Presentation # P1374)

うつ病と極端な血圧は有害な血管イベント率が最大であることの予測因子である

Depression and extremes of blood pressure predict highest rates of harmful vascular events

うつ症状と極端な血圧は既存の心疾患、糖尿病または脳卒中の患者における有害な血管イベント率が最大であることの予測因子となる、と2015年ESC Congressで発表された。スタディは、スコットランドに居住する既存の心疾患、糖尿病または脳卒中患者35,537人を対象とした。4年間の追跡期間中、3,939人（11%）の患者が少なくとも1つの重大な有害イベントを発現した。重大な有害イベントの予測において、うつ病は収縮期血圧（SBP）と有意な相互作用を有していた（p=0.03）。血圧が正常でうつ症状がない者に比べ、高血圧とうつ症状の両方を有する患者は4年間の重大な有害イベントのリスクが83%高く（ハザード比[HR]=1.83；95%信頼区間（CI）=1.46-2.30、p<0.001）、低血圧とうつ症状の両方を有する者はそのリスクが36%高かった（HR=1.36；CI=1.15-1.62、p<0.001）。この結果は、年齢、性別、ボディーマスインデックス（BMI）、総コレステロール値、社会経済的状態、抗うつ薬の使用および合併疾患数などの血管イベントリスクに影響し得る因子で補正された。これらの結果から、血圧モニターの仕方に重点的に取り組むこと、およびうつ症状を合併する患者に治療を提供することが健康上の転帰を改善し得ることが示唆される。

Full Text

Depressive symptoms and extremes of blood pressure predict the highest rates of harmful vascular events in patients with existing heart disease, diabetes or stroke, according to research presented at ESC Congress 2015 by Dr. Bhautesh Jani, clinical academic fellow in the Institute of Health and Wellbeing, University of Glasgow, UK.

The study in more than 35,000 patients found that the risk of further stroke or heart attack, heart failure or dying due to heart disease at four years was 83% higher in depressed patients with hypertension and 36% higher in depressed patients with hypotension, compared to those with normal blood pressure and no depressive symptoms.

"Previous studies have shown that patients with existing heart disease, diabetes or stroke are more likely to suffer from further heart attack or stroke than the general population, particularly those who have extremes of blood pressure or have depressive symptoms but until now the effects of having both together were unknown," said Dr. Jani. "This is the first study which has specifically investigated the relationship between depressive symptoms and extreme blood pressure in influencing the rate of heart attack, stroke, heart failure and heart disease related deaths in patients with existing heart disease, diabetes or stroke."

The study included 35,537 community dwelling patients with existing heart disease, diabetes or stroke from Scotland, UK. In 2008-09 depression was assessed using the hospital anxiety and depression score (HADS-D). Systolic (SBP) and diastolic (DBP) blood pressure were recorded and patients were classified as very high (SBP>160, DBP>100), high (SBP 140-159, DBP 90-99), normal (SBP 130-139, DBP 80-89), tightly controlled (SBP 120-129, DBP 80-84) or low (SBP<120, DBP<80) blood pressure. The occurrence of major harmful events (further stroke or heart attack, heart failure or dying due to heart disease) was recorded over a period of four years.

During the four year follow up period 3,939 patients (11%) had a least one major harmful event. Depression had a significant interaction with SBP (p=0.03) in predicting a major harmful event. Dr. Jani said: "The relationship between depression and blood pressure is an area of ongoing medical research and various physiological theories are under review to explain the nature of this relationship."

Patients with the combination of high blood pressure and depressive symptoms had 83% higher risk of a major harmful event at four years (hazard ratio (HR) =1.83; 95% confidence interval (CI) 1.46-2.30, p<0.001) and those with low blood pressure and depressive symptoms had a 36% higher risk (HR=1.36; CI=1.15-1.62, p<0.001) than those with normal blood pressure and no depressive symptoms. The results were adjusted for factors that can influence risk of vascular events such as age, sex, body mass index (BMI), total cholesterol levels, socioeconomic status, use of antidepressants and the number of existing medical conditions.

"In our study, patients with a combination of depression and high or low blood pressure had the highest rate of a major harmful vascular event at four years," said Dr. Jani. "One explanation for our results may be that these patients had the most severe form of existing heart disease, diabetes or stroke, which was not recognized and hence had the worst outcomes."

He concluded: "Our findings suggest that focusing resources on monitoring blood pressure and providing treatment in patients with associated depressive symptoms could improve health outcomes by reducing the risk of further strokes or heart attacks, having heart failure or dying from heart disease. They also indicate that patients with high or low blood pressure might benefit from screening and treatment for depression. To date there are no studies showing that treatment of depression changes or improves cardiovascular outcomes and more research is needed in this area. Studies are also needed to further understand how blood pressure and depression interact."

The study was sponsored by Chief Scientist Office, Scottish Government. The authors had no conflicts to report.

Conference News