Ivabradineによる心拍数低下により冠動脈イベントが減少する

BEAUTIFULトライアル：Ivabradineは安定冠動脈疾患および左室機能低下を有する患者の心筋梗塞および血行再建術施行率を減少させる初めての抗狭心症治療薬である

BEAUTIFUL:Ivabradine is first antianginal treatment to reduce myocardial infarction and revascularization in patients with stable coronary disease and left ventricular dysfunction

BEAUTIFULトライアル：morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with CAD and left ventricULar dysfunction（冠動脈疾患および左室機能不全を有する患者に対するIf電流阻害薬ivabradineの有病率と死亡率に対する効果の評価）の結果、ivabradineを用いて心拍数を低下させることにより、洞調律患者の心筋梗塞、心筋梗塞による左室収縮不全および血行再建術施行率を減少させる、とミュンヘンで開催された2008年European Society of Cardiology学会で発表された。左室駆出率40%未満の安定した患者10,917人を、5mgのivabradine（目標用量の7.5mgを1日2回投与まで増量）またはプラセボを投与する群に無作為に割り付けた。患者らは心血管系治療薬による至適治療を継続して受けた。スタディの対象全体で一次複合エンドポイント（心血管死、心筋梗塞による入院、心不全の新規発症または増悪による入院の合計）においてivabradineの有効性は認められなかった（p=0.94）。しかし、事前に定義されたサブグループの患者（心拍数70bpm以上）において、ivabradineは致死性および非致死性心筋梗塞による入院を36%（p=0.001）、冠動脈血行再建術施行を30%（p=0.016）減少させた。またこの試験の結果、ivabradineは安全で忍容性が高く、ルーチンに処方される全ての心血管治療薬と併用可能であることも確認された。

Full Text

The landmark BEAUTIFUL (morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with CAD and left ventricULar dysfunction) trial shows that heart rate reduction with ivabradine reduces myocardial infarction, associated left ventricular systolic dysfunction and revascularization in patients who are in normal sinus rhythm according to a featured presentation at the European Society of Cardiology Congress 2008 in Munich.

Commenting after the results presentation, the Chairman of the BEAUTIFUL Executive Committee, Professor Kim Fox said, "Ivabradine was always known to relieve ischemia. With the BEAUTIFUL results, ivabradine is the first antianginal treatment shown to reduce myocardial infarction (MI) and revascularization and to have a good tolerability profile even when used with other drugs. This is the gold standard for any antianginal, anti-ischemic drug".

The BEAUTIFUL trial was initiated in December 2004, under the guidance of an independent Executive Committee with the first patient being enrolled in early 2005. 10,917 patients with left ventricular ejection fractions less than 40% were recruited in 781 centers in 33 countries across 4 continents. The mean heart rate in these patients was 71 bpm and half of the patients had a heart rate more than 70 bpm. The results of the BEAUTIFUL study have shown that these patients with heart rate > 70 bpm are more likely to die or suffer from another cardiovascular event. The increase in risk is 34% for cardiovascular death, 46% for myocardial infarction, 56% for heart failure and 38% for coronary revascularization.

In the overall study population treatment with ivabradine did not result in a significant reduction of the primary composite end point (Cardiovascular death, admission to hospital for acute MI and admission to hospital for heart failure). However in patients with baseline heart rate more than 70 bpm, ivabradine significantly reduced the risk of hospitalization for fatal and non-fatal myocardial infarction by 36% (p=0.001) and the risk of coronary revascularization by 30% (p=0.016). What is important to note is that most of these patients were already receiving the guidelines-recommended cardiovascular therapy: antiplatelet agents (94%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (91%), ƒÀ-blockers (87%), as well as lipid-lowering agents (76%). Hence the results of BEAUTIFUL constitute a step further in the management of these coronary patients with heart rate above 70 bpm because, for the first time it has been shown that pure heart rate reduction with ivabradine further reduces coronary events even in patients receiving the current optimal cardiovascular therapy. This study also confirms that ivabradine is safe and well tolerated and can be used with all routinely prescribed cardiovascular drugs.

Commenting on the results the Chairman of the Steering Committee, Prof Roberto Ferrari said, "Often a lot of investigations are performed in coronary patients but a simple heart rate measurement is not done. BEAUTIFUL has reinforced the need to measure heart rate in all CAD patients and if the heart rate is more than 70 bpm to reduce it by using ivabradine on top of background therapy."

BEAUTIFUL results with ivabradine can be explained by its well-documented ability to relieve myocardial ischemia in patients with chronic stable angina. New research has demonstrated that ivabradine improves endothelial dysfunction and prevents the progression of atherosclerosis.

"Half of the CAD patients have a resting heart rate more than 70 bpm. These patients can now benefit from a treatment that will greatly reduce their chances of having another heart attack or needing further surgery", concluded Professor Kim Fox, the Chairman of the BEAUTIFUL Executive Committee.

PCIとCABGの相対的なメリットは未だに解決されていない

SYNTAXトライアル：最も困難な病変の患者に対する薬剤溶出ステントとバイパス手術を比較したトライアルの結果、安全性は同等であったがPCIの有効性に関しては複雑な結果が得られた

SYNTAX: Trial comparing PCI with drug-eluting stent and bypass surgery in the most complex patients reports comparable safety outcomes but mixed efficacy for PCI group

最も困難な病変の患者に対するパクリタキセル溶出ステントを用いた経皮的冠動脈形成術（PCI）と冠動脈バイパス術（CABG）を比較したSYNTAX（TAXusを用いた経皮的冠動脈形成術とバイパス手術の相乗作用）トライアルの1年間のデータから複雑なメッセージが得られた：安全性は同等であり、PCIに割り付けられた患者の方が脳卒中の合併症発現率が低いが再血行再建術施行率はこれらの患者において高かった。PCIとCABGの直接比較において研究者らは、死亡（4.3%対3.5%、p=0.37）または心筋梗塞（4.8%対3.2%、p=0.11）のリスクに統計学的な有意差がないことを明らかにした。脳卒中のリスクはバイパス手術群で有意に高かった(4.8%対3.2%，p=0.11)。総合すると、これら3つ（死亡、心筋梗塞、脳卒中）のデータポイントから、左主幹動脈病変および多枝病変を有する患者に対するPCIとバイパス手術の安全性は同等であることが示された。この結果はミュンヘンで開催された2008年European Society of Cardiology学会のHot Lineセッションで発表され、Lancetオンライン版に掲載された。

Full Text

One-year data from the SYNTAX trial comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in the most complex patients has produced mixed messages: higher rates of revascularization for patients randomized to PCI, but lower rates of stroke. There were no statistically significant differences in rates of death or myocardial infarction between PCI and CABG.

The results of SYNTAX have been eagerly anticipated because the study is the first randomized comparison of PCI with drug-eluting stents vs. bypass surgery in patients with the most complex coronary artery disease -- left main stenosis and three-vessel disease. One-year data from the SYNTAX randomized trial were presented by Patrick Serruys and Friedrich Mohr in a Hot Line session at the European Society of Cardiology Congress 2008 in Munich and published online in The Lancet. They revealed findings for the primary endpoint, focusing on the safety and effectiveness of the two therapies and whether either group experienced more heart attack, stroke, or death, or was more likely to require repeat revascularization procedures (either a second PCI or bypass surgery) by the end of the first year.

All patients in the trial were assessed by a multidisciplinary team that included an interventional cardiologist and cardiac surgeon. If both felt they could offer equivalent revascularization, patients were randomized in a 1:1 fashion to PCI (which used a paclitaxel-eluting coronary stent) or CABG.

The trial enrolled 1800 patients in its randomized arm from 62 EU sites and 23 US sites.

In its head-to-head comparison of PCI vs. bypass surgery, SYNTAX found no statistically significant difference in risk of death (4.3% vs. 3.5%, respectively; p=0.37) or heart attack (4.8% vs. 3.2%, respectively, p=0.11). The risk of stroke was significantly greater for bypass surgery (0.6% for PCI vs. 2.2% for bypass; p=0.003). Taken together as a composite, these three data points (death, heart attack, and stroke) show that PCI and bypass surgery are equally safe options for patients with left main and multi-vessel coronary artery disease.

Other findings from the 12-month data showed that the rate of symptomatic graft occlusion was 3.4% in the CABG group, and the rate of stent thrombosis in the PCI group 3.3% (P=0.89).

"The study failed to meet its primary endpoint for non-inferiority," conceded investigator Patrick Serruys of Rotterdam, Netherlands, adding that the outcome was nevertheless "hypothesis generating". He said: "The results for the first time open the way for drug-eluting stents in patients with more complex anatomy and advanced disease who have traditionally been treated with CABG."

"The good news is that both PCI and CABG have improved," said discussant Christian Hamm from Bad Nauheim, Germany.

The "all comes" design of SYNTAX meant that patients who were not considered "eligible" for the randomized trial were enrolled into two registries, 192 to a PCI registry and 644 to a CABG registry.

Results from the registry analysis were also presented yesterday and showed that the total MACCE rate in the PCI registry was 20.4% at 12 months, and in the CABG 8.8%.

"The registry shows that, for patients not considered eligible for CABG, PCI is a viable option," said principal investigator Friedrich Mohr of Leipzig, Germany. "The surgical results are excellent for patients who are not candidates for PCI."

Conference News

GISSI-HF心不全トライアルの総合結果

GISSI-HFトライアル：ロスバスタチンは原因に関係なく慢性心不全患者の臨床転帰に影響しなかったが魚油単独のサプリメントは有益であった

GISSI-HF: Rosuvastatin did not affect clinical outcomes in patients with chronic heart failure of any cause but a simple fish oil supplement showed benefit

ロスバスタチンは原因に関係なく慢性心不全患者の臨床転帰に影響しなかった（ロスバスタチンは安全な様であった）が魚油単独のサプリメントは有益であったとのGISSI-HFトライアルの結果が、2008年European Society of Cardiology学会で発表されLancetオンライン版に掲載された。New York Heart Associationクラス II～IVの慢性心不全患者4,574人（平均年齢68±11歳）を、心不全の原因または左室駆出率を問わず、ロスバスタチン1日10mg（2,285人）とプラセボ（2,289人）を比較する二重盲検無作為化トライアルに組み入れた。患者らは中央値で3.9年間追跡調査された。一次エンドポイント（死亡までの期間、または死亡および心血管疾患による入院までの期間の合計）は両群間で差がなかった。同じトライアルの別の群における結果では、魚油単独のサプリメントは心不全患者に有益である可能性が示唆された。n-3多価不飽和脂肪酸（n-3 PUFA、1日1g）の投与を受けた患者においては、死亡および心血管系が原因の入院の相対リスクが8%低下した（p=0.009）。

Full Text

Rosuvastatin (10 mg daily) did not affect clinical outcomes in patients with chronic heart failure of any cause, in whom the drug seemed to be safe, but a simple fish oil supplement benefitted these patients according to results from the GISSI-HF trial presented at the European Society of Cardiology Congress 2008.

Large observational studies, small prospective studies and post-hoc analyses of randomized clinical trials have suggested that statins could be beneficial in patients with chronic heart failure. However, previous randomized controlled trials have been methodologically weak. This trial investigated the efficacy and safety of the statin rosuvastatin in patients with heart failure.

4,574 patients (mean age 68±11 yr) with chronic heart failure of New York Heart Association class II--IV, irrespective of cause and left ventricular ejection fraction, were included in a double-blind randomized trial testing rosuvastatin 10 mg daily (n=2,285) against placebo (n=2,289). Patients were followed-up for a median of 3.9 years. Primary endpoints were time to death, and time to death or admission to hospital for cardiovascular reasons.

According to the intention to treat analysis, 657 (29%) patients died from any cause in the rosuvastatin group (28.8%) and 644 (28%) in the placebo group (adjusted hazard ratio [HR] 1.00, [95.5% CI 0.898--1.122], p=0.943). No differences were found also with respect to the other primary end-point: 1305 (57%) patients in the rosuvastatin group died or were admitted to hospital for cardiovascular reasons and 1283 (56%) in the placebo group (adjusted HR 1.01, [99% CI [0.908--1.112], p=0.903).

A separate arm of the same study found that a simple fish oil supplement (n-3 PUFA) can benefit patients with heart failure. Several epidemiological and experimental studies suggested that n-3 PUFA could exert favorable effects on the atherotrombotic cardiovascular disease including arrhythmias.

The GISSI researchers enrolled 6,975 patients with chronic heart failure of New York Heart Association class II-IV, assigned to n-3 PUFA 1 g daily or placebo. Patients were followed up for a median of 3.9 years. Primary end-points were time to death and time to death or admission to hospital for cardiovascular reasons. Analysis was by intention-to-treat population.

Among the GISSI findings: 955 (27%) patients died from any cause in the n-3 PUFA group and 1014 (29%) in the placebo group (relative risk reduction 9%, p=0.041). 1981 (57%) patients in the n-3 PUFA group and 2053 (59%) in the placebo group died or were admitted to hospital for cardiovascular reasons (relative risk reduction 8%, p=0.009). In absolute terms, 56 patients needed to be treated for 3.9 years to avoid one death or 44 to avoid one event like death or admission to hospital for cardiovascular reasons. In a per-protocol analysis performed in about 5000 full complier patients, the relative risk of death was reduced by 14% (p=0.004). Safety was excellent.

GISSI is endorsed by the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), Firenze, Italy; Ist.Ricerche Farmacologiche Mario Negri, Milan, Italy and the Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy. The GISSI-HF trial was planned, conducted and analyzed by the GISSI group, which has full ownership of the dat

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新世代の薬剤溶出ステントの有効性が示された

LEADERSスタディ：生分解性biolimusステントは'real world'のスタディで冠動脈形成術を施行される患者に対し安全で有効なようである

LEADERS: Biodegradable biolimus stent appears safe and effective in patients undergoing percutaneous coronary intervention in 'real world' study

この種のスタディでは初めてであるが、外側の表面のみに生分解性ポリマーを適用した薬剤溶出ステント（DES）は、日常臨床と同じ状況下において、最も広く用いられているDESと同様に安全で有効であることが示された、と2008年European Society of Cardiology学会で発表されLancetオンライン版に掲載された。LEADERS（Limus Eluted from A Durable versus ERodable Stent coating）スタディでは、1,707人の患者（2,472病変）を生分解性ポリマーを用いたbiolimus溶出ステントまたは耐久性ポリマーを用いたシロリムス溶出ステントを埋め込む群に無作為に割り付けた。9ヵ月後に、biolimus溶出ステント群とシロリムス溶出ステント群の患者のうち一次エンドポイントに到達したのは同じ割合であった（9.2%対10.5%；RR=0.88；95%信頼区間 0.64～1.19；非劣性p=0.003）。Biolimusおよびシロリムス溶出ステント群の死亡率（2.6%対2.8%；p=0.74）、心臓死（1.6%対2.5%；p=0.22）、心筋梗塞（5.7%対4.6%；p=0.30）、または臨床上適応とされた標的血管血行再建術（4.4%対5.5%；p=0.29［p値は優性に対する値］）は同等であった。Biolimus溶出ステントはまた、このスタディの主要な血管造影上のエンドポイントであるステント内内径狭窄率においても非劣性を示した（20.9%対23.3%；p=0.001）。

Full Text

In the first study of its kind, a drug-eluting stent (DES) with a biodegradable polymer applied only to the outer surface has been demonstrated as safe and effective as one of the most established and widely used types of DES with a durable polymer, in equivalent conditions to everyday clinical practice. Results were presented in a Hot Line session at the European Society of Cardiology Congress 2008 and published online in The Lancet.

The LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) study randomly assigned 1,707 patients with 2,472 lesions to treatment with either a biolimus-eluting stent with a biodegradable polymer or a sirolimus-eluting stent with a durable polymer. The study involved a broad range of patients for whom a stenting procedure was considered suitable, designed to reflect routine clinical practice.

Nine months after the procedure, a similar proportion of patients with biolimus-eluting stents and sirolimus-eluting stents reached the primary endpoint (9.2% vs 10.5%; RR=0.88; 95% CI 0.64 to 1.19; p=0.003 for noninferiority). Regarding individual safety and efficacy outcomes at 9 months, patients in the biolimus- and sirolimus groups had similar rates of death (2.6% vs 2.8%; p=0.74), cardiac death (1.6% vs 2.5%; p=0.22), MI (5.7% vs 4.6%; p=0.30), or clinically indicated TRV (4.4% vs 5.5%; p=0.29) (p values for superiority). Biolimus-eluting stents were also non-inferior to sirolimus-eluting stents in in-stent percent diameter stenosis (20.9% versus 23.3%, p=0.001 for noninferiority), the principal angiographic endpoint of the study.

"The results from LEADERS are significant, as they demonstrate for the first time that a drug-eluting stent with a biodegradable polymer is just as safe and effective as a conventional drug-eluting stent with a durable polymer, under conditions which resemble those of routine clinical practice", commented LEADERS Principle Investigator Professor Stephan Windecker, University Hospital, Bern, Switzerland. "The next stage will be to investigate whether a biodegradable polymer leads to a lower risk of stent thrombosis in the longer term".

テルミサルタンは心保護作用を有する

TRANSCENDトライアル：テルミサルタンはACE阻害薬に忍容性のない患者において軽度の心保護作用を有する

TRANSCEND: Telmisartan has modest cardioprotective effect for patients unable to tolerate ACE inhibitors

アンジオテンシン受容体拮抗薬（ARB）テルミサルタンは、アンジオテンシン変換酵素（ACE）阻害薬に忍容性のない心血管疾患のハイリスク患者における心血管死、心筋梗塞（MI）または脳卒中の発現を減少させるが、その効果は軽度であったと報告された。TRANSCENDトライアル：Telmisartan Randomized Assessment Study in ACE-Intolerant Subjects With Cardiovascular Disease（ACE阻害薬に忍容性のない心血管疾患患者におけるテルミサルタンの無作為化評価スタディ）トライアルが2008年European Society of Cardiology学会で発表され、Lancetオンライン版に掲載された。一次エンドポイントである心血管死、MI、脳卒中、または心不全による入院は、ARB群とプラセボ群とで同等であった（15.7%対17.0%；p=0.22）。しかし、エンドポイントを心血管死、MIまたは脳卒中（さらに心不全による入院は含まない）とすると、有害事象発現率はテルミサルタン群で低かった（13.0%対14.8%；p=0.048）。この複合エンドポイントの軽減は、主にテルミサルタン群でMI発現率が低いことによりもたらされた（3.9%対5.0%；p=0.06）。このトライアルによりまた、テルミサルタンの糖尿病新規発症（11.0%対12.8%，p=0.08）、左室肥大（5.0%対7.9%；p<0.001）、およびあらゆる心血管系疾患による入院（30.3%対33%；p=0.025）に対する軽度の有益性も示された。

Full Text

An international study led by Canadian researchers has found that the angiotensin receptor blocker telmisartan reduced the outcome of cardiovascular death, myocardial infarction or stroke in people who are unable to tolerate angiotensin-converting enzyme (ACE) inhibitors.

Dr. Salim Yusuf and Dr. Koon Teo, professors in the Michael G. DeGroote School of Medicine at McMaster University and clinicians at Hamilton Health Sciences, led the study. Results were presented today at the European Society of Cardiology Congress in Munich, Germany and published online in The Lancet.

The TRANSCEND (Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease) study enrolled nearly 6,000 people worldwide who are intolerant to ACE inhibitors, and evaluated whether telmisartan - compared to placebo - would reduce the risk of major cardiovascular events. A high proportion of patients received proven therapies, such as statins, anti-platelet agents and beta-blockers. Physicians were also free to use other medications that could lower blood pressure.

The researchers found that the outcome of cardiovascular death, myocardial infarction or stroke was modestly reduced when patients took telmisartan. In addition, fewer patients receiving telmisartan were hospitalized for any cardiovascular reason compared to placebo. Telmisartan was also remarkably well tolerated, and fewer patients on telmisartan discontinued the medication compared to placebo.

The primary endpoint of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure was similar between the ARB and placebo arms (15.7% vs. 17.0%, hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.81-1.05, p = 0.22). However, when the outcome included cardiovascular death, heart attack or stroke (and not hospitalization for heart failure), the incidence of adverse events was lower in the telmisartan group (13.0% vs. 14.8%, HR 0.87, 95% CI 0.76-1.0, p = 0.048). The reduction in this composite endpoint was driven primarily by a reduction in the incidence of myocardial infarction (3.9% vs. 5.0%, p = 0.06), whereas the incidence of cardiovascular death, stroke, and heart failure seemed to be fairly similar.

The trial did show a modest benefit of the drug on the prespecified composite secondary endpoints of new diabetes mellitus (11.0% vs. 12.8%, p = 0.08), left ventricular hypertrophy (5.0% vs. 7.9%, p < 0.001) and any cardiovascular hospitalization (30.3% vs. 33%, p = 0.025). There was no difference in all-cause mortality (12.3% vs. 11.7%, p=0.49). "The TRANSCEND study demonstrates the value of telmisartan in people who are unable to tolerate angiotensin converting enzyme inhibitors," said principal investigator Dr. Yusuf, director of the Population Health Research Institute at McMaster University.

"Although the benefit is of moderate size, there is an impact on a range of outcomes including the composite of cardiovascular death, myocardial infarction and strokes, as well as cardiovascular hospitalizations. Given the large proportion of people who are unable to tolerate an ACE inhibitor, the use of telmisartan would be clinically important." "The remarkable tolerability of telmisartan is emphasized by the fact that fewer individuals stop medication if they were receiving telmisartan compared to placebo," said Dr. Teo, the project director. "This is particularly noteworthy, as all the individuals enrolled in the study were unable to tolerate an ACE inhibitor, which is a closely related class of agents." The TRANSCEND study enrolled people with a history of cardiovascular disease or diabetes with end-organ damage who were intolerant to ACE inhibitors.

The study was conducted in 630 hospitals in 40 countries. It was coordinated by the Population Health Research Institute at McMaster University and Hamilton Health Sciences. The study was sponsored by Boehringer-Ingelheim, the manufacturers of telmisartan.

血管手術におけるフルバスタチンの心保護作用

DECREASE IIIスタディ：フルバスタチンは待機的大血管手術の周術期の循環器系予後を改善する

DECREASE III: Fluvasatatin improves perioperative cardiac outcomes after elective major vascular surgery

DECREASE IIIスタディ：Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo III（オランダにおけるストレスエコーを用いた心臓リスク評価 III）スタディの結果、フルバスタチン徐放製剤をベータ遮断薬に併用することにより、待機的大血管手術を施行されスタチンを初回投与されたハイリスク患者の周術期の循環器系予後が有意に改善する、と2008年European Society of Cardiology学会で報告された。患者（年齢中央値65.7歳、男性75%、冠動脈疾患の既往39%、脳卒中の既往29%、糖尿病20%）は、徐放性フルバスタチン（1日80mg；250人）またはマッチさせたプラセボ（247人）を術前30日より開始し術後30日以上継続する群に無作為に割り付けられた。フルバスタチン投与によりベースラインの総コレステロールおよびLDLコレステロールがそれぞれ20%と21%減少したのに対し、プラセボではそれぞれ4%および3%の減少であった（両方ともp<0.001）。同様にフルバスタチンは炎症マーカーである高感度C反応性蛋白およびインターロイキン-6をそれぞれ21%および33%減少させたのに対し、プラセボ群では＋3%および-4%の変化であった（両方ともp<0.001）。一次エンドポイントである初回血管手術後30日以内の心筋虚血性イベントに達したのは、フルバスタチンを投与された患者において有意に少なかった（心筋虚血と診断されたのはフルバスタチン群で10.9%であったのに対し、プラセボ群では18.9%であった；p=0.016）。

Full Text

Annually, approximately 40 million people undergo noncardiac surgery in the European Union. Of these patients approximately 400,000 (1%) will suffer a perioperative myocardial infarction (PMI) while approximately 133,000 (0.3%) die because of cardiac complications. In particular in patients undergoing noncardiac vascular surgery the incidence of perioperative cardiac complications is high with cardiac mortality rates exceeding 2%. Indeed perioperative cardiac events are the major cause of adverse outcome in vascular surgery patients.

The pathophysiology of a PMI is complex. While cardiac oxygen demand / supply mismatch in patients with coronary artery disease might be counteracted by appropriate beta-blocker use or coronary revascularization in these patients, coronary plaque instability leading to plaque rupture and thrombosis remains a significant problem. Recent retrospective studies suggested a potential beneficial role of statins in the prevention of PMI, in particular by "stabilizing" coronary plaques due to their pleiotropic, anti-inflammatory effects. Therefore the aim of the randomized, double blind, Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) III trial was to assess the cardioprotective effect of fluvastatin XL on top of beta-blocker therapy in vascular surgery patients.

Between June 2004 and April 2008 497 statin-naive patients (median age 65.7 years, 75% men, 39% prior coronary artery disease, 29% prior stroke, 20% diabetic) scheduled for vascular surgery were included in the trial at Erasmus MC Rotterdam, the Netherlands. Patients were randomized to receive either placebo or fluvastatin extended at a dose of 80 mg once daily. Treatment was started at the outpatient clinic on the day of randomization, median 37 days prior to the surgical procedure and was continued at least during the first 30 days after surgery. Inflammatory markers at baseline, including hs-CRP and IL-6 were assessed in patients allocated to fluvastatin or placebo. At hospital admission levels of hs-CRP and IL-6 were significantly lower in patients on fluvastatin (respectively 6.00 mg/L vs 4.66 mg/L, p=0.030 and 8.45 pg/ml vs 5.75 pg/ml, p=0.024). The primary analysis was intention-to-treat and involved all patients who were randomly assigned to either fluvastatin or placebo. Directly after surgery, study treatment was temporarily discontinued in 115 (23%) patients for a median duration of 2 days because of the inability to take the study drug orally. A total of 34 patients discontinued study medication because of laboratory abnormalities; 16 (3.2%) because of ALAT exceeding 3x upper limit of normal, 13 (2.6%) because of CK exceeding 10x upper limit of normal, and 5 (1.0%) because of a combination of elevated ALAT and CK.

Myocardial ischemia was detected in 74 (14.9%) patients within 30 days of the initial vascular surgical procedure. A total of 27/250 (10.9%) patients allocated to fluvastatin reached the primary endpoint compared to 47/247 (18.9%) patients allocated to placebo treatment (OR 0.53; 95% CI 0.32-0.88). Hence, the number needed to treat (NNT) to prevent one patient experiencing myocardial ischemia was 12.5 patients.

A total of 18 (3.6%) patients died within 30 days after surgery of which 12 (2.4%) were attributable to cardiovascular causes. 25 (5.0%) patients experienced a nonfatal myocardial infarction during that same period. The combined endpoint of cardiovascular death and nonfatal myocardial infarction was reached in 37/497 (7.4%) patients. A total of 12/250 (4.8%) patients allocated to fluvastatin therapy reached the combined endpoint, compared to 25/247 (10.1%) allocated to placebo. Hence, fluvastatin therapy was associated with a 52% relative reduction in the incidence of cardiovascular death or MI (OR 0.48; 95% CI 0.24-0.95). The NNT for the composite endpoint of cardiovascular death or nonfatal MI is 18.9 patients.

The proportion of patients experiencing any adverse event was similar between the fluvastatin and placebo groups. The proportion of patients experiencing a CK rise > 10x the upper limit of normal was 4.1% in the fluvastatin group and 3.0% in the placebo group. The median peak CK level was 141 U/Lin patients on fluvastatin and 113 U/L in patients on placebo (p=0.24). The proportion of patients with significant increase in ALAT levels, ie > 3x times upper limit of normal, was 3.1% in the fluvastatin group and 5.2% in the placebo group. The median peak ALAT level was 23 U/L in patients on fluvastatin and 24U/L in patients on placebo.
The study authors conclude that fluvastatin XL therapy was associated with improved postoperative cardiac outcome in high-risk patients undergoing elective vascular surgery.

Conference News

大動脈弁狭窄は脂質低下では改善しない

SEASスタディ：シンバスタチン／エゼチミブの併用による強力な脂質低下療法は大動脈弁狭窄の進行を抑制しない

SEAS: Intensive lipid-lowering therapy with simvastatin/ezetimibe combination does not affect the progression of aortic valve stenosis

無症候性の軽度～中等度大動脈弁狭窄患者においてシンバスタチンとエゼチミブの併用療法による強力なLDLコレステロール低下療法は大動脈弁狭窄の進行を抑制しないが心血管虚血性イベントのリスクは軽減しうる。SEAS：Simvastatin and Ezetimibe in Aortic Stenosis（大動脈弁狭窄におけるシンバスタチンとエゼチミブ）スタディの結果が2008年European Society of Cardiology学会で発表され、New England Journal of Medicineに掲載された。軽度～中等度の大動脈弁狭窄を有し脂質低下療法の適応のない患者1,873人（平均年齢67歳）を、シンバスタチン（1日40mg）とエゼチミブ（1日10mg）の併用にて強力にコレステロールを低下させる群またはプラセボ群に無作為に割り付けた。複合一次エンドポイントである主要な心血管イベント（LDL低下療法333人対プラセボ355人；ハザード比［HR］0.96；95%信頼区間［CI］0.83～1.12）または二次エンドポイントである大動脈弁疾患イベント単独（308人対326人； HR 0.97；95% CI 0.83～1.14）は二群間で有意差がなかった。この併用療法により動脈硬化イベント単独は軽減した(15.7%対20.1%、p=0.02)。治療群では癌発症率が高かった(11.1%対7.5%、p=0.01)が、これは患者数が少なかったため偶然認められたと考えられる。

Full Text

Results from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study indicate that intensive LDL-cholesterol lowering with the combination of simvastatin and ezetimibe does not affect the progression of aortic valve stenosis, but can reduce the risk of cardiovascular ischemic events in subjects with mild-to-moderate asymptomatic aortic stenosis, when compared with placebo. The use of simvastatin and ezetimibe in such patients was generally well tolerated and safe. The results were presented at the European Society of Cardiology Congress 2008.

The SEAS study is the first large-scale randomized trial to assess the effects of lowering LDL-cholesterol in patients with aortic stenosis. The study was initiated and designed by academic researchers in Scandinavia, and carried out at 173 clinical centers in Norway, Denmark, Sweden, Finland, Germany, UK and Ireland. It included 1,873 patients with mild to moderate aortic stenosis without symptoms who were not considered to have a clear indication for treatment with cholesterol-lowering drugs. Patients were randomly assigned to receive either intensive cholesterol lowering with the combination of simvastatin (40 mg daily) and ezetimibe (10 mg daily) or matching placebo. The first patient was included in 2001. The study was completed according to the study plan when the last patient included had been followed for 4 years (March 2008). Vital status at the end of the study was established for all patients. All data have been checked for completeness and the data file for analysis was closed on 30 June 2008.

The primary endpoint of the SEAS study was "major cardiovascular events", which is the composite of events associated with aortic valve disease and with atherosclerotic disease. The secondary endpoints were the two separate components of the primary endpoint: "aortic valve disease events" (surgical valve replacement, hospitalization because of heart failure, and cardiovascular death) and "atherosclerotic disease events" (non-fatal myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, hospitalization because of unstable angina pectoris, non-hemorrhagic stroke and cardiovascular death). Subsidiary outcomes included echocardiographic evidence of aortic stenosis progression and safety.

Compared with placebo, the combination of simvastatin and ezetimibe reduced LDL-cholesterol by an average of 61%, corresponding to a reduction of about 2 mmol/L (76 mg/dl), and this effect was sustained throughout the study. 688 patients had one or more primary endpoint events. No significant difference was observed between the treatment groups for the combined primary endpoint (333 patients with an event on LDL-lowering treatment versus 355 on placebo; hazard ratio [HR] 0.96; 95% confidence interval [CI] 0.83 to 1.12). Nor was there a significant difference for the secondary endpoint of aortic valve disease events alone (308 versus 326; HR 0.97; 95% CI 0.83 to 1.14). The combination of simvastatin and ezetimibe did, however, produce a statistically significant 22% (95% CI 3% to 37%; p=0.02) proportional reduction in the secondary endpoint of atherosclerotic events alone: 148 (15.7%) in the simvastatin plus ezetimibe group versus 187 (20.1%) in the placebo group.

The study therapy was generally well tolerated, with no significant differences between the treatment groups in the proportions of patients who stopped taking study treatment (irrespective of whether it was active or placebo). In the subsidiary safety analyses, a total of 175 patients were recorded with a serious adverse event attributed to cancer. More of these events were observed among patients assigned the combination of simvastatin and ezetimibe than among those assigned placebo (105 [11.1%] versus 70 [7.5%]; unadjusted p=0.01), this included patients with recurrent cancer and cancer prior to randomization as well as cancer diagnosed more than 2 weeks after withdrawal from the study. There were also slightly more cancer deaths (39 [4.1%] versus 23 [2.5%]; unadjusted p=0.05). These apparent differences were not related to any particular type of cancer and did not become significantly larger with more prolonged treatment.

The observed differences in cancer in the SEAS study are based on small numbers and could have occurred as a result of chance. In order to assess their relevance, the SEAS data have been provided to an independent academic group for combined analysis with data on cancer from the two other large trials of simvastatin and ezetimibe, which are still in progress. The SHARP (Study of Heart and Renal Protection) study is a randomized placebo-controlled trial of simvastatin and ezetimibe in 9400 patients with chronic kidney disease. The IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) study is a randomized double-blind trial of simvastatin and ezetimibe compared to simvastatin alone which has recruited 12,000 of a planned 18,000 patients with acute coronary disease.

In combination, the SHARP and IMPROVE-IT studies involve about 4 times as many cancers as in the SEAS study. The analysis of SHARP and IMPROVE-IT does not support the suggestion of an increase in cancer that was raised by the subsidiary analyses of the relatively small numbers of cancers in the SEAS study. Independent analysis of these data was initiated and has been conducted and interpreted by the Clinical Trial Service Unit (CTSU) at the University of Oxford, UK. The CTSU also designed and is conducting the SHARP trial, which is funded by a research grant to the University of Oxford from MSD and Schering-Plough academic. Both the SHARP study and the analyses of cancer data have been conducted by the CTSU independently of the pharmaceutical companies.

The scientific leadership of the SEAS study was a Steering Committee consisting of 14 academic representatives of centers in each of the participating countries and two members (a statistician and a coordinator) representing the funders. The SEAS study is funded by the pharmaceutical companies Merck Sharp & Dohme (MSD) and Schering-Plough who market the drugs being tested. All clinical endpoint events were adjudicated by an independent committee that was blinded to the study treatment allocation. The study was monitored by an independent Data Safety and Monitoring Board. Data collection was performed by MSD, and the data were analyzed by statisticians at Ulleval University Hospital in Oslo, Norway, and at MSD.

FX06は心再灌流傷害を軽減する可能性がある

FIREトライアル：フィブリン由来のペプチドは炎症を阻害することにより心筋損傷を軽減しSTEMI後の血管機能を保護する可能性がある

FIRE: A fibrin-derived peptide may reduce damage to the heart muscle by inhibiting inflammation and protecting vascular function following STEMI

フィブリン由来のペプチドFX06は再潅流に成功した急性ST上昇心筋梗塞（STEMI）の心筋壊死を軽減する可能性があるとのFIRE：FX06 In ischemia and Reperfusion（虚血および再潅流に対するFX06）トライアルの結果が、2008年European Society of Cardiology学会で発表された。FX06を再潅流療法中に患者に静脈内投与し、心筋保護効果が心臓核磁気共鳴画像で評価された。FX06は総梗塞サイズを21%減少させたが、FX06とプラセボの差は統計学的に有意ではなかった（21.68g対27.34g、p=0.21）。しかし、FX06はプラセボと比較しnecrotic core zoneを58%減少させた（1.77g対4.2g、p=0.019）。4ヵ月後にはFX06とプラセボとで総梗塞サイズ（15.37g対19.32g、p=0.36）およびscar mass（1.79g対2.84、p=0.16）の有意差はもはや認められなかった。主要な心有害事象もまたFX06群において少なかった。研究者らは、今回の成績はより大規模なトライアルで確認する必要があり、心臓死および心不全の新規発症に関する今後のトライアルの必要性を示唆した。

Full Text

Data presented at the European Society of Cardiology Congress demonstrates the effectiveness of a peptide called FX06 in preventing reperfusion injury following a myocardial infarction. While reperfusion is well established as a standard of care, it paradoxically causes additional damage to heart muscle in patients surviving from these attacks - a phenomenon termed "reperfusion injury". FX06 is a novel compound intended to prevent that damage.

Professor Dan Atar, the Coordinating Investigator of the FIRE (FX06 In ischemia and REperfusion) trial, a Phase II clinical study of FX06, presented the results of the trial on September 2nd in the Hot Line III Session at the European Society of Cardiology Congress in Munich, Germany.

"Re-establishment of blood flow, either by catheter-based balloon-intervention (PCI) or by thrombolysis, is necessary and life-saving in the treatment of acute myocardial infarctions. However, such interventions can lead to further damage to the heart muscle due to blood vessel dysfunction and inflammation," said Dan Atar, Professor of Cardiology at the Aker University Hospital, University of Oslo, Norway. "Based on the FIRE results, FX06 has been shown to reduce damage to the heart muscle by inhibiting inflammation and protecting vascular function. We predict that FX06 may become a novel treatment for STEMI patients undergoing PCI, representing a major advance in acute cardiac care."

The Phase II clinical trial was completed in March 2008, with data indicating a statistically significant reduction in myocardial necrosis following intravenous application of FX06 concurrent with reperfusion. FX06 is a peptide that binds to VE-cadherin, a target on the surfaces of endothelial cells, which form the inner cell layer of blood vessels, thereby preserving blood vessel function. This leads to reduced inflammation, reduced edema and reduced infarct sizes.
The FIRE trial was conducted between October 2006 and March 2008 as a randomized, double-blind, placebo-controlled study involving 234 patients from 26 leading centers of interventional cardiology in Europe. The study evaluated infarct size in patients undergoing percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction (STEMI). FX06 was administered intravenously to patients during reperfusion treatment, and the effect on heart muscle preservation was then assessed using cardiac magnetic resonance imaging. The primary endpoint was reduction in infarct size at five days after myocardial infarction.

While FX06 reduced the total infarct size by 21%, this difference between the FX06 and placebo groups was not statistically significant (21.68 g vs. 27.34 g; p=0.21). However, FX06 significantly reduced the necrotic core zone by 58% compared with placebo (1.77 g vs. 4.2 g; p=0.019). At 4 months, there were no longer significant differences between FX06 and placebo in total infarct size (15.37 g vs. 19.32 g; p=0.36) or scar mass (1.79 g vs. 2.84; p=0.16). Major adverse cardiac events in the FX06 group were also lower compared to the placebo group, which may indicate an effect of the drug on adverse patient outcome after an infarction.

高齢者に対する集中治療は有益でない

TIME-CHF：心不全の高齢患者に対する集中治療は有益でない

TIME-CHF: Elderly patients with heart failure do not benefit from intensive medical therapy

TIME-CHF：Trial of Intensified (BNP-guided) versus standard（symptom-guided）Medical therapy in Elderly patients with Congestive Heart Failure（うっ血性心不全の高齢患者に対する集中治療［BNPを指標にする］対標準［症状を指標にする］）スタディにおいて、心不全の管理に症状のみでなくナトリウム利尿ペプチドレベルを使用しても死亡およびあらゆる原因による入院を減少させることができなかった、と2008年European Society of Cardiology学会で発表された。しかし、結果は年代により有意に異なった。収縮能低下による心不全（駆出率≤45%）の患者499人をN末端脳型ナトリウム利尿ペプチド（NT-BNP）を指標にする群または症状を指標にする群に無作為に割り付け、75歳以上対60～74歳の群に層別化した。標準的な治療と比較しNT-BNPを指標とした集中治療は、一次エンドポイントである無入院生存期間を改善しなかった（ハザード比［HR］0.92、p=0.46）が、より疾患特異的なエンドポイントである心不全による入院のない生存期間は改善した（HR=0.66、p=0.008）。若年群においてNT-BNPを指標とした集中治療により全死亡率は低下し（HR=0.38、p=0.01）心不全による入院のない生存期間は改善した（HR=0.41、p=0.002）が、75歳以上の群においてはこれらの変化は認められなかった。これらの結果から、若年患者の結果に基づいた一般的な勧告は後期高齢患者には必ずしも直接当てはめることはできない可能性のあることが示唆された。

Full Text

Intensified, BNP-guided therapy was no more effective than a standard, symptom-guided approach in elderly heart failure patients in reducing the number of deaths and all-cause hospitalizations. However, the response to this intervention differed significantly between patients aged 60-74 years and those aged ≥75 years. This indicates the need for specific data in this large subset of very old heart failure patients who have been largely excluded from large treatment trials.

The study was carried out in 15 hospitals in Switzerland and Germany and included 499 heart failure patients with reduced pump function of the heart aged ?60 years. The study was called TIME-CHF, standing for the Trial of Intensified (BNP-guided) versus standard (symptom-guided) Medical therapy in Elderly patients with Congestive Heart Failure. Patients in both groups were well treated according to current guidelines, but doses of medication were significantly increased in the BNP-guided group. Increase in medication took place within the first 6 months after study inclusion and patients were followed up for another 12 months. This study has several aspects that may be relevant for the treatment of heart failure patients, particularly since it included a population that is representative for patients as seen in daily practice. Patients were on average 77 years old (82 years in the group aged ≥ 75 years) and had many diseases other than heart failure, i.e. app. 80% had 2 or more additional diseases. Previous studies had largely excluded such patients.

Symptoms and quality of life of patients in both intervention groups improved with treatment, irrespective of age. Death rate in all patients was lower than expected. This indicates that all patients with heart failure seem to profit from current standard therapy. With more intensified therapy, younger patients showed lower death rate and less hospitalizations due to cardiac reasons, including heart failure, than with standard therapy. However, this was not the case in older patients, where patients with intensified therapy had similar death and hospitalization rate, but worse quality of life than with standard treatment. Therefore, general treatment recommendations, which are based on results in younger patients, may not necessarily be directly applicable to very old patients. This particularly applies to patients with relevant diseases other than heart failure. Studies testing interventions in these very old patients, such as TIME-CHF, are needed to define the best therapies. In addition, it may not be beneficial to push doses to the limits in the very elderly and in those with other relevant health problems.

The intervention reduced the disease specific endpoint of death and heart failure hospitalizations, but not all-cause hospitalizations. This study indicates that the net benefit of treatment might be smaller than expected from the large treatment trials, particularly in patients who are likely to be hospitalized or die due to reasons other than heart failure. This might explain why death and hospitalization rates in the general heart failure community over the last two decades decreased at a lesser rate than was expected based on results from studies. In addition, TIME-CHF shows how important it is to study patients as seen in daily practice since the conclusion may not be exactly the same.

The findings need to be confirmed before it can be generally recommended to use different therapies in heart failure patients depending on their age. Nevertheless, it may help to better define individual needs for heart failure patients and to boost the urgently needed studies in this large heart failure population of very old patients.

ペリンドプリルとカルシウム拮抗薬併用により予後が改善する

EUROPAトライアル：すでにカルシウム拮抗薬を投与されている安定した冠動脈疾患患者にペリンドプリルを追加することは有益である可能性がある

EUROPA: Patients with stable coronary artery disease already receiving a calcium channel blocker may benefit from adding perindopril

EUROPAトライアルの新たな解析により、安定した冠動脈疾患患者におけるカルシウム拮抗薬（CCB）とペリンドプリルの”相乗効果”が示された。EUROPA：EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease（安定冠動脈疾患患者におけるペリンドプリルの心イベント減少効果に関するヨーロッパのトライアル）においては17%の患者がスタディ期間中を通してCCBを投与された。1,022人はペリンドプリル群に1,110人はプラセボ群に割り付けられた。つまり、3,095人はプラセボを投与されCCBは投与されず、3,326人はペリンドプリルを投与されCCBは投与されなかった。トライアルの一次エンドポイントを再度見直してみると、心血管死、心筋梗塞、または蘇生された心停止はペリンドプリルとCCBを併用された患者において少なかった。（併用群4.89%対ペリンドプリル単独投与群6.58%；プラセボとCCB併用群7.45%；プラセボ単独投与群7.98%；全ての比較においてp<0.05）。ペリンドプリルとCCBの併用によりまた、全死亡率が46%（p<0.01）、心血管死亡率が41%（p=0.09）、致死性および非致死性心筋梗塞が28%（p=0.01）、心不全による入院が54%（p=0.25%）減少した。

Full Text

The EUROPA trial (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease, Lancet 2003;362(9386):782-8) showed that perindopril significantly reduced the primary composite end point of cardiovascular (CV) death, myocardial infarction (MI), and cardiac arrest, in patients with stable coronary artery disease (CAD) in comparison with placebo and on top of other therapies. In the ASCOT-BPLA trial in hypertensive patients at risk of CV events, amlodipine ± perindopril therapy reduced risk of death and CV events in comparison with beta-blocker ± thiazide.

The goal of this study was to study the effect of the ACE inhibitor perindopril compared with placebo in patients with stable CAD receiving calcium channel blockers (CCB) on the risk reduction in major cardiac events and death and to assess the synergistic effects between perindopril and CCB. Among 12,218 EUROPA patients, 2,122 patients received CCB throughout the study: 1,022 patients in the perindopril group (Per/CCB+) and 1100 patients in the placebo group (Pl/CCB+).

Baseline characteristics were similar in all groups. Looking at the trial's primary endpoint, the percentage of patients experiencing cardiovascular death, MI, or resuscitated cardiac arrest was lowest in those who were given perindopril plus CCBs (4.89% vs. 6.58% for perindopril with no CCBs; 7.45% for placebo plus CCBs; 7.98% for placebo with no CCBs; p<0.05 for all comparisons). Perindopril plus CCBs also reduced the risk for all-cause mortality by 46% (p<0.01), cardiovascular mortality by 41% (p=0.09), fatal and nonfatal MI by 28% (p=0.10), and hospitalization for HF by 54% (p=0.25).

Synergy was considered when Hazard ratio (HR) of perindopril+CCB was inferior to HR (Perindopril alone) x HR (CCB alone). The calculation showed that the effect between perindopril and CCB was synergistic for all end points studied.

In patients with stable CAD already receiving a CCB, addition of perindopril provides significant reduction in all-cause mortality and major cardiac events. The synergistic action between perindopril and CCB, which underlies the clinical benefit, deserves further investigation.

Prasugrelは糖尿病患者に臨床上有益である

TRITON-TIMI 38トライアル：急性冠症候群を有する糖尿病患者はprasugrelを投与されることにより心筋梗塞発症が抑制される

TRITON-TIMI 38: Diabetics with acute coronary syndromes are less likely to suffer a myocardial infarction if treated with prasugrel

TRITON-TIMI 38トライアルのサブグループ解析の結果、急性冠症候群と診断された糖尿病患者は、prasugrelを投与されることにより心筋梗塞を発症する確率がクロピドグレルを投与されたのに対し40%低下した（8.2%対13.2%、p<0.001）ことが示された。さらに、一次エンドポイントである心血管死、非致死性心筋梗塞および非致死性脳卒中はprasugrelで治療された患者においてクロピドグレルで治療された患者よりも30%少なかった（12.2対17.0%、p<0.001）。この心血管イベントの減少は、糖尿病治療の種類にかかわらず全ての糖尿病患者において同様に認められた（インスリン治療対非インスリン治療、p=0.001）。Prasugrelで治療された糖尿病患者においてはクロピドグレルで治療された患者と比較し、ステント血栓症発現率が有意に低く、相対リスクは48%減少した（3.6%対2.0%、p=0.007）。この結果はミュンヘンで開催された2008年European Society of Cardiology学会のHot Lineセッションで発表され、同時にCirculation誌に掲載された。

Full Text

Patients who were diabetic and diagnosed with acute coronary syndromes were 40 percent less likely to suffer a myocardial infarction if they were treated with prasugrel vs. clopidogrel, according to a sub-group analysis of the TRITON-TIMI 38 trial (8.2 percent vs. 13.2 percent, p<0.001). In addition, according to this same analysis, the combined rate of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke was reduced by 30 percent in diabetes patients treated with prasugrel compared to those treated with clopidogrel (12.2 percent vs. 17.0 percent, p<0.001). In patients without diabetes, there was also improvement in outcomes with prasugrel, with the primary endpoint occurring in 9.2 percent of patients treated with prasugrel and 10.6 percent of patients treated with clopidogrel (p=0.02).

The diabetic sub-group analysis was presented by Stephen Wiviott, M.D., Assistant Professor of Medicine at Harvard Medical School and investigator with the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham & Women's Hospital, Boston, USA, at the Congress of the European Society of Cardiology (ESC) in Munich, Germany. In addition, the manuscript was simultaneously published online in Circulation, the medical journal of the American Heart Association.

"The results observed from this sub-group analysis showed that antiplatelet therapy with prasugrel resulted in significantly greater reduction of cardiovascular events among patients with diabetes when compared to those who were treated with clopidogrel," said Wiviott.

The reduction of cardiovascular events was consistent across the sub-group of diabetes patients regardless of diabetic therapies (insulin versus no insulin). The study showed a significant relative risk reduction in the primary endpoint of cardiovascular death, non-fatal heart attack and non-fatal stroke with prasugrel, 37 percent for insulin treated and 26 percent (p=0.001) for non-insulin treated diabetics. There was also a significantly lower rate of stent thrombosis among diabetes patients treated with prasugrel, resulting in a 48 percent relative risk reduction in stent thrombosis compared with clopidogrel (3.6 percent vs. 2.0 percent, p=0.007).

"These findings are interesting in view of previous studies that showed higher levels of platelet aggregation in insulin-treated diabetes patients after dual antiplatelet therapy compared to diabetes patients not treated with insulin," said Dr. Wiviott.

The main TRITON-TIMI 38 clinical trial, previously published in the New England Journal of Medicine in November 2007 (Vol. 357, No. 20), compared prasugrel with clopidogrel in patients with ACS undergoing percutaneous coronary intervention (PCI). In the primary analysis of the trial, prasugrel reduced the risk of the composite endpoint of cardiovascular death, heart attack or stroke by 19 percent, with an increased risk of major bleeding compared with clopidogrel (2.4 percent vs. 1.8 percent).

In this sub analysis, the rates of major bleeding events were similar for prasugrel (2.5 percent) and clopidogrel (2.6 percent) among patients with diabetes, regardless of diabetes therapies (insulin versus no insulin).

Dronedaroneは心房細動の患者を脳卒中から保護する

ATHENAスタディ：ATHENAスタディのpost-hoc解析において、dronedaroneは心房細動患者の脳卒中リスクを軽減することが示された

ATHENA: Dronedarone reduced the risk of stroke in patients with atrial fibrillation in post-hoc analysis of ATHENA study

ATHENA：A Trial with dronedarone to prevent Hospitalization or dEath in patieNts with Atrial fibrillation/flutter（dronedaroneを用いて心房細動／粗動患者の入院または死亡を予防するスタディ）の新たな解析の結果、dronedaroneは抗血栓薬を含む標準治療で適切に治療されている心房細動または粗動患者において脳卒中のリスクを低下させることが示された、と2008年European Society of Cardiology学会で発表された。過去のスタディではdronedaroneを標準治療に追加することにより、プラセボを追加するのと比較し、複合一次エンドポイントである心血管疾患による入院またはあらゆる原因による死亡が統計学的に有意に24%減少した(p=0.00000002)ことが示された。今回のスタディでは、75歳以上の患者（心血管リスクファクターの有無にかかわらず）、または心房細動／粗動に加え心血管リスクファクター（高血圧、糖尿病、脳血管イベントの既往、左房サイズ>50mmまたは左室駆出率<40%）をひとつ以上有する70歳超の患者4,628人をdronedarone 400mgを1日2回またはプラセボ内服群に無作為に割り付けた。このnon-prespecified二次エンドポイントに関する脳卒中post-hoc解析の結果、dronedaroneは脳卒中（虚血性または出血）のリスクをプラセボと比較し34%低下させた（脳卒中イベントそれぞれ46件 対 70件、p=0.027）。この効果はスタディの早期に認められ、経過観察期間中維持された（12～30ヵ月）。

Full Text

The results of a post-hoc analysis of the data from the ATHENA study were presented at the clinical trial update session of the European Society of Cardiology Congress 2008, in Munich, Germany. Previous results from the landmark ATHENA study have shown that the investigational medicine dronedarone on top of standard therapy decreased the combined primary endpoint of the risk of cardiovascular hospitalizations or death from any cause by a statistically significant 24% (p=0.00000002) as compared to placebo.

The ATHENA stroke post-hoc analysis on non-pre-specified secondary endpoints showed that dronedarone decreased the risk of stroke (ischemic or hemorrhagic) compared to placebo by 34% (46 vs. 70 stroke events respectively; p=0.027) in atrial fibrillation / atrial flutter patients adequately treated by standard therapy including antithrombotics. The significant reduction in stroke risk with dronedarone was incremental to background anti-thrombotic therapy like oral anticoagulants and / or anti-platelet agents. Similar to the ATHENA primary endpoint of CV hospitalizations or death, this effect appeared early and was maintained during the study follow-up (12 to 30 months).

"ATHENA is a landmark trial that will lead to a paradigm shift in the management of atrial fibrillation as it is the first time that an anti-arrhythmic drug has shown a significant impact on cardiovascular outcomes. As stroke is one of the leading complications of atrial fibrillation, and a major cause of death and long-term disability, these new results demonstrate the unique profile of dronedarone beyond its pure rhythm and rate-controlling effects," said Professor Stuart Connolly, Mc Master University, Department of Cardiology, Hamilton Canada, co-principal investigator of the ATHENA study.

The most frequently reported adverse events of dronedarone vs. placebo in the ATHENA trial as seen in the pre-specified safety analysis, were gastrointestinal effects (26% vs. 22%), skin disorders (10% vs. 8%, mainly rash) and a mild increase in blood creatinine (4.7% vs. 1%) due to inhibition of tubular secretion of creatinine in the kidneys. The mechanism of blood creatinine increase was well defined in a separate study of healthy volunteers. In the ATHENA trial, compared to placebo, dronedarone showed a low risk of pro-arrhythmia and no excess of hospitalizations for congestive heart failure. There was a similar rate of study drug discontinuation between the 2 study groups.

The landmark ATHENA study is the only double-blind, anti-arrhythmic, morbidity-mortality study in patients with atrial fibrillation. It was conducted in more than 550 sites in 37 countries and enrolled a total of 4,628 patients.

The patients studied in ATHENA were either 75 years of age or older (with or without cardiovascular risk factor) or above 70 years of age with at least one additional cardiovascular risk factor (hypertension, diabetes, previous cerebrovascular event, left atrium size greater than 50 mm or left ventricular ejection fraction lower than 40%). Patients were randomized to receive dronedarone 400 mg BID or placebo, with a maximum follow-up of 30 months.

The ATHENA study objectives were to show a potential benefit of dronedarone on the primary composite endpoint of all-cause mortality combined with cardiovascular hospitalization as compared to placebo. The pre-specified secondary endpoints were death from any cause, cardiovascular death and hospitalization for cardiovascular reasons. The pre-specified safety endpoint was the incidence of treatment emergent adverse events (between first study drug intake and last study drug intake plus 10 days) including: all adverse events, serious adverse events, adverse events leading to study drug discontinuation.

The ATHENA stroke post-hoc analysis on a non-pre-specified secondary endpoint was conducted in order to confirm the consistent benefit of dronedarone in atrial fibrillation or atrial flutter patients in reducing major cardiovascular complications like stroke, which is a leading cause of cardiovascular hospitalizations or death in this patient population.

若年アスリートに心臓超音波検査のスクリーニングは不要

若年アスリートの心疾患検索に心臓超音波検査を含むプレ参加プログラムは有能な手段ではあるが12誘導心電図で十分な可能性がある

Pre-participation program, including echocardiography, is an efficient way to identify young athletes with cardiac disease but 12-lead ECG may be sufficient

イタリアで施行されたスタディの結果、若年アスリートの心疾患検索に心臓超音波検査を含むプレ参加プログラムは有能な手段ではあるが12誘導心電図で十分であると2008年European Society of Cardiology学会で発表された。突然死の原因となる心疾患を有する者をタイムリーに発見する最も有用な方法を探すために研究者らは、プレ参加の12誘導心電図の結果心疾患がなく競技に参加できるとされたアスリート4,450人に心臓超音波検査で器質的な心疾患の評価を行った。4,450人中、肥大型心筋症（HCM）と診断された者はいなかった。心筋炎（4人）、僧帽弁逸脱（3人）、マルファン症候群（2人）、大動脈弁逆流（2人）、および不整脈原性右室心筋症（1人）などの他の異常が発見されたのはわずか12人であった。さらに、4人のアスリートはHCMとアスリートハートの”グレイゾーン”に当たるボーダーラインの左室壁厚（13mm）が認められた。このうち2人は、引き続き行われれた遺伝子解析または平均8年間の臨床上の変化の結果HCMと診断された。

Full Text

Studies conducted in Italy suggest that a pre-participation program, including echocardiography, is an efficient way to identify young athletes with cardiac disease.

Sudden and unexpected deaths in young competitive athletes are uncommon but highly visible events, which raise concern and ethical issues in both the lay public and medical community. Which is the best strategy to timely identify individuals with cardiac disease responsible for sudden death (primarily, hypertrophic cardiomyopathy - HCM) is largely debated. Namely, the extent to which sophisticated testing, such as echocardiography, is needed is still undefined.

To address this question, researchers carried out an echocardiographic assessment of the structural cardiac diseases in a population of 4,450 athletes, initially judged free of cardiac disease and eligible for competition on the basis of pre-participation screening with 12-lead ECG.

None of the 4,450 athletes showed evidence of HCM. Other cardiac abnormalities were detected in only 12 athletes, including myocarditis (n=4), mitral valve prolapse (n=3), Marfan's syndrome (n=2), aortic regurgitation with bicuspid valve (n=2), and arrhythmogenic right ventricular cardiomyopathy (n=1). In addition, 4 athletes were identified with borderline left ventricular wall thickness (i.e., 13 mm) in the "gray-zone" between HCM and athlete's heart. In 2 of these athletes, subsequent genetic analysis or clinical changes over an average 8-year follow-up resulted, respectively, in a diagnosis of HCM.

The pre-participation screening program including 12-lead ECG appears to be efficient in identifying young athletes with HCM, leading to their timely disqualification from competitive sports. These data also suggest that routine echocardiography is not an obligatory component of large population screening programs designed to identify young athletes with HCM.

新たな治療により動脈硬化性プラークが予防される

Darapladibを用いたLp-PLA2阻害により、プラークの脆弱性のキーとなる壊死性コアの拡大が予防される

Lp-PLA2 inhibition with darapladib prevented necrotic core expansion, a key determinant of plaque vulnerability

Darapladibを用いたリポ蛋白関連ホスホリパーゼA2（Lp-PLA2）阻害により、プラークの脆弱性のキーとなる壊死性コアの拡大が予防される、と2008年European Society of Cardiology学会のfeatured presentationで発表された。Lp-PLA2は冠動脈病変の壊死性コア内で豊富に発現し、その酵素活性生成物は炎症および細胞死にかかわりプラークを破裂しやすくしている可能性がある。このスタディにおいては、血管造影により冠動脈疾患が認められた患者330人にdarapladib（経口、1日160mg）またはプラセボを12ヵ月間投与し、冠動脈アテロームの変形能および血漿hs-CRPに対する効果を比較した。その他の治療は両群間で同等であり、12ヵ月後のLDLコレステロールには差がなかった。一方、Lp-PLA2活性はdarapladibにより59%阻害された（p<0.001対placebo）。12ヵ月後、プラーク変形能または血漿hsCRPは両群間で差がなかった（それぞれp=0.22およびp=0.35）。しかし、プラセボ投与群においては壊死性コア量が有意に増加した（4.5±17.9 mm^3，p=0.009）のに対し、darapladibはこの増加を抑制し（-0.5±13.9 mm^3，p=0.71）、結果として-5.2 mm^3の有意差が認められた（p=0.012）。これらの結果から、Lp-PLA2阻害は新たな治療アプローチとなる可能性のあることが示唆された。

Full Text

A twelve month study of treatment with darapladib concluded that, Lp-PLA2 inhibition with darapladib prevented necrotic core expansion, a key determinant of plaque vulnerability. These findings suggest that Lp-PLA2 inhibition may represent a novel therapeutic approach. In contrast, despite adherence to a high level of standard of care treatment, necrotic core continued to expand among patients receiving a placebo.

Lipoprotein-associated phospholipase A2 (Lp-PLA2) is expressed abundantly in the necrotic core of coronary lesions and products of its enzymatic activity may contribute to inflammation and cell death, rendering plaque vulnerable to rupture.

This study compared the effects of 12 months of treatment with darapladib (oral Lp-PLA2 inhibitor, 160 mg daily) or placebo on coronary atheroma deformability (IVUS-palpography) and plasma hs-CRP in 330 patients with angiographically documented coronary disease. Secondary end points included changes in necrotic core size (IVUS-radiofrequency), atheroma size (IVUS-greyscale), and blood biomarkers.

Background therapy was comparable between groups, with no difference in LDL-cholesterol at 12 months (placebo: 88±34 and darapladib: 84±31 mg/dL, p=0.37). In contrast, Lp-PLA2 activity was inhibited by 59% with darapladib (p<0.001 versus placebo). After 12 months, there were no significant differences between groups in plaque deformability (p=0.22) or plasma hsCRP (p=0.35). In the placebo-treated group, however, necrotic core volume increased significantly (4.5±17.9 mm^3, p=0.009), whereas darapladib halted this increase (-0.5±13.9 mm^3, p=0.71), resulting in a significant treatment difference of -5.2 mm^3 (p=0.012). These intra-plaque compositional changes occurred without a significant treatment difference in total atheroma volume (p=0.95).