クロピドグレルを凌ぐticagrelorの有益性

PLATO：新たな経口抗血小板薬はクロピドグレルと比較し、急性冠症候群患者の心血管イベントを軽減する

PLATO: New oral antiplatelet agent reduces cardiovascular events when compared to clopidogrel in patients with acute coronary syndromes

急性冠症候群患者を抗血小板治験薬であるticagrelorで治療することにより、クロピドグレルと比較し、心血管（CV）イベント（CV死、心筋梗塞、または脳卒中）を有意に軽減したことがphase3 PLATO（Platelet Inhibition and Patient Outcomes：血小板抑制と患者の予後）スタディにおいて示された、とESC 2009ホットラインセッションで報告され、New England Journal of Medicineに掲載された。PLATOはticagrelorとアスピリンの併用とクロピドグレルとアスピリンの併用をhead-to-headで比較したアウトカムスタディである。全ての大陸から選出した43ヵ国893施設の患者18,624人を組み入れた。全ての患者は急性冠症候群により入院しており、3分の1はST上昇心筋梗塞であり3分の2にはST上昇がなかった。入院直後に患者らは、無作為化二重盲検試験の形で、ticagrelor（90mgを1日2回）またはクロピドグレル（1日75mg）を6～12ヵ月内服する長期抗血小板療法を開始された。その結果、ticagrelorによりクロピドグレルと比較し、CVイベントは11.7%から9.8%に減少した（p<0.001、RRR=16%）が、重大な出血は増加しなかった。このエンドポイントに関する有効性はCV死および心筋梗塞の減少によるものであり、脳卒中に関しては差がなかった。

Full Text

The presentation of the PLATO (A Study of Platelet Inhibition and Patient Outcomes) trial, showed that ticagrelor reduced the rate of cardiovascular (CV) events (CV death, myocardial infarction or stroke) from 11.7% to 9.8% compared clopidogrel (p<0.001, RRR = 16%), without an increase in major bleeding. This efficacy endpoint was driven by a statistically significant reduction in both CV death and myocardial infarction (MI) with no difference in stroke. Ticagrelor is the first antiplatelet agent to demonstrate a reduction in CV death across all major acute coronary syndromes (ACS) patient types.

For every 1,000 patients admitted to the hospital because of an ACS event, use of ticagrelor instead of clopidogrel, for up to one year, led to 14 fewer deaths, or 11 fewer MI's, or 8 fewer cases of stent thrombosis, without an increase in major bleeds. In the PLATO study, the reduction in risk of cardiovascular events appears early and the benefit over clopidogrel grows with time. Ticagrelor demonstrated a consistent benefit
across multiple secondary efficacy endpoints including CV death and total mortality; myocardial infarction; the composite of myocardial infarction, stroke, and total mortality; and a composite of cardiovascular death, myocardial infarction, stroke, transient ischemic attack, recurrent cardiac ischemia, severe recurrent cardiac ischemia, and other arterial thrombotic events.

"Ticagrelor is the first antiplatelet therapy to achieve a significant reduction in CV mortality in ACS patients versus clopidogrel and perhaps most importantly without an increase in major bleeding," commented Professor Lars Wallentin, co-chair of the PLATO Executive Committee. "PLATO has redefined what is possible in the prevention of recurrent events in patients with acute coronary syndromes."

The PLATO study confirmed the clinical safety profile of previous ticagrelor studies by showing an efficacy advantage without an increase in major bleeding. Across all the important patient subgroups (e.g. gender, weight, history of stroke/TIA) in PLATO, ticagrelor showed no difference versus clopidogrel in the incidence of major bleeding. When minor bleeding was added, ticagelor showed a small increase in PLATO defined major plus minor bleeding versus clopidogrel. At continuous ECG monitoring wile in hospital, but not at later follow-up in the outpatient setting, pauses in the heart rhythm were seen more frequent with ticagrelor. However such pauses were not associated with any symptoms or clinical consequences for the patient. Transient symptoms of dyspnoea were reported more often by patients on ticarelor but only one in 100 ticagrelor treated patients overall stopped taking study medication due to dyspnoea.

PLATO was a head-to-head outcomes study of ticagrelor plus aspirin versus the active comparator, clopidogrel plus aspirin, and was designed to establish whether ticagrelor could achieve meaningful cardiovascular endpoints in ACS patients. 18,624 patients at 893 sites in 43 countries across all continents were successfully recruited. All patients were admitted to hospital because of acute coronary syndrome, one third with ST-elevation myocardial infarction and two thirds without ST-elevation. Shortly after admission to hospital, the patients started their long-term anti-platelet treatment with either ticagrelor (90 mg twice daily) or clopidogrel (75 mg daily) in a randomized, double blind fashion for 6 - 12 months. The PLATO study was led by the Executive Committee co-chairs, Professor Lars Wallentin, Sweden (Uppsala Clinical Research Center) and Professor Robert Harrington, USA (Duke Clinical Research Institute).

The PLATO study was sponsored by AstraZeneca, which has developed and manufactures ticagrelor. Ticagrelor is the first reversibly binding oral adenosine diphosphate (ADP) receptor antagonist. It selectively inhibits P2Y12, a key target receptor for ADP. ADP receptor blockade inhibits the action of platelets in the blood, reducing recurrent thrombotic events. Ticagrelor is the first in a new chemical class, the CPTPs (cyclopentyl-triazolo-pyrimidines) and is chemically distinct from the thienopyridines, such as clopidogrel and prasugrel.

The study design of PLATO was published in the April 2009 edition of the American Heart Journal (James, S. et al. in Am. Heart J. 2009; 157: 599-605).

Conference News

心房細動においてdabigatranはワルファリンよりもより有効である

RE-LY：心房細動患者の脳卒中予防において経口抗凝固薬dabigatranはワルファリンよりも有効である

RE-LY: Oral antithrombin dabigatran more effective than warfarin in preventing stroke in patients with atrial fibrillation

抗凝固薬dabigatranはワルファリンと比較し、心房細動（AF）患者の脳卒中および末梢塞栓イベント予防効果が高かったとのRE-LY（Randomized Evaluation of Long-term anticoagulant therapY：長期抗凝固療法無作為評価）スタディの結果が、バルセロナで開催されたESC 2009ホットラインセッションで発表された。RE-LYスタディでは、脳卒中リスクの高い心房細動患者18,113人において、2つの用量のdabigatran（150mgおよび110mgを1日2回）と現在の標準療法であるワルファリンを比較した。このスタディには44ヵ国951以上の施設が参加した。患者は2年以上にわたり組み入れられ、さらに1年間追跡された。高用量のdabigatranにより、ワルファリンと比較し、年間の一次エンドポイント（脳卒中および末梢塞栓イベント）が34%減少し（p<0.001）、出血性脳卒中イベントが74%（p<0.001）減少した。低用量のdabigatranの脳卒中予防効果はワルファリンと同様であったが、重大な出血は有意に少なかった。高用量のdabigatranにより二次エンドポイントであるMIのリスクは増加した（p=0.048）。

Full Text

The anticoagulant dabigatran is more effective than warfarin in the prevention of stroke in patients with atrial fibrillation, according to results from the RE-LY study (Randomized Evaluation of Long-term anticoagulant therapY).

"Although researchers have been looking for a replacement for warfarin for several decades, nothing has been successful as an oral blood thinner," says Professor Stuart Connolly, Director of the Division of Cardiology at McMaster University, Canada, and one of the leading investigators of the study.

The RE-LY study compared two doses of dabigatran with the current standard therapy, warfarin, in 18,113 patients with atrial fibrillation at increased risk of stroke. The study included more than 951 centers in 44 countries. Patients were enrolled over a two-year period and then followed for one further year. The study was designed to evaluate whether either of two doses of dabigatran were non-inferior to warfarin (i.e., at least as good as warfarin). The results show, however that the higher dose of dabigatran 150 mg twice daily, significantly reduces the risk of stroke by 34% compared to warfarin. The lower dose, 110 mg twice daily, had a similar effect to warfarin in the prevention of stroke, but with significantly less major bleeding.

According to Professor Connolly, although warfarin has been the gold standard for reducing stroke in atrial fibrillation for more than 20 years, it has many problems; these include a need for monitoring by blood test measurement, and a significant risk of increased bleeding, which makes it unsuitable for many patients. "Several new drugs have been recently studied to see if they could replace warfarin," says Professor Connolly. "None, however, has been satisfactory. Either they were not effective enough, they had too many side effects or they caused too much bleeding. This is the first time in more than 50 years that a new oral blood thinner has been developed which has been found to be both safer and more effective than existing therapy."

The RE-LY study was coordinated by the Population Health Research Institute of McMaster University and sponsored by Boehringer-Ingelheim.

Conference News

低用量アスピリンは推奨されない

AAA：無症候性血管イベントを有する患者に対するルーチンのアスピリン投与にエビデンスはない

AAA: No evidence for the routine use of aspirin in people with asymptomatic vascular events

無症候性の患者に対する血管イベント一次予防目的のアスピリン投与は支持されないとのAAA（Aspirin for Asymptomatic Atherosclerosis：無症候性動脈硬化患者に対するアスピリン）スタディの結果がESC 2009ホットラインセッションで発表された。このスタディは、足関節上腕血圧比（ABI）低値から無症候性動脈硬化症と考えられた患者に対するアスピリンの効果を評価するためにデザインされた初めてのプラセボコントロール無作為化試験である。臨床的に明らかな心血管疾患のない、スコットランド中部の50～75歳の男女28,980人にABIスクリーニング検査を施行した。ABI低値（3,350人、ABI≦0.95）の患者がトライアルに組み入れられ、1日100mgのアスピリンまたはプラセボを内服する群に無作為に割り付けられた。平均8.2年後の一次エンドポイント（致死性または非致死性の初回冠動脈イベントまたは脳卒中の合計、または血行再建術）はアスピリン群とプラセボ群とで統計学的有意差はなかった（HR 1.03、95%CI 0.84～1.27）。同様に、二次エンドポイント（一次エンドポイントの合計または狭心症、間欠性跛行または一過性脳虚血発作で定義した初回結果イベントおよび総死亡率）も両群間で有意差はなかった。

Full Text

The routine use of aspirin for the primary prevention of vascular events in people with asymptomatic disease cannot be supported, according to results from the Aspirin for Asymptomatic Atherosclerosis (AAA) study. The study is the first placebo-controlled randomized trial designed to determine the effect of aspirin in asymptomatic atherosclerosis as reflected by a low ankle brachial index (ABI). Results found no statistically significant difference in primary endpoint events between those subjects allocated to aspirin or placebo (HR 1.03, 95% CI 0.84-1.27).

Joint first author Professor Gerry Fowkes from the Wolfson Unit for Prevention of Peripheral Vascular Diseases in Edinburgh said: "It is possible that in the general population, aspirin could produce a smaller reduction in vascular events than this trial was designed to detect, but it is questionable whether such an effect, together with aspirin related morbidity, would justify the additional resources and health care requirements of an ABI screening program."

The benefits of antiplatelet therapy in the prevention of future cardio- and cerebrovascular events is well established in patients with a clinical history of arterial vascular disease However, evidence in primary prevention is limited with studies suggesting that any benefit of aspirin must be weighed against the risk of bleeding. The aim of the AAA trial was to determine the effectiveness of aspirin in preventing events in people with asymptomatic atherosclerosis detected by ABI screening.

The study recruited 28,980 men and women aged 50 to 75 years who were free of clinically evident cardiovascular disease in central Scotland; all were given an ABI screening test. Those with a low ABI (3350 subjects,≤0.95 ABI) were entered into the trial and randomized to once daily 100 mg aspirin or placebo. Participants were followed for a mean of 8.2 years and outcomes ascertained by annual contact, general practitioner records, linkage to discharges from Scottish hospitals, and death notification. The primary endpoint was a composite of initial fatal or non-fatal coronary event or stroke, or revascularization. There were two secondary endpoints: all initial vascular events defined as a composite of a primary endpoint event or angina, intermittent claudication or transient ischemic attack and all-cause mortality.

Results showed that 357 participants had a primary endpoint event (13.5 per 1000 person years, 95%CI 12.2-15.0), 181 in the aspirin group and 176 in the placebo group. A vascular event comprising the secondary endpoint occurred in 578 participants, but again no statistically significant difference was found between the aspirin and placebo groups (288 vs. 290 events). All-cause mortality was similar in both groups (176 v 186 deaths). An initial event of major bleeding requiring admission to hospital occurred in 34 (2%) of subjects in the aspirin group and 20 (1.2%) in the placebo group.

Commenting on the results (and on the use of ABI as a screening method), Professor Fowkes said: "Although the AAA trial was not of screening per se, the results would suggest that using the ABI as a tool to screen individuals free of cardiovascular disease in the community is unlikely to be beneficial if aspirin is the intervention to be used in those found to be at higher risk. Other more potent antiplatelets might be considered, but only if increased effectiveness in avoiding ischemic events is not matched by increased bleeding."

Conference News

ACSに対するotamixabanの有効性の複合結果

SEPIA-ACS1 TIMI 42：otamixabanは非ST上昇急性冠症候群患者の治療薬として有望である

SEPIA-ACS1 TIMI 42: Otamixaban shows promise for the treatment of patients with non-ST-elevation acute coronary syndromes

ESC 2009で発表された静注抗凝固治験薬otamixabanのphase IIトライアルの結果、急性冠症候群（ACS）の現在の標準治療薬と比較し、死亡、二度目の心筋梗塞（MI）、または他の冠動脈疾患のリスクを軽減する可能性が示された。このスタディ（SEPIA-ACS1 TIMI 42）は、世界36ヵ国のACS患者3,241人（平均年齢61歳、女性31%）を組み入れた。患者は5つの用量のotamixaban群またはヘパリンと比較対照薬（静注抗血小板薬eptifibatideの併用）の群に無作為に割り付けられた。患者は7日間（一次エンドポイント）およびその後6ヵ月間にわたり追跡された。最も低用量の群を除いた全てのotamixaban群においてヘパリンとeptifibatide併用群よりも死亡率、二度目のMI、または他の冠疾患発現率が低い傾向にあった。特に、中等用量のotamixaban投与群患者においては、死亡または虚血性合併症発現率がヘパリンとeptifibatide併用群と比較し、40%低かった。これらの有益性は180日間にわたり持続した。中等用量otamixaban投与群における出血発現率はヘパリンeptifibatide併用群と同等であった。

Full Text

Data from a phase II trial of an investigational intravenous drug designed to block the formation of blood clots shows potential to reduce the risk of death, a second heart attack, or other coronary complications compared with the current standard of care in patients presenting with acute coronary syndromes.

Otamixaban inhibits the activity of Factor Xa, a key enzyme involved in the process of blood coagulation. It has already shown promising results when tested in patients undergoing elective angioplasty. In this trial, otamixaban was studied in high-risk patients with acute coronary syndromes (ACS). Otamixaban was compared with heparin, a standard and very commonly used blood thinner for acute coronary syndromes. Heparin, however, has many limitations, including thinning the blood to an unpredictable degree and therefore needing frequent monitoring. "There is intense interest in finding a more effective, reliable, and safe replacement for heparin," said study lead Marc S. Sabatine, MD, MPH, an Investigator in the TIMI Study Group and a cardiologist at Brigham and Women's Hospital, who presented the findings at the European Society of Cardiology meeting in Barcelona.

Sabatine, along with Professor Eugene Braunwald, Chairman of the TIMI Study Group, and colleagues studied the use of otamixaban in 3241 patients from 36 countries around the world who presented with ACS. The study (called SEPIA-ACS1 TIMI 42) was designed to identify the optimal dose of otamixaban. Patients were randomized into one of 5 doses of otamixaban or a comparator of heparin plus the intravenous platelet inhibitor eptifibatide. Researchers tracked the incidence of death, a second heart attack, additional coronary complications, and bleeding through 7 days (the primary endpoint) as well as over the following 6 months.

At the end of the study, Dr. Sabatine and colleagues found that in all of the otamixaban arms except the lowest one, the rate of death, a second heart attack, or additional coronary complications tended to be lower with otamixaban than with heparin plus eptifibatide. Specifically, patients receiving intermediate doses of otamixaban had a significant, 40% lower rate of death or ischemic complications compared with treatment with heparin plus eptifibatide. These benefits persisted through 180 days. The rates of bleeding in intermediate doses of otamixaban were similar to the rate in patients treated with heparin plus eptifibatide.

"The data show that intermediate doses of otamixaban may offer a substantial reduction in major coronary complications in patients presenting with an acute coronary syndrome, with bleeding rates comparable to current therapy," says Sabatine. "These findings will need to be tested in a large phase III trial to establish the definitive role of otamixaban in the treatment of acute coronary syndromes." Otamixaban is under development at sanofi-aventis, the company that sponsored the study. Dr. Sabatine has received honoraria and consulting fees from sanofi-aventis and honoraria from Bristol-Myers Squibb. Dr. Braunwald has received research support from Johnson & Johnson and honoraria and consultant fees from sanofi-aventis.

Conference News

遠隔地患者に対するPCIのための移送有益性

NORDISTEMI：長時間の移送により治療が遅延する地域のSTEMI患者に対する血栓溶解術直後の血管形成術は予後を改善する

NORDISTEMI: Immediate angioplasty after fibrinolysis improves outcome of STEMI in areas with very long transfer delays

ノルウェイにおけるST上昇心筋梗塞遠隔治療（NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction ：NORDISTEMI）の結果がESC 2009において発表され、急性ST上昇心筋梗塞（STEMI）により受診した地方の患者は血栓溶解療法直後に移送し血管形成術を施行した方が、血栓溶解療法後保存的治療を行い地域病院でフォローするよりも予後が良好であることが示された。NORDISTEMIは、PCIを施行するのに長距離の移送を必要とする（距離中央値158km、移送時間中央値130分）ノルウェイの遠隔地域で施行された無作為化多施設スタディである。18～75歳のSTEMI患者計266人に血栓溶解療法を施行し、直後に移送し血管形成術/PCIを施行する群、または地域病院で標準的な管理を行い救助の適応のある場合または臨床的に増悪を認めた場合には移送する群に無作為に割り付けた。その結果、一次複合エンドポイント（死亡、再梗塞、脳卒中または12ヵ月以内の新たな虚血）は早期侵襲治療群において有意な低下は示さなかった（HR 0.72、95%CI 0.44～1.18、p=0.19）。しかし、死亡、再梗塞、または12ヵ月時点での脳卒中の合計は早期侵襲治療群において保存的治療群と比較し有意に少なかった（6.0%対15.9%、HR 0.36、95%CI 0.16～0.81、p=0.01）。出血および梗塞サイズは二群間で差がなく、移送に伴う合併症は少なかった。

Full Text

Results from the NORwegian study on DIstrict treatment of ST-Elevation Myocardial Infarction (NORDISTEMI) show that patients presenting with acute ST-elevation myocardial infarction (STEMI) in rural areas have a better treatment outcome with thrombolysis followed by immediate transfer for angiography than with thrombolysis and conservative, community-hospital follow-up.

NORDISTEMI is the first trial to study the effect of early PCI after fibrinolysis in rural areas with very long transfer delays. The median transfer distance to PCI was 158 km, and median transfer time was 130 minutes. Thrombolysis was given as pre-hospital treatment in 58% of patients; adjunctive anti-thrombotic medication was in accordance with the latest European guidelines. The results of the study suggest that in areas with long transfer delays an early invasive strategy (with angiography following thrombolysis) might be preferable to a more conservative approach.

The NORDISTEMI was a randomized, open, multicentre study conducted in Norway between February 2005 and April 2009. It compared two different strategies after fibrinolysis in a region with long transfer distances to PCI (100-400 km): to transfer all patients for immediate coronary angiography and intervention, or to manage the patients more conservatively.

A total of 266 STEMI patients, aged 18-75 years, received thrombolytic therapy and were randomized to either immediate transfer for angiography/PCI or to standard management in the community hospitals with urgent transfer only for a rescue indication or with clinical deterioration. All patients received aspirin, tenecteplase, enoxaparin and clopidogrel as anti-thrombotic medication.

The results showed a reduction in the primary composite endpoint of death, reinfarction, stroke or new ischemia within 12 months in the early invasive group, but the reduction did not reach statistical significance (hazard ratio 0.72, 95% CI 0.44-1.18, p=0.19). However, the composite of death, reinfarction or stroke at 12 months was significantly reduced in the early invasive group compared to the conservative group (6.0% versus 15.9%, hazard ratio 0.36, 95% CI 0.16-0.81, p=0.01). No significant differences in bleeding or infarct size were observed, and transfer-related complications were few.

Says associate professor Sigrun Halvorsen, the principal investigator of the study: "Our study indicates a potential for improving reperfusion strategies for patients living in rural areas with long transport distances. This may be achieved by applying a well-organized pharmaco-invasive approach, including pre-hospital thrombolysis and rapid transfer to a PCI centre".

NORDISTEMI is the first trial to study the effect of early PCI after fibrinolysis in rural areas with very long transfer delays.

Conference News

高齢者には初期治療としてのPCIは血栓溶解療法よりも有効性が高い

TRIANA：非常に高齢のAMI患者には初期治療としてPCIを施行した方が血栓溶解療法よりも有効性が高いことが示唆された

TRIANA: Primary angioplasty may be more effective than thrombolysis in very elderly patients with AMI

非常に高齢の急性心筋梗塞（AMI）患者には初期治療としてPCIを施行した方が血栓溶解療法よりも有効性が高いことが、スペイン心臓協会の後援で施行された無作為化トライアルTRIANA（TRatamiento del Infarto Agudo de miocardio eN Ancianos）スタディの結果示唆され、ESC 2009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75歳以上で発症後6時間未満の急性心筋梗塞患者226人を対象に施行され、2005～2007年にスペインの23の病院において組み入れられた。このスタディは患者の組み入れ率不良のために早期に終了したが、一次エンドポイント（30日間の死亡、再梗塞または障害を伴う脳卒中）は両群間で差がなかった（血栓溶解療法群で25.4%に対し血管形成術群で18.9%、p=0.21）。両群ともにイベント発現率が予測より高かったにもかかわらず、患者組み入れが遅かったために有意差の検出力は十分ではなかった。しかし、あらかじめ指定された二次エンドポイントにおいては、血管形成術群のほうが再虚血に対するカテーテル施行率が有意に低かった（0.8%対9.7%、p<0.001）。

Full Text

Primary angioplasty is superior to thrombolysis in the treatment of very old patients with acute myocardial infarction (AMI), according to results from the TRIANA (TRatamiento del Infarto Agudo de miocardio eN Ancianos) study, a randomized trial sponsored by the Spanish Society of Cardiology.

The trial was designed to compare the two principal available treatments to open blocked coronary arteries in AMI patients: immediate primary PCI with angioplasty, and thrombolysis with clot-dissolving drugs. The trial was performed in 226 patients all aged 75 years or older and all with acute myocardial infarctions (AMIs) of less than six hours' evolution. They were recruited in 23 Spanish hospitals between 2005 and 2007.

The study, which was closed prematurely because of slow patient recruitment, found no differences between the two groups in its primary endpoint — the incidence of death, reinfarction or disabling stroke at 30 days (25.4% in the thrombolysis group and 18.9% in the primary angioplasty group, p=0.21). Despite the higher-than-anticipated rate of events in both arms, the study became underpowered to detect such differences because of its reduced recruitment. However, in a pre-specified secondary endpoint there was a significantly lower need of new catheterization for recurrent cardiac ischemia in the primary angioplasty arm (0.8% versus 9.7%, p<0.001).

Reviewing the findings principal investigator Professor Héctor Bueno from the Hospital General Universitario "Gregorio Marañón" in Madrid reported that:

- The effect of primary angioplasty on reducing recurrent ischemia was so strong that it could still be easily detected in the study, despite its limited statistical power.
- Contrary to what might have been anticipated, there was no clear evidence that thrombolysis, which is considered controversial in older patients because of their increased bleeding risk, was unsafe in a population whose median age was 81 years; the study found no intracranial bleeding directly related to the use of thrombolysis, and no significant differences between groups in major bleeding (4.5% versus 3.8%; p=0.78), or need for transfusions (3% vs. 5.3%, p=0.35).
- There was no increase in renal failure associated with primary angioplasty (6.1% versus 7.5% with thrombolysis), a feared complication of catheterization in older patients.

Professor Bueno added: "All efficacy outcomes showed concordant trends in favor of primary angioplasty, suggesting that the potential advantage of an invasive strategy over thrombolysis in very old patients is because of its greater efficacy rather than its superior safety. However, patients in both groups tended to have a comparable prognosis one year later."
The TRIANA study was funded by the Fondo de Investigaciones Sanitarias (Instituto Carlos III, Ministry of Health, Spain), and unrestricted grants from Sanofi, Medtronic, Boston Scientific, Guidant, and Johnson & Johnson.

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

バルサルタンはアジア人の高血圧患者に有益性をもたらす

KYOTO HEART Study：バルサルタンは高リスクの日本人高血圧患者の罹患率および死亡率を減少させる

KYOTO HEART Study: Valsartan reduces morbidity and mortality in Japanese patients with high risk hypertension

KYOTO HEARTスタディの結果、従来の高血圧治療にアンジオテンシン受容体拮抗薬（ARB）バルサルタンを追加することにより日本人の心血管イベントの高リスク高血圧患者の心血管予後が改善することが示された、とESC 2009ホットラインセッションで発表され同時にEuropean Heart Journalオンライン版に掲載された。しかし、2つの治療群間の血圧に有意差はなく、この有益性は降圧効果のみでは説明できないことが示唆された。3.000人以上の日本人患者（女性43%、平均年齢66歳）をバルサルタン追加群またはARB以外の降圧剤使用群に無作為に割り付けた。全ての患者が血圧コントロール不良であり、心血管リスクファクターを1つ以上有していた。バルサルタン群において明確な有益性が認められたため、このスタディは3.27年の観察期間中央値の後早期に終了した。ARB以外の治療群と比較し、バルサルタン群においては、心血管または脳血管イベントを発症した患者が有意に少なかった（83人対155人；HR 0.55、95%CI 0.42～072、p=0.00001）。この一次エンドポイント発現率の有意差は、主に狭心症（22件対44件；HR 0.51、95%CI 0.31～0.86、p=0.01） および脳卒中/一過性脳虚血発作（25件対46件；HR 0.55、95%CI 0.34～0.89、p<0.05）の発現が少ないことによるものであった。

Full Text

The KYOTO HEART Study, which took place in Japan between January 2004 and January 2009, shows that the addition of valsartan to conventional antihypertensive treatment to improve blood pressure control is associated with an improved cardiovascular outcome in Japanese hypertensive patients at high risk of CVD events.

It remains to be determined whether the evidence found in Western countries for the benefit of blockade of the renin-angiotensin system could be directly applied in East Asian populations as a long-term strategy. The KYOTO HEART Study was designed to investigate the add-on effect of valsartan (an angiotensin II receptor antagonist, ARB) versus non-ARB optimal antihypertensive treatment on cardiovascular morbidity and mortality in Japanese hypertensive patients with uncontrolled blood pressure and high cardiovascular risks.

The KYOTO HEART Study was a multicentre, prospective, randomized comparison study with a response-dependent dose titration scheme. More than 3000 Japanese patients were assessed for eligibility (43% female, mean age 66 years); all had uncontrolled hypertension and one or more cardiovascular risk factors (such as diabetes, smoking habit, lipid metabolism abnormality, a history of ischemic heart disease, cerebrovascular disease or peripheral arterial occlusive disease, obesity (BMI>25) and left ventricular hypertrophy on electrocardiogram). 3031 patients were randomized to receive either additional treatment with valsartan or non-ARB conventional therapies.

The primary endpoint was a composite of defined cardio- or cerebrovascular events such as stroke/transient ischemic attack, myocardial infarction, hospitalization for heart failure, hospitalization for angina pectoris, aortic dissection, lower limb arterial obstruction, emergency thrombosis, transition to dialysis, or doubling of serum creatinine levels.

The study was prematurely stopped after a median observation time of 3.27 years. This was for ethical reasons because of unequivocal benefit in the valsartan group.

- Compared with non-ARB arm, fewer individuals in the valsartan arm reached a primary endpoint (83 vs. 155; HR 0.55, 95% CI 0.42-072, p=0.00001). This difference in primary endpoint rate was mainly attributable to reduced incidences of angina pectoris (22 vs. 44; HR 0.51,95% CI 0.31-0.86, p=0.01), stroke/TIA (25 vs. 46; HR 0.55, 95% CI 0.34-0.89, p<0.05).

- Differences in acute myocardial infarction (7 vs. 11), heart failure (12 vs. 26), arteriosclerosis obliterance (11 vs. 12), and aortic dissection (3 vs. 5) were not significant. In addition, rates of all-cause mortality (22 in valsartan arm vs. 32 in non-ARB arm) and cardiovascular mortality (8 vs. 13) were not significant.

- Blood pressure at baseline was 157/88 mmHg in the both groups. Mean blood pressure during the treatment period was 133.1/76.1 mmHg in the valsartan add-on arm and 133.3/76.0 mmHg in the non-ARB arm.

Says principal investigator Professor Hiroaki Matsubara, "The KYOTO HEART Study was first designed to evaluate whether the addition of valsartan to conventional antihypertensive treatment to improve blood pressure control influences the cardiovascular outcome in Japanese high-risk hypertensive patients. The study showed that valsartan has the additional benefits of cardiovascular event prevention for hypertensive patients in East Asia with metabolic syndrome or high-risks."

Conference News

薬剤溶出ステントの安全性が明らかになった

ISAR-TEST-4：生分解性ポリマー薬剤溶出ステントの1年後の成績は永久ポリマーを基盤とした薬剤溶出ステントの成績と同等であった

ISAR-TEST-4: One-year outcomes with a biodegradable polymer drug-eluting stent are similar to those with permanent polymer-based drug-eluting stents

生分解性ポリマーを薬剤溶出ステント（DES）に使用することによりステント血栓症のリスクを軽減する可能性があるとの考えを支持する新たな研究結果が、ESC 2009で発表され、European Heart Journalに掲載された。新規発症の未治療冠動脈病変に対しPCI施行の選別をかけていない患者を、生分解性ポリマーDES（1,299人）または永久ポリマーDES（Cypher-652人またはXience-652人）を留置する群に無作為に割り付けた。一次エンドポイントは、12ヵ月以内の心臓死、標的血管に基づく心筋梗塞（MI）、または標的病変（TLR）に対する再血行再建であった。30日後の臨床転帰は両群間で差が無かった；心臓死、標的血管またはTLRに基づくMIは生分解性ポリマー群で4.4%、永久ポリマー群で4.5%に認められた（p=0.87）。明らかなステント血栓症は各々の群で5例ずつ（0.4%）認めた。6～8ヵ月後の冠動脈造影では、後期ステント内狭窄およびステント留置セグメント内再狭窄発症率に両群間の差はなかった（それぞれp=0.49、p=0.85）。一次エンドポイントは生分解性ポリマー群で13.8%および永久ポリマー群で14.4%であり、非劣性のクライテリア（相対リスク0.96、95%CI 0.78～1.17、p-非劣性=0.005；p-優越性=0.66）に合致した。

Full Text

There's new support for the idea of using biodegradable polymers on drug-eluting stents (DES) to potentially reduce stent-thrombosis risk: results from the ISAR-TEST-4 study found a novel rapamycin-coated stent with a disappearing polymer to be equally as effective as the Cypher and Xience (permanent-polymer) stents, with at least a signal of improved safety. Dr. Julinda Mehilli of Deutsches Herzzentrum in Munich, Germany presented 12-month results from the 2603-patient trial during a Hotline session at the European Society of Cardiology (ESC) 2009 Congress. Results were published online simultaneously in the European Heart Journal.

Drug-eluting stents (DES), which slowly release medication to inhibit the build-up of scar tissue, have proved very successful in preventing restenosis of stented coronary arteries. However, several studies have shown persistent risk of blood clot formation inside DES over a longer time period after implantation than observed with bare metal stents. Additionally, recent serial angiographic studies have reported that scar tissue accumulation can be seen up for up to two years after implantation of DES. There is increasing evidence that the risk of both late in-stent blood clot and neointimal scar formation may be caused by a delayed healing process or a persisting inflammatory response to the permanent polymer used to control drug-release from the surface of the stent.

The ISAR-TEST-4 study is a randomized trial designed and conducted at two tertiary referral cardiology centers - Deutsches Herzzentrum and 1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, both in Munich, Germany - with the aim of assessing the efficacy and safety of a biodegradable polymer DES in a non-selected cohort of patients undergoing PCI in de novo native-vessel coronary lesions. First results indicate that safety and efficacy outcomes at one year are comparable with those of permanent polymer-based drug-eluting stents
Patients were randomly assigned to receive either a biodegradable polymer DES (n = 1299) or a permanent polymer DES (Cypher, n = 652, or Xience, n = 652). The primary endpoint was a composite of cardiac death, myocardial infarction (MI) related to the target vessel, or revascularization related to the target lesion (TLR) at one year.

The biodegradable polymer DES was developed in the setting of the Individualized Drug-Eluting Stent System to Abrogate Restenosis (ISAR) project. The stent platform consists of a sand-blasted, stainless-steel stent that is coated on-site with a mixture of rapamycin, biodegradable polymer, and shellac resin (a biocompatible resin widely used in the coating of medical tablets).

Primary endpoint results showed that the biodegradable polymer DES was non-inferior to the permanent polymer DES (a rate of 13.8% vs. 14.4%, relative risk 0.96, 95% CI 0.78-1.17, p-non-inferiority=0.005; p-superiority=0.66). No significant difference was observed between the biodegradable and permanent polymer DES according to cardiac death or MI (6.3% vs. 6.2%, P=0.94), TLR (8.8% vs. 9.4%, P=0.58) or stent thrombosis (definite/probable: 1.0% vs. 1.5%, P=0.29). Nor was there a significant difference in subgroup analysis of the biodegradable polymer DES versus the individual permanent polymer DES arms.

Investigator Dr. Julinda Mehilli from the Deutsches Herzzentrum in Munich said: "The one-year clinical efficacy of the biodegradable polymer rapamycin-eluting stent is comparable to permanent polymer-based DES. These results now provide a framework for testing the potential clinical advantage of biodegradable polymer DES over the medium- to long-term."

Conference News

左冠動脈主幹部病変の治療には近年PCIが多く施行されている

GRACE Registry：プロテクトされていない左冠動脈主幹部病変に対しPCIとCABGは相補的な治療であるようである

GRACE Registry: PCI and CABG appear to provide complementary treatment options in patient with unprotected left main coronary disease

急性冠イベントに関する国際登録研究（Global Registry of Acute Coronary Events：GRACE）の解析の結果、急性冠症候群（ACS）を呈する患者においてプロテクトされていない左冠動脈主幹部病変（ULMCD）患者はまれではあるが、経皮的冠動脈インターベンション（PCI）はこれらのよりリスクの高い患者において多く施行されている血行再建療法であることが示された。冠動脈バイパス術（CABG）はリスクの低い患者に対ししばしば遅れて施行され良好な6ヵ月生存率を得ている。今回解析を行った43,018人中1,799人は有意なULMCDを有し、PCIのみ（514人）、CABGのみ（612人）を施行されたかまたは血行再建術を施行されなかった（673人）。8年間のスタディ期間中にGRACEリスクスコアはPCIにおいてCABGよりも20ポイント高いまま不変であったが、時間とともにCABGよりもPCIでの血行再建術が着実に増加した。PCIを施行される患者は心停止後または心原性ショックを伴った急性心筋梗塞であることが多かった；PCIを施行された患者の48%が入院当日に血行再建されたのに対しCABG群では5.1%であった。血行再建術非施行群と比較し、血行再建術施行により早期院内死亡が多い傾向にあり、PCIでは有意であった（HR 2.60、95%CI 1.62～4.18）が、CABGでは有意ではなかった(HR 1.26、95%CI 0.72～2.22）。これらの結果はESC 2009で発表されEuropean Heart Journalに掲載された。

Full Text

Launched in 1999, the Global Registry of Acute Coronary Events (GRACE) is the world's largest international database tracking outcomes of patients presenting with acute coronary syndromes (ACS), including myocardial infarction or unstable angina. GRACE data are derived from 247 hospitals in North America, South America, Europe, Asia, Australia and New Zealand, and from more than 100,000 patients with ACS. Data from 43,018 ACS patients in the Registry were analyzed to determine the optimal revascularization strategy for unprotected left main coronary disease, which has so far been little studied.

Results of the analysis showed that unprotected left main coronary disease (ULMCD) in ACS is associated with high in-hospital mortality, especially in patients presenting with ST-segment elevation myocardial infarction (STEMI) and/or hemodynamic or arrhythmic instability. Percutaneaous coronary intervention (PCI) is now the most common revascularization strategy in this population, and is preferred in higher-risk patients. Coronary artery bypass grafting (CABG) is often delayed and is associated with the best 6-month survival. The two approaches therefore appear complementary in this high-risk group.

Of the 43,018 patients in the analysis, 1799 had significant ULMCD and underwent PCI alone (n=514), CABG alone (n=612), or no revascularization (n=673). Mortality was 7.7% in hospital and 14% at six months.

Over the eight-year study period, the GRACE risk score remained constant, 20 points higher in PCI than in CABG, but there was a steady shift to more PCI than CABG revascularization over time. Patients undergoing PCI presented more frequently with acute myocardial infarction, after cardiac arrest, or in cardiogenic shock; 48% of PCI patients underwent revascularization on the day of admission vs. 5.1% in the CABG group. After adjustment, revascularization was associated with an early hazard of hospital death compared with no revascularization, significant for PCI (HR 2.60, 95% CI 1.62-4.18) but not for CABG (HR 1.26, 95% CI 0.72-2.22).

From discharge to six months, both PCI (HR 0.45, 95% CI 0.23-0.85) and CABG (HR 0.11, 95% CI 0.04-0.28) were significantly associated with improved survival in comparison with an initial strategy of no revascularization. CABG revascularization was associated with a five-fold increase in stroke compared with the other two groups.

Says investigator Professor Gilles Montalescot from the Hôpital Pitié-Salpétrière in Paris: "The results show that CABG surgery and PCI are not used in similar types of patients and provide complementary treatment options in ACS."

Conference News

Rolofyllineは急性心不全に効果がなかった

PROTECT Study：Rolofyllineは急性心不全患者において有効性を示すことができなかった

PROTECT Study: Rolofylline does not demonstrate efficacy for patients with acute heart failure

PROTECTパイロットスタディでは有望な結果が認められたにもかかわらず、大規模なPROTECTトライアルではrolofyllineとプラセボとで非代償性心不全（HF）患者において差が認められなかった。24～48時間後の中等度から著明な呼吸困難の改善はrolofylline群の方がプラセボ群よりも多くの患者において認められたが、これは、永続的な腎機能障害に対する有効性の欠如により相殺された。このトライアルは、体液過負荷、腎機能障害（推定GFR 20～80ml/min）および血漿BNPまたはNT-proBNPレベル上昇（それぞれ>500pg/mLまたは>2,000pg/mL）の徴候発現後24時間以内にHFとして入院した患者2,033人に対するrolofyllineの効果を評価したものである。治療に成功したのはrolofylline群患者の40.6%に対し、プラセボ群患者では36.0%であり、治療無効と分類されたのはrolofylline群患者の21.8%に対し、プラセボ群患者では19.8%であり、その他の患者は不変であった（オッズ比=0.92、95%CI 0.78～1.09；p=0.348）。60日以内の死亡または心血管疾患および腎疾患による再入院は、rolofyllineおよびプラセボ患者でそれぞれ30.7%および31.9%であった（ハザード比および95%CI 0.98、0.83～1.17、p=0.861）。永続的な腎機能障害はプラセボ群患者の13.7%およびrolofylline患者の15.0%にそれぞれ発現した。重大な神経学的イベントはrolofylline群患者において多く認められた。

Full Text

Despite the promising findings of the PROTECT Pilot study, the larger PROTECT trial found no difference with rolofylline versus placebo with respect of the primary and main secondary end-points of the study. Although more rolofylline patients than placebo patients experienced moderate or marked dyspnea improvement at 24 and 48 hours from randomization, this was counterbalanced by a lack of effect on persistent renal impairment. Lastly, the risk of important neurological events was increased in patients on rolofylline.

Acute heart failure (HF) is the most common cause of hospitalization for patients over 65 years. Its prevalence continues to rise as the population ages. It carries a high cost and a dismal prognosis with an in-hospital mortality rate of 3-8%, a 60-90 day mortality rate of 9-13%, and a short-term re-hospitalization rate of 25-30%. Despite this, there have been no significant recent advances in medical treatment. The cornerstones remain intravenous diuretics to manage congestion, often in conjunction with morphine and intravenous vasodilators, such as nitrates, to relieve dyspnea.

Many patients hospitalized for HF have underlying chronic kidney disease or worsening renal function on admission or during their hospital course. Worsening renal function (WRF) and resistance to loop diuretics are consistently associated with poorer outcomes, including longer length of stay, higher in-hospital and post-discharge mortality rates, and increased readmission rates. Recently, adenosine has been implicated as an important mediator of both WRF and diuretic resistance as it causes a reduction in renal blood flow and glomerular filtration rate (GFR) and decreases sodium excretion. In the previously published PROTECT-Pilot study1, rolofylline treatment, at the 30 mg dose, was associated with trends toward better symptom improvement, lesser WRF, and fewer deaths or readmissions for HF or renal dysfunction over the next 60 days.

PROTECT (A Placebo-controlled Randomized study of the selective A1 adenosine receptor antagonist KW-3902 for patients hospitalized with acute HF and volume Overload to assess Treatment Effect on Congestion and renal function Trial) was aimed at the assessment of the effects of rolofylline on symptoms, renal function and short-term morbidity and mortality in 2,033 patients hospitalized for HF within 24 hours with signs of fluid overload, impaired renal function (estimated GFR 20-80 ml/min) and high BNP or NT-proBNP plasma levels (>500 pg/mL or >2000 pg/ml, respectively). Patients were randomized 2:1 to rolofylline 30 mg/day or placebo, administered as a 4 hours daily infusion repeated for 3 days. Dyspnea was assessed on a 7-point Likert scale daily for the first 7 days (or until discharge, if earlier) and then at 14 days, after enrollment. Blood samples for measurements of serum creatinine were collected daily until day 7 (or until discharge, if earlier) and at day 14 after enrollment. Deaths were captured to day 180 and rehospitalizations were captured up to day 60 after enrollment.

The primary end-point of PROTECT was a three category ordered outcome of treatment success, patient unchanged, or treatment failure. Treatment success was defined as a moderate to marked better dyspnea at 24 and 48 hours after the start of study drug compared to baseline, in the absence of any criteria for treatment failure. Treatment failure included any of the following criteria: death or readmission for HF any time through Day 7; or worsening symptoms and/or signs of HF occurring >24 hours after the start of study drug to Day 7 or discharge, whichever occurred first, or persistent renal impairment as defined by a serum creatinine (SCr) increase of≥ 0.3 mg/dL from randomization to Day 7, confirmed at Day 14, or the initiation of hemofiltration or dialysis through Day 7. Patients were categorized as unchanged if they did not meet criteria for either treatment success or treatment failure.

Secondary end-points were: time to death or rehospitalization for cardiovascular or renal causes through Day 60 and the proportion of subjects with persistent renal impairment defined as a SCr increase of ≥ 0.3 mg/dL from randomization to Day 7, confirmed at Day 14, or the initiation of hemofiltration or dialysis or death through Day 7.

Enrollment in PROTECT was concluded in January 2009 and the main results became available in June 2009. Six hundred seventy seven patients were randomized to placebo and 1,356 patients received rolofylline (placebo to rolofylline 1:2 randomization). The placebo and rolofylline groups were well balanced with respect to the main baseline characteristics. Follow-up was complete in all but 1 patient at 60 days and 4 patients (0.2%) at 180 days.

No significant difference was found between rolofylline and placebo with respect to the primary end-point. Treatment success was achieved by 40.6% patients on rolofylline, compared with 36.0% of the patients on placebo, 21.8% of the patients were classified as treatment failure with rolofylline versus 19.8% with placebo, the remainder being unchanged (OR=0.92, 95% CI=0.78-1.09; p=0.348). There were no significant differences between the treatment groups in either secondary endpoint. Death or rehospitalization for cardiovascular or renal causes at day 60 occurred in 30.7% and 31.9% of the rolofylline and placebo patients (hazard ratio and 95% CIs, 0.98, 0.83-1.17, p=0.861). Persistent renal impairment occurred in 13.7% of placebo patients and 15.0% of rolofylline patients, respectively.

With regards to the components of the primary end-point, moderate or marked better dyspnea at both 24 and 48 hours was observed in 52.0% of patients in the rolofylline treated group versus 45.4% of patients in the placebo group. However, this was partially counterbalanced by the higher rate of persistent renal impairment in the rolofylline group.

Serious adverse events (SAE) occurred in 13.8% of rolofylline and 14.7% placebo patients and cardiac SAEs occurred in 7.2% and 9.0%, respectively. The rate of central nervous system SAEs was 1.5% in the rolofylline group versus 0.6% in placebo, including more patients experiencing seizures.

In conclusion, despite the promising findings of the PROTECT Pilot study, the larger PROTECT trial found no difference with rolofylline versus placebo with respect of the primary and main secondary end-points of the study. Although more rolofylline patients than placebo patients experienced moderate or marked dyspnea improvement at 24 and 48 hours from randomization this was counterbalanced by a lack of effect on persistent renal impairment. Lastly, the risk of important neurological events was increased in patients on rolofylline.

Conference News

心原性ショックを伴ったAMI患者におけるabciximabの効果は失望させられる結果であった

PRAGUE-7 Study：GP IIb/IIIa阻害薬abciximabは心原性ショックを伴った急性心筋梗塞患者に対し有益ではない

PRAGUE-7 Study: GP IIb/IIIa inhibitor abciximab shows no benefit in patients with acute myocardial infarction and cardiogenic shock

心原性ショックを伴った急性心筋梗塞患者に対する初回経皮的冠動脈インターベンション（PCI）の際に、GP IIb/IIIa阻害薬abciximabをルーチンにup-frontで使用することは有益ではないとのPRAGUE-7スタディの結果がESC 2009ホットラインセッションで発表された。80人の患者が移送中またはカテ室で直に標準的な抗血栓薬および抗凝固薬を投与され冠動脈造影を施行された。その後患者らはup-frontでabciximabをボーラス投与後に点滴を12時間施行される群または標準的な周術治療を施行される群に無作為に割り付けられた。PCI中のabciximabの使用はインターベンションの術者の裁量に任された。Abciximabはup-front治療群患者全員に使用されたのに対し、標準治療群患者で使用されたのは35%であった。一次エンドポイント（30日間の死亡／再梗塞／脳卒中／新規の腎不全の合計）に達したのはup-front治療群患者のうち17人（42.5%）であり、標準治療群患者のうち11人（27.5%；p=0.24）であった。入院中に死亡したのはup-front群患者のうち15人（37.5%）であり、それに対し標準治療群患者では13人（32.5%；p=0.82）であった。他の項目に関しては両群間で有意差はなかった。

Full Text

Routine upfront use of the GP IIb/IIIa inhibitor abciximab during primary percutaneous coronary intervention (PCI) was of no benefit in patients with acute MI (AMI) complicated by cardiogenic shock, according to the results of the PRAGUE-7 study reported during a hotline session at the European Society of Cardiology Congress 2009.

The outcome of patients with acute myocardial infarction (AMI) complicated by cardiogenic shock is generally very poor. Although early mechanical revascularization by primary PCI has been shown as superior to medical treatment, the mortality range remains high (at about 45-60%). Registries have shown further therapeutic benefit from the administration of glycoprotein (GP) IIb/IIIa inhibitors during PCI in AMI patients with cardiogenic shock. However, there are no randomized data to support this approach in these high risk patients. The PRAGUE-7 study was designed to determine whether the routine upfront administration of abciximab (a IIb/IIIa GP inhibitor) improves outcome when compared with conventional selective administration.

This study, which is part of a series of randomized trials in cardiology and cardiac surgery performed in the Czech Republic, enrolled 80 of these most critically ill patients (AMI complicated by cardiogenic shock) but failed to show any benefit from the routine upfront administration of abciximab to all patients (before coronary angiography) over a more conventional selective use of abciximab during subsequent primary PCI.

All 80 patients in this open-label multicentre trial received standard antithrombotic and anticoagulant treatment (either during transport or directly at the catheterization laboratory) and coronary angiography. Patients in the upfront treatment group (group A) received a bolus of abciximab immediately after randomization followed by an infusion for 12 hours. PCI was performed immediately after coronary angiography. Group B received standard therapy with optional abciximab administration during PCI according to the interventional cardiologist.

The study's primary endpoint was a 30-day combined outcome of death/reinfarction/stroke/new renal failure. Secondary objectives were left ventricular ejection fraction assessed by echocardiography on day 30, major bleeding complications, myocardial blush grade after PCI, and TIMI-flow after PCI.

Results showed that PCI was technically successful in 90% of group A and 87.5% of group B patients. Abciximab was used in 100% of group A and 35% of group B. The primary endpoint was reached in 17 group A patients (42.5%) and 11 group B patients (27.5%) (p=0.24). Fifteen patients (37.5%) died during hospitalization in group A and 13 patients in group B (32.5%) (p=0,82). Ejection fraction among survivors after 30 days was 44 ± 11% (A) vs. 41 ± 12% (B) (p=0.205). Major bleeding occurred in 17.5% (A) vs. 7.5% (B) (p=0.310) and stroke in 2.5% (A) vs. 5% (B). No differences were found in TIMI-flow and MBG after PCI.

PRAGUE- 7 was supported by a grant from Lilly.

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).

Conference News

中等量の飲酒はAFのリスクを上昇させない

高血圧性心疾患患者において週10単位を超えるアルコールを飲むことにより心房細動のリスクが上昇する

Drinking more than 10 alcohol units per week increases the risk of atrial fibrillation in persons with hypertensive heart disease

高血圧のエンドポイント減少を目的としたロサルタン治療（Losartan Intervention For Endpoint reduction in Hypertension：LIFE）スタディの結果がESC 2009で発表され、大量のアルコール摂取により高血圧および左室肥大を有する患者において新規発症の心房細動のリスクが上昇することが示された。この二重盲検無作為化パラレルグループスタディでは、心電図上左室肥大の認められた高血圧患者9,193人を組み入れた（男性46%；平均年齢67歳、平均血圧174/98mmHg）。患者はロサルタンまたはアテノロールを基本とした降圧療法を受け、平均4.8年間追跡された。ベースライン時点で8,831人がAF既往歴および心電図上AF所見を有しておらず、従って、スタディ中にAFを発症するリスクを有していた。353人において新規発症のAFが心電図上認められた。これは、ベースラインの飲酒量が週10単位を超えるもので5.7%（20人）であり、飲酒量の少ない者または飲酒をしない者において3.9%（333人）であった。飲酒量が週10単位を超えることで新規発症のAFのリスクが増加した（p=0.042）。飲酒量が週10単位を超えることにより新規発症のAFのリスクが、AF新規発症の他のリスクと関係なく80%増加した（HR 1.8[1.2、2.9]、p=0.009）。

Full Text

The Losartan Intervention For Endpoint reduction in Hypertension (LIFE) study shows that high intake of alcohol is associated with an increased risk of new-onset atrial fibrillation (AF) in hypertensive patients with left ventricular hypertrophy, measured by electrocardiography (ECG).

Binge drinking can induce atrial fibrillation. Long-term moderate alcohol consumption appears not to increase the risk of new-onset AF; a threshold effect has, however, been suggested with a significantly increased risk of AF among the heaviest drinkers with an alcohol intake of more than 28-35 drinks per week.

People with atrial fibrillation (AF) have increased risk of hospitalization or death due to stroke, myocardial infarction or heart failure. The incidence of new-onset AF is increased in persons with hypertension and even more if left ventricular hypertrophy has developed. Medical treatment of hypertension reduces new-onset AF and treatment with the angiotensin receptor blocker losartan is more effective than the beta-1 selective blocker atenolol in this respect. However, it is unclear how smoking and alcohol intake influence the risk of new AF during antihypertensive treatment.

In LIFE, a double-blinded, randomized, parallel-group study, 9,193 hypertensive patients (46% men; mean age 67 years, mean blood pressure 174/98 mmHg) with ECG-documented left ventricular hypertrophy, received either losartan- or atenolol-based blood pressure lowering therapy, and were followed for a mean time of 4.8 years. The study was funded by Merck & Co and took place in Scandinavia, the United Kingdom and the United States in 1995-2001. At baseline 8,831 patients neither had a history of AF nor AF by ECG, and were thus at risk of developing this condition during the study.

ECG confirmed new-onset AF in 353 patients. This occurred in 5.7% of patients with baseline alcohol intake above 10 units per week (n = 20) versus 3.9% patients with lower or no alcohol intake (n = 333). Intake of alcohol above 10 units per week increased the risk for new-onset AF in univariate Cox regression analysis, with hazard ratio (HR) (95% CI) 1.6 (1.0, 2.5) p=0.042. In multivariate Cox regression, intake of alcohol above 10 units/week resulted in an 80% increased risk of new-onset AF (HR 1.8 (1.2, 2.9), p = 0.009) independently of the other factors associated to risk of new-onset AF (age, male gender, treatment allocation to losartan versus atenolol, and change over time in systolic blood pressure, Cornell ECG measure of left ventricular hypertrophy and heart rate). Smoking was not associated with more new atrial fibrillation, and the effect of alcohol did not interact with the effect of smoking.

"Our results show that an intake of alcohol above 10 units per week increases the risk of new-onset AF, hence drinking up to 10 alcohol units/week does not increase the risk of new-onset atrial fibrillation in hypertensive patients with ECG left ventricular hypertrophy" says Inger Ariansen.

Conference News

高用量のクロピドグレルはPCIの合併症を減少させる

CURRENT OASIS-7：二倍用量のクロピドグレルは血管形成術を施行されるACS患者に有益である

CURRENT OASIS-7: Double doses of clopidogrel shows benefit in ACS patients undergoing angioplasty

画期的なクロピドグレルの最大量使用による再イベント減少／血管形成術に際しての最大量抗血小板療法（CURRENT-OASIS 7：Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS）トライアルの結果、高用量のクロピドグレルは経皮的冠動脈形成術を施行される急性冠症候群（ACS）患者の合併症を有意に軽減することが示された。患者は、不安定狭心症または心筋梗塞にて病院に到着次第、可能な限り速やかに高用量または標準量のクロピドグレルを1ヵ月間投与される群に無作為に割り付けられた。高用量群は初日の血管形成術施行前になるべく早く600mgのクロピドグレルを内服し、その後1日150mgを7日間ののちに1日75mgを内服した。標準療法群は初日に300mg内服した後に30日後まで1日75mgを内服した。高用量療法により、血管形成術を施行された68%の患者（25,087人中17,232人）のステント血栓リスクが30%減少し、心筋梗塞リスクがさらに22%減少した。PCIを施行されなかった高用量群の7,000人に有益性は認められなかった。この結果はESC 2009ホットラインセッションで発表された。

Full Text

A landmark international study led by McMaster University researchers found high doses of the antiplatelet agent clopidogrel significantly reduce complications in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).

An international group of researchers from 39 countries found patients undergoing angioplasty benefited from a more aggressive antiplatelet regimen in which they were given double the standard dose for about a week.

"The superiority of the high dose clopidogrel regimen in reducing stent thrombosis and related heart attacks in those undergoing PCI is clear in our study and will be of great relevance to interventional cardiologists," said interventional cardiologist Dr. Shamir R. Mehta, an associate professor of medicine in the Michael G. DeGroote School of Medicine at McMaster University and the principal investigator of the trial.

The investigators simultaneously evaluated the optimal dose of aspirin and found that 300 mg of aspirin resulted in similar outcomes to 100 mg of aspirin and was not associated with higher rates of bleeding. There was also no benefit of the higher dose of clopidogrel in the 7,000 individuals not undergoing PCI.

Mehta presented results of the CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent EveNTs/Optimal Antiplatelet Strategy for InterventionS) trial at the annual European Society of Cardiology Congress in Barcelona, Spain, where the prevention of heart disease is the focus of this year's presentations by researchers from around the world.

CURRENT-OASIS 7 is a Phase III, multicentre, multinational, randomized, parallel-group trial which enrolled 25,087 patients scheduled to undergo angiography within 72 hours of arriving in a hospital emergency department or coronary care unit with unstable angina or a myocardial infarction. Of these, about 17,000 were suitable for angioplasty and underwent the procedure.

As soon as possible after their arrival, patients were randomly assigned to the high dose or standard dose of clopidogrel for a month. High-dose patients received 600 mg of clopidogrel on the first day - as early as possible before angioplasty - then 150 mg once a day for seven days, followed 75 mg daily for the remainder of the month. Those patients on the standard regimen received 300 mg on day one, followed by 75 mg once a day until day 30. Patients in both groups were randomly assigned to aspirin, either high-dose (300-325 mg once daily) or low-dose regimen (75-100 mg once daily).

The more intensive high-dose 600 mg clopidogrel regimen reduced the risk of stent thrombosis by an incremental 30 per cent and the risk of heart attack by a further 22 per cent over and above the standard regimen in 68 per cent of patients (17,232 out of 25,087) undergoing angioplasty. There was an increase in major bleeding, but no increase in cerebral hemorrhage or those that were fatal.

"What this implies is that the combination of high-dose clopidogrel combined with usual doses of aspirin may be the optimal treatment strategy in PCI patients," said Dr. Salim Yusuf, chair of the CURRENT-OASIS 7 steering committee, a professor of medicine in the Michael G. DeGroote School of Medicine and director of the Population Health Research Institute at McMaster University and Hamilton Health Sciences.

The CURRENT-OASIS 7 study was sponsored by Sanofi-Aventis and Bristol-Myers Squibb but was independently conducted by the Population Health Research Institute along with an international steering committee.

Conference News

再同期療法により軽症の無症状患者の心不全リスクが軽減する

MADIT-CRT：再同期療法により軽症の無症状患者の心不全リスクが軽減する

MADIT-CRT: Resynchronization therapy reduces risk of heart failure in asymptomatic patients with mild disease

無症状または軽症状を有する心不全患者を、除細動器付き植込み型心臓再同期装置（CRT-D）に無作為に割り付けられた患者は、標準的な植込み型除細動器（ICD単独）に割り付けられた患者と比較し、心不全または死亡のリスクが34%低い（HR 0.66；p=0.001）との多施設心臓再同期療法付き自動除細動器植込みトライアル（MADIT-CRT：Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy）の結果がESC 2009で発表された。このトライアルではNew York心機能クラスIまたはIIの左室機能低下（左室駆出率<30%）を伴いQRS幅>130msの虚血性または非虚血性心疾患患者を対象とした。トライアルは、心臓再同期療法に優位性が認められた（p=0.001）ため4.5年間で終了し、その間に1,820人の患者が組み入られた。患者はCRT-DまたはICD単独を受ける群に3：2の割合で無作為に割り付けられ、全ての患者がトライアルの期間を通じて最大限の心不全薬物療法を受けた。男性および女性、若年患者および高齢患者、心機能不全の軽症患者およびそれよりも重症の患者、虚血性および非虚血性全ての患者サブグループにおいてCRT-D療法の優位性が認められた。

Full Text

Asymptomatic or mildly symptomatic cardiac patients randomized to an implanted cardiac resynchronization device with defibrillator (CRT-D) have a 34% lower risk of heart failure or death than those receiving a standard implanted cardioverter defibrillator (ICD-only) (HR 0.66, p=0.001), according to results from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) study.

The MADIT-CRT study was a randomized trial designed to determine if CRT-D therapy would reduce the primary endpoint (all-cause mortality or heart failure events, whichever occurred first) when compared to patients receiving ICD-only therapy. The study population involved cardiac patients in New York Heart Functional Class I or II (no or mild symptoms) who had either ischemic or non-ischemic heart disease with left ventricular dysfunction (ejection fraction <30%) and QRS duration of >130ms on ECG.

Cardiac resynchronization therapy (CRT) with or without a defibrillator is indicated for use in patients with severe heart failure (New York Heart Association Class III/IV), and CRT has been shown to reduce symptoms, mortality and hospitalization in very sick cardiac patients. The question that remained was whether CRT would improve heart function and slow or prevent the development of heart failure in the less severe NYHA class I/II cardiac patients (moderately high risk, but with no or mild symptoms) by intervening early in the course of the disease before the development of advanced symptoms.

The MADIT-CRT trial enrolled and followed 1820 patients from 110 centers in Europe, Canada, and the USA during a 4.5-year period between December 2004 and 22 June 2009, when the trial was officially ended because of the superiority of the cardiac resynchronization therapy (p=0.001). Patients were randomized in a 3:2 fashion to receive either CRT-D or ICD alone, and all patients received optimal medical therapy for heart failure during the trial.

The superiority of CRT-D therapy was found to be present in all patient sub-groups, including those with ischemic and non-ischemic types of heart disease, as well as in males and females, younger and older patients, and those with mild and more advanced heart dysfunction.

Commenting on the results, the study's principal investigator, Professor Arthur J Moss from the University of Rochester Medical Center, New York, USA, said: "Cardiac resynchronization therapy was dramatically effective in this large study population, with a 34% reduction in the risk of all-cause mortality or heart failure. The benefit is dominated by a 41% reduction in heart failure events. These results validate a new indication for cardiac resynchronization therapy in the prevention of heart failure in at-risk asymptomatic or mildly symptomatic cardiac patients. It seems likely that this preventive CRT-D therapy will have widespread application and utilization."

Conference News

ヨーロッパの循環器医は心臓再同期療法の有効性を確信している

ヨーロッパCRT調査：ヨーロッパにおいて心臓再同期療法はガイドラインで推奨されているよりもより一般的になっている

European CRT Survey: Use of cardiac resynchronization therapy in Europe more common than guidelines recommend

ヨーロッパの循環器医は、心臓再同期療法（CRT）単独または除細動機能付き（CRT-D）によるCRTの有効性を、強力なエビデンスに基づく適応ではない患者に対しても確信しているとESC 2009ホットラインセッションで発表された。ヨーロッパCRT調査には、平均年齢68歳（31%は75歳以上）の患者2,438人を組み入れた。CRT療法を受ける患者には高齢者や洞調律でない者または軽度の心不全のみの患者や心電図上定義された心室dyssynchronyを有さない患者なども含まれた。CRT-PおよびCRT-Dを挿入された患者群間の患者背景に差は認められた；理由は多くあったが、人口統計学および経済因子は一部を構成していた。若年患者、男性および虚血性疾患患者はCRT-Dデバイスを植え込まれる確率が高かった。データから、今回のスタディのコホートは無作為化臨床試験に組み入れられたコホートと著明に類似している（CRTを受ける女性の割合は少なかった）ことが示された。しかし、今回の調査の患者はより高齢で、症状の軽い者が多かった。相当数の患者がnarrow QRSであり、心房細動を有する頻度が高かった。合併症率は無作為化トライアルで報告されたのと同様であった。

Full Text

The European cardiac resynchronization therapy (CRT) Survey is a joint initiative taken by the Heart Failure Association (HFA) and European Heart Rhythm Association (EHRA) of the European Society of Cardiology. Its primary objective is to describe current European practice and routines associated with the implantation of a CRT device with or without an ICD (implantable cardioverter defibrillator) capability in patients with heart failure.

The data collected from the survey provide useful information in CRT for heart failure on patient demographics and selection, clinical characteristics, diagnostic criteria, implantation routines and techniques, short-term outcomes, adverse experience, and assessment of adherence to guideline recommendations. These data should be useful for benchmarking individual patient management and national practice against wider experience. The data from randomized trials of CRT are limited and based largely on selected patients at high-volume centers with experienced operators. In contrast, the European CRT Survey describes current routine practice in CRT implantation based on a wide range of sampling.

Data were collected between 1st November 2008 and 30th June 2009 from 140 volunteer centers in 13 countries (Austria, Belgium, France, Germany, Ireland, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK). Information was provided on consecutive patients successfully implanted with a CRT device with or without an ICD (CRT-P, CRT-D). All patients agreeing to participate will have a follow-up visit approximately one-year after CRT implantation.

The survey enrolled 2438 patients, with a mean age of 68 years (31% were 75 years or older). There are characteristic differences between those receiving CRT-P and CRT-D; the reasons are many, but it is clear that demographic and economic factors play a part. However, the Survey data show that younger patients, men and those with ischemic etiology are more likely to receive a CRT-D device.

The data also show that the cohort is remarkably similar to the cohorts recruited in randomized clinical trials (with a low proportion of women receiving CRT). However, patients in the Survey were older, and more frequently had mild symptoms. A substantial number had a narrow QRS complex (although a broadening is a typical finding in many trials) and more frequently had atrial fibrillation. However, in this real-world population, complication rates were similar to those reported in the randomized trials.

Says lead author Dr. Nigussie Bogale from Stavanger University Hospital in Norway: "This European CRT Survey represents a reasonably large sample reflecting current European practice in the use of CRT devices in the management of patients with heart failure. Our findings show that many patients who do not strictly conform to current guideline recommendations frequently receive a CRT device. Clinicians, researchers and healthcare providers should find these data useful in designing strategies for patient management, trial design and resource allocation."

Conference News

イルベサルタンは心房細動患者の心不全発症を減少させる

ACTIVE-I：イルベサルタンは心房細動患者の心不全および塞栓イベントを減少させる

ACTIVE-I: Irbesartan linked to reduced heart failure complications and embolic events in patients with atrial fibrillation

心房細動クロピドグレルトライアルにおけるイルベサルタンによる血管イベント予防（ACTIVE-I ：Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events）スタディがESC 2009で発表され、降圧剤イルベサルタンが心房細動患者の心不全合併症および脳卒中、他の塞栓イベントおよび一過性脳虚血発作の合計リスクを軽減させたことが明らかになった。このスタディは二つの複合主要エンドポイントを調査した：心血管死、心臓発作または脳卒中の合計であったが、両群間で差はなかった（両群ともに年間5.4%）。しかし、この合計と心不全による入院率は、有意ではないが低い傾向にあった（イルベサルタン群年間7.3%対プラセボ群年間7.7%）。この差は心不全による入院が14%と有意に少ないためであった（イルベサルタン群年間2.7%対プラセボ群年間3.2%）。脳卒中、非中枢神経系塞栓、および一過性脳虚血発作発現率も13%と有意に低かった（イルベサルタン群年間2.9%対プラセボ群年間3.4%）。心血管疾患による入院および入院日数の有意な減少も認められた。イルベサルタンとプラセボの忍容性は同様であった。

Full Text

Most research in atrial fibrillation (AF) has focused on reducing stroke and other embolic events. Yet heart failure occurs more frequently in AF patients, but has not been the focus of intervention research.
In a major international trial, researchers from McMaster University in Canada, found that the hypertension drug irbesartan reduced the risk of heart failure complications and the combination of stroke, other embolic events and transient ischemic events in patients with atrial fibrillation.

Although strokes are frequent in AF patients (and have been the focus of much research), heart failure is even more common, but no intervention has been shown to reduce this complication.

The findings of the ACTIVE-I (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) study was presented at the European Society of Cardiology in Barcelona, Spain, by Dr. Salim Yusuf. Dr. Yusuf is a professor of medicine in the Michael G. DeGroote School of Medicine at McMaster University and director of the Population Health Research Institute at McMaster University and Hamilton Health Sciences.

"The approach to the management of AF patients should be multidimensional," said Yusuf, the chair of the ACTIVE-I steering committee. "While antithrombotic drugs are important in preventing stroke and other complications, complimentary approaches to reducing these and other complications by lowering blood pressure or controlling heart rhythm are important."

The ACTIVE-I study is part of a larger program of research into atrial fibrillation and involves randomizing over 9,000 patients (enrolled at more than 500 centers in 41 countries) to receive irbesartan or placebo for 4.1 years. The study was completed in June, 2009.

The difference in systolic blood pressure between the groups was approximately 3 mm Hg. The study examined two co-primary outcomes: the composite of cardiovascular death, heart attack or stroke which was unchanged (5.4 per cent/year in each group), but this composite plus heart failure hospitalization tended to be non-significantly lower (7.3 per cent/year irbesartan vs. 7.7 per cent/year placebo). The latter difference was due to a significant reduction in hospitalizations for heart failure (2.7 per cent/year irbesartan vs. 3.2 per cent/year placebo) by 14 per cent. There was also a significant reduction in stroke, non-central-nervous-system embolism, and transient ischemic attacks (2.9 per cent/year irbesartan vs. 3.4 per cent/year placebo) by 13 per cent. There was a significant reduction in hospital admissions and the number of days in hospital for cardiovascular reasons. Irbesartan was similarly tolerated compared to placebo.

"The modest BP lowering with irbesartan in the trial likely occurred because patients were already receiving several BP-lowering drugs before entering the trial, and this was intensified to a greater extent in the placebo group during the trial," said Dr. Stuart Connolly, a professor of medicine in the Michael G. DeGroote School of Medicine at McMaster University, a member of the Population Health Research Institute and the principal investigator of the trial.

"When one considers that the difference in systolic BP between groups was less than 3 mm Hg, the 13 per cent to 14 per cent relative risk reduction in heart failure and cerebrovascular and other embolic events is clinically important, and suggests that more aggressive BP lowering may have an even larger benefit."

"By demonstrating the reduction in cardiovascular hospitalizations, the ACTIVE I study highlights the importance of multiple approaches in tackling the total burden of disease in patients with AF," said Dr. Marc Pfeffer, Dzau Professor of Medicine, Harvard University Medical School at the Brigham and Women's Hospital in Boston. Dr. Pfeffer is the U.S. National Coordinator and a member of the ACTIVE Executive Committee.

Conference News

ICDの遠隔調査の効果

TRUST trial：植込み型除細動器の追跡監視は病院受診と比較し、家でモニターすることにより改善した

TRUST trial: Follow-up surveillance of implantable defibrillators is improved by home monitoring compared to hospital visits

植込み型除細動器（ICD）装着患者は遠隔監視および年一回の受診により安全にモニターすることができる―Lumos-Tはルーチンの外来でのデバイスフォローアップを安全に軽減することができる（TRUST：Lumos-T Safely Reduces Routine Office Device Follow Up）―とのトライアル結果がESC 2009で発表された。TRUSTは従来どおりのまたは遠隔監視による追跡調査を前向きに評価した初めてのかつ最大規模（患者1,443人を組み入れ）のスタディであった。患者・医師間の意思疎通に関係のない自動送信は、監視を維持し注目すべき有意なデータを迅速に送信できるため、臨床的に適切な介入ができる。遠隔監視を用いることにより、不必要な受信を省き、カレンダー上3ヵ月おきのチェックを厳守させることができた。TRUSTトライアルの結果、従来の診療のように患者自身が物理的に診察室に訪れる必要のある従来の診療と全く異なり、患者のデータがいつでもどこからでも遠隔監視できる可能性のあることが示された。しかし、従来の診療であれ遠隔監視であれ、カレンダーベースのチェックで検出できる重要なイベント数は総じて少ない。イベントは予定されたチェックとチェックの間に起こりがちであり、いつ発現したかは、心臓または装置の不具合を遠隔監視している方が（中央値<3日）、従来の診療（>30日）よりも遥かに速く検出された。

Full Text

Patients receiving implantable cardioverter defibrillators (ICDs) can be monitored safely through remote monitoring with only one annual follow-up visit according to results form the TRUST (Lumos-T Safely Reduces Routine Office Device Follow Up) trial presented at the 2009 ESC Congress.

The number of patients receiving life saving implantable cardioverter defibrillators (ICDs) is increasing and affects millions worldwide. These devices collect important system and patient data and monitoring their function is very important but is practiced inconsistently. Routine conventional follow-up visits every 3 to 6 months are recommended but, for some patients, this is sometimes difficult to adhere to. The problem with conventional follow-up visits is that no surveillance occurs in between visits. A means of intensive device monitoring without overburdening device clinics is desirable and this role is fulfilled by Home Monitoring.

Automatic transmission, independent of patient or physician interaction, has the ability to maintain surveillance and rapidly bring to attention significant data, enabling clinically appropriate intervention. This form of technology was tested in the TRUST (Lumos-T Safely Reduces Routine Office Device Follow Up) trial. TRUST is the first and largest study (enrolling 1,443 patients) prospectively assessing follow up both conventionally and with remote monitoring.

This current report shows that patients could be monitored safely with only one annual scheduled hospital visit and three monthly checks performed via remote monitoring. Remote monitoring cut out unnecessary hospital visits by almost a half. The use of remote monitoring secured greater follow-up adherence to the three monthly calendar based checks. The TRUST trial showed patient data may be monitored remotely anytime and from anywhere, as opposed to in the conventional care which relies on patients to present themselves physically in their physician's office. However, calendar based checks overall, whether conventionally or remotely, picked up few important events. These were more likely to occur in between scheduled checks, and when they occurred were detected much faster by remote monitoring (median <3 days) of cardiac and/or device problems compared to >30 days with conventional care.

The TRUST trial proves that remote monitoring provides physicians with an important tool for managing patients with implantable device therapy efficiently. It performs daily surveillance, helps to maintain continuity of follow up, and identifies the exceptional group of patients requiring in-clinic attention. Patient convenience is improved since unnecessary follow-up visits are avoided and necessary in-office evaluation is facilitated.

Niraj Varma, M.D., TRUST principal investigator, stated at the ESC Congress that: "The data demonstrates yet another benefit that Home Monitoring brings to patients, as well as physicians." Dr. Varma continued, "Based on the results TRUST, a large-scale clinical trial, I believe that remote monitoring may improve physician's ability to care for patients with implanted cardiac devices and enhance patient safety."

The technology tested was Biotronik Home Monitoring, an automatic, wireless system that performs daily telemetric surveillance of the patient and the technical status of the implanted device, without requiring patient activation.

Conference News

糖尿病患者の非侵襲的リスク同定

心臓磁気共鳴画像により糖尿病患者の主要な有害心臓イベントを予測することができる

Cardiac magnetic resonance imaging predicts major adverse cardiac events in diabetic patients

糖尿病患者の主要な有害心臓イベント（MACE）は心臓磁気共鳴（CMR）画像により予測できるとESC 2009で発表された。この前向きスタディは狭心症で来院しCMRアデノシン灌流およびガドリニウム遅延造影（LGE）画像検査を施行された糖尿病患者170人を対象とした。164人（男性101人および女性63人）において良質のCMR画像が撮影でき追跡調査が可能であった。これら164人の患者は臨床的に心筋梗塞歴のないスタディ群（114人）および心筋梗塞の既往のあるコントロール群（50人）に分割した。追跡調査中央値26ヵ月後に心筋灌流欠損およびLGE陽性の者が32%（114人中36人）存在し、26%（114人中30人）がMACEを経験した。MACEを経験した者は有意に高齢であり、過去に冠動脈血行再建術を施行された率が高く、CMRで評価した左室駆出率が低かった（それぞれp=0.03；p=0.05およびp=0.03）。LGEが存在することによりMACEのハザード比がLGEの存在しない場合と比較し3.5倍増大した（HR 3.5；p=0.01）。心筋灌流欠損によりMACEのハザード比が2.5倍増大した（HR 3.1；p=0.04）。

Full Text

Major adverse cardiac events (MACE) can be predicted by cardiac magnetic resonance (CMR) imaging in patients with diabetes according to a study presented at the 2009 ESC Congress.

Cardiac magnetic resonance imaging provides a noninvasive means to predict moderate to high risk of cardiac events in diabetic patients. It also detects silent myocardial ischemia, according to the results of a study conducted in Hong Kong, where 7.7% of the population is affected by diabetes. Late gadolinium enhancement (LGE) presence was associated with an increase in cardiac events, including death.

As cardiovascular complications are now the leading cause of illness and death in diabetic patients, the burden of cardiovascular disease and premature mortality is expected to rise correspondingly, accounted for an estimated 50% to 80% of all deaths in those with diabetes mellitus (DM). Unfortunately, it has been reported by Rosenmann that a larger population of diabetic patients has asymptomatic myocardial infarction, estimated to be 9.1% compared with only 4.1 % of silent myocardial infarction in non-diabetic patients and patients with silent myocardial infarction are doing worse. There is a clear need to identify diabetic patients at high risk of cardiovascular events who may benefit from more intensive medical or revascularization treatment strategies.

The prevalence of diabetes mellitus has increased tremendously over the past decades. Estimates from the World Health Organization predict that by the year 2015, 300 million people around the world will be diagnosed with diabetes. The Asian/Pacific region accounts for 46% of the global burden of diabetes and China is estimated to contribute almost 38 million people to the diabetic population in the year 2025. The age-adjusted prevalence of diabetes mellitus in Hong Kong was found to be 7.7% whereas the crude prevalence ranged from less than 1% in subjects younger than 30 years to more than 20% in the middle-age group.

Cardiac magnetic resonance imaging (CMR) provides a noninvasive means of comprehensive assessment in myocardial perfusion reserve, to detect myocardial ischemia and characterization of myocardial scar by late gadolinium enhancement (LGE) imaging in a one-stop shop fashion.

Silent myocardial infarction in diabetic patients identified by late gadolinium enhancement by contrast enhanced cardiac magnetic resonance imaging, is the strongest incremental prognostic factor for the development of future major adverse cardiac events (MACE).

This prospective study consisted of 170 diabetic patients presenting with angina who underwent CMR adenosine perfusion and LGE imaging. Good quality CMR imaging and follow up were successful in 164 patients (101 male and 63 female). The 164 patients were divided into the study group (n=114) that consists of patients without clinical history of myocardial infarction and the control group (n=50) with a past history of myocardial infarction. Cox regression analyses were performed to associate the presence of myocardial ischemia by positive adenosine perfusion study and LGE with major adverse cardiovascular events (MACE), including cardiovascular death, occurrence of new myocardial infarction, unstable heart failure requiring hospitalization, significant ventricular arrhythmic events and unstable angina between the study group and the control group respectively.

At a median follow-up of 26 months, positive myocardial perfusion defect and LGE was present in 32% (36 of 114 patients) and 26% (30 of 114 patients) experienced MACE respectively. Patients with MACE were significantly older, had more prevalence of having previous coronary revascularization procedures and lower left ventricular ejection fraction as assessed by CMR (p=0.03; p=0.05 & p=0.03 respectively).

The presence of LGE was associated with a 3.5 fold hazards increase for MACE (hazard ratio, 3.5; p=0.01) compared with patients without LGE. The presence of perfusion defect was associated with a 2.5 fold hazards increase for MACE (hazard ratio, 3.1; p=0.04). Adjusted with other clinical risk factors including age, left ventricular ejection fraction and myocardial perfusion imaging, LGE was the strongest multivariable predictor of the development of MACE.

Furthermore, diabetic patients without history of myocardial infarction but silent myocardial infarction identified by positive LGE had a cardiac event rate similar to that of patients with clinical evidence of prior MI.

These results have further proven the hypothesis that diabetic patients with silent myocardial infarction are a high risk population for future MACE and justify more intensive management strategy.

In conclusion, cardiac magnetic resonance imaging provides a noninvasive means to identify moderate to high-risk diabetics. It detects silent myocardial ischemia by adenosine myocardial perfusion and identifies silent myocardial infarction. LGE by CMR provides incremental value in the risk stratification model in diabetic patients that is complementary to other well known risk factors model.

Conference News