Cangrelorはクロピドグレルよりも優れている（Abstract # 13-LB-15696）

CHAMPION PHOENIX: Cangrelorの他に類を見ない即効性の抗凝固作用は循環器領域において広く有用である可能性がある

CHAMPION PHOENIX: Uniquely fast anticoagulant action of cangrelor has potential for broad utility in cardiology

冠動脈ステント留置を施行された患者を対象とした大規模グローバルトライアルにおいて、治験中の抗凝固薬cangrelorは一般的に使用されているクロピドグレルよりも確実に優れていたとの第Ⅲ相CHAMPION PHOENIXスタディのデータが第62回American College of Cardiology学会で発表され、同時に*New England Journal of Medicine*オンライン版に掲載された。このトライアルでは新たな静注薬cangrelorと経口薬クロピドグレルによる標準治療を世界中の153施設の患者約11,000人において比較した。トライアルは全てのタイプの急性冠症候群、狭心症およびPCIを施行された他の疾患の患者を対象とした。Cangrelorの成績はクロピドグレルよりも有効性の計測値において有意に優れており（4.7%対5.9%）、つまり一次エンドポイント（総死亡、心筋梗塞、無作為化後48時間以内の虚血による血行再建術またはステント血栓）発現率が22%低下した。Cangrelorはまた重要な二次エンドポイント（48時間以内のステント血栓）発現率も38%低下した。安全性エンドポイントである48時間以内の重篤な出血の発現率は、両治療群ともに低く統計学的に同等であった（0.16%対0.11%）。有効性と安全性の結果は一般的に報告されるサブグループ全てにおいて一貫していた。

Full Text

The experimental anticoagulant drug cangrelor solidly outperformed commonly used clopidogrel in a large global trial of patients who underwent coronary stent procedures, according to data from the phase III CHAMPION PHOENIX study presented at the American College of Cardiology's 62nd Annual Scientific Session and simultaneously published online in the *New England Journal of Medicine*.

Cangrelor and clopidogrel interfere with the P2Y12 receptor, a platelet-surface protein that helps regulate blood clotting. Currently approved drugs in this class are effective in cutting down ischemic events in patients who need percutaneous coronary intervention (PCI), but they have important clinical limitations: they're slow to take effect, remain active for days and come only in pill form. For patients on recent anti-platelet therapy who need timely coronary intervention, that profile poses risk of surgical bleeding if the drug is still active or risk from postponing surgery until the drug's effect wears off. Additionally, oral drugs present problems for anyone who urgently needs stenting and is in no condition to swallow or absorb a pill. Cangrelor is administered intravenously, takes effect rapidly and wears off an hour after the infusion ends.

CHAMPION PHOENIX, a randomized double-blind trial, pitted the novel IV drug cangrelor against the oral clopidogrel standard of care in approximately 11,000 patients at 153 centers around the world. An "all-comers" clinical trial, it included a broad cross-section of patients with every type of acute coronary syndrome, angina and other conditions for which people undergo PCI, as long as they had no recent exposure to a P2Y12 inhibitor and could swallow a pill. Other exclusion criteria included recent use of anti-clotting agents called GP IIb/IIIa inhibitors or fibrinolytics and specific indications of high risk of bleeding.

Cangrelor performed significantly better than clopidogrel across efficacy measures: 4.7 percent vs. 5.9 percent, or a 22 percent reduction in the odds of the primary endpoint, which was composite incidence of death, myocardial infarction, ischemia-driven revascularization or stent thrombosis at 48 hours after randomization. Cangrelor also showed a 38 percent reduction in the odds of the key secondary endpoint, incidence of stent thrombosis at 48 hours. Both treatment arms showed a low, statistically comparable incidence for the safety endpoint of severe bleeding at 48 hours: 0.16 percent vs. 0.11 percent. The efficacy and safety results were consistent in all commonly reported subgroups.

"These are endpoints we worry about a lot in interventional cardiology and cardiology in general," said Deepak L. Bhatt, MD, MPH, chief of cardiology at VA Boston Healthcare System, senior physician at Brigham and Women's Hospital, professor of medicine at Harvard Medical School, Boston and, along with Robert A. Harrington, M.D., chairman of medicine at Stanford University School of Medicine, co-principal investigator. "This study examined a very wide spectrum of patients, which means the results really do apply to a substantial percentage of patients undergoing stent procedures around the world."

The company plans to file for approval with the Food and Drug Administration using data from CHAMPION PHOENIX and the earlier BRIDGE trial.

"The investigators feel the data are compelling," Dr. Bhatt explained. "The data we've shown are clear and consistent across all relevant subgroups or patient populations. This drug has several advantages, and nothing out there right now has quite the same biological properties."

The Medicines Company sponsored the CHAMPION PHOENIX trial and provided a research grant to the Duke Clinical Research Institute for the statistical analyses and event adjudication.

ACC2013特集

治験薬は血管形成術中の心筋傷害を軽減する（Abstract＃13-LB-15976）

SELECT ACS: InclacumabはNSTEMI患者のPCI後の心筋傷害を軽減する

SELECT ACS: Inclacumab reduces myocardial damage after PCI in patients with NSTEMI

治験中の抗炎症薬inclacumabの単回投与は血管形成術中の心筋傷害を軽減するとのスタディ結果が第62回American College of Cardiology学会で発表され、同時に*Journal of the American College of Cardiology*に掲載された。SELECT ACS第Ⅱ相試験は非ST上昇心筋梗塞（NSTEMI）を発症した患者530人（年齢中央値61歳）を対象とした。患者は、20mg/kgのinclacumab、5mg/kgのinclacumabまたはプラセボを血管形成術の1時間前に投与される群にランダムに割り付けられた。研究者らはトロポニンIおよびCK-MBを用いて心筋傷害を評価した。20mg/kgの inclacumabを投与された患者においてはプラセボ投与患者と比較し、16時間後のトロポニンI値が22.4%（*P* =0.066）そして24時間後のトロポニンI値が24.4%（*P* =0.05）低かった。CK-MB値はプラセボと比較し、16時間後に16.3%（*P* =0.088）そして24時間後に17.4%（*P* =0.055）低かった。血管形成術後24時間の時点で、プラセボ群では18.3%でCK-MBが 正常上限の3倍以上（多くの臨床試験で血管形成術後心筋梗塞を定義するのに用いる閾値）に上昇していた。これと比べ高用量のinclacumab投与患者におけるその割合は8.9%であった（*P* =0.051）。5mg/kgの用量は有効性のエンドポイントにおいて有意な効果は示さなかった。

Full Text

A single dose of an investigational anti-inflammatory drug, inclacumab, reduced myocardial damage during angioplasty in a study presented at the American College of Cardiology's 62nd Annual Scientific Session and simultaneously in the *Journal of the American College of Cardiology.*

In this trial, researchers compared a single dose of inclacumab administered one hour before angioplasty with a placebo. Inclacumab is a human monoclonal antibody that blocks p-selectin, a molecule found in platelets and the cells that line blood vessels. P-selectin is activated in response to inflammation, which can ultimately lead to tissue damage. The study met its primary endpoint: decrease in levels of troponin I, a protein found in the bloodstream when heart damage has occurred, after angioplasty.

"Our hypothesis was that by using the p-selectin antagonist inclacumab, we'd be able to demonstrate vascular benefit," said Jean-Claude Tardif, M.D., director of the Research Centre at the Montreal Heart Institute, professor of medicine at the University of Montreal and the study's lead investigator.

The SELECT-acute coronary syndrome phase II trial involved 530 patients with a median age of 61 experiencing a type of heart attack called non-ST-elevation myocardial infarction or NSTEMI. Patients were randomized to receive an infusion of inclacumab at 20 mg/kg, inclacumab at 5 mg/kg or placebo one hour before angioplasty.

Researchers measured heart damage using two standard molecular markers: troponin I and CK-MB. These markers are used clinically to diagnose myocardial infarction (MI). They were measured at baseline and at eight, 16 and 24 hours after PCI. The co-primary endpoints were the change in troponin I at 16 hours and 24 hours.

In patients receiving 20 mg/kg of inclacumab, troponin I levels dropped 22.4 percent more at 16 hours (P =0.066) and 24.4 percent more at 24 hours (*P* =0.05), compared with patients on placebo. CK-MB levels dropped 16.3 percent more at 16 hours (*P* =0.088) and 17.4 percent more at 24 hours (*P* =0.055), compared with patients on placebo.

Also, at 24 hours after angioplasty, 18.3 percent of patients on placebo had CK-MB increases of more than three times the upper limit of normal, a threshold that many clinical trials use to define a post-angioplasty MI. This compared with 8.9 percent of patients who received the higher dose of inclacumab (*P* =0.051).

The 5 mg/kg dose of inclacumab had no significant effects on the cardiac markers.
Researchers also measured p-selectin levels to see if they correlated with changes in CK-MB and troponin I. Levels did not drop significantly in the group that received 5 mg/kg inclacumab. However, levels dropped 19.2 percent with the 20 mg/kg inclacumab dose, compared with placebo (*P* =0.0002).

"It was exciting to see that a single administration of inclacumab would yield clinical benefit," Dr. Tardif said.

The researchers analyzed a subgroup of patients who were not taking antiplatelet drugs called glycoprotein 2b3a inhibitors. These are given to some patients to prevent blood clots but can increase the risk of bleeding. In patients not taking 2b3a inhibitors, those who received the 20 mg/kg dose of inclacumab experienced a 36 percent decrease in troponin I at 24 hours (P =0.008 compared with placebo).

"If we're able to confirm these results in potential future studies, this drug could become part of the therapeutic armamentarium in modern cardiology," Dr. Tardif said. "You could use this drug more widely, in all patients coming in with heart attacks, although that would require additional large studies."

The trial was sponsored by Hoffman-La Roche, Ltd. Dr. Tardif's institution has received financial support from Hoffman-La Roche.

余震の強度は心血管系の健康に直接影響する（Abstract # 13-A-13796）

日本における2011年の地震による余震は心筋梗塞および突然死を倍増した

Aftershock of the Japan 2011 earthquake linked to a doubling in myocardial infarctions and sudden death

地震およびそれに続く余震による急性の情動的および身体的ストレスは、心疾患率の低い人々においても心筋梗塞（MI）および突然死の誘因として重要である可能性があるとの研究結果が第62回American College of Cardiology学会で発表された。研究者らは日本における2011年の地震およびその後の津波を被った地域におけるMIと心臓突然死を発症した患者の誘因および臨床的特徴を評価した。最初の最大の地震は2011年3月11日に発生し震源地のマグニチュードは9.0であった。岩手ではこれにより震度5.6の地震が起きた。2つ目の地震は4月7日に発生した震度5.5の地震であった。それまでの年と比較し、この災害後4週間のMIおよび突然死発生総数は倍であった。津波の影響を受けた地域と内陸とで有意な差は認められなかった。これらの結果および心イベントと自然災害とを関連付けた他のスタディから、自動体外式除細動器の公共配置や病院における高度な災害計画などの予防措置をとることの必要性が強調される。筆者らはまた、高リスク患者には薬剤（即効性カルシウム受容体拮抗薬、β遮断薬、アスピリンおよびニトログリセリン舌下錠）を供給し手元に置かせることも提案している。

Full Text

Acute emotional and physical stress induced by earthquakes and subsequent aftershocks may be important triggers of myocardial infarction (MI) and sudden death, even in a population with low rates of heart disease, according to research presented at the American College of Cardiology's 62nd Annual Scientific Session.

Researchers assessed the incidence and clinical characteristics of patients with an acute MI and sudden cardiac death in the area affected by the 2011 earthquake and subsequent tsunami in Japan. Patients with myocardial infarction treated in all hospitals located in the disaster area were assessed retrospectively for four weeks before and eight weeks after the disaster. Subjects who experienced sudden death, defined as death within one hour after onset, prior to arrival at the hospital were also assessed by death certificate. For comparison with the previous year's case numbers, the same assessment was conducted in the corresponding area and time period for 2009 and 2010. There were no significant differences in age, gender, preexisting heart disease or in-hospital death between the before and after periods.

There were clear peaks in the incidence MI and sudden death in the week after each of the two major shocks of the Japan natural disaster. The first, main shock occurred March 11, 2011, with a magnitude of 9.0 in the epicenter. In Iwate, this produced seismic intensity—the strength of the shaking— of 5.6. The second happened at midnight on April 7 with a seismic intensity of 5.5 in the study area.

Researchers found a significant relationship between the number of MI and sudden death and seismic intensity. Compared to previous years, overall incidence of MI and sudden death four weeks after the disaster was significantly increased. In the study area, incidence of MIs, including sudden cardiac death, doubled. No significant differences in the increase of the prevalence rate were found between the tsunami-impacted and inland area.

"These data suggest that acute emotional and physical stress induced by the earthquake itself rather than the long-term environmental deterioration by the tsunami is an important trigger of heart attacks and sudden death. Several previous studies suggest the time of shocks, especially early morning, is important to the increase in heart attacks and sudden death," said Motoyuki Nakamura, M.D., professor of internal medicine, division of cardioangiology, Northern Iwate Heart Disease Registry Consortium, Iwate Medical University, Morioka, Iwate, Japan, and one of the study authors. "However, in our case, it's the intensity of the shocks themselves, rather than the time window, that appear to be related to the increased incidence as both earthquake shocks clearly increased the incidence in the present disaster regardless of time."

While the researchers did not study the underlying cause of the rise in MIs and sudden death, Dr. Nakamura speculates that the combination of emotional and physical stress, along with a shortage of food and water and increased dehydration, may have conspired to increase blood pressure, heart rate and blood clotting and may have resulted in plaque rupture.

Dr. Nakamura added that the death rate of patients admitted to the hospital did not increase after the disaster, suggesting that medical staff working in the field may have been able to maintain the usual quality of care for patients even amid insufficient medical staff, shortages that well preceded the disaster.

Researchers believe their findings and those of other studies linking cardiac events to natural disasters underscore the need to take preventive measures, such public distribution of automated external defibrillators, especially in areas with frequent earthquakes or other disasters, as well as advanced hospital disaster planning to address how to transfer patients to nearby hospitals and leverage other support services. Dr. Nakamura also suggests a supply of medications such as quick-acting calcium channel blockers, beta blockers, aspirin and sublingual nitroglycerin be kept on hand for high-risk patients to help prevent cardiac events.

This study was supported, in part, by the Japan Science and Technology Agency, Takeda Science Foundation and the Japanese Circulation Society.

ACC2013特集

オフポンプとオンポンプバイパス術技術は同等である（Abstracts # 13-LB-10677 and 13-LB-15974）

CORONARY trial：オンポンプバイパス術とオフポンプバイパス術に関する最大のスタディの結果、両者ともに安全に施行できることが証明された

CORONARY trial: Largest study of on-pump and off-pump bypass proves both can be done safely

人工心肺使用（オンポンプ）および人工心肺不使用（オフポンプ）で施行される冠動脈バイパス術を比較した結果、全体の技術に差はなかったが臨床的には明らかな差があったことが示されたとの研究結果が第62回American College of Cardiology学会で発表された。2007年10月以降、CORONARYトライアルでは、冠動脈疾患を有しCABGを予定された患者4,752人（平均年齢67.6歳、80.0%男性）を徹底的に評価し、確実にオフポンプまたはオンポンプ手術いずれもが適応であることを確認したあとでこれらのいずれかの手術に無作為に割り付けた。患者当たりの平均グラフト数は3.1であった。バイパス術後30日以内の死亡、心筋梗塞、腎不全および脳卒中からなる一次総アウトカムに関しては、統計学的に同等であった（オフポンプ患者9.9%およびオンポンプ患者10.3%）。同様に、この総アウトカムの個々のイベントについても差がなかった。オフポンプ手術の方が必要とする血液製剤の量、出血による再手術、肺合併症および急性腎障害が少なかったが、再血行再建術の施行がより多かった。この発現率はまれであった（オフポンプ群で2,375人中16人、あるいは0.7%に対しオンポンプ群で0.2%）。

Full Text

Two studies presented at the American College of Cardiology's 62nd Annual Scientific Session and simultaneously published online in the *New England Journal of Medicine* show similar efficacy for on- and off-pump heart bypass surgery.

In CORONARY, an international, multicenter trial of on-pump versus off-pump bypass surgery, enrolled 4,752 patients already scheduled to undergo a bypass procedure. The study is the largest to compare the two approaches.

For the primary endpoint of patients' composite outcomes of death, stroke, myocardial infarction or new kidney failure requiring dialysis within one year of surgery, researchers found no significant difference between patients receiving the off-pump and on-pump procedures (12.2 vs. 13.3 percent, $P = 0.24$.) The study previously looked at this primary endpoint for patients at 30 days and also found the two methods to be statistically neutral in the short-term, but conflicting results from other research studies raised uncertainty about patients' intermediate (one year post-surgery) and long-term outcomes.

"We found that both on-pump and off-pump bypass have similar results, even at one year," said Andre Lamy, M.D., lead author of the CORONARY study and professor in the division of cardiac surgery at McMaster University in Ontario. "Both surgical approaches are effective when provided by experienced surgeons."

Coronary artery bypass graft surgery (CABG) is one of the most commonly performed operations in the world and consumes more resources in cardiovascular medicine than any other procedure. In on-pump CABG, the patient's heart is stopped and blood is circulated through a heart-lung machine, where it is oxygenated and returned to the patient. In the off-pump technique, the surgeon uses a retractor to lift the still-beating heart and perform all coronary artery grafts. Off-pump CABG eliminates the need to insert a cannula into the aorta, cross-clamp the aorta, connect the patient to the heart-lung machine and stop and restart the heart.

The CORONARY study included patients from 79 centers in 19 countries who were scheduled to undergo CABG. Participants were randomly assigned to receive on-pump or off-pump CABG after a complete assessment to ensure they were appropriate for both techniques. In addition to the primary endpoint, researchers looked at the need for coronary revascularization between groups. This entails restoring blood flow to the heart through a repeat CABG or placement of a stent and indicates the initial CABG procedure was not successful. Again, results were similar between groups with 1.4 percent of patients in the off-pump group and 0.8 percent of patients in the on-pump group requiring this additional procedure.

The study also assessed the neurocognitive function and quality of life of patients in each group through the use of standardized scales.

"We found a transient improvement in neurocognitive function at hospital discharge among those receiving an off-pump bypass," Dr. Lamy said. "But at one year, our results are similar with both techniques."

According to Dr. Lamy, this transient difference in patients' neurocognitive functions came as a surprise to researchers, as smaller studies have shown evidence of short-term neurocognitive declines among patients receiving both types of bypass. Researchers found patients' quality of life to be similar after both on- and off-pump bypass.

The CORONARY study results differ from those emerging from another large trial that suggested improved outcomes at one year with on-pump surgery. According to Dr. Lamy, this discrepancy is likely related to surgeons' expertise in the two techniques, as well as the surgical risk of each patient.

"Compared to the other trial, our patients were older and sicker, and our surgeons were more experienced, particularly in performing off-pump bypass," he said.

Off-pump bypass requires a higher degree of surgical expertise since the operation occurs while the patient's heart is still beating. Thus, surgical expertise is a key factor affecting patient outcomes, and it is possible that other studies have not controlled for this, Dr. Lamy said.

All surgeons participating in the CORONARY study were required to have performed a minimum of 100 cases in the approach used, though the vast majority of surgeons in their study were highly experienced in both types of procedure, Dr. Lamy said.

"The CORONARY study shows that off-pump bypass is just as good as on-pump. Therefore, surgeons should tailor their surgical approach to their technical expertise and expected technical difficulty," Dr. Lamy said.

The CORONARY study will follow patients for five years. Researchers hope this continued evaluation will provide needed evidence about the success of on- and off-pump bypass beyond the first year.

The CORONARY study was supported by a grant from the Canadian Institutes of Health Research.

The second study is the large, multicenter trial—the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients, called GOPCABE. It was the first study to evaluate on-pump versus off-pump bypass surgery among patients aged 75 or older. The primary endpoint was individual patients' combined outcomes of death, stroke, heart attack, repeat revascularization or new renal replacement therapy within 30 days of surgery. Researchers found no significant difference in the primary endpoint between patients receiving the on-pump and off-pump procedures (8.2 vs. 7.8 percent, $P = 0.74$).

"Our study shows that coronary bypass surgery can be performed in the elderly population with excellent results, and this is equally true for both techniques," said Anno Diegeler, M.D., Ph.D., head of the department of cardiovascular surgery at the Heart Center Bad Neustadt in Germany and the study's lead investigator. "These findings suggest clinicians can select the lower cost off-pump procedure without risk to the patient."

Previous studies comparing the two techniques also found similar results for on-pump and off-pump CABG, but none of these studies focused exclusively on elderly patients. To address concerns that the elderly may not benefit equally from both techniques because of their higher risks, GOPCABE enrolled 2,539 patients aged 75 or older scheduled for elective, first-time CABG in 12 cardiovascular centers in Germany. Patients were randomized to receive on-pump or off-pump CABG. Results for all components of the primary endpoint were similar between the groups at 30 days. Patients had no significant differences in rates of death (2.8 vs. 2.6 percent), stroke (2.7 vs. 2.2 percent), heart attack (1.7 vs. 1.5 percent), and new renal replacement therapy (3.1 vs. 2.4 percent), and a slim difference in repeat revascularization (0.4 vs. 1.3 percent). At 12 months, researchers again found no significant difference in the composite endpoint between on- and off-pump (14.0 vs. 13.1 percent, $P = 0.483$).

Study results are important for surgeons who favor off-pump surgery, Dr. Diegeler said.

"For surgeons who prefer off-pump surgery, our study confirms that off-pump CABG is safe and the quality is equal to on-pump surgery for elderly patients. At 12 months, we had a survival rate of 93 percent among our off-pump patients and 92 percent for on-pump," he said. He notes that the surgeon's level of experience is critical in assessing the two techniques.

According to Dr. Diegeler, the similar result from both techniques is beneficial to facilities and patients in developing countries, where the on-pump procedure may come at a higher cost since instruments used in off-pump CABG can be re-sterilized, but components of the machine used in on-pump cannot.

While this study provides support for the efficacy and safety of both CABG techniques in the elderly, Dr. Diegeler said further work is needed to look at CABG outcomes in other special populations, including patients deemed high-risk for surgery.

The GOPCABE study was supported by a grant from MAQUET, in Rastatt, Germany.

ACC2013特集

DKクラッシュおよびキュロットステント施術が比較された（Abstract # 13-LB-10264）

DKCRUSH-III: 治療困難な分岐部病変において"ダブルキッシング"クラッシュステントを用いた際の有害事象は少ない

DKCRUSH-III: Fewer adverse events with “double kissing” crush stent in challenging bifurcation lesions

冠動脈分岐部病変を有する患者に対する治療は"ダブルキッシング"クラッシュとして知られるステント技術を用いた方がキュロットステント治療よりも有意に優れていたとのDKCRUSH-Ⅲトライアルの結果が第62回American College of Cardiology学会で発表された。キュロット技術は主幹動脈および分枝にオーバーラップするステントを留置する。DKクラッシュ技術は分枝ステントの小片を主幹動脈の方へ延長させる。この方法はバルーンを動脈内で拡張させることと"ダブルキス"させることの2点を取り入れている。今回の多施設スタディでは、非保護左主幹動脈末梢分岐病変の患者をDKクラッシュ（210人）またはキュロット（209人）ステントを施行する群に無作為に割り付けた。8か月後の追跡冠動脈造影の結果、ステント内再狭窄をDKクラッシュ群で12例に、キュロット群で22例に認めた（6.8%対12.6%）。1年後に主要な有害心事象を来したのはDKクラッシュ群患者の方がクロット群より少なかった（6.2%対16.3%）。標的病変および標的血管の再血行再建術施行率はキュロット法の方が明らかに高かった：標的病変においては6.7%対2.4%であり、標的血管においては10.5%対4.3%であった。この結果は*Journal of American College of Cardiology*のオンライン版に公表されており、印刷版4月9日号に掲載予定である。

Full Text

Patients with coronary bifurcation lesions that are linked with poor prognosis, fared significantly better with the stent technique known as double kissing crush than with culotte stenting, according to data from the DKCRUSH-III trial presented at the American College of Cardiology's 62nd Annual Scientific Session.

DKCRUSH-III is the first head-to-head comparison of double kissing (DK) crush and culotte stent techniques in coronary artery disease. The study focused on bifurcation lesions.

DK crush and culotte are two-stent procedures named for their configurations. The culotte technique places stents in the main artery and the side branch, overlapping them in the main vessel before the branch forks, akin to pants legs that meet at the seat. The DK crush technique extends a small piece of the branch stent into the main artery, where it is squeezed against the main artery's wall. This approach introduces two points where the balloons used in stenting inflate in the artery and connect for a "double kiss."

Bifurcation lesions are Y-shaped trouble spots, which account for about 15 percent of lesions treated with coronary stents. Bifurcation lesions present technical problems associated with higher rates of restenosis and lower rates of long-term favorable outcome. High morbidity and mortality are connected with unprotected left main coronary artery (ULMCA) disease. Approximately two-thirds of significant ULMCA disease involves the distal bifurcations. Such lesions magnify the challenge for the interventional cardiologist. The best treatment for this lesion type has been a matter of debate.

"Angiographic follow-up at eight months found 12 cases of in-stent restenosis in the side branch with DK crush and 22 with culotte [6.8 percent vs. 12.6 percent]," said Jun-Jie Zhang, M.D., an interventional cardiologist in the cardiovascular department of Nanjing First Hospital, Nanjing Medical University, in Nanjing, China. "Thus, we have to say that DK crush is superior to culotte stenting."

The multicenter study randomly assigned patients with ULMCA distal bifurcation lesions to treatment with DK crush (210 patients) or culotte (209 patients) stenting. At one year, major adverse cardiac events occurred in 6.2 percent of the DK crush patients and 16.3 percent of the culotte patients. The culotte approach had markedly higher rates of repeat intervention at the target lesion and the target vessel: 6.7 percent target lesion vs. 2.4 percent, and 10.5 percent target vessel vs. 4.3 percent. Clotting at the stent site was low in both groups.

"Although this trial did not include a bypass surgery group to contrast with the stenting techniques, the promising results achieved by DK crush were comparable with those after coronary artery bypass," Dr. Zhang said.

The study will extend clinical follow-up for participating patients to five years, and further research through the DKCRUSH-V study is ongoing.

The study was simultaneously published online in the *Journal of American College of Cardiology* and will appear in the April 9 print edition.

DKCRUSH-III was funded by the Jiangsu Provincial Outstanding Medical Program.

ACC2013特集

血栓溶解薬は血管形成術と同程度に有効である（Abstract # 13-LB-15699）

STREAM: 病院到着前のtenecteplase投与は一部の心筋梗塞患者において有益である

STREAM: Treatment with tenecteplase before hospital benefits some patients suffering myocardial infarction

血栓溶解療法は緊急血管形成術を行うことのできない一部の心筋梗塞患者において有益である可能性があるとのレイトブレイキングトライアルの結果が第62回American College of Cardiology学会で発表され、同時に*New England Journal of Medicine*に掲載された。Strategic Reperfusion Early After Myocardial Infarction（STREAM）トライアルにはST上昇心筋梗塞（STEMI）患者1,915人を組み入れた。患者は初めにカテーテルインターベンション（PCI）の施行できない状況で、地域病院または救急隊員により診察された。大規模な医療機関に転送される前に、患者は到着直後にPCIを施行される群、またはtenecteplaseとエノキサパリンとの併用および到着前のクロピドグレルおよびアスピリンによる薬物療法群にランダムに割り付けられた。大規模医療機関へ転送された時点で、tenecteplase患者の約3分の1が緊急血管形成術を必要とした。一次エンドポイント（総死亡、ショック、うっ血性心不全および30日以内の心発作の合計）は緊急PCI群とtenecteplase群とで同等であった（14.3%対12.4%、*P*=0.211）。心臓特異的死亡率または心疾患による再入院に関して差はなかった。Tenecteplase群の方が冠動脈造影上正常な血流を有する確率が高かった（58%対21%）。また同群はPCI施行群よりも冠動脈完全閉塞を有する率が低かった（16%対59%）。

Full Text

A clot-busting therapy may benefit some myocardial infarction patients who cannot have immediate angioplasty, according to research presented at the American College of Cardiology's 62nd Annual Scientific Session.

"Drug therapy before transfer is at least as effective as [angioplasty], and an urgent catheterization was avoided in two-thirds of patients," said Frans Van de Werf, M.D., Ph.D., professor of cardiology at University of Leuven, Belgium, and the study's lead investigator. "It gives [clinicians] time to consider other options, such as [coronary artery bypass graft] and medical therapy."

The Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial included 1,915 patients from 15 countries. All had ST-elevation myocardial infarction (STEMI). Patients were first seen in community hospitals or by emergency medical personnel. In these settings, immediate percutaneous coronary intervention (PCI) —the preferred first-line treatment for STEMI—was not possible until patients were transferred to a major medical center.

Before transfer, subjects were randomized to either angioplasty immediately after arrival or to drug therapy with tenecteplase plus enoxaparine, clopidogrel and aspirin before arrival. When patients on tenecteplase reached a medical center, about one-third needed urgent angioplasty. The other two-thirds did not. They received an angiogram an average of 17 hours after arrival. Based on the results of the angiogram, patients received either PCI or coronary artery bypass graft surgery under non-urgent circumstances.

The primary endpoint was a composite of all-cause mortality, shock, congestive heart failure and subsequent myocardial infarction within 30 days. Results were similar between the immediate PCI group and the tenecteplase group (14.3 vs. 12.4 percent, *P*=0.211). There were no differences in cardiac-specific mortality or cardiac rehospitalization.

Patients receiving tenecteplase were more likely to have normal blood flow on an angiogram, compared with the PCI-only group (58 vs. 21 percent). They were less likely than the PCI-only group to have an angiogram show complete blockage of an artery (16 vs. 59 percent). More tenecteplase patients than PCI-only patients eventually underwent coronary artery bypass graft surgery.

During the course of the trial, researchers halved the dose of tenecteplase in people ages 75 and older to minimize cranial bleeding, a common complication of clot-busting therapy. The incidence of such bleeding in the total study population was 0.5 percent after the dose reduction.

"We offer this pharmaceutical strategy with timely coronary angiography as an alternative to primary PCI," Dr. Van de Werf said. "We believe that it may be helpful in some early-presenting patients for whom immediate PCI is not possible."

The study was funded by Boehringer Ingelheim. Dr. Van de Werf's institution, the University of Leuven, received a grant from Boehringer Ingelheim to conduct the STREAM trial, as well as funding for a study of dabigatran in patients with a mechanical heart valve.

ACC2013特集

カテーテル弁置換術の安全性は開心術と同様である（Abstract # 13-LB-15857）

PARTNER: 脳卒中および死亡は経カテーテル的大動脈弁置換術と標準的な手術とで同等である

PARTNER: Midterm stroke and death rates comparable for transaortic valve replacement and standard surgery

高リスク高齢者において経カテーテル的大動脈弁置換術（TAVR）の3年後の総死亡率および心血管死亡率は開心術と比較し同等であり術後30日間の脳卒中リスクも上昇しないとのレイトブレイキング臨床試験の結果が第62回American College of Cardiology学会で発表された。第Ⅲ相多施設スタディPARTNERでは、高リスクのfaulty大動脈弁患者699人を標準治療（351人）またはTAVR群（348人）に割り付けた。3年後の総死亡率は両群間でほぼ同等であった：標準手術群44.8%に対しTAVR群44.2%。心血管死亡率もまた標準手術群で30.2%およびTAVR群で30.1%であり、統計学的には差がつかなかった。両群ともに症状は同様に改善し、それは3年間持続した。2年後または3年後の脳卒中リスクにも差はなかった。TAVR脳卒中率は1年後で6%、2年後では7.7%であり3年後では8.2%であったのに対し、標準的な手術ではそれぞれ3.2%、4.9%および9.3%であった。このスタディは*American Journal of Medicine*オンライン版で公表されており2013年8月号印刷版に掲載予定である。

Full Text

All-cause and cardiovascular mortality were similar for transaortic valve replacement compared to open-heart surgery in high-risk older patients at three years with no increased risk of stroke after 30 days, according to results from the PARTNER study presented at the American College of Cardiology's 62nd Annual Scientific Session.

The transcatheter aortic valve replacement (TAVR) system was investigated as an alternative to open-heart surgery for high-risk patients with severe aortic stenosis. Recovery from catheter-based valve replacement typically takes a few days compared with four to eight weeks for open-heart surgery, which may be a benefit in a high-risk patient population.

The multi-center PARTNER study assigned 699 high-risk patients with faulty aortic valves to standard surgery (351 patients) or TAVR (348 patients). At three years, all-cause mortality was nearly identical in both groups: 44.8 percent for standard surgery compared to 44.2 percent for TAVR. Cardiovascular mortality rates also were statistically indistinguishable at 30.2 percent for standard surgery and 30.1 percent for TAVR. Both groups displayed similar improvements in symptoms that have been maintained for three years.

"One of the concerns has been the durability of the valve, but there seems to be no structural deterioration thus far," said Vinod H. Thourani, M.D., associate professor of cardiac surgery and co-director of the Structural Heart and Valve Center at Emory University School of Medicine in Atlanta. "It works as it's supposed to work, and hemodynamic performance is excellent past the three-year mark and comparable to surgical valve replacement."

With the much higher stroke rate reported for TAVR at 30 days, the other concern in this study has been whether a higher stroke risk would persist beyond that 30-day periprocedural window. None appeared at two or three years. TAVR stroke rates were 6 percent at one year, 7.7 percent at two years and 8.2 percent at three years, compared with 3.2 percent, 4.9 percent and 9.3 percent for standard surgery.

"After 30 days, TAVR patients don't have that many strokes," Dr. Thourani said. "At three years the surgery group's stroke rate has caught up with and slightly surpassed the TAVR rate but not to statistical significance."

Leaks around the valve were common soon after the procedure and were overwhelmingly higher in the TAVR group, and even mild aortic leakage is associated with a higher mortality rate after any valve replacement procedure, Dr. Thourani noted.

"In these first-generation transcatheter procedures, we have equivalent midterm outcomes between TAVR and the gold-standard surgical valve replacement in high-risk patients with severe aortic stenosis," Dr. Thourani said. "However, paravalvular leak continues to increase mortality at three years. Physicians should adopt innovative imaging technologies for more accurate sizing to help decrease these leak rates during TAVR."

The phase III study will follow patients for five years to assess durability of the TAVR device and longer-term outcomes.

Edwards Lifesciences sponsored this clinical trial and provides funding to Emory University for the research. Dr. Thourani sits on the steering committee and the publications committee for the PARTNER study.

ACC2013特集

心疾患の起源がミイラにおいて発見された（Abstract # 13-LB-15977）

Horus study: 4,000年前まで遡ると多くの地域や生活習慣からミイラに動脈硬化があったことが分かった

Horus study: Atherosclerosis found in mummies from many geographies and lifestyles dating back 4,000 years

動脈硬化は近代の生活習慣の産物であるとしばしば考えられているが、この現象はさまざまな地理的位置や遺伝子背景および生活習慣を含む数千年にわたる疾患であるとのレイトブレイキングトライアルの結果が第62回American College of Cardiology学会で発表された。このHorus Studyは古代人における動脈硬化の証拠を調査した初めての系統的な研究である。研究者らの国際協力によりエジプト、ペルーおよび北米の4,000年近くの期間を経たミイラ137体の全身コンピュータ断層撮影（CT）が施行された。研究チームは調査したエジプト人76体の38%、ペルー人51体の25%、アナサジ族5体の40%、アレウト族5体の60%において、動脈硬化の証拠を明らかにした。科学的調査から推定した年齢に基づくと、これらのミイラの死亡時平均年齢は36歳であったが、動脈硬化を有する者の平均年齢は有意に高く43歳であった。このスタディの立案者らによると、古代人の平均寿命は約40歳であることから、一部の人々において動脈硬化は老化特有のものであるとの仮説が導かれる。

Full Text

While atherosclerosis is often considered a product of modern lifestyles, it is a condition that has spanned thousands of years, including a wide variety of geographic locations, genetic backgrounds and lifestyles, according to research presented at the American College of Cardiology's 62nd Annual Scientific Session.

The Horus Study is the first systematic search for evidence of atherosclerosis among ancient people. An international collaboration of researchers performed whole body computed tomography (CT) scans of 137 mummies from populations in Egypt, Peru and North America spanning a period of nearly 4,000 years. They found signs of atherosclerosis in 35 percent of the mummies and across all populations in the study.

"It is surprising that atherosclerosis is so easy to find in these ancient cultures across the globe over a very wide timespan and among people with very different genetics, lifestyles and diets," said Randall Thompson, M.D., St. Luke's Health System and one of the study authors. "One implication is that this disease that we think of in terms of modern lifestyles and diet is actually related to aging. Or, perhaps we don't understand the risk factors as well as we think we do."

A previous study by Thompson and his team, released in 2011, detailed the findings of atherosclerosis among Egyptian mummies, leading researchers to question whether something inherent to the ancient Egyptian culture, such as a rich, high-fat diet may have caused them to develop atherosclerosis. To further test this hypothesis, the study was expanded to include a variety of cultures, socioeconomic strata and time periods. In addition to the ancient Egyptians of 1900 B.C. to 200 A.D., mummies were included from the indigenous corn and potato farmers of ancient Peru living between 600 B.C. and 1500 A.D., the ancestral Hisatsinom forager-farmers living on the Colorado Plateau and the Unangan hunter-gatherers of the Aleutian Islands, who lived from 1750 to 1900 C.E. The Horus team found evidence of atherosclerosis among all groups, including 38 percent of the 76 Egyptians studied, 25 percent of 51 Peruvians, 40 percent of the five Hisatsinom examined, and 60 percent of the five Unangan.

"While it is hard to compare these numbers directly [with current data on atherosclerosis], atherosclerosis is common in ancient people," Dr. Thompson said, adding that people in modern times may have been "oversold the ability of diet to prevent or reverse cardiovascular disease."

Based on age estimates from scientific examination, the average age of the mummies in the study at time of death was 36, though those with atherosclerosis had a significantly higher average age of 43. According to Thompson, the average life span in ancient times was about 40, lending evidence to the hypothesis that atherosclerosis might be an inherent part of aging for some people.

Researchers speculate risk factors for ancient populations might have included chronic exposure to household cooking fires in small living quarters, which may have produced risks similar to that from smoking, and inflammation related to parasites and infections. Although stress is difficult to measure, historians know there were particular stressors inherent in ancient lifestyles.

"Certainly we have stress now in modern times. Sitting in traffic when we're late for work is stressful for us, but it's nothing like famine and pestilence; they had brutal lives," Dr. Thompson said.

The research team was most surprised to find atherosclerosis among a population not suspected to be as susceptible: hunter-gatherers. Because of this population's varied diet and high level of daily exercise, their risk factors for atherosclerosis would seem to be low. However, advanced atherosclerosis was found among mummies of the indigenous Aleutians, who even in 1900 were living traditionally: hunting seals, fishing and gathering berries and sea urchins. Three of the five mummified adults of this area had atherosclerosis, including a woman of approximately 50 years of age who had heavy calcifications of two of her three coronary arteries.

Study findings may have implications for modern day patients in terms of risk factors, prevention and treatment, notes Dr. Thompson. While these findings may point to genetic and age-related factors playing a large role in development of atherosclerosis, he said, this is all the more reason for patients today to address the factors they can control: quitting smoking, cutting down on alcohol, eating a healthy diet, exercising and following up with health care providers to monitor blood pressure and cholesterol levels.

The Horus Study is the culmination of an international collaboration between physicians, anthropologists and biologists from numerous medical centers as well as the Smithsonian Institution, the Metropolitan Museum of Art, and the British, Egyptian, Brooklyn, University of Pennsylvania, and Peruvian Peruchuco Museums. The study was funded by a grant from the National Endowment for the Humanities, the National Bank of Egypt, Siemens and the St. Luke's Hospital Foundation.

ACC2013特集

ジゴキシンは心不全患者の入院を減らす（Abstract # 13-LB-15819）

DIG:ジゴキシンは慢性心不全の高齢患者における全入院を減少させる

DIG: Digoxin reduces all cause hospital admissions in older patients with chronic heart failure

ジゴキシンは、左室駆出率の低下した慢性心不全（HFrEF）の外来高齢患者の全入院率を有意に低下させるとの研究結果が第62回American College of Cardiologyで発表され、同時に*American Journal of Medicine*オンライン版に公表され、2013年8月号の印刷版に掲載予定である。研究者らはDIG（Digitalis Investigation Group）トライアルのHFrEF患者6,800人の1995年以降の予後をレビューした。目的は30日以内の全ての原因による入院に対するジゴキシンの効果を調査することであった。患者は21～94歳であり、半数は65歳以上であった。ジゴキシンは30日以内の全ての原因による入院を34%減少させた。ジゴキシンによる治療は追跡開始後30日以内の総死亡を増加させなかった。他の強心薬とは異なり、ジゴキシンは死亡率を増加させないようであり、低用量では神経ホルモンを遮断することが明らかにされた。HFrEFの死亡率や入院を減少させる薬剤の多くもまた神経ホルモンを遮断するため、この結果は重要であると専門家らは述べている。これらの結果から、ジゴキシンは退院後間もない急性心不全の高齢患者の再入院を減少させるのにも役立つ可能性があると研究者らは確信している。

Full Text

Digoxin significantly reduces the likelihood of hospital admission due to all causes among ambulatory older patients with chronic heart failure and reduced ejection fraction (HFrEF), according to research presented at the American College of Cardiology's 62nd Annual Scientific Session.

Researchers reviewed patient outcomes from 1995 in the Digitalis Investigation Group (DIG) trial of 6,800 patients with HFrEF. Patients with HFrEF are at high risk for hospitalization and rehospitalization. The objective of the current study was to examine the effect of digoxin on 30-day all-cause hospital admission among these patients, aged 21 to 94 years, half of whom were age 65 or older and would be Medicare eligible.

Data show digoxin was associated with a 34 percent reduction in 30-day all-cause hospital admission. Digoxin is part of a group of drugs called positive inotropes that act to strengthen the heart muscle's contractions, thereby making the heart pump better. Unlike other positive inotropic drugs, digoxin does not seem to increase mortality and has been found to block neurohormones in low doses. Experts say this is important as most drugs that reduce mortality and hospitalization in HFrEF also block neurohormones. This study found that treatment with digoxin did not increase all-cause mortality during the first 30 days of follow-up.

"We have an approved drug, which is inexpensive, generally well-tolerated and known to reduce the long-term risk of hospitalization due to heart failure, that has now been demonstrated to reduce hospital admissions due to all causes within the first 30 days of use," said Ali Ahmed, M.D., M.P.H., professor of medicine and epidemiology in the UAB Divisions of Geriatrics and Cardiology and Birmingham VA Medical Center, and the study's lead investigator.

While this study assessed rates of hospital admission in older ambulatory chronic heart failure patients, the researchers believe that these findings suggest that digoxin may also help reduce readmission of older, acute heart failure patients recently discharged from a hospital.

"Because the effect of digoxin was more pronounced in high-risk sicker subgroups, such as those with New York Heart Association class III or IV symptoms or an enlarged heart, the kind of patients who were at a higher risk of hospital admission, and because of digoxin's favorable influence on heart pump and blood flow, it may be expected that digoxin would also be effective in patients who were recently hospitalized for acute heart failure as they have very high risk for re-admission," Dr. Ahmed said.

This could be significant as earlier studies have found an estimated 27 percent of Medicare beneficiaries with heart failure return to the hospital within 30 days of discharge. All told, nearly one out of three of these readmissions is related to heart failure rather than other reasons.

In addition to improving care and outcomes, the use of digoxin may also help hospitals avoid financial penalties for higher than usual rates of readmission. According to the Centers for Medicare and Medicaid Services, unplanned hospital readmissions alone cost the Medicare program an estimated $17 billion annually. In an effort to reduce Medicare costs under the Patient Protection and Affordable Care Act, Medicare now penalizes hospitals for higher-than-expected 30-day all-cause readmissions for patients with heart failure, heart attack and pneumonia, regardless of whether readmission is related to the condition causing the initial hospitalization.

"Hospitalizations account for about a quarter of the nearly $550 billion annual Medicare spending," said Dr. Ahmed. "Re-hospitalization costs about a sixth of that spending. We all knew that hospital readmission was a big problem for the U.S. health care system, but we only started paying serious attention to it after the new health care reform law made provision for financial penalties."

He adds that each time someone with heart failure goes to the hospital it also raises their risk of dying or having other poor outcomes. Because the present study draws on data from about 20 years ago—before the era of beta blockers and aldosterone antagonists—researchers say further research is needed to reevaluate digoxin among contemporary heart failure patients and to assess its use before hospital discharge in the acute heart failure setting.

"If we can replicate these results in hospitalized patients with acute heart failure and find that digoxin also reduces 30-day all-cause readmission as it did 30-day all-cause admission, then it provides a very simple, low-cost tool to reduce this burden for the patients and for our health care system," Dr. Ahmed said.

He estimates that one-third of heart failure patients receive digoxin today compared to two-thirds before the DIG trial was conducted, which he says is in part based on the fact that other heart failure medications such as beta blockers and aldosterone antagonists were subsequently shown to reduce both mortality and hospitalizations, and thus given greater priority. The Food and Drug Administration approved oral digoxin for the treatment of mild to moderate heart failure in 1997 following the DIG trial.

This study is published online in the *American Journal of Medicine* and will appear in the August 2013 print edition.

シルデナフィルは拡張期心不全患者に無効であった（Abstract # 13-LB-15755）

RELAX: 勃起不全治療薬は拡張期心不全患者を改善させなかった

RELAX: Erectile dysfunction drug shows no improvement in patients with diastolic heart failure

一般的に使用されている勃起不全治療薬の拡張期心不全治療効果に対する期待は大きかったが、有益性は認められなかったとのスタディ結果が第62回American College of Cardiology学会で発表された。RELAXスタディは拡張期心不全に対するシルデナフィルを用いた長期治療の効果を観察した初めての多施設トライアルである。スタディには拡張期心不全（LVEF≧50%、NYHAクラス2-3）の患者113人が組み入れられ、シルデナフィル20mgを1日3回3か月間内服しその後にさらに3か月間60mgを1日3回内服した。彼らはプラセボコントロール群（103人、年齢中央値68歳）と比較された。スタディの結果、一次エンドポイントである24週間後のピーク酸素摂取量の変化には有意差が認められなかった。6分間歩行検査、患者の健康状態に基づく臨床スコアおよびQOL、そして心臓超音波検査、MRIおよび血液検査によるバイオマーカーデータを含む心血管構造および機能検査などの他のアウトカムについてもまた、差はなかった。このスタディ結果は*Journal of the American Medical Association (JAMA)*オンライン版に掲載されており、3月27日号の印刷版に掲載予定である。

Full Text

Despite high expectations for a commonly used erectile dysfunction drug to treat patients with diastolic heart failure, no beneficial effects were found in a study presented at the American College of Cardiology's 62nd Annual Scientific Session.

The RELAX Study is the first multicenter trial to look at the effect of chronic therapy with sildenafil in diastolic heart failure. Sildenafil is a phosphodiesterase-5 (PDE-5) inhibitor, a class of drugs used to treat erectile dysfunction and certain types of pulmonary arterial hypertension. Positive results with sildenafil in smaller studies and animal models provided the impetus for the study. But, compared to the placebo, researchers found no beneficial effect of the drug on the primary endpoint of participants' maximum exercise capacity assessed by peak oxygen consumption nor on secondary endpoints of submaximal exercise capacity (as tested by six minute walk distance), clinical status, or cardiovascular structure and function.

"The results of our study were surprising and disappointing," said Margaret Redfield, M.D., professor of medicine at the Mayo Clinic in Rochester, Minn., and the study's lead author. "There was a lot of anticipation around this study based on other research, and we were hoping to find something that would help these patients, as there are currently few options for treatment."

While current treatment for diastolic heart failure includes recommendations for weight loss, smoking cessation and controlling blood pressure, there are no medications available specifically for its treatment. Because sildenafil can increase blood supply to the lungs, and in animal studies it improved heart and vascular structure and function, researchers believed the drug would improve heart and lung function for diastolic heart failure patients.

According to Dr. Redfield, while it is possible that factors such as insufficient drug dosage or duration contributed to their results, she thinks this is unlikely based on the outcomes of other studies finding benefits from sildenafil.

It is more likely that, compared to other types of heart failure, the disease process seen in diastolic heart failure is different and does not respond well to this category of drug, she said.

In the RELAX study, patients with diastolic heart failure were enrolled in nine primary centers that make up the Heart Failure Clinical Research Network as well as 16 associated centers. To meet inclusion criteria, participants had to do a cardiopulmonary exercise test and have heart and blood tests showing that they had severe limitations in exercise capacity and abnormalities in the structure and function of their hearts.

The study enrolled 113 patients with diastolic heart failure (LVEF ≥50%, NYHA class 2-3) who received 20mg sildenafil three times daily for three months, followed by 60 mg three times daily for another three months. They were compared to a placebo control group (n=103). The trial participant's medium age was 69 years.

The primary endpoint of the study was peak exercise capacity after 24 weeks of therapy with the drug sildenafil. Other outcomes of the study included how far participants could walk in a six-minute exercise test, a clinical score based on patients' health outcomes and quality of life, and cardiovascular structure and function tests including echocardiographs, MRIs and biomarker data from blood tests.

The study was a double-blind, placebo-controlled, randomized clinical trial. For all outcomes, study results were neutral, showing no beneficial effect of sildenafil on heart failure patients. Although sildenafil and other PDE-5 inhibitors are not labeled for heart failure, it is possible that some clinicians may be prescribing these drugs for their heart failure patients based on the results of preliminary studies, which suggest a benefit.

"RELAX study results should discourage this practice, particularly considering the high cost of the drug," Dr. Redfield said.

While Dr. Redfield does not believe a larger trial of PDE-5 inhibitors is warranted in the general population of patients with diastolic heart failure, she said further research is needed to ascertain their potential benefits with certain subgroups of patients. Other small studies have demonstrated benefits from the drug for patients with diastolic heart failure who also had high blood pressure, right ventricular dysfunction and pulmonary arterial hypertension.

"Given these results, future studies should be done with this subset of patients," Dr. Redfield said, noting that ongoing trials in the U.S. and in Europe are assessing the effect of PDE-5 inhibitors in heart failure with reduced ejection fraction.

The RELAX Study was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health, which funds the Heart Failure Clinical Research Network, now in its seventh year.

This study was published online in the *Journal of the American Medical Association (JAMA)* and in the March 27 print edition.

ACC2013特集

薬剤により糖尿病患者の狭心症は軽減する（Abstract # 13-LB-15927）

TERISA: Ranolazineの狭心痛軽減作用は血糖コントロール不良の患者において最も顕著であった

TERISA: Angina pain reduction effects of ranolazine most pronounced in patients with poor glucose control

Ranolazineは2型糖尿病患者の狭心症を軽減し、この効果は血糖コントロール不良な患者においてより顕著なようであるとの研究結果が第62回American College of Cardiologyで発表された。Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina（TERISA）トライアルには927人の患者（男性61%）が組み入れられ、ranolazine 1,000mgを1日2回内服群またはそれに匹敵させたプラセボを8週間内服する群に無作為に割り付けられた。全ての患者が2型糖尿病を有し、冠動脈疾患の確定診断を受け、1週間に1回以上の狭心発作を伴う安定狭心症を有していた。患者はすでに、他の狭心症治療薬を1または2剤内服していた。一次エンドポイントは第2～8週の自己報告の狭心症頻度であった。その結果、週当たりの胸痛発作はranolazine群において3.8回/週であり、プラセボ群の4.3回/週よりも少なかった（*P*=0.008）。重要な二次エンドポイントは、同じ時間枠内のニトログリセリン使用頻度であった。これもまたプラセボ群よりもranolazine群で低く、週当たり1.7回対2.1回であった（*P*=0.003）。このスタディ結果は*Journal of the American College of Cardiology*オンライン版に掲載されており、5月21日号の印刷版に掲載予定である。

Full Text

A commonly used anti-anginal drug reduces chest pain in patients with type 2 diabetes and appears to have a more pronounced effect in those with poorer glucose control, according to research presented at the American College of Cardiology's 62nd Annual Scientific Session.

Ranolazine is approved by the U.S. Food and Drug Administration for the treatment of chronic angina, or chest pain, both as first line therapy and as an add-on when symptoms are not relieved with other anti-anginal drugs, including beta-blockers, calcium channel blockers and nitrates. However, this randomized, double-blind, placebo-controlled trial is the first to evaluate the drug in patients with diabetes, coronary artery disease and angina.

People with diabetes are at increased risk for coronary artery disease. Patients with diabetes and coronary artery disease also tend to have a higher burden of chest pain or angina than those without diabetes.

The Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) trial included 927 patients, randomized to receive either 1000 mg ranolazine twice daily or matching placebo for eight weeks. To qualify for the study, patients had to have type 2 diabetes, established coronary artery disease and stable angina with at least one angina episode per week. Patients were already taking one or two other anti-anginal drugs.

The primary endpoint was self-reported angina frequency between weeks two and eight. Weekly episodes of chest pain were lower in the ranolazine arm at 3.8 episodes per week compared to 4.3 episodes per week with the placebo (*P*=0.008). A key secondary endpoint was how often people used sublingual nitroglycerin during the same timeframe. This was also lower in the ranolazine arm compared with placebo, 1.7 vs. 2.1 doses per week (*P*=0.003).

"Angina is associated with worse quality of life, increased risk of hospitalization and higher health care costs and appears to be more prevalent in patients with diabetes," said Mikhail Kosiborod, M.D., associate professor of medicine at the University of Missouri, Kansas City, cardiologist at St. Luke's Mid America Heart Institute and the study's lead author. "While ranolazine was shown to be effective in reducing angina in prior studies, this is the first time it has been prospectively evaluated in patients with diabetes—a high-risk and therapeutically challenging group."

Each patient was given an electronic diary in which to record angina episodes, sublingual nitroglycerin use and other information. This unique feature was a strength of the study, Dr. Kosiborod said.

"Patient-reported outcomes done with usual methods, such as paper entry, may result in a hoarding effect," he said. "Patients fill out a lot of information at one sitting, and there can be issues with data validity. In this study, they had daily prompts to use the electronic diary and were constantly monitored for compliance. There was 98 percent compliance with the diary in both arms."

The patient population was 61 percent male. Nearly all (96 percent) had hypertension, and 74 percent had a history of myocardial infarction. Most patients were taking statins (82 percent) and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (88 percent). Sixteen percent were smokers.

The researchers also found that ranolazine was especially effective in patients with worse glucose control, as measured by hemoglobin a1c (Hba1c) levels. The therapeutic superiority of ranolazine vs. placebo on reducing weekly angina frequency was more pronounced in patients with higher baseline Hba1c, regardless of the cut-point used. Prior data show that the drug may lower fasting glucose levels in people with diabetes, thus lowering Hba1c.

"Ranolazine is an effective anti-anginal drug in patients with diabetes and may also have a glucose-lowering effect," Dr. Kosiborod said. "If the glucose-lowering action of ranolazine is confirmed in future studies, patients with diabetes and angina may derive a dual benefit from this drug."

Researchers also completed a subgroup analysis of patients by geographic region. Angina frequency was not different between the ranolazine and placebo arms among patients enrolled in Russia, Ukraine and Belarus. Among patients enrolled in other countries, those treated with ranolazine experienced a significant reduction in angina frequency as compared with placebo (3.1 vs. 4.1 episodes per week; *P*=0.002).

"The reasons for this geographic difference are not clear," Dr. Kosiborod said. "It wasn't explained by differences in baseline characteristics but was driven by several sites located in Russia. We're exploring it."

Diabetes affects more than 347 million people worldwide. About 90 percent of diabetes is type 2 diabetes, in which the body does not use insulin effectively. Excess weight and a lack of physical activity are thought to be the main causes of type 2 diabetes. The U.S. Centers for Disease Control estimates that one in three American adults could have the condition by the year 2050.

The study was funded by Gilead Sciences, Inc. Saint Luke's Mid America Heart Institute received funding for the independent statistical analysis of the TERISA trial from Gilead Sciences.

The study was simultaneously published online in the *Journal of the American College of Cardiology*, and will appear in the May 21 print edition.

ACC2013特集

エプレレノンはMI後の予後を改善する可能性がある（Abstract # 13-LB-15932）

REMINDER:エプレレノンを標準治療に追加投与することによりMI後の心不全リスクが低下する可能性がある

REMINDER: Eplerenone may reduce risk of heart failure after MI when given in addition to standard treatment

薬剤エプレレノンは心筋梗塞（MI）後の心血管死亡および心不全のリスクを3分の1以上減少させるようであるとの研究結果が第62回American College of Cardiology学会で発表された。REMINDER（Reduction of heart failure morbidity in patients with acute ST-elevation myocardial infarction）は、ST上昇MI（STEMI）患者1,012人を対象とした無作為化二重盲検トライアルである。患者は心不全徴候または心不全歴を有さなかった。彼らはエプレレノンまたはプラセボを標準治療に加えて投与された。全体で、エプレレノン内服群はプラセボ内服群よりも予後不良率が38%低かった。追跡期間中央値10.5か月後の心不全、重症不整脈または死亡はエプレレノン投与群患者においてプラセボ投与群患者よりも頻度が低かった（18.4%対29.6%、*P* <0.0001）。また、1か月後にBNP/NT-proBNP上昇を認めたのはエプレレノン群患者でわずか16%であったのに対し、プラセボ群では25.9%であった（*P* <0.0002）。今回のスタディ対象患者は低リスク（死亡率0.4%）であり標準治療を受けていた。有害事象は両群で同等であった。

Full Text

The drug eplerenone appears to reduce the risk of cardiovascular mortality and heart failure after a myocardial infarction (MI) by more than one-third, according to research presented today at the American College of Cardiology's 62nd Annual Scientific Session.

The REMINDER (Reduction of heart failure morbidity in patients with acute ST-elevation myocardial infarction) trial was a randomized, double-blind trial of 1,012 patients with ST-elevation MI (STEMI). Patients had no signs or history of heart failure. They were given either eplerenone or placebo in addition to standard therapy. Overall, patients taking eplerenone were 38 percent less likely to have poor outcomes than those given a placebo.

Eplerenone counteracts aldosterone, which can increase blood pressure. The drug is currently approved to treat hypertension and as a treatment for patients who have heart failure several days after an MI.

"This is the first randomized trial to test a mineralocorticoid receptor agonist during the acute phase of heart attack, and the results suggest a clinical benefit," said Gilles Montalescot, M.D., Ph.D., lead investigator of the study and professor of cardiology and head of the Cardiac Care Unit at Pitié-Salpétrière Hospital, Paris.

Clinical trials and registries show that in the 30 days after a first MI, between 8.6 percent and 40 percent of patients will be diagnosed with heart failure.

The primary endpoint of the REMINDER trial included several outcomes:

- Cardiovascular mortality
- Rehospitalization or extended initial hospital stay due to heart failure
- Severe arrhythmias
- Ejection fraction of 40 percent or lower after one month
- An elevation of brain natriuretic peptide (BNP) and its associated protein, NT-proBNP, after one month

Patients who had one of these outcomes were considered to have reached the primary endpoint. After a mean follow-up of 10.5 months, patients on eplerenone had one of these outcomes less often than those receiving placebo (18.4 vs. 29.6 percent, *P* <0.0001). Also, only 16 percent of patients on eplerenone had an elevation of BNP/NT-proBNP after one month, compared with 25.9 percent receiving placebo (*P* <0.0002). Adverse events rates were similar in both groups.

"Eplerenone has the potential to reduce clinical and subclinical heart failure in STEMI patients," Dr. Montalescot said.

The study population was low-risk (the mortality rate was 0.4 percent) and was receiving standard treatment.

"Despite this, a benefit was observed with eplerenone to prevent adverse outcomes and subclinical heart failure," Dr. Montalescot said. "Confirmation in a higher-risk population with a longer follow-up would be important to support this new strategy."

The ongoing ALBATROSS [Aldosterone Blockade Early After Acute Myocardial Infarction] study is investigating this hypothesis, Dr. Montalescot added.

The study was funded by Pfizer, Inc. Dr. Montalescot indicated no conflict of interest.

ACC2013特集

待機的PCIは外科的なバックアップなしで安全に施行された(Abstract # 13-LB-15907)

MASS COMM: 院内緊急心臓外科手術の不可能な病院で施行される非緊急血管形成術は安全で有効である

MASS COMM: Non-emergency angioplasty at hospitals without on-site cardiac surgery is safe and effective

院内緊急心臓外科手術の不可能な病院で施行する非緊急血管形成術は、緊急心臓外科手術の可能な病院で施行される血管形成術と比較し、安全性および有効性は同等であるとの研究結果が第62回American College of Cardiology学会で発表された。計3,691人の患者が3:1の割合で無作為に割り付けられ、2,774人は緊急心臓外科手術の不可能な病院で、917人は外科的なバックアップのある病院に転送されPCIを施行された。対象の平均年齢は64歳であり、32%は女性、32%は糖尿病を有し、61%は急性冠症候群で来院した。血管形成術30日後および12か月後の総死亡率、心筋梗塞、再血行再建術または脳卒中などの予後は心臓外科を有さない病院群と有する病院群とで差はなかった。今回の結果から、心臓外科はなくとも適切な経験、確立された血管形成術プログラム、および必要とされるレベルの病院と術者の人数を有すれば、これらの病院を訪れた患者に血管形成術を施行することは受容できる選択であると筆者らは述べている。

Full Text

Non-emergency angioplasty performed at hospitals without on-site cardiac surgery capability is no less safe and effective than angioplasty performed at hospitals with cardiac surgery services, according to research presented at the American College of Cardiology's 62nd Annual Scientific Session.

Emergency surgery has become an increasingly rare event following percutaneous coronary intervention (PCI) or angioplasty. This study adds to the growing body of evidence supporting favorable outcomes for patients undergoing elective or non-emergency angioplasty at hospitals without cardiac surgery on-site. Researchers say there are several reasons why expansion of non-emergency PCI to hospitals without cardiac surgery programs may be viewed favorably.

"Among them are patient choice and patient and physician convenience afforded by providing the ability to remain in a local and familiar community. In addition, the added volume of PCI procedures at these hospitals could help to provide resources to support active primary PCI programs," said Alice Jacobs, M.D., professor of medicine at Boston University School of Medicine, and the study's lead investigator. "However, controversy continues to exist surrounding this expansion of services to treat patients in non-emergency settings, where timely access to angioplasty is less important to cardiovascular outcomes and the risk to benefit ratio may differ from the emergency setting."

Dr. Jacobs and her team conducted a prospective, randomized trial comparing the safety and effectiveness of non-emergency angioplasty at 10 hospitals in Massachusetts without on-site cardiac surgery services and seven hospitals with on-site cardiac surgery services. A total of 3,691 patients were randomly assigned in a 3:1 ratio to undergo angioplasty: 2,774 at hospitals without on-site cardiac surgery and 917 at hospitals with surgical backup. The mean age of study subjects was 64 years, 32 percent were women, 32 percent had diabetes and 61 percent presented with an acute coronary syndrome.

Rates of major adverse cardiac events, including death, heart attack, repeat angioplasty and stroke, were assessed at 30 days and 12 months post-angioplasty. Rates at 30 days were 9.5 percent for sites without on-site cardiac surgery compared to 9.4 percent for those with surgical services. Outcomes did not differ significantly between the non-surgical and surgical groups for all-cause mortality, heart attack, repeat angioplasty or stroke. At the 12-month follow up, major adverse cardiac events rates were 17.3 percent for sites without on-site surgery compared to 17.8 percent for sites with surgical services available, and rates of mortality, heart attack, repeat angioplasty and stroke did not differ between groups.

A random sample of 376 study subjects was selected to monitor clinical practice patterns between hospitals with and without cardiac surgery on-site. There were no significant differences between the two treatment groups with respect to procedure success rates, completeness of angioplasty or the proportion of lesions classified as meeting ACCF/AHA/SCAI PCI guidelines Class I or II recommendations for anatomic indications to perform PCI.

"While we did not directly compare all PCI procedures at hospitals with and without cardiac surgery, our results suggest that performance of angioplasty in hospitals without cardiac surgery but with the appropriate experience, established angioplasty programs and the required hospital and operator volume, is an acceptable option for patients presenting to these hospitals for care," Dr. Jacobs said.

This study was funded by the participating hospitals without on-site cardiac surgery service.

This study was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

ACC2013特集

バイオリムス溶出ステントはエベロリムス溶出ステントと同等である（Abstract＃13-LB-11492）

NEXT:バイオリムス溶出ステントを留置された患者の1年後の予後はエベロリムス溶出ステントを留置された患者のそれと同等である

NEXT: Outcomes of patients receiving biolimus-eluting stent comparable to everolimus stent at one year

日本でトップの薬剤溶出ステントと生物分解性コーティングを特徴とする新たなデバイスの比較において、この新規参入ステントの1年後の成績は統計学的に同等であったとのNEXTトライアルのデータが第62回American College of Cardiology学会で発表された。NEXTトライアルは、これら2つのステントを比較した最大の多施設、無作為化、オープンラベルスタディであり、3,235人の患者がバイオリムス溶出ステント（BES）またはエベロリムス溶出ステント（EES）に割り付けられた。スタディは日本における98の参加施設において薬剤溶出ステント挿入を予定された全ての患者を組み入れ、除外項目はなかった。1年後の標的病変血行再建率はBESで67%であったのに対しEESでは66%であり（両群ともに4.2%）、BESはEESに対し非劣性であるとの目的を達成した。明確なステント血栓の累積発生率は低く、BES群で0.25%であったのに対しEES群で0.06%であった。スタディ対象患者の多くは高齢であり（平均年齢69.2±9.8年）、糖尿病を有していたり（46%）すでに冠動脈内ステントを留置されたりしていた（51%）。解析の結果、これらのサブグループにおいて2つのステント群間の予後に差はなかった。初期成功率はBESおよびEESで非常に良好であり両群ともに99.6%であった。

Full Text

In a match-up of Japan's top drug-releasing stent and a new device featuring a biodegradable coating, the newcomer delivered statistically comparable one-year results, according to data from the NEXT trial presented at the American College of Cardiology's 62nd Annual Scientific Session.

The polymer coating on drug-eluting stents slowly releases a drug designed to prevent restenosis and subsequent target lesion revascularization. The polymer's drug greatly reduces restenosis and target lesion revascularization rates, but the coating itself retards healing in the stented artery and may trigger an inflammatory response that leads to late adverse effects. The clinical challenge is to retain the pros of the drug and minimize or eliminate the cons of the polymer. With a polymer coating that dissolves six to nine month after implantation, the biolimus-eluting stent (BES) may reduce late restenosis or stent thrombosis.

The NEXT trial assigned 3,235 patients to either BES or an everolimus-eluting stent (EES) in the largest multicenter, randomized open-label study comparing these two devices ever reported. BES was approved in Japan in 2011, while EES is the country's leading coronary drug-eluting device. The two eluted compounds belong to the same class of drugs. The study enrolled all patients scheduled for insertion of a drug-eluting stent at 98 participating centers in Japan, with no exclusion criteria.

"Our results suggest that BES could be the alternative to EES, a current gold standard second-generation drug-eluting stent," said Masahiro Natsuaki, M.D., of Kyoto University Graduate School of Medicine's Department of Cardiovascular Medicine. "Because the polymer will completely disappear one year after stent insertion, at least a three-year timeframe will be needed to demonstrate the potential advantage of BES over other available stents."

BES met the goal of non-inferiority to EES in target-lesion revascularization at one year, with target lesion revascularization in 67 BES patients vs. 66 EES patients (4.2 percent for both groups). The cumulative rates of definite stent thrombosis were low and similar at 0.25 percent in the BES group vs. 0.06 percent in the EES group. In a substudy of 528 patients, angiographic imaging confirmed similar rates of restenosis in both study arms, expressed as late lumen loss—a shrinkage of space inside the stented artery at 266 days + 43 days after the procedure: loss of 0.03+0.39mm in BES patients vs. 0.06+0.45mm in EES patients.

The study's other primary outcome is death or heart attack at three years after stent insertion, with multiple secondary outcome measures for that three-year timeframe. Interim two-year data also will be analyzed.

Many patients in this study were older (mean age 69.2±9.8 years), had diabetes (46 percent) or already had a coronary stent (51 percent). Analysis found no differences in outcomes for these subgroups between the two stent types. An earlier study's findings had raised concerns about acute success rate with BES—the ability to deliver all intended stents to the target site and achieve the target artery diameter. In this trial, acute success rates were very high for BES and EES at 99.6 percent in both groups.

Dr. Natsuaki observed that despite the study's all-comer design, the actual study population mostly included patients with stable coronary artery disease; the one-year rate of target lesion revascularization was lower than expected, leading to a relatively large margin of non-inferiority; and the high incidence of follow-up angiography inflated rates of target lesion revascularization. Nevertheless, "Given the equivalent one-year outcome, long-term clinical data for biodegradable-polymer BES compared with durable-polymer EES will have crucial implications for future development of improved metallic drug-eluting stents," he said.

The study was sponsored by Terumo Japan. Dr. Natsuaki indicated no conflict of interest.

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