新規経口抗凝固薬はワルファリンと比べても遜色はない(Abstract 1875)

新規経口抗凝固薬はワルファリンと同じように脳梗塞を予防するが出血を起こしにくい

New oral anticoagulants provide same stroke prevention as warfarin but cause less bleeding

非ビタミンK拮抗経口抗凝固薬（NOAC）は、ワルファリンと同じように脳梗塞を予防するが頭蓋内出血を起こしにくい、という43,000人超の心房細動患者を対象にした観察研究が2016年ESC Congressで発表された。研究では、NOAC（ダビガトラン、リバーロキサバン、アピキサバン）を"リアルワールド"においてワルファリンと比較した。1年以内の脳梗塞リスクは、NOAC群とワルファリン群で同等であり、2.0～2.5%の範囲であった。1年後の頭蓋内出血リスクは、ワルファリン治療群（0.6%）に比べ、ダビガトランおよびアピキサバン治療群で有意に低かった（0.3～0.4%）。

Full Text

The new oral anticoagulants provide the same stroke prevention as warfarin but cause less intracranial bleeding, reports an observational study in more than 43 000 patients presented at ESC Congress 2016 today by Dr. Laila Staerk, a research fellow at Herlev and Gentofte University Hospital, Denmark.

"Atrial fibrillation is associated with a five-fold risk of stroke, potentially leading to disability and death," said Dr. Staerk. "In the next four decades, the number of patients with atrial fibrillation is expected to triple so the number of Europeans diagnosed could rise to a staggering 25 to 30 million."

Patients with atrial fibrillation are treated life-long with oral anticoagulation to reduce their risk of stroke. But treatment with non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (warfarin) is a double-edged sword, because it lowers the risk of stroke at the cost of increased bleeding risk. Intracranial bleeding is a particular fear.

With several treatment options available the clinical question of which one to use has often been asked. Dr. Staerk said: "There has been a need to investigate safety and effectiveness of NOACs versus warfarin in a 'real world' population and our Danish registries provide this opportunity."

The current study compared the risk of stroke and intracranial bleeding with NOACs (dabigatran, rivaroxaban and apixaban) versus warfarin in a 'real world' setting. The study was conducted at The Cardiovascular Research Centre at Herlev and Gentofte University Hospital in Denmark. It included 43 299 patients with atrial fibrillation who were recruited from Danish nationwide administrative registries.

Some 42% of patients were taking warfarin, while 29%, 16% and 13% were taking dabigatran, apixaban and rivaroxaban, respectively. During follow up, stroke occurred in 1054 patients and there were 261 intracranial bleedings.

The researchers found that the risk of having a stroke within one year was similar between the NOAC and warfarin groups, and ranged from 2.0 to 2.5%. At one year the risk of intracranial bleeding was significantly lower in patients treated with dabigatran and apixaban (0.3 to 0.4%) compared to those treated with warfarin (0.6%).

Dr. Staerk said: "The inclusion and exclusion criteria in our study were broadly similar for patients initiating NOACs or warfarin, and this gave a straightforward opportunity to directly compare the treatment regimens, which is in contrast to the randomized trials. The results suggest that although they have similar effects in preventing stroke, dabigatran and apixaban were associated with a safer use regarding the absolute one-year risk of intracranial bleeding."

She added: "Our results complement the large randomized phase III trials by providing 'real world' data on stroke and intracranial bleeding with NOACs versus warfarin since fragile patients were not excluded from our nationwide cohort. For example, patients with increased risk of bleeding, liver disease, and chronic kidney disease are less represented in trials."

Dr. Staerk concluded: "Registry studies have some limitations such as the observational design, residual confounding, and confounding by drug indication. In the future it would be exciting to see a head-to-head randomized trial performed to compare the different NOAC treatments in patients with atrial fibrillation."

Velux Foundations supported the study.

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Nebivololはアントラサイクリン心毒性を予防する (Abstract 2102)

新しい心エコー法が心不全症状発現前に心筋障害を明らかにする

New echocardiographic techniques identify myocardial dysfunction before heart failure symptoms appear

Nebivololはアントラサイクリン心毒性を予防する、と2016年ESC Congressで発表された。アントラサイクリンは乳がん治療に広く用いられているが、心毒性が認められている。HER2陰性乳がん患者60人を対象に、ドキソルビシンによる化学療法が計画され、2群（コントロール群=30人、nebivolol治療群=30人）にランダム化割り付けされた。6サイクルの化学療法後、従来の心エコー法により左室駆出率が示され、左室内径短縮率および左室径に有意な変化は認めなかった。しかし、より新しい、さらに高感度の心エコー法（組織ドプラ法およびスペックル・トラッキング法）は、化学療法後の心臓障害を明らかにした。Nebivololで治療された患者では、心機能が保護され正常に保たれた。

Full Text

Nebivolol prevents anthracycline-induced cardiotoxicity, according to research presented at ESC Congress 2016 today by Professor Mirela Cleopatra Tomescu, a cardiologist at Victor Babes University of Medicine and Pharmacy, Timisoara, Romania.

"Breast cancer is a major public health problem worldwide, with a death rate of about 1 in 33 patients," said Professor Tomescu. "Anthracyclines are a class of powerful pharmacological agents widely used in the treatment of breast cancer but they have a toxic effect on the heart, inducing heart failure."

The goal of the current study was to find a method that detects cardiotoxicity accurately and early, and to see if a cardioprotective drug could prevent heart failure in these patients.

Depressed myocardial contractility is traditionally diagnosed using echocardiography, based on the estimation of left ventricular ejection fraction (LVEF) and fraction shortening (FS). However, these parameters are affected in the advanced stages of cardiotoxicity. New echocardiographic techniques, such as tissue Doppler, speckle tracking and strain rate imaging, allow the recognition of myocardial dysfunction before heart failure symptoms occur, and before the classical echocardiographic parameters are impaired.

For the cardioprotective drug, the researchers chose nebivolol, a cardioselective beta-blocker with anti-oxidant, anti-apoptotic and vasodilator properties, which is used to treat hypertension and heart failure.

The study group included 60 women with HER-2 negative breast cancer, with a mean age of 52 ± 13 years, scheduled to start chemotherapy with doxorubicin. They were randomly divided into two groups, the control group (n=30) and the nebivolol-treatment group (n=30). Nebivolol was administered at a dose of 5 mg once daily, for the duration of chemotherapy. Cytostatic treatment was performed with doxorubicin 70 mg/m^2, administered intravenously alone, every 21 days. There were six cycles of cytotoxic therapy. The average cumulative dose of doxorubicin was 520 ± 8 mg/m^2.

Echocardiography was performed at baseline and after six months of chemotherapy and included conventional two-dimensional echocardiography, tissue Doppler imaging, and speckle tracking imaging. There were no significant differences between groups in baseline clinical and echocardiographic characteristics. The cumulative dose of doxorubicin was similar in the two groups. No patient stopped chemotherapy, and no patient died during the study.

After six cycles of chemotherapy with doxorubicin, LVEF, FS, and left ventricular (LV) diameters did not change significantly in either group. In the control group, tissue Doppler imaging revealed significant alterations of LV diastolic function, assessed by a decrease of myocardial velocities. Speckle-tracking imaging assessed in the control group showed a statistically significant alteration of the LV systolic function, of longitudinal and radial strains, as well as of the strain rates. In the nebivolol treatment group, no significant changes in heart function were noted.

Professor Tomescu said: "Conventional echocardiography showed no change in heart function in either group following chemotherapy. But the newer, more sensitive echocardiographic techniques showed heart damage after chemotherapy. Patients who received nebivolol were protected and had normal heart function. Our study demonstrates the utility of new echocardiographic methods such as tissue Doppler and speckle tracking imaging in the early detection of ventricular dysfunction induced by cytostatic treatment."

She concluded: "Our finding that nebivolol treatment prevented anthracycline-induced cardiotoxicity is encouraging, but larger studies with a longer follow-up period are needed to confirm the results."

There were no sources of funding cited for this study.

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非虚血性心不全におけるICDの延命効果は示されなかった(Abstract 1220)

DANISH：非虚血性心不全における一次予防としてのICDは適切でない可能性がある

DANISH: ICDs may not be right for primary prevention in non-ischemic heart failure

非虚血性心不全患者に対する植込み型除細動器（ICD）は通常治療に比べ、二次転帰である心臓突然死を半減した（p=0.01）が総生存率は改善しなかった（p=0.28）、と2016年ESC Congressで発表され、同時に*New England Journal of Medicine*に掲載された。このDANISHトライアルの結果は、患者がCRTデバイスを植え込まれたか否かには関係がなかったが、68歳未満の患者においてはICD植込み例では全死亡が有意に少なく（p=0.01）、若年患者はICD植込みによる延命効果の可能性が示唆された。

Full Text

Placement of an implantable cardioverter-defibrillator (ICD) in patients with non-ischemic systolic heart failure did not improve overall survival compared to usual clinical care – although a secondary outcome, risk of sudden cardiac death, was halved with ICD placement, according to new research reported here.

Results of the DANISH trial, presented at ESC Congress 2016, with simultaneous publication in the *New England Journal of Medicine*, suggest a caveat to both European and American Heart Association guidelines which recommend ICDs for all heart failure, noted study investigator Lars Kober, MD, from Rigshospitalet, Copenhagen University Hospital in Copenhagen, Denmark.

"Prophylactic ICD implantation is a class 1 recommendation in patients with heart failure and reduced left ventricular systolic function in both European and American guidelines," he explained. "However, the evidence is much weaker for patients with non-ischemic etiology. Until now, there has been the limited data on ICDs in this population, and our trial fills that gap by suggesting ICDs should not be routinely implanted in all patients with systolic heart failure."

DANISH (which stands for DANish randomized, controlled, multicenter study to assess the efficacy of Implantable cardioverter defibrillator in patients with non-ischemic Systolic Heart failure on mortality) included stable patients with chronic, non-ischemic, symptomatic heart failure.

A total of 560 control patients were randomized to receive usual care (which included guideline-recommended medication including beta blockers, renin-angiotensin inhibitors, and mineralocorticoid-receptor antagonists), while 556 patients were randomized to receive an ICD.

There was an equal proportion of patients (58%) in both groups who also needed cardiac-resynchronization therapy (CRT). This was delivered via biventricular pacemakers in the control arm, and via a device combining CRT and ICD in the ICD arm.

After a median follow-up time of 67.6 months, the primary outcome of death from all causes occurred in 21.6% of the ICD patients and 23.4% of the controls – a non-significant difference (hazard ratio [HR] 0.87; 95% confidence interval 0.68 to 1.12; P=0.28).

Sudden death, a secondary outcome, occurred in 4.3% of the ICD patients and was almost doubled (8.2%) in the control group (HR 0.50; 95% CI 0.31 to 0.82; P=0.01).
The results were independent of whether or not a patient received a CRT device, but there was an important interaction with age, said Professor Kober.

"Patients younger than 68 years of age had a significant reduction in all-cause mortality if they received an ICD (HR 0.64; 95% CI 0.45 to 0.90, P=0.01), suggesting that younger patients may have a survival benefit with ICD implantation."

Device-related infections occurred in both groups, since 58% of the controls had received a biventricular pacemaker. However, in patients not receiving CRT there was an excess risk of device infection in the ICD group (5.1% vs. 0.8% in controls; HR 6.35; 95% CI 1.38 to 58.87; P=0.006). Inappropriate shocks are also another risk associated with ICDs, and these occurred in 5.9% of the ICD group.

Current American Heart Association guidelines include ICD implantation as a class 1A recommendation for primary prevention of all-cause mortality in patients with symptomatic systolic heart failure - with no differentiation between patients with ischemic and non-ischemic etiology, while European guidelines have a class IB recommendation specifically for patients with non-ischemic heart failure, he explained.

"Guidelines are based on multiple studies and ICD treatment should still have a class 1A recommendation for prevention of sudden cardiac death in non-ischemic heart failure also. However, patients with a high risk of non-sudden death may not benefit, and age should be an important factor in the decision to give an ICD, along with comorbidities," he concluded.

The study was supported by unrestricted grants from Medtronic, St. Jude Medical, TrygFonden, and The Danish Heart Foundation.

Prof. Kober has received honoraria from Novartis and Sanofi-Aventis outside the presented work.

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N-アセチルシステインはMI後の状態を引き上げる (Abstract 2227)

NACIAM：N-アセチルシステインはSTEMIに対しPCIを施行された患者の梗塞サイズを縮小する

NACIAM: N-acetylcysteine reduces infarct size in patients undergoing PCI after STEMI

ニトログリセリン（GTN）静注（IV）にN-アセチルシステイン（NAC）IVを併用することにより、ST上昇急性心筋梗塞（STEMI）に対し経皮的冠動脈形成術（PCI）を施行された患者の梗塞サイズが約3分の1に有意に縮小した、と2016年ESC Congressで発表された。NACIAMトライアルは、緊急PCIを施行され低用量GTN IVも施行されたSTEMI患者112人（平均年齢64歳）を対象とした。MI発症から1週間以内（早期）、および3か月後（後期）に再度施行された心臓磁気共鳴画像検査の結果、NAC投与群ではプラセボ投与群に比べ、梗塞サイズがそれぞれの時期において33%および50%少なかった（両方ともp=0.02）。

Full Text

The addition of intravenous (IV) N-acetylcysteine (NAC) to IV glyceryl trinitrate (GTN) significantly reduced infarct size by approximately one third in patients undergoing percutaneous coronary intervention (PCI) after ST-segment elevation acute myocardial infarction (STEMI), according to Hot Line research reported at ESC Congress 2016.

"Timely and effective myocardial reperfusion by PCI is the treatment of choice for limiting myocardial infarct size and improving clinical outcomes in patients presenting with STEMI. However, additional pharmacological interventions may help to reduce infarct size further," noted Sivabaskari Pasupathy, PhD candidate, from the University of Adelaide, in Adelaide, Australia, who presented the findings at ESC Congress 2016.

"Any intervention that actually reduces myocardial infarct size by approximately a third might reasonably be expected to substantially improve long-term outcomes."

NACIAM (N-AcetylCysteine In Acute Myocardial infarction), a placebo-controlled, double-blind trial, included 112 STEMI patients (mean age 64 years) from 3 Australian hospitals.

All patients underwent emergency PCI and also received low dose intravenous GTN. They were randomized pre-PCI to receive either high dose (15 grams/24 hours) NAC or an identical placebo, both delivered intravenously over 48 hours, "with the hypothesis that NAC might reduce infarct size, either by potentiating the effects of GTN or via 'scavenging' of reactive oxygen species," said Dr. Pasupathy.
Cardiac magnetic resonance (CMR) imaging performed within one week (early) and again 3 months post MI (late) showed that patients who received NAC had reductions in infarct size of 33% and 50% respectively compared to placebo (p=0.02 for both).

There was a similar but not significant trend towards reduction in creatine kinase release.

Additionally, myocardial salvage, measured at one week, was approximately doubled in patients who received NAC (60% vs. 27%, p<0.001), and there was also evidence of accelerated tissue reperfusion and hypochlorous acid "scavenging" in these patients.

Over 2 years of follow-up, the combination of cardiac readmissions and deaths was less frequent in NAC-treated (3 vs. 16 patients, P<0.01).

Safety endpoints including hypotension, bleeding, and contrast-induced nephropathy were similar in both groups.

"Intravenous NAC administration was associated with more rapid chest pain resolution, improved myocardial salvage, a favorable in-hospital safety profile, sustained infarct size reduction at 3 months post-STEMI, and promising clinical outcomes at 2 years," concluded Dr. Pasupathy. "While the results of this study are encouraging, we would prefer to regard NACIAM as the precursor of a follow-up study, sized for clinical end-points," she noted.

Supported by a grant-in-aid from Australian National Heart Foundation.

The authors reported no disclosures.

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CPAP治療による心血管系の有益性はない (Abstract 2224)

SAVE：冠動脈疾患患者に対するCPAP治療の心血管系への有益性は疑問である

SAVE: Cardiovascular benefit to CPAP treatment questioned in patients with coronary artery disease

冠動脈疾患および閉塞性睡眠時無呼吸を有する高齢患者に対し、持続性陽圧気道（CPAP）を用いた3年以上の夜間治療は、通常治療に比べ心血管系リスクをさらに軽減することはなかった。しかし重要なことに、CPAPは日中の眠気、健康関連QOL、気分ー特に抑うつ症状ーおよび出勤で定義された参加者のウェルビーイングを改善した。参加者は主に高齢者（約61歳）、過体重、習慣性いびき症の男性で、全員が冠動脈疾患または脳血管疾患を有していた。このSAVEスタディの結果は2016年ESC Congressで発表され、同時に *New England Journal of Medicine* に掲載された。

Full Text

More than 3 years of nightly treatment with a continuous positive airway pressure (CPAP) machine did not reduce cardiovascular risk more than usual care among elderly patients with coronary artery disease and obstructive sleep apnea (OSA).

Findings from the Sleep Apnea Cardiovascular Endpoints (SAVE) study were presented at ESC Congress 2016, with simultaneous publication in the *New England Journal of Medicine*.

"Given the level of risk of cardiovascular disease attributed to OSA in previous observational studies, we were surprised not to find a benefit from CPAP treatment," said the study's principal investigator Doug McEvoy, MD, from the Adelaide Institute for Sleep Health at Flinders University in Adelaide, Australia.

The SAVE study recruited sleep apnea patients with moderate-to- severe disease from 89 clinical centers in 7 countries.

Participants were predominantly elderly (approximately 61 years), overweight, habitually snoring males – all with coronary artery or cerebrovascular disease.

A total of 2,717 individuals were randomized to receive usual care alone, or usual care plus CPAP.

To be eligible, participants had to achieve a minimum 3 hours of sham-CPAP adherence per night in a one week run-in before the study started.

Usual care included concomitant CV risk management, based on national guidelines, as well as advice on healthy sleep habits and lifestyle changes to minimize OSA.

The study showed that 42% of patients assigned to CPAP had good adherence (an average of 4 or more hours per night). Mean apnea-hypopnea index (AHI, a measure of OSA severity) decreased from 29.0 to 3.7 events per hour when patients used CPAP, indicating good control of their OSA.

However, after a mean follow-up time of 3.7 years for 1,341 usual care and 1,346 CPAP patients included in the final analysis, there was no difference between groups in the primary outcome - a composite of death from any CV cause, myocardial infarction or stroke, and hospitalization for heart failure, acute coronary syndrome, or transient ischemic attack.

Specifically, 17.0% of patients in the CPAP group and 15.4% in usual-care had a serious CV event (hazard ratio 1.10; 95% CI 0.91 to 1.32; P=0.34).

"It's not clear why CPAP treatment did not improve CV outcomes," said Prof McEvoy.

"It is possible that, even though the average CPAP adherence of approximately 3.3 hours per night was as expected, and more than we estimated in our power calculations, it was still insufficient to show the hypothesized level of effect on CV outcomes."

Importantly though, CPAP did improve the wellbeing of participants, defined by symptoms of daytime sleepiness, health-related quality of life, mood – particularly depressive symptoms - and attendance at work.

Prof. McEvoy said that "While it is disappointing not to find a reduction in CV events with CPAP treatment, our results show that treatment of OSA in patients with CV disease is nevertheless worthwhile – they are much less sleepy and depressed, and their productivity and quality of life is enhanced."

"More research is needed now on how to reduce the significant risk of CV events in people who suffer from sleep apnea," he added.

"Given our finding of a possible reduction in cerebrovascular events in patients who were able to use CPAP for more than 4 hours per night, and of prior studies showing a stronger association between OSA and stroke than between OSA and coronary artery disease, future trials should consider targeting patients with OSA and stroke who can achieve a high level of compliance with CPAP."

The study was funded by the National Health and Medical Research Council (NHMRC) of Australia, Philips Respironics Foundation, and others.

Dr. McEvoy reports research equipment grants from ResMed and Air Liquide, speaker fees from Philips Respironics, and holds a Practitioner Fellowship and other grants from the NHMRC.

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幹細胞静脈内投与の期待されるベネフィット (Abstract 1232)

心不全における幹細胞注入は健康状態を改善したが心機能は改善しなかった

Infused stem cells in heart failure improved health status but not cardiac function

慢性非虚血性心筋症患者に対する間葉系幹細胞の静脈内単回投与は、器質的または機能的に有意な改善をもたらさなかったが、いくつかの臨床的に有意な改善をもたらした、との第II相ランダム化トライアルの結果が2016年ESC Congressで発表された。特に、プラセボに比べ、itMSC療法は、臨床概要および注入後90日の機能状態スコアに加え、6分間歩行試験（p=0.02）においても大きな改善を示した。過去の研究は、専ら幹細胞を直接心臓に注入する侵襲的なアプローチに焦点を当てていた。

Full Text

A single dose of mesenchymal stem cells delivered intravenously to patients with chronic non-ischemic cardiomyopathy was not associated with significant cardiac structural or functional improvements, but did result in several clinically relevant benefits, according to results from a phase II-a randomized trial.

The study, presented in a Hot Line session as ESC Congress 2016, "demonstrated that a more convenient and less invasive infusion strategy is safe, well-tolerated and shows improvements in multiple measurements of patient health status," reported investigator Javed Butler MD, from Stony Brook University, Stony Brook, NY, USA.

Previous work in this field has focused almost exclusively on the more invasive approach of injecting stem cells directly into the heart.

Prof. Butler and his colleague used "ischemia tolerant" mesenchymal stem cells (itMSCs) that were grown under chronic hypoxic conditions, with the aim of enhancing their potential benefits.

"The premise was that stem cells may have immune modulatory properties, which are enhanced when grown under hypoxic conditions," he explained.

This potential immune modulation and anti-inflammatory effect also opens the door to new methods of delivery, he added.

"Virtually all previous studies of stem cell therapy for heart failure have centered on the concept that the cells must be injected directly into the heart to trigger new growth, but if stem cells have anti-inflammatory benefits, direct cardiac delivery may not be necessary to repair and stimulate the dysfunctional viable myocardium."

The single-blind, placebo-controlled, crossover, multicenter study randomized patients with non-ischemic cardiomyopathy and left ventricular ejection fraction (LVEF) ≤40% to receive intravenous itMSC therapy (n=10) or placebo (n=12) for 90 days and then cross over to the other treatment.

The stem cells were donated by a health volunteer and grown under hypoxic conditions from the moment of extraction.

At 90-days post itMSC infusion, there were no major differences in primary safety endpoints of all-cause mortality, all-cause hospitalization, and adverse events.

Secondary endpoints of cardiac remodeling (left ventricular ejection fraction and ventricular volumes), assessed by cardiac magnetic resonance imaging, were also not different between groups at 90-days.

However, treatment with itMSCs resulted in improved health status and functional capacity – which were also prespecified secondary endpoints.

Specifically, compared to placebo, itMSC therapy resulted in statistically significant improvements in 6-minute walk test (an estimated 36m more than placebo, p=0·02) as well as greater improvements in Kansas City Cardiomyopathy Questionnaire scores (clinical summary score +5·22, p=0·02, and functional status scores +5·65, p=0·06) at 90-days post-infusion.

Additionally, itMSCs infusion resulted in significant alterations in several inflammatory cells, "supporting the immunomodulatory and anti-inflammatory mechanisms of itMSCs," noted Dr. Butler.

"To our knowledge, this trial represents the first experience with intravenously administered itMSCs in patients with any type of chronic cardiomyopathy," he concluded. "Further studies should explore the efficacy of serial dosing to produce more sustained immunomodulatory effects and thereby perhaps facilitate improvement in left ventricular structure and function, and in clinical outcomes."

The study was funded by Cardiocell LLC in San Diego, CA, USA.

Dr. Butler reports research support from the National Institutes of Health, PCORI and European Union; and is a consultant to Amgen, Bayer, Cardiocell, Novartis, Boehringer-Ingelheim, Relypsa, Z Pharma, PharmaIn, SC Pharma and Gilead.

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心臓再生療法のトライアルが新たな知見をもたらす (Abstract 1299)

CHART-1：心臓形成幹細胞療法により、一部の心不全患者は恩恵をこうむる可能性がある

CHART-1: Cardiopoietic cell therapy may benefit a subgroup of patients with heart failure

うっ血性心不全患者において心臓形成療法（骨髄由来幹細胞を用いて心臓の修復を促進する治療）は、シャム手術に比べ一次転帰は改善しなかった。しかし、この研究により新たな知見が明らかにされた、とCHART-1トライアルの研究者らは2016年ESC Congressで発表した。特に、左室拡張末期容積が200～370 mLの患者群におけるサブグループ解析からは、この細胞療法の好ましい効果が示された。筆者らは、このサブグループの患者は心臓形成療法の恩恵をこうむる可能性があると考えている。

Full Text

A therapy that uses bone-marrow stem cells to promote heart repair did not significantly improve the primary outcome over a sham procedure among patients with congestive heart failure. However, it revealed critical new insights, according to investigators of the CHART-1 trial.

Although findings of CHART-1 (Congestive Heart Failure Cardiopoietic Regenerative Therapy) were neutral in the overall patient population, an exploratory analysis identified a sub-group of patients who may benefit from cardiopoietic cell therapy, according to the principal co-investigator of the study Jozef Bartunek, MD, PhD, from OLV Hospital Aalst, Belgium.

"Within a well-defined patient population, based on baseline heart failure severity, this therapy showed benefit," said Prof. Bartunek, who presented the findings at ESC Congress 2016. "Lessons learned from CHART-1 will now provide the foundation for the design of the ensuing CHART-2 trial which will target these patients."

Cardiopoietic cell therapy involves the isolation of mesenchymal stem cells from a patient's own bone marrow. Exposing these cells to a "cardiogenic cocktail" turns them into cardiopoietic cells that are then injected into damaged heart tissue.

The CHART-1 study randomized patients with symptomatic ischemic heart failure from 39 hospital centers in Europe and Israel.

Patients received either a sham procedure (n=151) or cardiopoietic cells (n=120).

At 39 weeks there was no significant difference between groups for the primary efficacy endpoint, which was a composite of all-cause mortality, worsening heart failure events, Minnesota Living with Heart Failure Questionnaire total score, 6-minute walk distance, left ventricular end-systolic volume and ejection fraction.

However, a subgroup analysis of patients with severe heart enlargement at baseline (left ventricular end-diastolic volumes between 200 and 370 mL) suggested a positive effect of the cell treatment over sham.

"Outcomes for all components of the composite endpoint, including mortality and worsening heart failure, were "directionally consistent" said Prof Bartunek, adding that "the effect was also related to clinically meaningful improved quality of life, greater 6-minute walk distance, and reduced left ventricular end-systolic volume for cell treatment versus sham."

In addition, "we observed a modifying effect of treatment intensity with suggestion of a greater benefit at lower number of injections," he added. "Overall safety was demonstrated across the study cohort, with no difference in adverse clinical outcomes observed between the groups."

Ongoing analyses will evaluate 12-month clinical outcomes, said Prof Bartunek. "Insights from the CHART-1 trial have implications for targeting the patient population that should be considered for cardiopoietic cell therapy in future clinical trials or for broader clinical considerations. More generally, indices of heart failure severity and optimized therapeutic intensity should be considered."

The trial was funded by Celyad, SA (Mont-Saint-Guibert, Belgium).

Jozef Bartunek is a member of CVBA Cardiovasculair Onderzoek an institution which co-founded Cardio3Biosciences (currently Celyad). All consultancy/speakers fees and research contracts are directed to Cardiovasculair Onderzoek and Cardiac Research Institute, Aalst, BE.

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短期間の抗血小板薬2剤併用療法は有効である (Abstract 2218)

NIPPON：新たな薬剤溶出性ステント留置後の患者において、短期の抗血小板薬2剤併用療法は長期投与と同等である

NIPPON: Short-term dual antiplatelet therapy equivalent to longer course in patients with a newer drug-eluting stent

ある特定の薬剤溶出性ステント（DES）を留置された患者において、短期抗血小板薬2剤併用療法（DAPT）は、長期投与に比べ非劣性を示した、と2016年ESC Congressで発表された。トライアルの対象となったすべての患者は、生体吸収性ポリマー溶出のNoboriステントを留置され、アスピリン（1日81～162 mg）とクロピドグレル（1日75 mg）またはチクロピジン（1日200 mg）によるDAPTを施行された。今回のNIPPONスタディの結果から、正味の臨床的脳血管有害イベント－主要評価項目－発現率は、6か月および18か月のDAPT期間で同等であり、出血の合併症にも差がないことが示された。

Full Text

A short-term course of dual antiplatelet therapy (DAPT) is non-inferior to a longer course in patients who have undergone placement of a particular kind of drug-eluting stent (DES).

Results of the NIPPON (NoborI dual antiplatelet therapy as aPPrOpriate DuratioN) study, presented at ESC Congress 2016, showed similar rates of "net adverse clinical and cerebrovascular events" (NACCE) – the main outcome – with both 6 and 18-month DAPT durations, and no difference in bleeding complications.

"Based on these findings, a combination of short DAPT and a newer DES with bioabsorbable abluminal coating should be able to minimize the incidence of thrombotic events and bleeding complications simultaneously," concluded investigator Masato Nakamura, MD, PhD, of Toho University Ohashi Medical Center in Tokyo, Japan.

All patients in the trial had received the Nobori bioabsorbable abluminal-coated stent, with DAPT consisting of aspirin (81–162 mg/day) combined with clopidogrel (75 mg/day) or ticlopidine (200 mg/day).

The study enrolled 3,775 patients with coronary artery disease or acute myocardial infarction who had undergone percutaneous coronary intervention and stent placement at 130 Japanese institutions.

It incorporated broad inclusion criteria to reflect the real-world clinical setting.

However, an interim analysis showed slow enrollment and substantially lower events than expected, and the study was terminated early.

Results from only the first 2,772 patients to be followed for at least 18 months showed there was a 0.46% difference in occurrence of the primary endpoint among patients randomized to either short or long-term DAPT (1.92% vs. 1.45% respectively), confirming the non-inferiority of short-term therapy.

The rate of bleeding events was similar (0.73 % of the long-term and 0.96% of the short-term DAPT group), as was the rate of stent thrombosis (0.07% in both).

"The results of the present study should be interpreted with caution before trying to draw firm conclusions," cautioned Professor Nakamura. "The interpretation of the NIPPON trial is complicated by the fact that the event rate was lower than the expected incidence of the primary endpoint in both groups. Therefore, the statistical power may not have been adequate to fully assess the risk of primary endpoint."

Associations for Establishment of Evidence in Interventions Studies funded the research.

Dr. Nakamura has received research grant support and honoraria from Terumo Corporation, Sanofi, and Daiichi Sankyo.

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除細動前の抗凝固薬による新たな治療選択肢 (Abstract 5715)

ENSURE-AF：AF除細動においてエドキサバンはワルファリンと同等に安全かつ有効である

ENSURE-AF: Edoxaban is as safe and effective as warfarin at AF cardioversion

除細動施行前に抗凝固療法が必要な心房細動（AF）患者は、エドキサバン-非ビタミンK拮抗経口抗凝固薬-による治療により恩恵をこうむる可能性がある。このENSURE-AFトライアルは2016年ESC Congressで発表され、同時に*Lancet* に掲載された。エドキサバンは、よく管理された最適なエノキサパリン／ワルファリン療法に比べ、大出血および血栓塞栓発症率が同等であった。この結果は経食道心エコー（TEE）ガイド下、抗凝固薬による前治療、および併存疾患によらず同等であった。実臨床レベルでは、今回のスタディの結果、新たにAFと診断された抗凝固療法非施行患者は、TEE不可または3週間前から治療ができない場合には、除細動のわずか2時間前にエドキサバンを開始すればよいことが示された。

Full Text

Patients with atrial fibrillation (AF) who need anticoagulation before undergoing cardioversion may benefit from treatment with edoxaban - a non-vitamin K antagonist (VKA) oral anticoagulant (NOAC), according to results of the ENSURE-AF trial.

Edoxaban is "an effective and safe alternative" to standard therapy, which uses VKAs, said investigator Andreas Goette, MD, from St. Vincenz-Hospital, Paderborn, Germany, who presented the Hot Line results at ESC Congress 2016, with simultaneous publication in The *Lancet*.

While VKA anticoagulation works well, it has a major limitation in that it requires regular monitoring and dose adjustment to ensure that patients reach anticoagulation targets, explained Prof Goette. This can sometimes delay cardioversion for several weeks.

"At a practical level, our study results show that newly diagnosed non-anticoagulated AF patients can start edoxaban as early as two hours prior to their cardioversion procedure if they have access to transoesophageal echocardiography (TEE) or 3 weeks prior without."

Edoxaban was previously shown to be safe and effective compared to standard VKA therapy (enoxaparin/warfarin) among patients with AF in the ENGAGE AF-TIMI 48 study, but the impact of electrical cardioversion was not systematically assessed in that study.

ENSURE-AF, the largest randomized clinical trial of anticoagulation for cardioversion in patients with AF, "provides the largest prospective trial data for a NOAC in this clinical setting," noted Prof Goette. "Results suggest that edoxaban is an effective and safe alternative to standard enoxaparin/warfarin, a VKA therapy."

The phase 3b study, involving 239 study sites in 19 countries in Europe and the United States, included 2,199 patients with documented non-valvular AF who were scheduled for electrical cardioversion after anticoagulation therapy.

A total of 1,095 patients were randomized to receive edoxaban, while the remaining 1,104 received enoxaparin/warfarin (dosing varied depending on patient characteristics).

Of these 988 (90.2%) and 966 (87.5%) patients, respectively, were cardioverted either electrically or spontaneously, some with the use of transoesophageal echocardiography (TEE).

The primary efficacy objective of this study was to compare the incidences of the composite endpoint of stroke, systemic embolic event (SEE), myocardial infarction (MI) and cardiovascular (CV) death between the two groups at day 28 (ITT analysis).

This endpoint occurred at a comparable rate in both groups: 0.5% patients in the edoxaban arm vs. 1.0% in the enoxaparin/warfarin arm (OR=0.46; 95% CI, 0.12–1.43)
The primary safety outcome was a composite endpoint of major and clinically relevant non-major (CRNM) bleeding events at 30 days.

This also occurred at a comparable rate 1.5%and 1.0% respectively (OR=1.48; 95% CI, 0.64–3.55).

In short, "edoxaban had similar rates of major bleeding and thromboembolism compared to well-managed, optimized enoxaparin/warfarin therapy. The results were similar whether TEE-guidance was used or not, whether patients had received prior anticoagulation or not, and in patients with a broad range of associated comorbidities."

The study was funded by Daiichi Sankyo. Professor Goette has served as a consultant for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer, and a speaker for Astra Zeneca, Bayer, Berlin Chemie, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Pfizer, and Sanofi-Aventis.

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冠動脈分岐部病変に対するステント留置技術の比較(Abstract 5034)

BBK II：側枝にステント留置が必要な冠動脈分岐部病変にはキュロットステントが好ましい

BBK II: Culotte stenting preferred for coronary bifurcations when stenting of the site branch is needed

側枝にステント留置が必要な冠動脈分岐部病変には、TAPステント術に対しキュロットステント術を用いた治療の方が優れている、とのBBK IIトライアルの結果が2016年ESC Congressで発表され、同時に*European Heart Journal* に掲載された。一次エンドポイントは、9か月後のフォローアップ定量的冠動脈造影により評価した、分岐部病変の最大ステント径狭窄率であった。結果、キュロットステント群とTAPステント群の平均最大径狭窄率は、それぞれ21%対27%（p=0.038）であり、キュロットステント群が有意に優れていた。この差のほとんどすべては、側枝の狭窄率の差によるものであった。

Full Text

Coronary bifurcations are best treated with a technique known as culotte stenting, as opposed to T-and-protrusion (TAP) stenting, when there is need for a side-branch stent according to results of the BBK II (Bifurcations Bad Krozingen) trial.

The findings, presented at ESC Congress 2016, with simultaneous publication The *European Heart Journal*, are the first randomized results directly comparing these two commonly used techniques.

Coronary bifurcations lesions have to be treated in about 20% of all percutaneous coronary interventions, and so far several different technical approaches have been recommended, explained investigator Miroslaw Ferenc, MD, PhD from the University Heart Center Freiburg, in Bad Krozingen, Germany.

"Treatment is often challenging and requires a high level of interventional qualification. This is the first head to head comparison of the two most commonly used techniques in patients needing side branch stenting and having suitable anatomy for both techniques, and it not only provides angiographic follow-up but also demonstrated a clear signal with respect to clinical outcome.

"There was a statistically significant difference in the primary study endpoint favoring culotte stenting. The lower angiographic restenosis rate in the bifurcation lesion after culotte stenting as compared with TAP stenting was also associated with lower rate of target lesion revascularization (TLR) in the first year after PCI."

The study included 300 patients with stable or unstable angina and/or a positive stress test who were undergoing percutaneous coronary intervention and side-branch stenting of a coronary bifurcation lesion.

During the procedure, if a side branch stent was needed and the lesion was deemed amenable for both stenting techniques, patients were randomized to either TAP stenting (n=150) or culotte stenting (N=150).

The primary endpoint was maximal in-stent percent diameter stenosis of the bifurcation lesion assessed by follow-up quantitative coronary angiography at 9 months.

This showed a significant advantage to culotte stenting which resulted in a mean maximal percent diameter stenosis of 21% versus 27% in the TAP stenting group (P=0.038), said Dr. Ferenc.

This difference in the primary endpoint was driven almost entirely by differences in the side branch, where the mean percent diameter stenosis was 16% in the culotte arm versus 22% in the TAP (P=0.029). In contrast, there were no differences between techniques in the percent diameter stenosis in the main branch.

There were other important differences in favor of culotte stenting, added Dr. Ferenc.

These included a highly significant difference in binary in-stent restenosis at the bifurcation lesion (6.5% after culotte vs. 17% TAP; P=0.006) as well as a 6% vs. 12% target bifurcation lesion revascularization rate at 1 year (which just missed reaching statistical significance: P= 0.069). Again, both of these outcomes were driven by differences in the side, as opposed to the main branch, he said.

Death, target vessel myocardial infarction, and stent thrombosis were infrequent at 1 year, and did not differ significantly between the two study groups.

"Given the clear results of this trial together with the same trend for hard clinical endpoints, culotte stenting has now to be seen as the preferred approach for coronary bifurcations, when stenting of the site branch is needed," said Dr. Ferenc.

"Interventional cardiologists can use now culotte stenting with more confidence knowing that this technique is associated with a very low angiographic restenosis rate and lower rate of TLR as compared with TAP stenting - even though it is slightly more challenging and requires appropriate training."

This trial was exclusively supported by an unrestricted grant from the University Heart Center Freiburg - Bad Krozingen. Dr. Ferenc receives speaker honoraria from Boston Scientific, Biotronik, Abbott, and Medtronic.

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STEMIにおいてプラスグレルとticagrelorの有効性は同等である(Abstract 5028)

PRAGUE-18：STEMIにおいてプラスグレルとticagrelorの安全性および有効性は同等である

PRAGUE-18: Prasugrel and ticagrelor equally safe and effective in STEMI

ST上昇急性心筋梗塞（STEMI）患者において、抗血小板薬であるプラスグレルとticagrelorの安全性および有効性は同等であった、とのPRAGUE-18の結果が2016年ESC Congressで発表された。一次エンドポイントは死亡、再狭窄、標的病変緊急血行再建術施行、脳卒中、輸血を要する重症出血、または発症7日後の入院延長で定義された。中間解析において、エンドポイント発現率に両群間で差がなかった（プラスグレル群対ticagrelor 群でそれぞれ4.0% および4.1%；p=0.939）ことから、トライアルは予定より早期に中止された。これは、2剤を直接比較した初のランダム化試験である。

Full Text

The antiplatelet drugs prasugrel and ticagrelor had similar safety and efficacy among patients with acute myocardial infarction and ST segment elevations (STEMI), according to results of PRAGUE-18, the first randomized, head-to-head comparison of the drugs.

"Our findings confirm previous indirect - non-randomized- comparisons of these two drugs, based on analyses of various registries," commented Petr Widimsky MD, DrSc, from the Cardiocenter of Charles University, in Prague, Czech Republic. "Thus, both drugs are very effective and safe and significantly contribute to the excellent outcomes of patients with acute myocardial infarction in modern cardiology."

The Hot Line study, presented at ESC Congress 2016, randomized 1,230 STEMI patients to receive either prasugrel or ticagrelor prior to primary percutaneous coronary intervention (pPCI).

The primary end-point was defined as death, re-infarction, urgent target vessel revascularization, stroke, serious bleeding requiring transfusion, or prolonged hospitalization at 7 days.

The trial was halted prematurely after an interim analysis showed no difference in the rate of this endpoint between groups (4.0% and 4.1% in the prasugrel and ticagrelor groups, respectively; P=0.939).

There was also no difference between groups in the rate of the key secondary end-point, composed of cardiovascular death, non-fatal myocardial infarction or stroke within 30 days (2.7% and 2.5%, respectively; P=0.864).

"These study results offer more freedom to clinicians to select the antiplatelet agent added on top of aspirin for patients with STEMI who receive dual antiplatelet therapy," commented Prof. Widimsky.

Final follow-up will be at 1 year for all patients, and will be completed in 2017.

The PRAGUE acronym refers to a series of academic randomized trials coordinated by the Cardiocenter, Charles University Prague, starting with PRimary Angioplasty in patients with myocardial infarction transferred from General community hospitals to angioplasty Units of tertiary cardiology centers with or without Emergency thrombolysis (2000).

Administrative costs were covered by the Charles University Cardiovascular Research Program P35. The investigators have no relevant disclosures.

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機能的画像検査の広範な使用が推奨される (Abstract 4154)

CE-MARC 2：冠動脈疾患が疑われる患者において心臓MRIはより侵襲的な冠動脈造影を回避させる

CE-MARC 2: Cardiac MRI avoids more invasive angiography in suspected coronary artery disease

冠動脈疾患が疑われる患者を対象とした機能的画像検査-ガイドラインが指示する方法ではなく-を用いた初回研究の結果、不必要な血管造影が減少した、とのCE-MARC 2トライアルの結果が2016年ESC Congressで発表され、同時に*JAMA* に掲載された。心臓MRIおよび心筋シンチグラフィの両者は、ガイドラインが指示する方法よりも不必要な冠動脈造影施行率を有意に減少させ、主要な心血管イベントに関して不利益はなかった。この結果から、たとえ高リスク患者群であっても、機能的画像検査をより広範囲に活用すべきであることが示唆された。

Full Text

Initial investigation of patients with suspected coronary heart disease (CHD) using functional imaging - rather than guideline-directed care - resulted in significantly less unnecessary angiography, according to results of the CE-MARC 2 trial.

The findings, presented in a Hot Line session at ESC Congress 2016, and published simultaneously in *JAMA*, could have an important impact on referral rates for invasive coronary angiography, and potentially healthcare costs, said lead investigator John Greenwood, PhD, from the University of Leeds, in Leeds, United Kingdom.

"Rates of invasive angiography are considered too high among patients with suspected coronary heart disease," explained Professor Greenwood.

"Our findings show that both cardiovascular magnetic resonance (CMR) and myocardial perfusion scintigraphy (MPS) significantly reduced rates of unnecessary angiography compared to guideline-directed care, with no penalty in terms of major adverse cardiovascular events (MACE). This suggests that functional imaging should be adopted on a wider basis, even in high-risk patient subgroups."

The Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease 2 (CE-MARC 2) trial included 1,202 patients with suspected CHD from six UK centers.

The patients were randomized to functional imaging-based investigation with either CMR (n = 481) or MPS (n = 481), or to guideline-directed investigation (n=240) based on National Institute for Health and Care Excellence (NICE) guidelines.

In this latter group, those with a pre-test likelihood of 10%-29% (meaning low risk for CHD based on age, gender, symptom characteristics, and clinical history) were scheduled for cardiac computed tomography (CCT), those with a pre-test likelihood of 30% to 60% (intermediate risk) were scheduled MPS, and those with a high pre-test likelihood were sent directly to coronary angiography.

The primary end point was unnecessary coronary angiography within 12 months, (defined by absence of significant stenosis measured by fractional flow reserve or quantitative coronary angiography), with secondary end points of MACE, and positive angiography within this same time period.

Overall, 22% of the study population underwent coronary angiography within 12 months, with unnecessary angiograms occurring in 28.8% of the NICE guidelines group, 7.5% of the CMR group, and 7.1% of the MPS group, reported Professor Greenwood.

The adjusted odds ratio of unnecessary angiography for the CMR group versus the NICE guidelines group was 0.21 (95% CI, 0.12-0.34; P < .001), with no statistically significant difference between the CMR and MPS groups.

Between the three strategies, there was no difference in short-term MACE or positive angiography rates.

"Worldwide, MPS is the most commonly used test to assess suspected CHD, but CMR is increasingly recognized as having high diagnostic accuracy and prognostic value," noted Professor Greenwood. "Although the results of CE-MARC 2 showed no difference between the CMR and MPS strategies in terms of unnecessary angiography rates, our original CE-MARC study showed that CMR had a higher diagnostic accuracy compared to MPS (Lancet 2012; 379(9814):453-460) and was also a stronger predictor of risk for MACE (Annals of Internal Medicine 2016; 165(1):1-9)."

He concluded that "these results show that a broader use of functional imaging (CMR or MPS), in low, intermediate and high risk patient groups, could reduce the rates of invasive angiography that ultimately show no obstructive coronary disease. In addition, CE-MARC and CE-MARC 2 further support the role of CMR as an alternative to MPS for the diagnosis and management of patients with suspected CHD."

The trial was funded by grants and fellowships from the British Heart Foundation; the Leeds Teaching Hospital Charitable Foundation; the National Institute for Health Research, and the Scottish Funding Council. Professor Greenwood reported no relevant disclosures.

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アリロクマブは家族性高コレステロール血症のアフェレーシスを減少させる(Abstract 3166)

ODYSSEY ESCAPE：PCSK9阻害薬は家族性高コレステロール血症におけるアフェレーシス治療の必要性を減少させる

ODYSSEY ESCAPE: PCSK9 inhibitor reduces need for apheresis treatment in familial hypercholesterolemia

家族性高コレステロール血症ヘテロ接合体患者は、PCSK9阻害薬アリロクマブを用いることで、高価で時間のかかるアフェレーシス治療の必要性を軽減またはなくすことすら可能となる。アリロクマブ治療患者はプラセボ群患者に比べ、アフェレーシスを75%減らすことができた（$p < 0.0001$）。実際、アリロクマブを使用した患者の63.4%がアフェレーシスを完全にやめることができ（プラセボでは0人）、92.7%は少なくとも半減した（プラセボ群では14.3%）。この第3相ODYSSEY-ESCAPEトライアルの結果は2016年ESC Congressで発表され、同時に*European Heart Journal*に掲載された。

Full Text

Patients who have heterozygous familial hypercholesterolemia (HeFH), a condition that causes abnormally raised low-density lipoprotein cholesterol (LDL-C) levels and premature cardiovascular disease, can significantly reduce or even eliminate their need for expensive and time-consuming apheresis treatments with the PCSK9 inhibitor alirocumab.

Results of the phase 3 ODYSSEY-ESCAPE trial, reported in a Hot Line session at ESC Congress 2016, "suggest a role for alirocumab in the overall management of patients with HeFH undergoing regular lipoprotein apheresis therapy, with the potential to avoid apheresis treatments or delay the requirement for such treatments," said the study's lead investigator Patrick M. Moriarty, MD, from the University of Kansas Medical Center, in Kansas City, KS, USA.

The findings, published simultaneously in The *European Heart Journal*, have exciting implications for HeFH patients, many of whom struggle with weekly apheresis treatments, he explained.

"Being able to reduce or eliminate apheresis would be a major breakthrough for these patients who spend $50,000 to $75,000 a year, and 3-4 hours every 1-2 weeks to clear their blood of excess LDL-C. If our results are confirmed in other studies this could mark a new era for patients with familial hypercholesterolemia who have uncontrolled cholesterol levels and resistance to normal medical management."

The study included 62 HeFH patients from 14 centers in the US and Germany, who were undergoing apheresis either weekly or every 2 weeks.

They were randomized to receive subcutaneous injections of either alirocumab 150 mg (n=41) or placebo (n=21) every 2 weeks for 18 weeks while still continuing their regular lipid-lowering medications (LLT).

Apheresis treatments during the study were scheduled over 2 phases: Until week 6, the rate was fixed according to the patient's established schedule, but was then adjusted between weeks 7 through 18 based on individual needs. If a patient's LDL-C had dropped by 30% or more since the start of the study, apheresis was skipped.

At the end of the study, the alirocumab-treated patients had a 75% greater reduction in apheresis compared to those on placebo (P<0.0001).

In fact, 63.4% of patients on alirocumab eliminated apheresis altogether (compared to none in the placebo group), and 92.7% avoided at least half of the procedures (compared to 14.3% in the placebo arm).

"Reasons why apheresis rates reduced with placebo are unclear, but may reflect individual variation in LDL-C values, perhaps due to changes in diet or adherence to LLT, the small sample size, and the fact that patients were in a supervised clinical trial," noted Dr. Moriarty.

Adverse events were generally not serious, and were similar in both groups (75.6% of alirocumab vs. 76.2% of placebo patients).

"In the future, lipoprotein-apheresis centers may now add alirocumab to a patient's LLT and possibly not have to treat them with apheresis or at least treat them less often," predicted Dr. Moriarty. "Since the drug has already been approved for this patient population (HeFH and high CVD risk) it can be now considered part of standard care for these patients intolerant to other LLT. Both patients and health care providers will all be pleased to know there is potentially easier, more efficient, and less expensive means of treating dyslipidemia in these patients."

This study was supported by Sanofi and Regeneron Pharmaceuticals, Inc. The sponsor was involved in the study design, the writing of the report, and the decision to submit it for publication. Dr. Moriarty reports grants and personal fees from Regeneron and Sanofi, as well as from Amgen, Ionis, and Genzyme; personal fees from Duke, Esperion, Eliaz Therapeutics, Alexion, Aegerion, Amarin and Lilly; and grants from Pfizer, Catabasis, Novartis, and Kaneka.

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伏在静脈グラフトにおいて薬剤溶出ステントはより有効である(Abstract 5025)

BASKET SALVAGE：長期予後の点から薬剤溶出ステントは伏在静脈グラフトにおいて利点がある

BASKET SALVAGE: Long-term outcomes gives advantage to drug eluting stents in saphenous vein grafts

伏在静脈グラフトによる血行再建施行患者において、薬剤溶出ステント(DES)はベアメタルステント(BMS)よりも明らかに利点がある、とのBASKET SALVAGEトライアルの結果が2016年ESC Congressで発表された。一次エンドポイントである12か月以内の主要な心イベントは、BMS群に比べ、DES群において有意に頻度が低かった(2%対18%、p<0.001)。この差は主として、標的グラフトに対する再血行再建率がBMS群では12%であったのに対し、DES群ではそれがなく(p<0.001)、また、BMS群では非致死性心筋梗塞発症率が有意に高かった(12%対2%)ことによるものであった。

Full Text

Drug-eluting stents had a clear advantage over bare metal stents in patients undergoing revascularisation of saphenous vein grafts, results of the BASKET-SAVAGE trial show.

"This is currently the largest trial with long-term outcome data comparing these two types of stents in saphenous vein graft disease, and will reassure clinicians about the use of DES for this specific indication," noted principal investigator Raban Jeger, MD, from University Hospital, in Basel, Switzerland.

Findings from BASKET-SAVAGE, (which stands for Basel Kosten Effektivitäts Trial – SAphenous Venous Graft Angioplasty Using Glycoprotein 2b/3a Receptor Inhibitors and Drug-Eluting Stents) were presented in a Hot Line session at ESC Congress 2016.

The results address inconsistency in the published literature regarding long-term outcomes after stenting of saphenous vein grafts (SVG), added Prof. Jeger.

Saphenous veins from the legs may be used to bridge plaque-filled coronary arteries as part of coronary bypass surgery, but eventually they too can atherosclerotic and require stents to keep them open.

The BASKET-SAVAGE trial randomized 173 patients with SVG disease to undergo percutaneous coronary intervention (PCI) with either bare metal stents (BMS, n=84) or paclitaxel drug-eluting stents (DES, n=89). (The trial reached only 72% of its target sample size before being terminated early due to limited enrolment).

The patients were a median age of 72 years and had received their SVGs a median of 13 years earlier.

During the procedure, most patients also received glycoprotein IIb/IIIa inhibitors (74%) to prevent clotting, and distal protection devices (66%) to catch any dislodged plaque debris.

The primary endpoint, which was major adverse cardiac events (MACE) at 12 months, occurred significantly less often in the DES compared to the BMS group (2% vs. 18%, hazard ratio [HR] 0.15, P<0.001). This difference was driven largely by a 12% rate of repeat procedures in the target graft among BMS-treated patients compared to none in the DES group (HR 0.04, P<0.001), as well as a significantly higher rate of nonfatal myocardial infarctions in BMS-treated patients (12% vs. 2%, HR 0.24, P=0.025).

Longer follow-up to 3 years among a subgroup of patients showed that MACE rates were 67% lower in the DES compared with the BMS group (30% vs. 12%, HR 0.33, P=0.0012), and the safety profile was similar in both arms.

Due to different pathophysiology, SVG atherosclerosis is potentially more demanding to treat compared to coronary artery disease in native vessels, but combining distal protection devices and glycoprotein IIb/IIIa inhibitors with DES resulted in MACE rates comparable to those seen after native vessel stenting, said Prof. Jeger.

"DES should remain the standard of care in patients with SVG lesions undergoing percutaneous coronary interventions," he concluded.

The Swiss National Science Foundation, the Basel Cardiovascular Research Foundation, and Boston Scientific Germany. The investigators reported no relevant disclosures.

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DOCTORS：光干渉断層法は経皮的冠動脈インターベンション施行にさらに役立つ

DOCTORS: Optical coherence tomography sheds more light on percutaneous coronary intervention

光干渉断層法（OCT）は、経皮的冠動脈インターベンション（PCI）施行患者の冠動脈を可視化し、標準的な血管造影ガイド下PCIに比べ臨床転帰を改善する、と2016年ESC Congressで発表され、同時に*Circulation* に掲載された。血管造影ガイド下群に比べ、OCT群における冠血流予備量比（FFR）は有意に良好であった（p=0.005）。さらに、施術後FFR>0.90の患者数はOCT群において多かった（p=0.0001）。OCTにより、医師はステント植え込み前に血栓や石灰化をより多く確認することができた（それぞれp=0.0004およびp<0.0001）。これにより、抗血小板薬使用は、OCT群においてより頻度が高い結果となった（53.3%対35.8%）。

Full Text

Optical coherence tomography (OCT) can visualize the coronary arteries in patients undergoing percutaneous coronary intervention (PCI) and lead to better outcomes compared to standard angiography-guided PCI, according to new findings reported here.

Results of the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) study were presented in a Hot Line session at ESC Congress 2016, with simultaneous publication in *Circulation*.

In patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS), OCT "provided useful additional information beyond that obtained by angiography alone, and impacted directly on physician decision-making," reported the study's lead investigator Nicolas Meneveau, MD, PhD, from University Hospital Jean Minjoz, in Besançon, France.

OCT, which involves introducing an imaging catheter into the coronary artery to check vessel size, lesion characteristics, and stent positioning and expansion "led to a change in procedural strategy in half of cases," said Professor Meneveau.

However, "additional prospective randomized studies with clinical endpoints are required before it can be recommended for standard use."

The multi-center trial included 240 NSTE-ACS patients who were randomized 1:1 to standard fluoroscopy-guided PCI alone (angio group) or with the addition of OCT - performed an average of 3.8 times, before, during an after the procedure.

Overall, OCT was associated with better functional outcome than PCI guided by fluoroscopy alone, said Prof. Meneveau.

The primary endpoint of the study, which was fractional flow reserve (FFR) – a measure of blood flow and pressure in the coronary artery before and after the procedure - was significantly better in the OCT group as compared to the angio group (0.94 vs. 0.92, p=0.005).

In addition, the number of patients with a post-procedural FFR>0.90 was significantly higher in the OCT group (82.5% vs. 64.2%, p=0.0001).

Compared to angiography, OCT allowed clinicians to see significantly more thrombi (69% vs. 47%, p=0.0004) and calcifications (45.8% vs. 9%, p<0.0001) before stent implantation. This resulted in more frequent antiplatelet use in the OCT group (53.3% vs. 35.8%).

As well, OCT was also significantly more likely to reveal stent underexpansion (42% vs. 10.8%), incomplete lesion coverage (20% vs. 17%, and edge dissection (37.5% vs. 4%), compared to angio.

Stent malapposition, which is not visible under fluoroscopy alone, was observed in 32% of patients undergoing OCT.

These observations led to the more frequent use of post-stent overinflation in the OCT group (43% vs. 12.5%, p<0.0001) and a lower percentage of residual stenosis (7.0% vs. 8.7%, p=0.01).

The addition of OCT increased procedure time as well patients' exposure to fluoroscopy and contrast medium, but this did not increase complications such as peri-procedural myocardial infarction or impaired kidney function, added Prof. Meneveau.

"Findings of the DOCTORS study add to the cumulating body of evidence in favor of a potential benefit of OCT to guide angioplasty," he said. "The improvement in functional outcomes could translate into a clinical benefit in the longer term."

The DOCTORS study was funded by the French government's national hospital research program (Programme Hospitalier de Recherche Clinique 2013). Prof Meneveau receives consulting fees and speaker honoraria from St Jude Medical, Bayer, Daiichi Sankyo, Astra Zeneca, BMS-Pfizer, and speaker honoraria from Boehringer Ingelheim.

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抗凝固薬による出血に対する迅速かつ有効な中和剤(Abstract 5718)

ANNEXA-4：予備試験の結果において第Xa因子阻害剤は抗凝固作用を迅速に軽減した

ANNEXA-4: Factor Xa reversal agent quickly reduces anticoagulant activity in preliminary results

生命を脅かす可能性のある抗凝固作用を抑制するようデザインされた中和剤は、迅速に作用し忍容性は非常に良好であった、と現在進行中のANNEXA-4スタディの中間解析結果が2016年ESC Congressで発表され、同時に*New England Journal of Medicine* に掲載された。スタディ対象患者は、直接または間接fXa阻害剤投与後、18時間以内に急性大出血を来し緊急の中和作用を必要とした。リバロキサバン投与患者では、静注終了時にはfXa阻害活性がベースラインから89%低下しており、アピキサバン投与患者では同様に93%低下した。12時間後の臨床的止血効果は、79%の患者において"良から優"と評価された。

Full Text

A specially designed antidote to reverse acute, potentially life-threatening anticoagulant-related bleeding worked quickly, and was well-tolerated according to interim results of the ongoing ANNEXA-4 study.

Andexanet alfa reduced anticoagulant activity by roughly 90% within half an hour among patients with acute major bleeding while receiving a factor Xa (fXa) inhibitor, resulting in "excellent or good" hemostasis at 12 hours in most subjects, reported lead investigator Stuart J. Connolly, MD, from McMaster University, in Hamilton Ontario, Canada.

The **AN**dexanet Alfa, a **N**ovel Antidote to the Anticoagulation **E**ffects of F**XA** Inhibitors (ANNEXA-4) study was presented at ESC Congress 2016, with simultaneous publication in The *New England Journal of Medicine*.

"Andexanet is the first specific agent designed for reversal of factor X inhibitors. Although it has been shown to reduce anti-fXa activity in volunteers, until now we did not have experience in acutely bleeding patients. In these patients andexanet reduced the anticoagulant effect of the factor Xa inhibitors and was associated with effective hemostasis in most patients," according to Dr. Mark Crowther, ANNEXA-4 co-principal investigator, also from McMaster University.

The interim results include 67 patients, mean age 77 years, who required urgent reversal of acute major bleeding within 18 hours of receiving either a direct (apixaban, rivaroxaban, edoxaban) or indirect (enoxaparin) fXa inhibitor.

The primary site of bleeding was gastrointestinal 49% of patients, and intracranial in 42%.

For ethical reasons, the study was not randomized, and all patients received andexanet – first in an immediate bolus over 15-30 minutes, followed by a 2-hour infusion. Dosing was based on which fXa inhibitor they had been exposed to, and when.

Patients were assessed at baseline, end-of-bolus, and end of the 2-hour infusion, as well as at 4, 8, and 12 hours, and 3 and 30 days post-infusion.

Among 47 patients included in the efficacy assessment, there was an 89% decrease in anti-fXa activity from baseline to end-of-bolus for those exposed to rivaroxaban (n=26), and a corresponding 93% reduction for those exposed to apixaban (n=20).

At 12 hours, clinical hemostatic efficacy was rated as "good to excellent" in 79% of patients.

Thrombotic events occurred in 18% of subjects during 30-day follow up. "This rate of events is not unexpected considering the thrombotic potential of the patients and the fact that in most of them anticoagulation was discontinued at the time of bleeding and not restarted," said Dr. Connolly.

"This preliminary report of the ongoing ANNEXA-4 study shows us that andexanet rapidly reverses anti-factor Xa activity in acutely bleeding patients and this is associated with excellent or good hemostasis in most."

The study was funded by Portola Pharmaceuticals. Both Dr. Connolly and Dr. Crowther have received research support and fees for consulting and lecturing from Portola Pharmaceutical Co.

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