Investigation into revascularization techniques for diabetics with coronary artery disease

CLINICAL TRIAL

"...for patients with diabetes and advanced coronary artery disease, coronary artery bypass grafting was superior to percutaneous coronary intervention in that it significantly reduced rates of death and myocardial infarction."

It is not uncommon for individuals with diabetes to also suffer from coronary artery disease (CAD). Consequently, it seems necessary to determine which revascularization technique would be most appropriate in the treatment of these individuals. In a study conducted by Michael Farkouh (Mount Sinai School of Medicine, NY, USA) and colleagues, coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with drug-eluting stents were compared to identify which technique may be the most appropriate for diabetics with CAD.

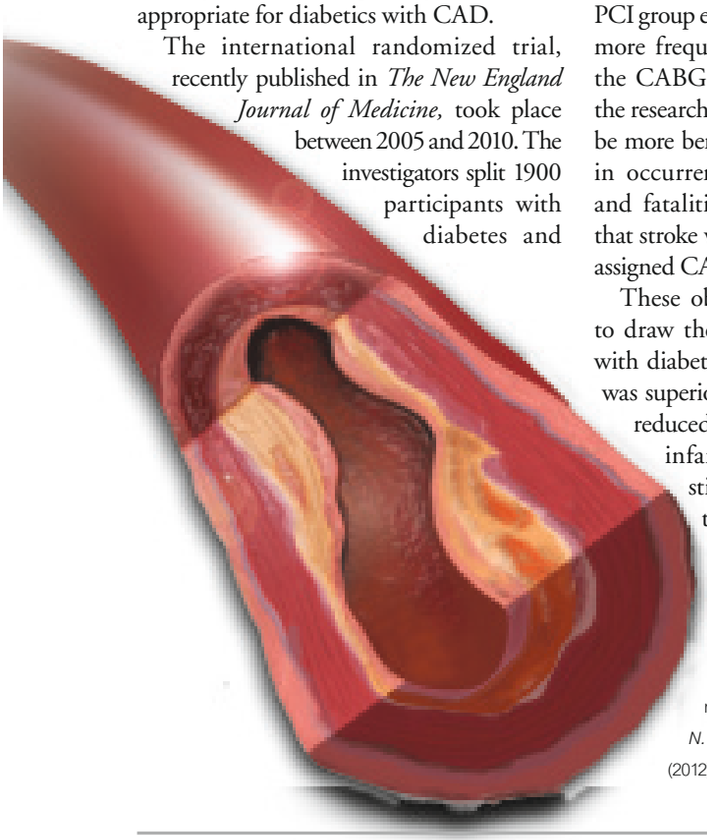
The international randomized trial, recently published in *The New England Journal of Medicine,* took place between 2005 and 2010. The investigators split 1900 participants with diabetes and multivessel CAD into two groups. One group was assigned to undergo CABG and the other was allocated PCI with drug-eluting stents.

The researchers followed the participants for 2 years or more and ensured that they had access to recommended medical treatments to control factors including glycated hemoglobin and low-density lipoprotein cholesterol. It was claimed in the study that "the primary outcome measure was a composite of death from any cause, nonfatal myocardial infarction or nonfatal stroke."

The results of the trial indicate that the PCI group experienced the primary outcome more frequently (26.6%) compared with the CABG group (18.7%). Furthermore, the researchers claim that CABG appears to be more beneficial owing to the differences in occurrences of myocardial infarction and fatalities. However, it was observed that stroke was more prevalent in the group assigned CABG.

These observations led the researchers to draw the conclusion that "for patients with diabetes and advanced CAD, CABG was superior to PCI in that it significantly reduced rates of death and myocardial infarction." However, as stroke is still a significant risk after CABG, there is still opportunity for the development of better strategies.

– Written by Hannah Branch



Source: Farkouh ME, Domanski M, Sleeper LA *et al.* Strategies for multivessel revascularization in patients with diabetes. *N. Engl. J. Med.* doi:10.1056/NEJMoa1211585 (2012) (Epub ahead of print).

Phase I study demonstrates efficacy of radiosurgery in kidney cancer

The results of a recent Phase I trial examining the use of stereotactic radiosurgery to treat kidney cancer suggest that this noninvasive treatment modality may be an important advance in the treatment of kidney cancer patients that have limited alternative treatment options. There are an estimated 65,000 new cases of kidney cancer each year within the USA according to the American Cancer Society. Surgical removal of cancerous tissue is a typical treatment approach if the cancer has not spread at the time of diagnosis. However, some patients may not be suitable candidates for surgery and it is these patients that stereotactic radiosurgery may be applicable to. This is because stereotactic radiosurgery is noninvasive and does not require any anesthetic; it is performed in three treatments using the Cyberknife® (Accuray, CA, USA) system to deliver targeted radiation doses.

The trial results were presented at the 54th Annual Meeting of the American Society for Radiation Oncology in Boston in an abstract entitled, "Stereotactic Radiosurgery for Renal Cancer: Phase I Safety and Toxicity." The study included 20 patients aged between 58 and 92 years who received initial treatment doses of 600 cGy per fraction, with increases in treatment of 200 cGy per fraction to total doses of 24, 32 and 48 Gy being included in the study. The patients were followed for 2–41 months post-treatment. Within the study, the limiting levels of toxicity were defined as National Cancer Institute common toxicity criteria Grade 3 or higher gastrointestinal/genitourinary acute radiation toxicity. Of the patients that received treatment, 94% had decreased or stable disease, with limited side effects.

> "This study is … intended to offer patients a noninvasive, highly focused ablative radiation with surgical precision with little to no side effects..."

Describing the significance of the results, lead investigator Lee Ponsky from University Hospitals Case Medical Center said, "This study is a unique partnership between a surgeon and radiation oncologist, intended to offer patients a noninvasive, highly focused ablative radiation with surgical precision with little to no side effects … We are very excited about these results and cautiously optimistic about the future potential of this therapy."

The study authors emphasized that further studies are required on this possible treatment and that, following on from the results of the study, a Phase II study is to be carried out with 12 further patients with the aim of increasing the dose and determining the most effective treatment dose.

– Written by Sean Fitzpatrick

Source: University Hospitals Case Medical Center Seidman Cancer Center: www.uhhospitals.org/about/media-news-room/current-news/2012/10/stereotactic-radiosurgery-shows-promise-for-kidney-cancer

Minimally invasive uterine fibroids treatment receives US FDA approval

It has been announced at the recent 41st Advancing Minimally Invasive Gynecology Worldwide Global Congress, held in Las Vegas (NV, USA) that a new minimally invasive treatment system has received US FDA approval for uterine fibroids. Halt Medical Inc.'s (CA, USA) Acessa™ system was already approved and in use in Europe and Canada, but has now received FDA approval to treat all fibroid symptoms and types.

> "This new minimally invasive option will increase patient satisfaction and can reduce the number of postprocedure complications..."

Worldwide, fibroids are one of the leading causes of hysterectomy procedures. Emphasizing the significance of the approval, Jeffrey Cohen, Halt Medical's Chief Executive Officer, said, "It's estimated that 97% of women with fibroids choose to suffer with their symptoms rather than having their uterus removed … Gynecologists will have an alternative to hysterectomy for their fibroid patients."

As an alternative to hysterectomy, Acessa is a same-day procedure where radiofrequency energy is delivered to the fibroids via a hand piece. Following application of radiofrequency energy, the fibroid is reabsorbed by healthy surrounding tissue.

Halt Medical believes that this new minimally invasive option will increase patient satisfaction and can reduce the number of postprocedure complications compared with hysterectomy as a result of this milestone approval for the company.

– Written by Sean Fitzpatrick

Source: Halt Medical: www.haltmedical.com/news/70-acessa-by-halt-medical-receives-fda-approval-for-treating-uterine-fibroids

Study indicates Alzheimer's risk may be reduced by short-term hormone use

A new study recently published in the journal *Neurology* has suggested that women could reduce their risk of developing Alzheimer's disease by 30% if they started taking hormone therapy within 5 years of menopause.

Alzheimer's disease is the most common cause of dementia in people aged 65 years and over. The research, which was a collaborative effort by scientists at institutes including John Hopkins University (MD, USA), Weill Cornell Medical College (NY, USA) and McGill University Faculty of Medicine (Montreal, Canada), was supported by the National Institute on Aging (NIH, MD, USA). A total of 1768 women, aged 65 years and older, were monitored for 11 years. Each woman supplied the date they began menopause and a complete history of their hormone therapy use.

Hormone therapy, consisting of either estrogen and a progestin, or simply estrogen alone, was used by 1105 women of the 1768. A total of 176 women developed Alzheimer's disease dementia at some stage during the study: 89 out of the 663 women who had not taken hormone therapy and 87 out of the 1105 women who had.

Study author Peter Zandi from John Hopkins University remarked "This has been an area of debate because observational studies have shown a reduced risk of Alzheimer's disease with hormone therapy use, while a randomized controlled trial showed an increased risk. Our results suggest that there may be a critical window near menopause where hormone therapy may possibly be beneficial. On the other hand, if started later in life, hormone therapy could be associated with an increased risk of developing Alzheimer's disease."

> "There may be a critical window near menopause where hormone therapy may possibly be beneficial."

A 30% lower risk of developing Alzheimer's dementia was discovered in women who began using hormone therapy within 5 years of menopause compared with women who did not use hormone therapy at all. Hormone treatment began 5 or more years after menopause, however it did not alter the risk of development of the disease in hormone users compared with women who did not use hormones. Interestingly, the researchers found that combined estrogen and progestin therapy started when the user was 65 years of age or older appeared to lead to an increased risk of the user developing Alzheimer's dementia.

Victor Henderson at Stanford University (CA, USA) commented on the findings "While this well-designed study supports the possibility that short-term hormone use may reduce the risk of Alzheimer's disease, more research is needed before we can make new clinical recommendations for women and their use of hormone therapy."

– Written by Madeleine Nowak

Sources: Shao H, Breitner JC, Whitmer RA *et al.* Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. *Neurology* 79(18), 1846–1852 (2012); American Academy of Neurology press release: www.aan.com/press/index.cfm?fuseaction=release.view&release=1112; American Academy of Neurology: http://patients.aan.com/disorders/index.cfm?event=view&disorder_id=844

Molecular flag identified in women with breast cancer that could predict their response to tamoxifen

Researchers at the University of Manchester's Paterson Institute for Cancer Research (Manchester, UK) have recently discovered a molecular flag in women with breast cancer that can be used by doctors to help predict how a patient will respond to treatment with the drug tamoxifen.

Tamoxifen is used in complementary (adjuvant) hormone therapy, with radiotherapy and chemotherapy, to treat types of breast cancer where the hormone estrogen is essential for tumor growth. In these patients, who have estrogen receptor-positive breast cancer, tamoxifen is used to block the hormone and has been shown to increase breast cancer survival rates by up to one-third. A total of 70% of breast cancer sufferers are estrogen receptor positive, the most common form of the disease. However, not all patients respond positively to hormone therapy (approximately one-third do not) or develop resistance to tamoxifen.

Lead author Göran Landberg from the University of Manchester, said "The identification of molecular flags to classify subgroups of breast cancer and so determine the best treatment for each patient is of increasing importance in cancer therapy. Tamoxifen has been shown

to be highly effective in some breast cancer patients when used alongside traditional cancer therapies but, in a third of cases, the result has not been what we would hope. If we can predict which patients will respond to tamoxifen, and those who won't, then this is clearly advantageous as it means the correct treatment is provided instantly, which will improve disease outcomes."

The study, recently published in the journal *PLoS ONE*, investigated the tumor growth signals sent by connective tissue surrounding the tumor. The team analyzed tissue microarrays of two breast cancer cohorts. This included samples from 564 women with invasive breast cancer. Some of the women were treated with tamoxifen and some were not. They discovered that connective tissue cells, fibroblasts, differed between patients and could indicate how a patient might respond to treatment with tamoxifen.

"Testing patients for the pERK flag could help doctors determine whether tamoxifen is an appropriate treatment for their patient..."

Study author, Susan Busch (University of Manchester) discussed the findings: "We discovered that women who had low levels of a protein known as pERK in their cancer-associated fibroblasts did not respond to tamoxifen. Testing patients for the pERK flag could help doctors determine whether tamoxifen is an appropriate treatment for their patient or whether alternative therapies should be explored, so saving time and money."

The researchers intend to continue studying molecular flags in cancer-associated fibroblasts in the hope of understanding how these cells encourage the tumor to grow. Understanding this could lead to new therapies developed to block these signals and conquer drug resistance.

– Written by Madeleine Nowak

Sources: Busch S, Rydén L, Stål O, Jirström K, Landberg G. Low ERK phosphorylation in cancer-associated fibroblasts is associated with tamoxifen resistance in pre-menopausal breast cancer. *PLoS ONE* 7(9), e45669; University of Manchester press release: www.manchester.ac.uk/aboutus/news/display/?id=8967

Memantine may hold the key to slowing cognitive decline for brain tumor patients undergoing radiation therapy

Research presented at the 54th Annual Meeting of the American Society for Radiation Oncology (ASTRO) in Boston (MA, USA), details how memantine has been shown to decrease the rate of cognitive decline reported in brain cancer patients treated with whole-brain radiation therapy (WBRT). The Phase III trial has exhibited a decrease in the decline of recognition memory, global function, executive function and processing speed in sufferers.

"By the end of the trial period, it was found that patients who received memantine had a 17% reduction in the rate of cognitive decline..."

The researchers measured the length of time before patients undergoing WBRT started experiencing a decline in cognitive function. In total, 508 patients were tested that had received WBRT from March 2008–July 2010. The patients were split into a placebo group and another group that received 20 mg of memantine a day. This dosage was initiated within 3 days of the start of WBRT and continued for 24 weeks. By the end of the trial period, it was found that patients who received memantine had a 17% reduction in the rate of cognitive decline compared with the placebo group that had not received it.

"...memantine may prevent the changes that occur in the brain following radiation therapy..."

Several tests were conducted to evaluate the level of cognitive function in both groups; the Controlled Oral Word Association test was undertaken at weeks 8 and 16 and, at the end of the 24 weeks, both the Trail Making Test Part A, as well as the Hopkins Verbal Learning Test-Revised Delayed Recall, were conducted. For the patients that survived until the end of the 24-week trial period, patterns in these three tests all demonstrated the same positive correlation for memantine and a decrease in cognitive decline.

Memantine is a *N*-Methyl-D-aspartate receptor antagonist that has previously been provided to people suffering from Alzheimer's disease. "We are excited to see that adding memantine to the treatment plan for brain tumor patients helps preserve their cognitive function after WBRT even 6 months after treatment," discussed Nadia N Laack, co-author of the study Mayo Clinic (FL, USA). "Our findings suggest that memantine may prevent the changes that occur in the brain following radiation therapy, impacting future treatment practices for these patients and suggest a role for further study in other patient populations receiving radiation to the brain."

– Written by Natasha Galukande

Source: American Society for Radiation Oncology Press Release: www.astro.org/News-and-Media/News-Releases/2012/Memantine-delays-cognitive-decline-in-brain-tumor-patients-who-receive-whole-brain-radiation-therapy.aspx

Liraglutide versus exenatide: which is the superior drug?

Type 2 diabetics are sometimes prescribed glucagons-like peptide-1 receptor agonists in order to improve their glycemic control while decreasing body weight. Such drugs include exenatide and liraglutide. To determine the safety and efficacy of these drugs, Guntram Schernthaner (Rudolfstiftung Hospital, Vienna, Austria) and colleagues conducted a study aimed at comparing the impact of once-daily liraglutide with once-weekly exenatide in individuals with Type 2 diabetes.

The research published in *The Lancet* involved a trial that took place in 19 different countries between 11 January 2010 and 17 January 2011. The investigators selected 912 participants who had Type 2 diabetes, were older than 18 years of age and were undergoing treatment with oral antihyperglycemia medication and lifestyle intervention. The participants were randomly assigned into groups, in which they would receive injections of 1.8 mg liraglutide once per day or 2 mg exenatide once per week. The group stated that "the primary end point was change in glycated hemoglobin from baseline to week 26" and they analyzed the findings by treatment intentions.

All but one of the participants were incorporated into the intention-to-treat analysis. The researchers claim that the levels of glycated hemoglobin were subject to more change in those treated with liraglutide compared with those treated with exenatide. Furthermore, it appeared that adverse effects including diarrhea and nausea were more common among the liraglutide group; however, in both groups, these adverse events decreased in prevalence with time.

After analyzing the results, the group concluded that both liraglutide and exenatide were associated with improved glycemic control. They further claimed that greater reductions were observed among those being administered liraglutide. The investigators state that their findings, in addition to injection-related factors, such as frequency, could potentially aid healthcare advisors to decide which treatment option is best to prescribe for Type 2 diabetics.

– Written by Hannah Branch

Source: Buse JB, Nauck M, Forst T *et al*. Exenatide once weekly versus liraglutide once daily in patients with Type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* doi:10.1016/S0140-6736(12)61267-7 (2012) (Epub ahead of print).

Research investigates the effectiveness of bevacizumab in bowel cancer patients

Bevacizumab, also known as Avastin® (Genentech, CA, USA) has been shown to increase survival in bowel cancer in 10–15% of patients and has been licensed for use in several other carcinomas including lung, kidney and ovarian cancers. However, it has been difficult to predict which patients will benefit from the angiogenesis-inhibiting drug. Research published in *Clinical Cancer Research* has indicated that comparing levels of specific VEGF-acting proteins could help to identify those that will respond best to the drug.

Bevacizumab inhibits the VEGF-A protein, of which VEGF165 and VEGF165b are two major forms. While VEGF165 is involved in tumor angiogenesis, VEGF165b has the opposite effect and limits angiogenic growth.

Researchers from the University of Bristol (UK) measured the amounts of VEGF165 and VEGF165b found in patient tumor samples. The team found those patients with low levels of VEGF165b survived for 3 months longer without disease progression compared with patients not on bevacizumab. In comparison, patients with higher levels of VEGF165b saw no benefit from the drug and survived no longer than those patients not on bevacizumab.

Lead author, David Bates (University of Bristol's School of Physiology and Pharmacology, UK) commented: "Avastin has shown great potential for a minority of people with bowel cancer, but it has been impossible to predict who will benefit from the drug. Currently, Avastin is not approved by NICE for patients with advanced bowel cancer because they feel that the benefit to an unknown minority of patients does not justify the cost of treatment."

The initial results of the study have prompted calls for further investigation. Bates hopes that future research can move towards a better understanding of who will respond best to the drug: "We now need to look at cancer samples from a large group of patients about to start taking Avastin and determine if the amount of VEGF165b can accurately identify those patients that will benefit and so potentially open a new treatment option for some people with advanced bowel cancer."

–Written by Jitesh Patel

Sources: Bates DO, Catalano PJ, Symonds KE *et al*. Association between VEGF splice isoforms and progression-free survival in metastatic colorectal cancer patients treated with bevacizumab. *Clin. Cancer Res.* 18(22), 6384–6391 (2012); University of Bristol. Press release: www.bristol.ac.uk/news/2012/8868.html

Can we trust β-blockers to reduce mortality?

Two studies published within a fortnight of each other are questioning four decades of β-blockers as a standard therapy for heart disease and high blood pressure.

A study published in the *Journal of the American Geriatrics Society* (*JAGS*)by a team from The University of Maryland (MD, USA) found that β-blocker use did not extend the life of patients. Their data were in concurrence with a paper from a team at the New York School of Medicine (NY, USA) who published in *The Journal of the American Medical Association (JAMA)* just a few days later.

For patients who have had a myocardial infarction (MI), β-blocker treatment remains the standard therapy for coronary artery disease (CAD). Part of their mode of action blocks β-1 receptors in the heart from binding adrenaline and noradrenaline. Inhibition of this normal hormone-receptor interaction slows the heart and reduces contractile force to lower blood pressure. Almost 200 million prescriptions for β-blockers were written in the USA in 2010.

The *JAMA* observational study consisted of 44,708 patients with CAD risk factors only, known prior MI or known CAD without MI, and was led by Sripal Bangalore (New York School of Medicine). The primary outcome focused on a composite of cardiovascular death, nonfatal MI or nonfatal stroke with an interquartile range follow-up of 35–45 months. The paper reports that event rates were not significantly different in patients with β-blocker use compared with those without β-blocker use for the outcome tested, even in the cohort with prior MI (16.93 vs 18.60%, respectively). For the CAD patient cohort who had not experienced MI, event rates were also not significantly different between those with β-blocker use and those without (12.94 vs 13.55%, respectively). In the cohort with CAD risk factors only, the event rates were found to be higher with β-blocker use versus without (14.22 vs 12.11%, respectively), summarizing that the use of β-blockers was not associated with a lower risk of composite cardiovascular events.

Although the paper published in *JAGS*, led by Ilene Zuckerman, focused on the effect of drug compliance on death rates in heart attack patients, it had a surprising finding; while expected data showing patients complying with their drug regime of statins, anticoagulants or hypertensives were 30% less likely to die than noncompliers, the magnitude of effect for the mortality outcome was smallest for patients taking β-blockers. The study summarized that regardless of whether or not the patients stuck to their β-blocker regime, their risk of death was the same. Taken with the *JAMA* paper, the results are hard to ignore. Reza Tabrizchi at the Memorial University of Newfoundland (NL, Canada), however, notes that there are several limitations to this trial, "The patient sample size had to be reduced by 36% for propensity score matching; it is not clear what kind of real-life outcome was missed in the cohorts not included."

The authors of the *JAMA* paper go some way to explaining their findings, which differ to earlier β-blocker studies. A meta-analysis published in the *British Medical Journal* in 1999 observed a 23% reduction of death with β-blocker use; however most of the trials performed predated routine reperfusion or medical therapy for MI. Reperfusion therapy involves surgically or pharmacologically opening the blocked arteries and has been shown to significantly reduce damage to the heart. As β-blockers are useful for controlling arrhythmias from a damaged heart, a reperfused myocardium, suffering fewer arrhythmias, would benefit less from β-blocker therapy.

Data, therefore, seems to suggest that as reperfusion therapy has now become routine for patients following heart attacks, any benefits from β-blocker therapy may have disappeared. Josh Bloom of the American Council on Science and Health (NY, USA) believes that as β-blockers are low risk and have prevailed for 40 years, prescriptions are unlikely to stop overnight. However, "some individuals have reported nonresponsiveness to the beneficial actions of β-blockers," added Tabrizchi, "this is an important limitation when considering these two papers."

– Written by Tanya Stezhka

Sources: Bangalore S, Steg G, Deedwania P *et al.* β-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 308(13), 1340–1349 (2012); Zuckerman IH, Yin X, Rattinger GB *et al.* Effect of exposure to evidence-based pharmacotherapy on outcomes after acute myocardial infarction in older adults. *J. Am. Geriatr. Soc.* 60, 1854–1861 (2012); Freemantle N, Cleland J, Young P, Mason J, Harrison J. β-blockade after myocardial infarction: systematic review and meta-regression analysis. *BMJ* 318(7200), 1730–1737 (1999); Bloom J. β blockers are busted – what happens next?: www.newscientist.com/article/mg21628900.200-beta-blockers-are-busted--what-happens-next.html

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