New fears of radiation exposure during cardiac computed tomography angiography

The authors of a new study have raised fears of potential exposure to high doses of radiation during cardiac computed tomography (CT) angiography (CCTA). Furthermore, current methods available to reduce radiation exposure are frequently not used.

The Prospective Multicenter Study on Radiation Dose Estimates of Cardiac CT Angiography in Daily Practice I (PROTECTION I) suggests that the benefits of utilizing CCTA should be weighed against the radiation exposure, which increases the risk of cancer. Although the risk of cancer is still small, it appears that many clinicians are still unfamiliar with the magnitude of radiation received during the CCTA and with the factors contributing to the overall radiation dose.

Jörg Hausleiter and colleagues from the Technischen Universität München, Munich, Germany, investigated the daily dose of radiation and factors contributing to it. They also investigated the use of currently available strategies to reduce exposure.

A total of 1965 patients who underwent CCTA between February and December 2007 were studied. Independent risk factors associated with radiation dose were identified. Dose-length product (DLP) was utilized, as it most accurately reflects the total dose of radiation exposure during the entire CT scan.

Medium DP was 885 mGy × cm, which corresponds to an estimated radiation dose of 600 chest x-rays: high variability in DLP was observed between study sites (range of median DLPs per site).

Factors which have an effect on the overall dose of radiation included patient weight, absence of stable sinus rhythm, scan length, the use of electrocardiographically controlled tube current modulation, 100-kV tube voltage, sequential scanning, experience in cardiac CT number of CCTAs per month, and type of 64-slice CT system.

> *"An improved education of physicians and technicians performing CCTA on these dose-saving strategies might be considered to keep the radiation dose 'as low as reasonably achievable' in every patient undergoing CCTA."*

"The study demonstrates that radiation exposure can be reduced substantially by uniformly applying the currently available strategies for dose reduction, but these strategies are used infrequently," the authors explained. "An improved education of physicians and technicians performing CCTA on these dose-saving strategies might be considered to keep the radiation dose 'as low as reasonably achievable' in every patient undergoing CCTA."

"As CCTA is being used more frequently worldwide for diagnosing coronary artery disease, all strategies for reducing radiation exposure will finally reduce the patient's lifetime cancer risks. Although the associated risk is small [estimated lifetime attributable risk of death from cancer after an abdominal CT scan is 0.02%] relative to the diagnostic information for most CT studies, this risk needs to be realized, especially when repeated CT scans are being performed."

Source: Hausleiter J, Meyer T, Hermann F: Estimated radiation dose associated with cardiac CT angiography. JAMA 301(5), 500-507 (2009).

in the news...

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Monitoring BNP levels to guide heart failure therapy gives mixed results

Monitoring BNP levels to guide heart failure therapy has only minimal benefits, report Matthias Pfisterer (University Hospital Basel, Switzerland) and colleagues in the *Journal of the American Medical Association*.

The Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) examined 499 patients aged ≥60 years with a left-ventricular ejection fraction ≤45%, New York Heart Association (NYHA) class II–IV, a recent HF hospitalization and BNP levels ≥2 times the upper limit of normal. The study found no improvement in all-cause outcome over conventional symptom-guided therapy, and only a benefit in hospital-free survival in heart failure patients under the age of 75 years.

> *"While the BNP level may prove to be a useful tool for guiding therapy, it may be the method of reduction of BNP levels that matters most in improving outcomes for patients."*

Subjects received evidence-based pharmacotherapy; dosages were titrated either with the aim of achieving BNP levels of <400 pg/ml in patients younger than 75 years and <800 pg/ml in older patients, or with the aim of minimizing dyspnea. Doses of drugs were uptitrated to a significantly greater extent in the BNP-guided group versus the symptom-guided group.

The study population was then divided into two age groups – under and over 75 years. After a follow-up of 18 months, the BNP-guided strategy and symptom-guided strategies had similar outcomes with respect to all-cause hospitalization and survival.

However, BNP-guided therapy was found to significantly improve survival without hospitalization for heart failure in patients under the age of 75 years (72 vs 62%, respectively).

Ileana Piña (Case Western Reserve University, OH, USA) and Christopher O'Connor (Duke University, NC, USA) believe that reducing BNP levels may not in itself be the key: "While the BNP level may prove to be a useful tool for guiding therapy, it may be the method of reduction of BNP levels that matters most in improving outcomes for patients."

Source: Pfisterer M, Buser P, Rickli H et al.*: BNP-guided vs symptom-guided heart failure therapy.* JAMA *301, 383–392 (2009).*

New treatment guidelines for irritable bowel syndrome released

New guidelines for the management of irritable bowel syndrome (IBS) are being released by the American College of Gastroenterology, providing clinicians with an up-to-date, comprehensive and practical set of recommendations for the diagnosis and treatment of the disease.

IBS is a common gastrointestinal disorder, the symptoms of which can include cramping, abdominal pain, bloating, constipation and/or diarrhea. Despite being the most frequently diagnosed disease by gastroenterologists, IBS is also one of the most misunderstood.

Following an increased understanding of the disease in recent years, it was deemed necessary to update the American College of Gastroenterology guidelines on the management of IBS, last published in 2002. "The College recognized that in the span of five to six years there has been a remarkable explosion in knowledge that's become available that's helped us to understand the cause and management of IBS," says William Chey, who, along with Philip Schoenfeld, helped to develop the new evidence-based recommendations.

> *"With effective counseling, medications and dietary and lifestyle interventions, the vast majority of patients with IBS can effectively manage their disease."*

Included in the updated guidelines are recommendations relating to the screening and diagnosis of IBS patients, as well as information about the different medications currently available to treat the disease and the possible side effects of these. Dietary changes that patients have found helpful are also listed.

Chey notes that nowadays, with effective counseling, medications and dietary and lifestyle interventions, the vast majority of patients with IBS can effectively manage their disease.

Source: University of Michigan Health System www.med.umich.edu

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in medicine.
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Live *Salmonella*-based vaccine could fight infant pneumonia

Researchers from Arizona State University's Biodesign Institute (AZ, USA) have come up with two novel vaccine strains that draw on the properties of an unlikely vaccine carrier – *Salmonella typhimurium*.

Generally associated with causing sickness rather than safeguarding the body against it, *S.typhimurium* is one of over 2000 strains or serotypes of the *Salmonella* constellation of bacteria responsible for causing serious, sometimes fatal diseases, to which children under 2 years of age are particularly vulnerable.

This study, published in the *Proceedings of the National Academy of Science of the USA*, offers new promise in the battle against *Streptococcus pneumoniae*, a prodigious killer causing more than 2 million annual fatalities worldwide.

Group leader Roy Curtiss hopes to recruit *Salmonella's* appetite for infection and use it to speed delivery of a suite of key antigens – surface proteins of *S. pneumoniae*, the causative agent of bacterial pneumonia. In the body, such antigens stimulate an immune response, but the additional pathogenic ingredients necessary to cause the disease are absent.

In addition to triggering a powerful, protective immune response, *Salmonella*-based vaccines offer an inexpensive alternative that may be administered orally in a single dose – a significant advantage in the developing world. The novel vaccine strains designed by Curtiss and his team require mannose and/or arabinose – sugars that are unavailable in the human body. Therefore, after approximately seven cell divisions the bacterium runs out of the sugar and, unable to sustain the integrity of its cell wall, it bursts.

"We've got the *Salmonella* on a string," Curtiss enthused. "We can decide when to snap the string, and they're gone."

In comparison with attenuated *Salmonella* produced through deletion mutation, Curtiss' RASV delayed attenuation strains provoked significantly greater anti-PspA immune response (measured in serum antibody levels) as well as conferring greater protection from *Streptococcus pneumoniae* infection. Indeed, in critical proof-of-concept mouse studies, a 20% higher protection rate was achieved even in the presence of a tenfold increase in the challenge dose of pneumonia pathogen.

An initial version of the new vaccine is scheduled to begin the first preclinical trials in human subjects early in 2009.

Source: Li Y, Wang S, Scarpellini G et al.*: Evaluation of new generation Salmonella enterica serovar Typhimurium vaccines with regulated delayed attenuation to induce immune responses against PspA.* Proc. Natl Acad. Sci. USA *106(2), 593–598 (2009).*

REOLYSIN® enters clinical trial in patients with metastatic colorectal cancer

Patients are being enrolled for a clinical trial in the UK assessing the anticancer effect of REOLYSIN®, a proprietary formulation of the human reovirus developed by Oncolytics Biotech Inc. (AB, Canada). The trial is led by Prof. Alan Melcher of St James's University Hospital (Leeds, UK).

The natural habitat of reovirus is water supplies and sewage, and the virus is believed to also inhabit the respiratory and bowel systems of humans. Most people have been exposed to reovirus before reaching adulthood, although the infection is typically asymptomatic. Normal cells can clear the virus effectively using dsRNA-dependent protein kinase (PKR). However, many cancer cells have an activated Ras pathway, which leads to PKR deficiency, and reovirus has been demonstrated to multiply well in many cancer cell lines that have an activated Ras pathway, and eventually kill these cells.

Up to 20 patients with histologically proven colorectal cancer and being scheduled for surgical resection of liver metastases are expected to be enrolled in this open-label, nonrandomized, single-center clinical trial (REO 013). The patients will receive intravenous REOLYSIN for 5 consecutive days prior to their scheduled surgical resection. Oncolytics will provide REOLYSIN, while the University of Leeds (UK) will cover other costs.

"This study allows us to assess a resected tumor after REOLYSIN treatment has been administered, providing us with vital information about how effective REOLYSIN delivery really is in patients," said Melcher. "REOLYSIN will be given to patients before their planned operation, which is part of the patient's standard clinical care. In addition to a possible benefit to patients, this data will tell us more about how REOLYSIN kills cancer cells, helping to guide future research and development of the agent."

Researchers will examine the resected liver metastatic tumors to assess the presence, replication and anticancer effects of REOLYSIN. The safety profile and immune responses to REOLYSIN will also be evaluated.

"We are pleased that our UK colleagues are sponsoring additional clinical research using REOLYSIN," said Brad Thompson, President and Chief Executive Officer of Oncolytics. "With the US National Cancer Institute trials underway, three REOLYSIN trials are now being sponsored by our collaborators." Oncolytics also plans other human clinical trials using REOLYSIN alone and in combination with radiation and chemotherapy in cancer treatment.

Source: Oncolytics Biotech Inc., AB, Canada: www.oncolyticsbiotech.com

Drug approvals December/January (up to February 10th 2009).					
Trade name	**Generic name**	**Indication**	**Region**	**Manufacturer**	**Date approved**
Oncology					
Vidaza™	Azacitidine	To treat adults with higher-risk myelodysplastic syndrome and acute myeloid leukemia	EU	Celgene	Dec 2008
Not yet determined	Degarelix	For patients with advanced prostate cancer	USA	Ferring Pharmaceuticals Inc.	Dec 2008
	Fludarabine phosphate 10 mg	For the treatment of adult patients with B-cell chronic lymphocytic leukemia whose disease has not responded to or has progressed during or after treatment with at least one standard alkylating-agent-containing regimen	USA	Antisoma	Dec 2008
Tasigna®	Nilotinib	For use in patients with certain forms of Philadelphia chromosome-positive chronic myeloid leukemia who are resistant to Novartis' Gleevec® (imatinib)	Japan	Novartis	Jan 2009
Neurology					
Ryzolt™	Tramadol hydrochloride extended-release tablets 100, 200 and 300 mg	For the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time	USA	Labopharm Canada Inc.	Dec 2008
Zolpimist™	Zolpidem tartrate 5 and 10 mg oral spray	For the short-term treatment of insomnia characterized by difficulties with sleep initiation	USA	NovaDel Pharma Inc.	Jan 2009
Copaxone®	Glatiramer acetate	For the treatment of patients with a clinical isolated syndrome suggestive of MS	EU	Teva Pharmaceutical	Jan 2009
Zavesca®	Miglustat	For the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease	EU	Actelion Ltd	Jan 2009
Cardiology					
Trilipix™	Fenofibric acid	In combination with a statin to reduce TGs and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal As monotherapy to reduce TG in patients with severe hypertriglyceridemia As monotherapy to reduce elevated LDL-C, Total-C, triglycerides and Apo B, and to increase HDL-C in patients with primary hypercholesterolemia or mixed dyslipidemia	USA	Abbott Laboratories	Dec 2008
Nexterone®	Amiodarone HCl injection	For the treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy	USA	Prism Pharmaceuticals Inc.	Jan 2009
Co-Dio®	Valsartan/hydrochlorothiazide	Hypertension	Japan	Novartis	Jan 2009

CHD: Coronary heart disease; G-CSF: Granulocyte colony-stimulating factor; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MS: Multiple sclerosis; PUVA: Psoralen plus ultraviolet A light; TG: Triglyceride.

Drug approvals December/January (up to February 10th 2009) (cont.)

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Atacand® Plus	Candesartan cilexetil 32 mg combined with a diuretic (hydrochlorothiazide), in doses of either 12.5 mg or 25 mg	For the treatment of hypertensive patients who are not optimally controlled by monotherapy alone	USA	AstraZeneca	Feb 2009
Hematology					
RiaSTAP™	Fibrinogen concentrate (human)	To treat acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia	USA	CSL Behring	Jan 2009
Soliris®	Eculizumab	For the treatment of all patients in Canada with paroxysmal nocturnal hemoglobinuria.	Canada	Alexion Pharmaceuticals, Inc.	Jan 2009
ATryn®	Antithrombin alfa	For the prevention of blood clots in patients with hereditary antithrombin deficiency	USA	GTC Biotherapeutics	Feb 2009
Nplate™	Romiplostim	For the treatment of chronic immune thrombocytopenic purpura in patients who do not respond sufficiently to current treatments, such as corticosteroids and immunoglobulin. The drug is only approved for use as second-line therapy for adult nonsplenectomized immune thrombocytopenic purpura patients where surgery is contra-indicated	EU	Amgen	Feb 2009
Urology					
Gelnique™	Oxybutynin chloride gel 10%	For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency	USA	Watson Pharmaceuticals, Inc.	Jan 2009
Rheumatology					
Enbrel®	Etanercept	For the treatment of chronic severe plaque psoriasis. The approval covers patients between 8 and 17 years of age who cannot use other systemic therapies	EU	Wyeth	Jan 2009
Savella™	Milnacipran HCl	For the management of fibromyalgia	USA	Forest Laboratories, Inc. & Cypress Bioscience, Inc.	Jan 2009
RoActemra®	Tocilizumab	Treatment of adults with moderate-to-severe rheumatoid arthritis who do not respond to disease-modifying antirheumatic drugs or tumour necrosis factor antagonists	EU	Roche	Jan 2009
Allergy & immunology					
AllerNaze™	Triamcinolone acetonide, USP nasal spray 50 µg	For the once-daily treatment of nasal symptoms associated with both seasonal allergic rhinitis and perennial allergic rhinitis in adults and children 12 years of age and older	USA	Collegium Pharmaceutical, Inc.	Jan 2009

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Drug approvals December/January (up to February 10th 2009) (cont.).					
Trade name	**Generic name**	**Indication**	**Region**	**Manufacturer**	**Date approved**
Oralair®		Sublingual tablets for desensitization to grass pollens for patients between 5 and 17 years of age	Germany	Stallergenes S.A.	Jan 2009
Xolair®	Omalizumab	For treating severe bronchial asthma in adults who are uncontrolled despite use of standard medications	Japan	Novartis	Jan 2009
Dermatology					
Epiduo™	Adapalene and benzoyl peroxide gel 0.1/2.5%.	For the treatment of acne vulgaris	USA	Galderma Laboratories	Dec 2008
Stelara™	Ustekinumab	For the treatment of moderate-to-severe plaque psoriasis in adults who failed to respond to other systemic therapies including ciclosporin, methotrexate and PUVA	EU	Johnson & Johnson	Jan 2009
Vectical™	Calcitriol 3 mcg/g	Mild-to-moderate plaque psoriasis	USA	Galderma Laboratories L.P	Jan 2009
Gastroenterology & hepatology					
Kapidex™	Dexlansoprazole delayed release capsules 30 mg	For maintaining healing of erosive esophagitis, and for treating heartburn associated with nonerosive gastroesophageal reflux disease	USA	Takeda Global Research & Development Center Inc.	Jan 2009
Kapidex™	Dexlansoprazole delayed release capsules 60 mg	For healing of all grades of erosive esophagitis	USA	Takeda Global Research & Development Center Inc.	Jan 2009
Diagnostics					
Lusedra™	Fospropofol disodium injection 35 mg/ml	For monitored anesthesia care sedation in adult patients undergoing diagnostic or therapeutic procedures.	USA	Eisai Medical Research Inc.	Dec 2008
Vasovist®	Gadofosveset trisodium	A contrast agent in magnetic resonance angiography to evaluate aortoiliac occlusive disease in adults with known or suspected peripheral vascular disease.	USA	EPIX Pharmaceuticals, Inc.	Dec 2008
Other					
Mozobil™	Plerixafor injection	To be used in combination with G-CSF to mobilize hematopoietic stem cells to the bloodstream for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma	USA	Genzyme Corporation	Dec 2008
Casodex®	Bicalutamide	For boys with familial male-limited precocious puberty (testotoxicosis)	USA	AstraZeneca Pharmaceuticals	Dec 2008
Arimidex®	Anastrozole tablets 1 mg	For male pubertal patients with gynecomastia and female pediatric patients with McCune–Albright syndrome with progressive precocious puberty	USA	AstraZeneca Pharmaceuticals	Dec 2008

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Drug approvals December/January (up to February 10th 2009) (cont.).

Trade name	Generic name	Indication	Region	Manufacturer	Date approved
Latisse™	Bimatoprost ophthalmic solution	For the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness	USA	Allergan, Inc.	Dec 2008
Zingo™	Lidocaine hydrochloride monohydrate powder intradermal injection system	To treat the pain associated with blood draws to include adults	USA	Anesiva, Inc.	Jan 2009
Lucentis®	Ranibizumab	For subfoveal wet age-related macular degeneration	Japan	Novarits	Jan 2009
Alli	Orlistat	Obesity	EU	GlaxoSmithKline Plc	Jan 2009
Jespect® Ixiaro®	-	To prevent Japanese encephalitis	Australia	Intercell/Novartis	Feb 2009

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