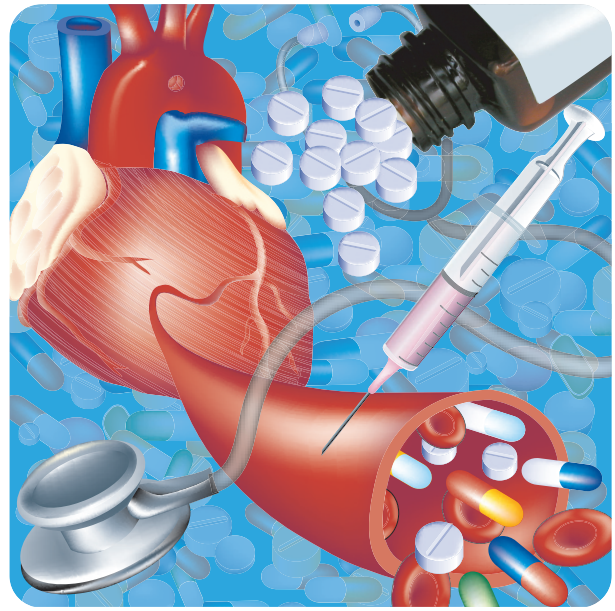
As the controversy of the Vioxx withdrawal continues and the facts accumulate, researchers continue to investigate the possible mechanisms for the associated adverse cardiovascular events

Continuing investigations of Vioxx® and its associated adverse cardiovascular events

Rofecoxib (Vioxx®), a selective cyclooxygenase-2 (COX-2) inhibiting nonsteroidal anti-inflammatory drug (NSAID) made by Merck & Co., was voluntarily withdrawn from the market on the 30th September 2004. The drug was used primarily to treat arthritis and acute pain, but safety concerns over the increased risk of adverse cardiovascular events associated with prolonged usage halted its utilization.



The results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, which was designed to test the long-term usage of the drug for the prevention of colorectal polyps, were the deciding factor in the withdrawal of rofecoxib. It was revealed that there was a significantly increased risk of myocardial infarction in those taking the drug compared with those taking placebo.

> 'How do we retain the usefulness of these drugs, which work and which are particularly valuable to people who suffer gastrointestinal effects with NSAIDs?'

It has been suggested that the risk associated with taking rofecoxib was detected many years ago and that there should have been more prompt action when reports of adverse reactions were received. The US Food and Drug Administration (FDA) had delayed any action on pre-approval reports from Merck that suggested there were cardiovascular risks associated with the drug. It was not until 2001, 2 years after the approval of rofecoxib, that the FDA decided to discuss these previously mentioned concerns. Then in 2002, the FDA insisted that Merck include precautions regarding the cardiovascular risks in the drug information leaflets.

Since the withdrawal of rofecoxib, there has been a vast amount of information revealed regarding its associated risks, and many comments from experts on how this was neglected for such a long time. Dr Eric J Topol, Cleveland Clinic Foundation, USA, noted in an article in the October 21st issue of the *New England Journal of Medicine* that the FDA did not act quickly enough to the many reports of adverse cardiovascular events associated with rofecoxib use. Topol commented that, "the FDA's passive position of waiting for data to accrue is not acceptable, we are dealing with an enormous public health issue."

A study published in a recent issue of *Science* has revealed the possible mechanism of how rofecoxib and other COX-2 inhibitors may be linked to cardiovascular risk and the development of heart disease. Dr Garret FitzGerald, lead investigator from the University of Pennsylvania, USA, suggests that the risks seen with rofecoxib are a class effect and that all other COX-2 inhibitors may have the same associated risks.

Through studies in mice, FitzGerald and his team found that when COX-2 is activated, it results in the upregulated production of prostacyclin PGI2, which has atheroprotective properties. PGI2 limits activation of clot-causing blood platelets that have the potential to damage artery walls. This effect is mediated through estrogen acting upon estrogen receptor subtype a. It was found that the protective effect of estrogen in female mice was no longer apparent when the PGI2 receptor had been removed. The results from this study suggest that when COX-2 inhibitors are used, the protection of pre-menopausal women from cardiovascular risk is removed. Furthermore, these findings reveal the possible reason for a known incidence of heart disease in pre-menopausal females compared with post-menopausal females.

FitzGerald thoughtfully queries, "How do we retain the usefulness of these drugs, which work and which are particularly valuable to people who suffer gastrointestinal effects with NSAIDs?"

Priority Paper Alerts

Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial.
Nissen SE, Tuzcu EM, Libby P *et al*.: *JAMA* 292(18), 2271–2273 (2004).
Reports the results of the CAMELOT trial, which compared the effects of antihypertensive drugs amlodipine or enalapril vs placebo in patients with coronary artery disease. Efficacy measurement was based on a comparison of cardiovascular events for amlodipine/enalapril vs placebo and also amlodipine vs enalapril. Results showed that both drugs reduce adverse cardiovascular events, with a more significant reduction with amlodipine.

Effect of anti-TNFα therapy on arterial diameter and wall shear stress and HDL cholesterol.
Irace C, Mancuso G, Fiaschi E, Madia A, Sesti G, Gnasso A: *Atherosclerosis* 177(1), 113–118 (2004).
Examines the effect of TNFα therapy in rheumatoid arthritis patients following infliximab treatment. Results show that after infliximab treatment, the arteries studied demonstrated vasoconstriction and increased wall shear stress. Furthermore, lipid profile of the patients was examined, showing that HDL cholesterol is reduced by TNFα therapy.

Association between congestive heart failure and hospitalization in patients with Type 2 diabetes mellitus receiving treatment with insulin or pioglitazone: a retrospective data analysis.
Rajagopalan R, Rosenson RS, Fernandes AW, Khan M, Murray FT: *Clin. Ther.* 26(9), 1400–1410 (2004).
Examines the suggested association between pioglitazone therapy in Type 2 diabetes patients and congestive heart failure. The prospective analysis revealed that there was a significantly lower incidence of congestive heart failure and also hospitalization rates in patients receiving pioglitazone therapy compared with insulin therapy.

Catheter ablation for atrial fibrillation in congestive heart failure
Hsu LF, Jais P, Sanders P *et al*. *N. Engl. J. Med.* 351(23), 2373–2383 (2004).
Prospectively examines catheter ablation therapy for atrial fibrillation in patients with heart failure. Demonstrates that catheter ablation significantly improves cardiac function and also quality of life in patients with congestive heart failure and atrial fibrillation.

Combination surgery: robotically assisted keyhole angioplasty

A report from the American Heart Association's Scientific Sessions 2004 has highlighted the efficacy and safety of a new technique – robotically enhanced minimally invasive direct coronary artery bypass (MIDCAB) – raising hopes for wider implementation of the procedure in the near future.

> 'No complications were found with this approach, but we need to be certain that it could be done safely'

The surgery involves cutting three holes in the chest; two small holes for the camera and a light, and a larger hole for the surgical instruments. The surgical instruments are connected to a computer, which detects the movements of the surgeon and subsequently translates them into movement in the surgical instruments.

Dr De Bruyne, coauthor of the report, describes how although the pioneering approach was carried out on only 12 patients, it shows immense potential as a future strategy for treatment of cardiovascular disease. The combination procedure has many advantages i.e., reduced scarring, pain and recovery time. De Bruyne describes how "patients with diabetes often have long lesions in their left descending artery that are difficult to treat with angioplasty but can be helped with bypass surgery". De Bruyne claims that there were "no complications found with this approach, but we need to be certain that it could be done safely". All patients were involved in a follow-up program, which detected no reports of chest pain, heart attack or death.

However, much larger trials must be carried out before a full analysis of the combination surgery can be completed.

Obesity and risk of atrial fibrillation

Results of a study published in the *Journal of the American Medical Association* describe how obesity may be a risk factor for atrial fibrillation. Wang and colleagues of the Framingham Heart Study, MA, USA, describe how long-term follow-up data from participants of the Framingham Heart Study was used to assess the affect of BMI on atrial fibrillation incidence rates, assessing risk by assigning each individual to one of three body mass index (BMI) categories. All participants were free from atrial fibrillation at baseline.

The interesting results showed that 526 of the 5282 participants developed atrial fibrillation. There was a 4% increase in risk of developing atrial fibrillation for every 1 unit of BMI increase above normal. Individuals in the obese category were shown to have an approximately 50% greater risk of developing atrial fibrillation.

This study shows that obesity must now be considered as a serious risk factor for the development of atrial fibrillation and that focus on prevention of obesity may reduce the number of patients suffering from this condition, in addition to a growing list of other associated disorders. "Although our study was observational, it raises the intriguing possibility that weight reduction may decrease the risk of atrial fibrillation," the authors of the study concluded.

Elevated inflammatory enzyme significantly linked to ischemic stroke

Investigators of a study presented at the American Heart Association's Scientific Sessions 2004 report that a high level of the enzyme lipoprotein-associated phospholipase A2 (Lp-LA2), which is associated with inflammatory events in atherosclerosis, has been found to be a risk factor for ischemic stroke.

Lp-LA2 aids the processing of low-density lipoprotein cholesterol into products within atherosclerotic plaques, and also produces inflammatory signals within the plaques, resulting in an increase in inflammation. Inflammation in the blood vessels leads to the development of atherosclerosis, the underlying cause of heart attacks.

The investigators of the ongoing Atherosclerosis Risk in Communities (ARIC) study describe the finding that participants of the study with the highest levels of the enzyme had a significantly increased risk of ischemic stroke. "These ARIC findings illustrate that Lp-LA2 can be an independent and significant warning - above and beyond standard risk factors - identifying individuals with an increased risk of stroke. Lp-LA2 may prove to be a useful independent diagnostic measure, and ongoing research is evaluating whether Lp-LA2 is an important therapeutic target to reduce stroke," said Christie M Ballantyne, director of the Center for Cardiovascular Disease Prevention at Baylor College of Medicine and lead investigator of ARIC. The study was carried out by looking at the relationship between Lp-LA2, other cardiovascular risk factors and an additional inflammatory molecule that is known to be involved in atherosclerosis, C-reactive protein, in a series of stored blood samples from the participants. It was found that a raised level of Lp-LA2 and C-reactive protein in the blood was synergistic in predicting stroke risk.

GlaxoSmithKline are now looking into the role of inhibitors against this enzyme in possibly reducing the risk of stroke and coronary heart disease, which would have great therapeutic potential.

Results from the CART-2 trial

A Phase IIb trial of the anti-inflammatory drug AGI-1067 (AtheroGenics Inc.), has been completed. The positive results of the trial have shown that treatment with the drug significantly reduces atherosclerotic plaque volume. Its mechanism of action is thought to involve inhibition of molecules that are involved in the inflammatory process, such as vascular cell adhesion molecule 1, through blockage of signalling pathways in the endothelial cells lining blood vessels, ultimately reducing the risk of atherosclerosis development.

The results from the trial of the investigational drug were analyzed at two centers; the Montreal Heart Institute (MHI) under the direction of Jean-Claude Tardif, Principal Investigator of Canadian Antioxidant Restenosis Trial-2 (CART-2), and the Cleveland Clinic Foundation (CCF) under the direction of Steven Nissen.

Commenting on the results of the trial, Tardif said "I consider these final data encouraging. Given the regression signal in the AGI-1067 group, as well as the drug's ability to reduce myeloperoxidase, a biomarker closely associated with major adverse cardiac events, I believe we have enhanced our chances of seeing positive results in the phase III Aggressive Reduction of Inflammation Stops Events (ARISE) trial. "

Rob Scott, Senior Vice President of Clinical Development and Regulatory Affairs and Chief Medical Officer at AtheroGenics said "We are pleased with the results of the CART-2 study and believe these data provide good evidence that, in contrast to current therapies, AGI-1067 has the ability to regress plaque in coronary arteries when dosed over a 12-month period. We believe that AGI-1067 is showing its potential to be a leader in the next generation of oral cardiovascular therapeutics."

The results of this trial bring a hope that this new drug may be added to the current atherosclerosis treatments and complement their actions.

Tissue-engineered blood vessels in heart bypass surgery

Tissue-engineered blood vessels (TEVs) have been reported to have potential for use in heart surgery. A study, conducted by researchers at the University of Buffalo, (NY, USA), describe how the artificially produced vessels were created and implanted in sheep after just 2 weeks of development.

The vessels were shown to function successfully, demonstrating mechanical strength, and long-term viability without clotting. Furthermore, the vessels were found to have excellent remodeling propreties. “We found that the vessels were very reactive. They dilate or constrict mechanically in response to chemical compounds, which is how native vessels adapt to changing flow rate" said Stelios Andrelias, co-author of the study that appears in the *American Journal of Physiology*. He added "It is no stretch to extrapolate that these TEVs could remain functional in the long term because the animals presented no adverse effects."

The research shows that TEVs have the potential for use in a wide range of surgical applications. There is a hope that they might one day be used in coronary bypass surgery. A patent application has now been filed on the novel, tissue-engineered vascular vessel and the method for making it.

Chylomicrons in coronary heart disease

A study carried out by researchers at the University of Alberta, USA, has shown that chylomicron remnants accumulate in blood vessel walls and may therefore contribute to the development of coronary artery disease.

Chylomicrons are produced after a meal when the fat and cholesterol has been metabolized. It is broken down quickly, and therefore in a fasting blood sample will only account for approximately 3% of the total cholesterol present in the blood.

As LDL cholesterol accounts for approximately 70% of the total cholesterol in the blood, it is widely believed that accumulation of LDL cholesterol, as opposed to any other type of cholesterol, is the main reason for the development of heart disease. However, these findings put this theory into doubt, highlighting the importance of chylomicrons in the development of heart disease.

Dr Spencer Proctor and his research group studied the mechanism of chylomicron breakdown with unique imaging techniques. They investigated how chylomicrons are formed and their delivery pathway in rabbits. They discovered that chylomicrons rapidly accumulate in the arteries when they are processed.

"We believe understanding chylomicrons and their metabolism may answer all questions about cholesterol and the role it plays in the development of diabetes, obesity, and other cardiovascular diseases."

There are still many questions that need to be answered regarding the role of chylomicrons in the development of heart disease. "At the moment, not enough is known about chylomicron remnants and their pathways. As a first goal, I'd like to see a greater awareness among clinicians about the significance of chylomicrons to cardiovascular disease and how to test their metabolism in humans."

Promotion of heart muscle growth by molecule thymosin β-4

A molecule has shown great promise for use in the treatment of heart attack after reports from researchers at the University of Texas Southwestern Medical Center, Dallas, USA describe the findings of their research. Dr Deepak Srivastava, lead researcher and professor of pediatrics and molecular biology, describes the results of the study in a recent issue of *Nature*. The investigation aimed to elucidate the action of peptide thymosin β-4 on cardiomyocytes. It was found that the molecule promotes growth of heart muscle and also survival of cardiac cells, giving protection from tissue damage and scarring, and improving cardiac function. Thymosin β-4 is a naturally occurring peptide that is being developed by RegeneRx Biopharmaceuticals, Inc.

Srivastava said "Our original interest was in trying to understand how the heart forms. We found that thymosin β-4 induced cells to migrate and also made them survive longer."

The next progression would be to implement the findings from this study into a clinical trial of thymosin β-4 into heart attack patients, pending approval from the US Food and Drug Administration. This raises the possibility for implementation of the molecule into the treatment of myocardial damage. There are however some doubts about the effectiveness of using adult cells in treatment, moving the focus away from the controversies surrounding the use of stem cells for repair of heart attack damage.

Srivastava added, "If it works, it will be phenomenal."

Alcohol linked to prevention of coronary heart disease

There is a possibility that moderate alcohol consumption may be associated with reduced risk of heart disease. Alcohol appears to reduce plaque build up in the coronary arteries, an indication that it may aid in the reduction of coronary atherosclerosis.

Dr Jacqueline Witteman, Erasmus Medical Center, Rotterdam, and colleagues used data from the Rotterdam Coronary Calcification Study to look at how alcohol consumption was associated with the deposits of coronary calcium, an indicator of plaque build up. The coronary calcification of each individual was scored by the Agatston method, using electron beam computed tomographic scans. Individuals were assessed according to the amount of alcohol they consumed per day, one or fewer drinks, one to two drinks or more than two drinks per day. It was found that those individuals who consumed the most amount of daily alcohol had the least calcium deposits, and those who did not drink had the highest amount of deposits. "To our knowledge this is the first study assessing the effect of alcohol consumption on coronary atherosclerosis in a general population of asymptomatic subjects," note the researchers in the *Archives of Internal Medicine*.

An inverse relationship between alcohol consumption of up to two drinks per day and coronary calcification was detected. The authors discuss their findings, "Our results show a significant inverse association between alcohol consumption and coronary calcification, even after adjustment for blood lipid values," and suggest that the protective effect is mediated by an increase in high-density lipoprotein levels.