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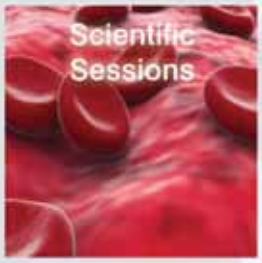

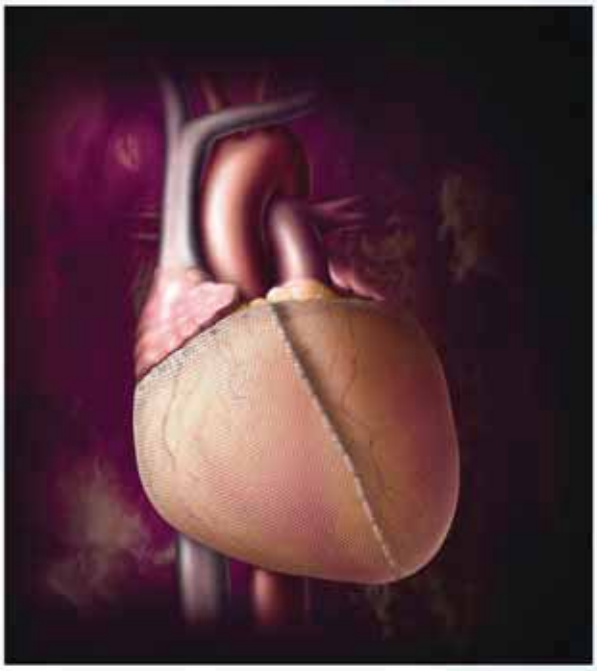

HIGHLIGHTS FROM THE

ACC.10
59th Annual Scientific Session

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Catheter Ablation of Atrial Fibrillation: 2010 State-of-the-Art

Douglas L. Packer, MD, Mayo Clinic, Rochester, MN, discussed several approaches to ablative treatment of atrial fibrillation (AF), noting that the primary underpinning of AF ablation is pulmonary vein isolation (PVI) and that everything else is ancillary. Dr. Packer noted, "The key is knowing whether or not you have pulmonary vein isolation—whether you have entrance block or whether you have exit block." See page 8.

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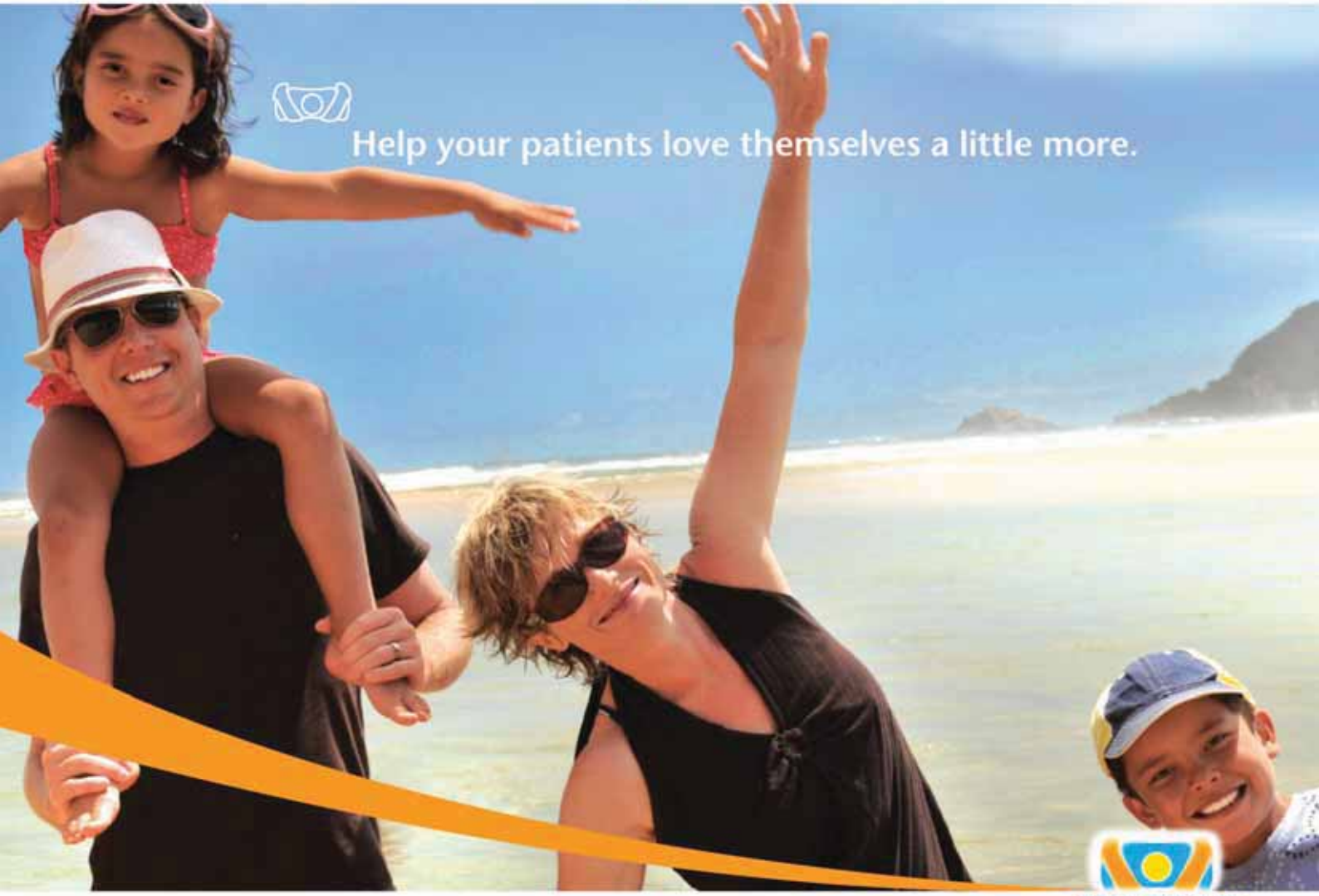

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References: 1. CRESTOR® package insert **2.** Jones P, Davidson MH, Stein EA, *et al.* Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR* Trial). *Am J Cardiol* 2003;**92**:152-160. **3.** Schuster H, Barter PJ, Stender S, *et al.* Effects of switching statins on achievement of lipid goals. Measuring Effective Reduction in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *Am Heart J* 2004;**147**:705-712. **4.** Rosenson RS. Statins: can the new generationn make an impresssion? *Expert Opin Emerg Drugs* 2004;**9**(2):269-279. **5.** Shepherd J, Hunninghake DB, Stein EA, *et al.* Safety of rosuvaststin. *Am J Cardiol* 2004;**94**:882-888.

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Dear Healthcare Practitioner,

It is with great pleasure that AstraZeneca brings you the MD Conference Express Report from the American College of Cardiology's 59th Annual Scientific Session held in Atlanta, Georgia USA 14 - 16 March. This publication is a summary of the important scientific sessions which took place at this event.

We hope you will find the articles both beneficial and informative. Furthermore, we hope they assist you in staying abreast of the latest medical developments worldwide. We are very pleased to include in this edition of the MD Conference Express CPD Accreditation. The articles written in the MD Conference Express are by independent medical journalists and the views expressed are not necessarily those of AstraZeneca South Africa.

We look forward to continued involvement in the field of cardiovascular medicine with our range of products.

Kind regards,

Tracy Riley
CRESTOR Brand Manager

AstraZeneca Pharmaceuticals (Pty) Ltd
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5 Leeuwkop Road Sunninghill 2157 South Africa
Private Bag X30 Sunninghill 2157 South Africa

TEL: +27 (0) 11 797-6000
FAX: +27 (0) 11 797-6001
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References:
1. Steyn K, Fourie JM (ed). Heart disese in South Africa. Media Data Document. Heart and Stroke Foundation. July 2007.
2. Steyn K, Fourie J (eds). Chronic diseases of lifestyle in South Africa: 1995-2005. Technical Report.
Cape Town: South African Medical Research Council 2006. Pg 11.
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Dear Colleagues,

The 2010 American College of Cardiology (ACC) Scientific Session held March 14-16, 2010, in Atlanta, Georgia, attracted participants from over 100 countries and included 17 joint sessions with international societies which addressed major health issues as it pertains to individual nations and to global health. A total of 2,296 faculty presented at this year's meeting, 473 of whom represented our international community. Additionally, there were a total of 1,900 poster presentations. The diversity of attendees and presenters enhances the annual meeting as place to both present original research and to learn about the most cutting edge science in cardiovascular care.

There are many factors that contribute to the burden of cardiovascular disease. This year's meeting focused on several topics related to cardiovascular health including hypertension, dyslipidemia, heart failure, and arrhythmias. There were also a variety of sessions that focused on scientific advancements and new techniques related to intervention as part of the i2 Summit.

Comprehensive Clinical Trial Sessions, where innovative science was presented for the first time, provided attendees with the latest developments in pharmaceutical therapies, equipment, and advances in procedures in the many areas of treatment, diagnosis and prevention. Clinical trial highlights included results from ACCORD, NAVIGATOR, EXPLORE-Xa, JET-STENT, and EVEREST II among others. Spotlight sessions provided practical take-home messages for the practicing clinician in the areas of imaging, electrophysiology, congenital cardiology and interventional approaches. Overall, this was a very well-rounded meeting that covered a broad range of important topics in cardiology.

This issue of *MD Conference Express*® provides a peer-reviewed summary of some of the main findings presented in Atlanta. Each article has been carefully verified against primary sources, and reviewed by an independent medical board to ensure fair balance and integrity of the data. We hope that you will find it to be a useful instrument in implementing new information from the Scientific Session/ i2 Summit into your practice. For more information about *MD Conference Express*, please visit www.mdconferencexpress.com. For more information about the American College of Cardiology, please visit www.acc.org.

We wish you all the best in the coming year and hope to welcome you in New Orleans for the ACC's Scientific Session 2011, where a carefully crafted program is already being prepared.

James McClurken, MD, FACC

Annual Scientific Session Program Committee Chair

Dear Practitioner,

We are pleased to share with practicing clinicians highlights from the 59th Annual Scientific Sessions of the American College of Cardiology/i2 Summit held in Atlanta, GA, March 14-16, 2010. Over 1,707 abstracts were presented at this year's meeting, including 125 featured abstracts from ACC, 35 featured abstracts from the i2 Summit, and 30 late-breaking clinical trials. The articles selected for this issue of *MD Conference Express*® represent the most newsworthy and cutting edge items of relevance to a broad array of practitioners.

The scope and quality of the abstracts presented continue to make the ACC Scientific Sessions an exciting and innovative forum where advances in research can be translated into practical applications for the clinician. This year's meeting saw the first presentation of the ACCORD Trial, a large, randomized, double-blind, placebo-controlled trial evaluating the effects of intensive blood pressure control and combination lipid therapy with a statin and a fibrate in patients with type 2 diabetes at high risk for cardiovascular events followed for 5 years. In the blood pressure arm of the study, an intensive control goal of 120 mmHg systolic blood pressure did not reduce the rate of major cardiovascular events compared with a standard control goal of 140 mmHg systolic blood pressure. Additionally, combination lipid therapy (statin + fibrate) did not reduce the rate of major cardiovascular events compared with statin therapy alone. Also of great interest to clinicians were the findings from the NAVIGATOR trial evaluating the effect of nateglinide and valsartan on the rate of major cardiovascular events in patients with impaired glucose tolerance. While there was no evidence of cardiovascular-related benefit of long-term treatment with either drug, valsartan was associated with a decrease in the incidence of diabetes.

Other highlighted late-breaking clinical trials in this issue include results from the JETSTENT trial that demonstrated that rheolytic thrombectomy plus stenting was associated with better clinical outcomes at 6 months and improved myocardial perfusion compared with direct artery stenting alone in patients with ST-elevation myocardial infarction. This benefit occurred without adding to the burden of stroke and major bleeding. This issue of *MD Conference Express* also offers findings from the Phase II, EXPLORE-Xa trial which investigated the safety and tolerability of three doses of the oral direct factor Xa inhibitor betrixaban compared with warfarin in patients with atrial fibrillation/flutter.

In addition to learning about the results of top late-breaking clinical trials, this issue also contains new information in selected, challenging areas of cardiovascular medicine, including catheter ablation of atrial fibrillation, bleeding and acute coronary syndromes, and optimizing diabetes management, as well as current updates on 3D echocardiography and stenting.

We hope that you will find the articles and practical perspectives contained in the pages of this edition of *MD Conference Express* to be useful in your clinical practice. For more information about *MD Conference Express* please visit www.mdconferencexpress.com.

Robert P. Giugliano, MD, SM
Associate Physician
Cardiovascular Division
Brigham & Women's Hospital
Associate Professor in Medicine
Harvard Medical School
Boston, MA

Marc P. Bonaca, MD
Cardiovascular Fellow
Cardiovascular Division
Brigham and Women's Hospital
Boston, MA

MD CONFERENCE EXPRESS

HIGHLIGHTS FROM THE
American College of Cardiology 59th Annual Scientific Session

March14 - 16, 2010, Atlanta, GA

STAFF

President	Jennifer Goodwin
Vice President, Publishing	Beth Johnson
Production Assistant	Lauren Valone
Medical Writers	Heather Q. Sinclair Maria Vinall

SALES

Jennifer Goodwin Tel.: +1-617-515-9797

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reports [at] goodwingroupintl.com
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PUBLISHER

The Goodwin Group
Connecting the World of Medicine

98 Oxford Street
Suite #1
Arlington, MA 02474 USA
Tel.: +1-617-515-9797
E-mail: reports [at] gooodwingroupintl.com

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Catheter Ablation of Atrial Fibrillation: 2010 State-of-the-Art

Written by Maria Vinall

Douglas L. Packer, MD, Mayo Clinic, Rochester, MN, discussed several approaches to ablative treatment of atrial fibrillation (AF), noting that the primary underpinning of AF ablation is pulmonary vein isolation (PVI) and that everything else is ancillary. Dr. Packer noted, "The key is knowing whether or not you have pulmonary vein isolation—whether you have entrance block or whether you have exit block." Persistent potentials may remain after ablation, and the question that needs to be answered is whether they are coming from the left superior pulmonary vein or another location, such as the left atrial appendage or the vein of Marshall. One way to answer that question, to avoid overablating, and to confirm entrance or exit block is by pacing at sites that are candidate sources of the potentials and at different locations (eg, laterally or septally) on the vein.

Short- to mid-term clinical success rates using PVI with and without linear ablation in the treatment of paroxysmal AF are quite good (range 80% to 90%); however, in the case of persistent or permanent AF, the success rate within and between techniques varies widely [Brooks AG et al. *Heart Rhythm* 2010]. Prashanthan Sanders, PhD, University of Adelaide, Adelaide, Australia, discussed whether ablation of AF provided a long-term cure or palliation.

Although there have been only a few long-term AF outcome studies, we have learned several things—most importantly, that although most recurrences are early, there is an attrition rate that is probably related to the underlying substrate, such as hypertension [Shah AN et al. *J Cardiovasc Electrophysiol* 2008; Sawhney N et al. *Am J Cardiol* 2009]. This tells us, said Prof. Sanders, that in addition to performing the ablation, clinicians should be aggressively treating the underlying risk factors and monitoring patients over time. At this point, the primary purpose of AF ablation remains symptom control. In order to determine whether ablation can result in a long-term cure, it will be necessary for new studies to clearly delineate both the type of AF and the procedure that was used.

Samuel Asirvatham, MD, Mayo Clinic, Rochester, MN, discussed the complications that are associated with ablation and how they can be avoided. He noted that although the risk of pulmonary vein stenosis can be minimized by not ablating within the pulmonary vein, it still may occur. One of the reasons for this is that there is no anatomical boundary that can be used to identify the beginning of the pulmonary vein and the end of the left atrium. Another reason is that the electrical signals that come from the catheter mapping can be confusing and can lead to overablation. To avoid ablation in the pulmonary vein, it is necessary to have accurate knowledge of the pulmonary vein ostium and to correct for the interpretation of the electrical signals.

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Other areas that may be damaged during ablation include the coronary arteries, the aorta, the phrenic nerve, and the esophagus. Catheter entrapment into the mitral valve apparatus is also a recognized complication, which can best be managed by pushing (versus pulling on) the catheter and then reversing the maneuver that caused it to become lodged. In summary, said Dr. Asirvatham, knowledge of the anatomy and an appreciation of its potential complexity and variability is important in avoiding these complications.

David J. Callans, MD, University of Pennsylvania, Philadelphia, PA, discussed some recent and upcoming advances in imaging during ablation. Second-generation image integration takes preprocedure CT or MRI angiograms and incorporates them directly into electroanatomic mapping (*EAM*) systems. The result is excellent anatomy and the ability to see the patient's unique anatomical variations. This is a strategy that is particularly useful in extrapulmonary vein procedures. Having all of the information in the catheterization laboratory is also very helpful, and one way of doing this is called "fast mapping." Fast

mapping is a way of constructing the atrial geometry within the context of the procedure itself that corrects for the limitations of impedance-based systems. As with most technology, there is a tradeoff, and in this case, it is static images. "3D echocardiography is probably the most perfect 3D imaging in terms of its anatomic correctness," said Dr. Callans. "However, its tradeoff is that it can not currently be integrated into the EAM environment." Lastly, he noted that magnetic and robotic navigation promise better catheter stability and a reduction in fluoroscopy exposure for both the operator and the patient.

Looking to the future, Dr. Callans believes that the ultimate imaging for ablation procedures would be direct visual imaging. Two endoscopy-based products that are currently under development (one by Cardiofocus the other by Voyage Medical) would allow clinicians to see in "real time." A major advantage to real-time imaging is that it makes visual verification of lesion formation possible, which should make gaps in the ablation less likely to occur. Whether by advanced imaging or direct visual imaging, Dr. Callans believes that we need an improved understanding of catheter contact and force and lesion verification. With improved technology, however, will come increased cost and eventually the need for some quantification of effectiveness.

Suneet Mittal, MD, Columbia University, New York, NY, used the current guidelines [Calkins H et al. *Heart Rhythm* 2007] as the framework for his discussion of the role of monitoring, antiarrhythmic drug (AAD) therapy, and anticoagulation postablation. Current guidelines call for delaying arrhythmia monitoring to assess the efficacy of catheter ablation for at least 3 months postprocedure, called a 'blanking period,' because early recurrences of AF are common during that time. Dr. Mittal presented data from a study in 72 patients who received 3 months of continuous ECG monitoring after PVI, which confirmed the early recurrence of AF during the first few weeks after PVI and indicated that a waiting period of 3 months is justified to identify patients with AF recurrences that do not foreshadow procedure failure (Figure 1). In this study, freedom from any AF within the first 2 weeks following ablation was shown to predict long-term AF freedom (Figure 2) [Joshi S et al. *J Cardiovasc Electrophysiol* 2009].

AAD therapy is common during the first 1 to 3 months after ablation. "Although data are limited, probably the best study to evaluate the use of AADs," said Dr. Mittal, "is the 5A Study." Results from this study indicated that in patients with paroxysmal AF who were undergoing PVI, 6 weeks of AAD therapy after AF ablation is well tolerated and reduces the incidence of clinically significant atrial arrhythmias and the need for cardioversion/hospitalization for arrhythmia management [Roux JF et al. *Circulation* 2009]. Longer-term studies are still needed.

Current guidelines call for the use of warfarin for all patients for at least 2 months after ablation, with the decision to extend the use of warfarin beyond this period being based on the patient's risk factors for stroke. Discontinuation of warfarin therapy generally is not recommended in patients with a CHADS score ≥2. Dr. Mittal reviewed the results of several studies that have questioned these recommendations [Bunch TJ et al. *J Cardiovasc Electrophysiol* 2009; Oral H et al. *Circulation* 2006; Themistochakis S et al. *J Am Coll Cardiol* 2010], which demonstrated a low risk of stroke in patients who were undergoing successful AF ablation. "Better stroke risk stratification systems are needed in these patients," said Dr. Mittal.

Figure 1. 3-Months Continuous ECG Monitoring Following PVI.

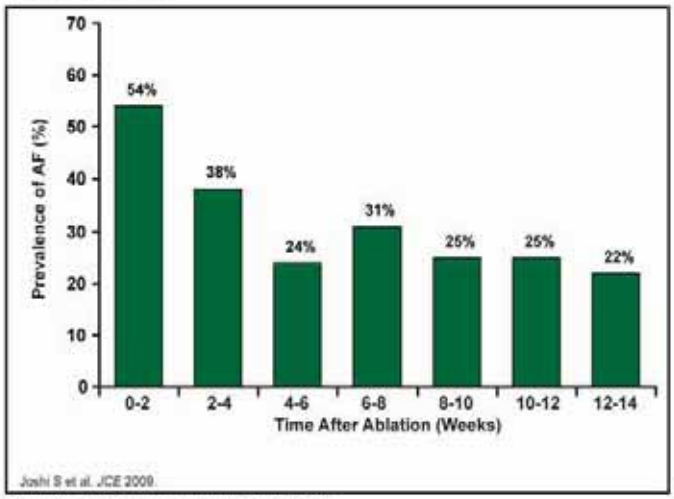

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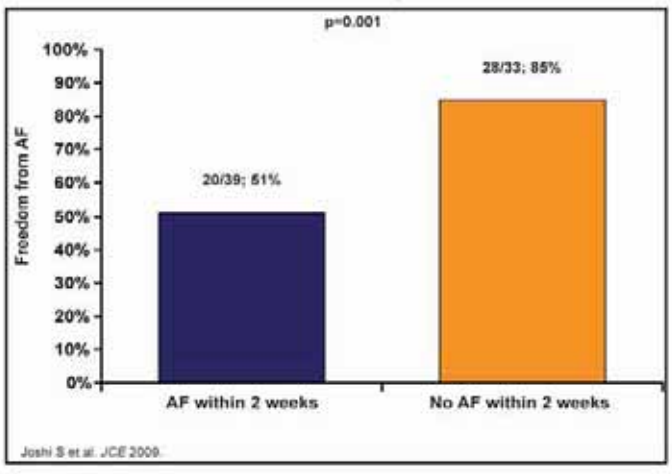
Figure 2. 3-Month Continuous ECG Monitoring Following PVI: AF Within 2 Weeks Following Ablation.



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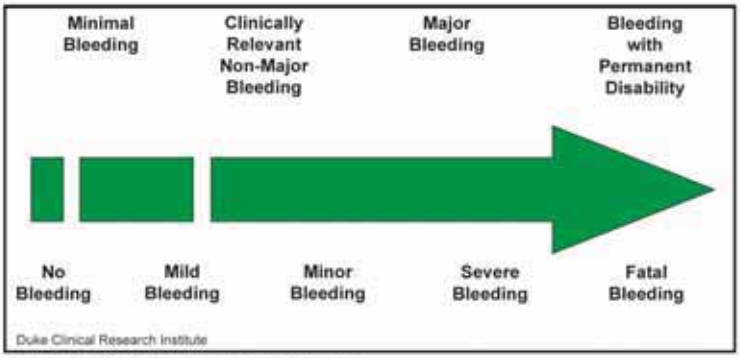
Bleeding and Acute Coronary Syndromes

Written by Maria Vinall

Bleeding classification systems offer a common language that facilitates comparisons across data sets in multicenter/multinational clinical trials and registries. John H. Alexander, MD, Duke University Medical Center, Durham, NC, described commonly used bleeding definitions while evaluating their advantages and limitations. The four major scales that are used in clinical trials today are: TIMI, GUSTO, ISTH, and ACUITY; however, several of the recent major trials have added subdefinitions that were not included in the original scales. In addition, recent large trials have utilized trial-specific definitions (eg, PLATO and CURRENT). Regardless of the scale that is used, however, bleeding should be seen as a continuum (Figure 1). The best bleeding definition depends on the context. Different levels of bleeding may be expected in acute inpatient trials versus long-term trials in stable outpatients, in large phase III trials versus smaller dose-ranging trials, and in data-intensive clinical trials versus large, simple registries. A bleeding definition should be evaluated the same way as a good clinical trial endpoint: it should reflect clinical importance; be sufficiently common in the population to be detected; and be influenced by the intervention that is being studied, easily ascertainable and objectively defined, and standardized across trials/registries.

"Ultimately, as clinicians, we are interested in the net clinical benefit between ischemic events and bleeding caused by antiplatelet and anticoagulant therapy," concluded Dr. Alexander. Choosing a primary bleeding definition should be done with this thought in mind.

Figure 1. Bleeding Severity Continuum.



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There appears to be a strong association between bleeding and longer-term adverse cardiovascular outcomes, although a causal relationship between bleeding and mortality remains controversial. John W. Eikelboom, MD, McMaster University, Montreal, Canada, discussed some of the trials that have shown a direct long-term relationship between bleeding severity and adverse outcomes—cardiovascular outcomes, in particular—and identified some challenges for clinicians to better manage bleeding risk. Studies that have helped to define the relationship between bleeding and poor outcome include the OASIS-5 trial, in which >90% of excess deaths occurred in patients with bleeding [Budaj A et al. *Eur Heart J* 2008]; the OASIS-2 and -4 trials [Eikelboom JW et al. *Circulation* 2006]; and ACUITY [Mehran R et al. *Eur Heart J* 2010 (in press)].

This relationship may be explained by several factors, including stopping effective therapies in response to bleeding and the potential effects of stored red blood cells. Koch and colleagues have shown that in patients who are undergoing cardiac surgery, transfusion of red cells that had been stored for more than 2 weeks is associated with a significantly increased risk of postoperative complications, as well as reduced short- and long-term survival [Koch CG et al.

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N Engl J Med 2008]. These results are consistent with those from other studies [Eikelboom J et al. *Am Heart J* 2010 (in press)]. It has been suggested that this effect is due, among many other factors, to the depletion of 2,3-DPG in stored red cells [Heaton A et al. *Br J Haematol* 1989]. Key challenges for clinicians include accurately identifying patients who are at the highest bleeding risk and identifying and implementing strategies that minimize bleeding while still yielding a net benefit for patients. Challenges for researchers include defining and establishing a cause-and-effect relationship between bleeding and subsequent adverse outcomes and controlling for potential confounding, since patients who are more likely to bleed are also more likely to have other adverse events due to the presence of more comorbid conditions.

Richard G. Bach, MD, Washington University School of Medicine, St. Louis, MO, discussed the development and clinical application of the CRUSADE bleeding risk score for patients with non-ST-segment elevation myocardial infarction (NSTEMI) [Subherwal S et al. *Circulation* 2009]. The CRUSADE score combines eight predictors into a simple validated prediction tool for major bleeding that preserves discrimination across treatment subgroups and complements ischemic risk prediction tools for global risk assessment that enable clinicians to consider all the potential adverse outcomes in patients with NSTEMI prior to the initiation of treatment. The CRUSADE score is limited, in that history of prior bleeding or bleeding diathesis was not collected, and it may underestimate the rate of bleeding in populations of patients who died within 48 hours or in a coronary artery bypass (CABG) population, because bleeding was censored at the time of CABG. Nevertheless, the CRUSADE bleeding score can assist clinicians who are evaluating patients with NSTEMI to quantitatively estimate the risk of major bleeding prior to deciding on therapeutic interventions. A web-based tool to calculate the CRUSADE score is available at www.crusadebleedingscore.org.

Jean-Pierre L. Bassand, MD, University of Besançon, Besançon, France, noted that there have been dramatic improvements in outcomes of acute coronary syndrome (ACS) treatment over the last 30 years, mostly due to antiplatelet agents, anticoagulants, revascularization/reperfusion/thrombolysis, long-term treatment/secondary prevention, and implementation of guidelines. However, these improvements have been accompanied in many cases by increases in major bleeding (Figure 2). Data from the GRACE Registry indicate that advancing age, female gender, history of bleeding or renal insufficiency, the use of GPIIb/IIIa blockers, and percutaneous interventions (PCI) are some of the factors that are associated with an increased risk of bleeding in patients with NSTEMI (Moscucci M et al. *Eur Heart J* 2003), as are excess use and incorrect dosing of unfractionated heparin, low-molecular-weight heparin, and GPIIb/IIIa blockers [Alexander KP et al. *JAMA* 2004], which appear to be even more common in the very patients who are already at risk of bleeding for other reasons [Alexander KP et al. *Circulation* 2006]. Recently, it has been suggested that bleeding risk may have a genetic component. In particular, CYP2C19*17 carrier status has been shown to be significantly associated with enhanced response to clopidogrel and an increased risk of bleeding [Sibbing D et al. *Circulation* 2010].

The challenge remains to develop therapies that inhibit platelet activation more effectively without increasing bleeding complications. The inhibition of the platelet protease-activated receptor-1 (PAR-1) for thrombin has been shown to inhibit thrombin-mediated platelet activation without increasing bleeding in preclinical models and small-scale clinical trials [Angiolillo DJ et al. *Eur Heart J* 2010]. Results from the TRA20P-TIMI 50 [NCT00526474] and TRACER [NCT00527943] trials, which are due in approximately 1 to 2 years, are anxiously awaited.

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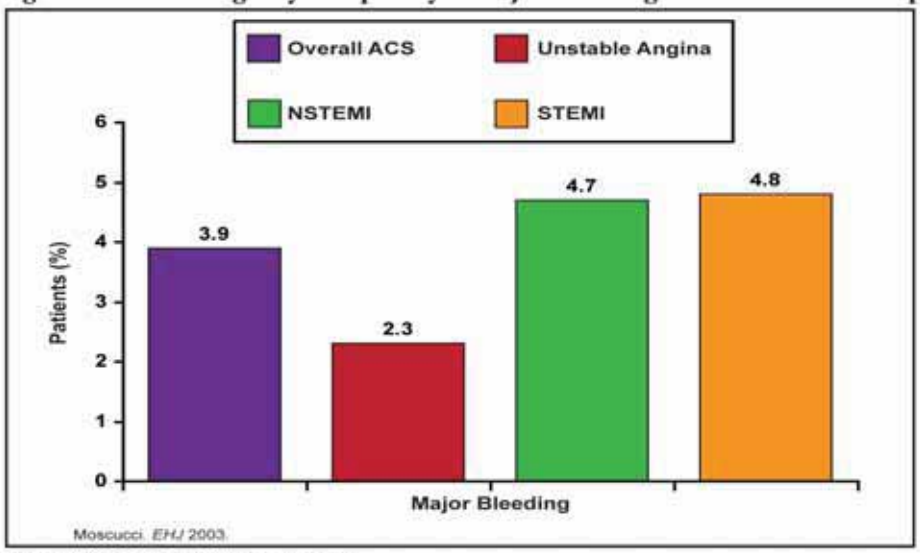
Figure 2. GRACE Registry: Frequency of Major Bleeding in Overall Patient Population.



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Deepak L. Bhatt, MD, Boston Healthcare System and Harvard Medical School, Boston, MA, discussed the current strategies that are available to decrease the risk of ACS-associated bleeding. Gastrointestinal (GI) bleeding is the most common form of chronic major bleeding that occurs in patients with ACS. The OCLA and COGENT trials have attempted to determine if prophylactic use of proton pump inhibitors (PPI) reduces the risk of GI bleeding and affects survival outcome. While omeprazole has been shown to significantly decrease inhibition of the platelet P2Y12 receptor by clopidogrel [Gilard M. *J Am Coll Cardiol* 2008], it is unclear whether this translates to increased rates of clinical adverse ischemic events. Preliminary results from the COGENT trial [Bhatt. TCT Sept 2009] have shown that GI bleeding events are reduced with PPI treatment versus placebo and that survival curves with respect to composite cardiovascular events after 1 year do not appear to differ.

The increasing use of the radial approach to PCI may offer some protection from excess bleeding. Compared with the femoral approach, the use of radial-PCI was associated with a similar rate of procedural success (OR, 1.02; 95% CI, 0.93 to 1.12) but a significantly lower risk for bleeding complications (OR, 0.42; 95% CI, 0.31 to 0.56). The reduction in bleeding complications was more pronounced among patients aged <75 years, women, and patients who were undergoing PCI for ACS [Rao SV et al. *J Am Col Cardiol* 2008].

In the 1-year results from the HORIZONS-AMI trial, patients with acute STEMI who were undergoing PCI and treated with the thrombin inhibitor bivalirudin had significantly lower rates of protocol-defined major bleeding (5.8% vs 9.2%; HR, 0.61; 95% CI, 0.48 to 0.78; p<0.0001) as well as trial-defined net adverse clinical events (bleeding + ischemic events) than patients who were assigned to heparin plus a GPIIb/IIIa inhibitor (15.6% vs 18.3%; HR, 0.83; 95% CI, 0.71 to 0.97; p=0.022) [Mehran R et al. *Lancet* 2009]. These results (and similar findings with other recent antithrombotic therapies, such as fondaparinux and dabigatran) offer the hope that future antithrombotic treatment strategies will be able to simultaneously reduce bleeding and ischemic complications, thus resulting in a win-win situation for patients.

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Results from the ACCORD Lipid Study

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid study (NCT00000620) does not support the use of combination fibrate and statin therapy compared with statin therapy alone to reduce cardiovascular (CV) risk in high-risk patients with type 2 diabetes mellitus (DM). However, subgroup analyses suggest a treatment interaction that is associated with combination therapy and gender and a possible interaction between combination therapy and severe dyslipidemia.

Henry N. Ginsberg, MD, Columbia University, New York, NY, discussed findings from the ACCORD Lipid Study. The lipid substudy was a randomized, placebo-controlled, double-blind trial that included 5518 participants with stable type 2 DM for >3 months who were at high risk for cardiovascular disease (CVD) events (defined as clinical or subclinical disease or having ≥2 risk factors in addition to type 2 DM; Table 1). All patients were taking simvastatin 20 to 40 mg/day and were randomized to receive either fenofibrate 54 to 160 mg/day (based on estimated glomerular filtration rate) or placebo. The mean follow-up was 4.7 years.

Table 1. Additional Inclusion Criteria for the ACCORD Lipid Study.

Age
≥40 years with history of clinical CVD
≥55 years for all other participants
Lipid Profile
~ Low-Density Lipoprotein (LDL) Cholesterol 60 to 180 mg/dL
~ High-Density Lipoprotein (HDL) Cholesterol
<55 mg/dL for women/blacks
<50 mg/dL for all other participants
~ Triglycerides
<400 mg/dL if on lipid therapy
<750 mg/dL for all other participants

The primary outcome was the first occurrence of a major CV event (defined as nonfatal myocardial infarction [MI], nonfatal stroke, or CV death). Secondary outcomes included the individual components of the primary outcome, an expanded macrovascular outcome (defined as a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure), major coronary disease events (defined as a combination of a fatal coronary event, a nonfatal MI, or unstable angina), hospitalization or death due to heart failure, all stroke, and death from any cause.

There was no significant difference between fenofibrate and placebo for the primary outcome or the prespecified secondary outcomes. The most common adverse event was severe muscle aches/pains, which was similar in both groups regardless of creatine kinase level (40% for both groups). Elevations of creatine kinase were unusual and not different between the two treatment groups. Other serious adverse events were uncommon. Both groups demonstrated increased serum creatinine levels over the course of the study, but the incidence of elevated creatinine was 50% to 100% higher in the fenofibrate group. In contrast to the increases in creatinine in the fenofibrate group, the incidence of both micro- and macroproteinuria was lower in participants who were treated with fenofibrate.

There was evidence of an interaction between gender and fenofibrate + simvastatin combination therapy, suggesting a potential harm for women (9.1% event rate over five years for the fenofibrate group vs a 6.6% event rate over five years for the placebo group) and potential benefit for men (11.2% for fenofibrate vs 13.3% for placebo) with regard to the primary outcome of major CV events (p=0.01 for interaction). When patients with both low HDL levels (≤34 mg/dL) and high triglyceride levels (≥204 mg/dL) were compared with all other participants, a weak heterogeneity was observed, but this interaction did not reach statistical significance (p=0.057 for interaction). However, there was a suggestion of benefit in the subgroup with severe dyslipidemia (12.37% for fenofibrate vs 17.32% for placebo); there was no benefit of fenofibrate in all other participants (10.11% for fenofibrate vs 10.11% for placebo).

While the primary endpoint was not achieved in the ACCORD Lipid study, the interactions that were noted during the subgroup analyses merit further investigation. Whether or not there are gender-specific differences in benefit that are associated with fenofibrate combination therapy has not been established. Additionally, the nonsignificant interaction that was detected in those with significant dyslipidemia requires clarification.

Further Reading: The ACCORD Study. Group *N Engl J Med*. 2010; published online ahead of print.

Results from the ACCORD BP Trial

Intensive blood pressure (BP) control did not reduce the rate of a composite outcome of major cardiovascular (CV) events in high-risk patients with type 2 diabetes mellitus (DM), according to the Action to Control Cardiovascular Risk in Diabetes (ACCORD; NCT00000620) Blood Pressure Trial. William C. Cushman, MD, VA Medical Center, Memphis, TN, presented the results of the ACCORD BP Trial.

The ACCORD BP Trial included 4733 patients with stable type 2 DM > 3 months (average duration 10 years), with hemoglobin A1c 7.5% to 11%, who were considered to be at high risk for CVD (defined as clinical or subclinical disease or ≥ 2 CV risk factors, in addition to DM). Patients were randomized to receive either intensive therapy (n=2362) (initial 2-drug therapy of thiazide-type diuretic plus an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB), or a β-blocker was recommended with drugs added or titrated at each visit in order to achieve a systolic BP (SBP) of <120 mmHg) or standard therapy (n=2371) (where therapy was intensified if SBP was ≥160 mmHg at one visit or ≥140 mmHg during two consecutive visits; therapy was down-titrated if SBP was <130 mmHg at one visit or <135 mmHg during two consecutive visits). The target SBP for the intensive therapy group was <120 mmHg, and the target SBP in the standard therapy group was <140 mmHg.

The primary outcome was the first occurrence of a major CV event (defined as nonfatal myocardial infarction [MI], nonfatal stroke, or CV death). Secondary outcomes included an expanded macrovascular outcome (defined as a combination of the primary outcome plus revascularization or hospitalization for congestive heart failure), major coronary disease events (defined as a combination of a fatal coronary event, a nonfatal MI, or unstable angina), hospitalization or death due to heart failure, all stroke, death from any cause, or death from CV causes.

The rate of serious adverse events, although infrequent, was significantly higher in those who were treated with intensive therapy compared with those who received standard therapy (3.3% vs 1.3%, respectively; p<0.001). Additionally, the mean estimated glomerular filtration rates were significantly lower in the intensive therapy group (75 vs 81mL/min/1.73m^2; p<0.001), but the incidence of end-stage renal disease was no different. One year from study end, the mean SBP averaged 119.3 mmHg versus 133.5 mm Hg for intensive and standard groups, respectively, which amounted to a difference of 14.2 mmHg.

The annual rate of the composite of fatal and nonfatal CV events was similar in both groups (1.87% vs 2.09% per year for standard therapy; p=0.20). There was no difference in death from any cause between the two groups. Interestingly, the prespecified secondary outcomes of total stroke (p=0.01) and nonfatal stroke (p=0.03) were lower in the intensive therapy group. No interaction within predefined subgroups was found, although there was a trend (p<0.08) for modification of effect by randomization to intensive or standard glycemia intervention, with benefit in the standard group.

These results failed to demonstrate that lower target SBP (<120 mmHg), through the use of intensive therapy, reduces the rate of fatal and nonfatal CV events (composite primary endpoint) in high-risk patients with type 2 DM.

Further Reading: The ACCORD Study Group *N Engl J Med* 2010; published online ahead of print.

Results from the NAVIGATOR Trial

There is no evidence of cardiovascular (CV) benefit that is associated with long-term treatment with nateglinide and valsartan in patients with impaired glucose tolerance and cardiovascular disease (CVD) or CV risk factors. However, valsartan therapy is associated with a reduction in the incidence of diabetes. Rury R. Holman, MB, ChB, FRCP, Churchill Hospital, Oxford, United Kingdom, and Robert M. Califf, MD, Duke Translational Medicine Institute, Durham, NC, presented results from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR; NCT00097786) Trial.

NAVIGATOR was a double-blind, randomized, multicenter, controlled trial that included 9306 patients with impaired glucose tolerance, defined as fasting plasma glucose (FPG) ≥95 mg/dL and <125 mg/dL and either known CVD if ≥50 years old or ≥1 risk factor for CVD if ≥55 years old. The use of any antidiabetic agent within the last 5 years was an exclusion. Patients were randomized in a 2x2 factorial design to either valsartan (an angiotensin receptor blocker) 160 mg daily or placebo, and to either nateglinide (a short-acting secretagogue) 60 mg 3 times daily or placebo. All study subjects participated in a lifestyle modification program throughout the duration of the study.

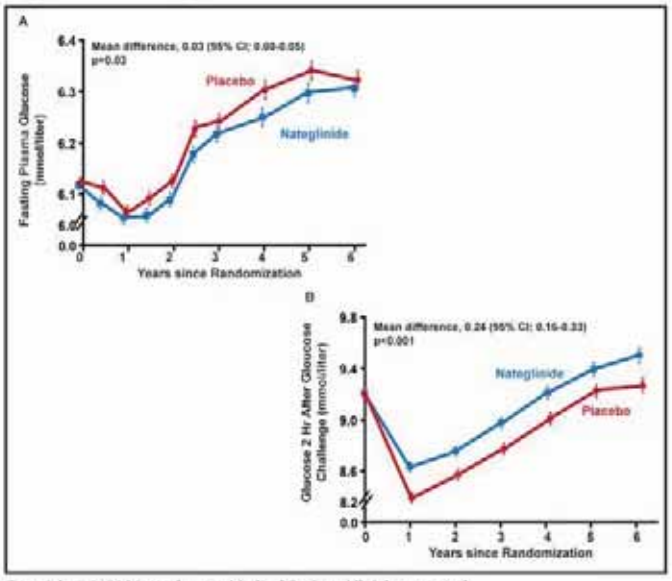
One-quarter of participants had known CVD at baseline. The mean age was 64 years, and the median follow-up was 6.5 years for vital status and 5.0 years for incident diabetes. On average, patients in this study were obese at baseline (average BMI 30.5 kg/m^2). The three coprimary endpoints for both comparisons of this study were:

1. The incidence of diabetes, defined as fasting plasma glucose (FPG) ≥126 mg/dL (≥7.0 mmol/L) and/or 2-hour plasma glucose ≥200 mg/dL (≥11.1 mmol/L), confirmed by oral glucose tolerance test within 12 weeks;

2. An extended CV composite outcome of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization for heart failure, revascularization or unstable angina;
3. The core CV composite outcome of CV death, nonfatal MI, nonfatal stroke, or hospitalization for heart failure.

Dr. Holman discussed findings from the nateglinide arm of NAVIGATOR. There was no significant difference between nateglinide (n=4645) and placebo (n=4661) with regard to the extended CV composite outcome or the core CV composite outcome. There was a nonsignificant increase in incident diabetes with nateglinide (36% vs 34%; p=0.05). While patients who were treated with nateglinide demonstrated lower FPG levels over the course of the study (p=0.03), plasma glucose levels 2 hours post-glucose challenge were significantly higher (p<0.001) in the nateglinide group compared with placebo (Figure 1). "These results were unexpected, based on nateglinide's mechanism of action, and the reason for this disparity is unclear," said Dr. Holman. However, these findings may be due to a decline in drug response over time or an acute withdrawal reaction, as the study drug was withheld on the day of the oral glucose tolerance test.

Figure 1. Changes in Mean Plasma Glucose Levels.



Adverse events did not differ between the two treatment groups, with the exception of hypoglycemic events. Nateglinide therapy was associated with an increased risk of hypoglycemia compared with placebo (19.6% vs 11.3%; p<0.001). Of the events in the nateglinide group, 21 were deemed severe, 214 were moderate, and 676 were mild versus 12, 104, and 411 in the placebo group, respectively.

Mean body weight and waist circumference were also higher in the nateglinide group, despite an overall trend in mean body weight reduction throughout the duration of the study. Ten percent of participants lost 5% of their baseline weight by 6 months.

Dr. Califf presented the details of the valsartan (n=4631) versus placebo (n=4675) comparison of NAVIGATOR. He began by pointing out that the difference in the use of concomitant beta-blockers, calcium channel blockers, and diuretics from baseline to last study visit was greater in the placebo arm than in the valsartan arm (p<0.001).

Valsartan did not significantly reduce the incidence of the extended or core CV outcomes. However, there was a 14% relative reduction in the incidence of diabetes in the valsartan group. The cumulative incidence of diabetes was 33.1% in the valsartan group versus 36.8% in the placebo group, amounting to an absolute reduction of 3.8% (HR, 0.86; 95% CI, 0.80 to 0.92; p<0.001). Additional exploratory outcomes of CV death and total mortality were not significantly different.

As with the nateglinide arm of the trial, patients in the treatment arm demonstrated lower FPG over the course of the study. Contrary to the nateglinide results, glucose levels 2 hours post-glucose challenge were also lower in the valsartan treatment arm compared with placebo (p<0.001).

Treatment with valsartan significantly reduced mean sitting blood pressure throughout the duration of the study (p<0.001 for systolic and diastolic measurements). However, hypotension-related adverse events were more common in those who received valsartan (42.4%) than in those who received placebo (35.9%; p<0.001). Other common adverse events were nasopharyngitis, back pain, and arthralgia.

No major safety concerns were identified during the course of the NAVIGATOR study. The rates of major CV events were comparable in all arms of this study, and neither treatment appeared to impact the incidence of CV outcomes. Nateglinide therapy was associated with a higher incidence of hypoglycemia, while valsartan therapy was associated with a higher incidence of hypotension-related adverse events. Valsartan therapy, in combination with lifestyle modification, did reduce the incidence of diabetes in patients with impaired glucose tolerance and CVD or CV risk factors.

Dr. Califf concluded that NAVIGATOR demonstrates that the risks and benefits of therapies can not be predicted accurately based on biology and intermediate measures. Instead, they must be empirically demonstrated with proper randomized clinical trials. While lifestyle modification continues to be the key to diabetes prevention and management, it is important to investigate pharmaceutical options as well, especially in the presence of comorbidities, such as CVD.

Results From the EVEREST II Trial

Percutaneous mitral valve repair using the MitraClip System is a safe and effective treatment for patients with significant mitral regurgitation (MR). Two established strategies for the treatment of significant MR are medical management, which controls symptoms but does not address underlying pathophysiology or disease progression, and surgical repair or replacement, which is effective but invasive. Thus far, there is an unmet need for a less invasive treatment option, particularly among the elderly and in the presence of comorbidities. Ted E. Feldman, MD, Evanston Hospital, Evanston, IL, presented findings from the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II; NCT00209274), which investigated a noninvasive mitral repair option for MR.

EVEREST II was a randomized, multicenter, controlled trial that included 279 patients (MitraClip Device, n=184; Control of Surgical Repair/Replacement, n=95) with moderate to severe (3+) or severe (4+) MR according to American College of Cardiology/American Heart Association guidelines who were candidates for mitral valve surgery. Patients in both groups were well matched at baseline. It is important to note that 73% of patients had degenerative MR and 27% of patients had functional MR in both groups.

The primary safety endpoint was major adverse event (MAE) rate at 30 days using a superiority hypothesis and per-protocol cohort. The primary effectiveness endpoint was clinical success rate or freedom from the combined outcome of death, mitral valve surgery or reoperation for mitral valve dysfunction, or MR >2+ at 12 months using a noninferiority hypothesis and per-protocol cohort. Additional analyses included intention-to-treat (ITT) for safety (MAE rate at 30 days) and effectiveness (freedom from composite of death, mitral valve surgery > 90 days or reoperation for mitral valve dysfunction >90 days postindex procedure, or MR >2+ at 12 months) and clinical benefit assessment using MR severity, left ventricular function, NYHA Functional Class, and quality of life (SF-36) survey as measures of clinical benefit.

The MitraClip device demonstrated superiority over control with regard to safety (p<0.0001). MAEs were observed in 9.6% of patients in the device group compared with 57.0% in the control group, an observed difference of 47.4% at 30 days (Table 1). Additionally, the MitraClip device was noninferior to control with regard to clinical success rate at 12 months (72.4% for the device group vs 87.8% for the control group; p=0.0012). Results of the safety and clinical success rates in the ITT analysis were similar to those of the per-protocol cohort. The device group demonstrated safety superiority (p<0.0001) and effectiveness noninferiority (p=0.0005) compared with control in the ITT analysis.

Table 1. EVEREST II - 30-Day MAEs.

30 Day MAE, non-hierarchical	# Patients experiencing event	
	Device Group (n=136)	Control Group (n=79)
Death	0	2 (2.5%)
Major Stroke	0	2 (2.5%)
Re-operation of Mitral Valve	0	1 (1.3%)
Urgent/Emergent CV Surgery	0	4 (5.1%)
Myocardial Infarction	0	0
Renal Failure	0	0
Deep Wound Infection	0	0
Ventilation >48 hrs	0	4 (5.1%)
New Onset Permanent AF	0	0
Septicemia	0	0
GI Complication Requiring Surgery	1 (0.7%)	0
All Transfusions ≥2 units*	12 (8.8%)	42 (53.2%)
Total % of Patients with MAE	9.6%	57.0%
	p<0.0001* (95% CI, 34.4% to 60.4%)	
*p<0.0001 if include major bleeding only		

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Clinical benefit was observed in the MitraClip and mitral valve surgery patients through 12 months. These patients demonstrated improvements in left ventricular function, NYHA Functional Class, and quality of life.

Based on these findings, the MitraClip procedure may be a feasible therapeutic option for selective patients with significant mitral regurgitation, and surgery remains an option after MitraClip procedure. Results from EVEREST II are promising with regard to safety, efficacy, and clinical benefit. However, MitraClip is an investigational device only and is not currently available for sale in the United States.

The Safety and Tolerability of Betrixaban Therapy

The oral direct factor Xa inhibitor betrixaban, at doses of 40 mg, 60 mg, and 80 mg once daily, is safe and well tolerated compared with dose-adjusted warfarin in patients with nonvalvular atrial fibrillation (AF) or atrial flutter. Michael D. Ezekowitz, MD, PhD, Vice President, Lankenau Institute for Medical Research, Thomas Jefferson Medical College, Wynnewood, PA, presented results from the Phase II, randomized, multicenter EXPLORE-Xa Trial (NCT00742859).

Dr. Ezekowitz pointed out a few important characteristics of betrixaban, including its effective half-life of approximately 20 hours and the fact that it is being codeveloped with an antidote. No dose adjustments for renal impairment or major drug interactions were anticipated during this trial, because betrixaban is excreted mostly unchanged through bile, with minimal renal excretion, and it is not a substrate for the CYP450 system.

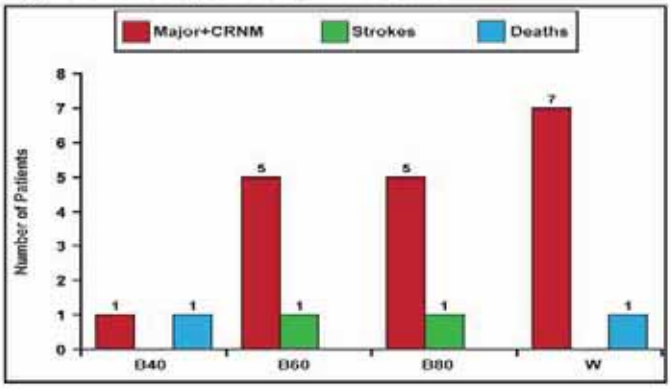
In EXPLORE-Xa, 508 patients with nonvalvular AF and at least one risk factor for stroke were randomized to receive betrixaban 40 mg (n=127), 60 mg (n=127), or 80 mg (n=127) or open-label warfarin (n=127) with an international normalized ratio goal of 2 to 3. The mean age was 74 years, and the median follow-up was 4.9 months (minimum follow-up 3 months; maximum follow-up 12 months). Patients were excluded from participation in the study if they had active endocarditis, AF due to reversible cases or mechanical heart valve, scheduled major surgery or pulmonary vein ablation, or repeated systolic blood pressure >160 mmHg; had received hemodialysis within one year; or experienced a recent ischemic stroke, systemic embolic event, or acute coronary syndrome within 30 days. The primary endpoint was occurrence of major or clinically relevant nonmajor bleeding. The secondary endpoints were time to occurrence of any bleeding (major, clinically relevant nonmajor, and minimal) and time to occurrence of death, stroke, myocardial infarction (MI), or other systemic embolism.

At 3 months, the rate of major or clinically relevant nonmajor bleeding in the betrixaban 40-mg group (n=1) was significantly less than in the warfarin group (n=4). Bleeding rates in the groups that received betrixaban 60 mg (n=4) and 80 mg (n=5) were comparable with rates that were observed in the warfarin group. The number of strokes and deaths was low in all treatment groups (Figure 1). Patients who received the 40-mg betrixaban dose demonstrated a slight increase in d-dimer from baseline, and there was a trend toward a dose response with d-dimer activity across the dose spectrum.

Adverse events were equally distributed among the groups, with the exception of gastrointestinal adverse events. The incidence of vomiting, nausea, and diarrhea was more common in patients who received betrixaban. There was no difference in the incidence of alanine aminotransferase >2x the upper limit of normal in any of the groups (2.4% for betrixaban and warfarin groups).

Betrixaban 40 mg, 60 mg, and 80 mg appear to be well tolerated in patients with AF or atrial flutter. There was a dose-dependent effect on the primary endpoint of major or clinically relevant nonmajor bleeding that was associated with betrixaban therapy. More comprehensive evaluation in a larger study population is needed to determine the safety and efficacy of betrixaban therapy.

Figure 1. Bleeds, Strokes, and Deaths.



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Pooled Analysis of the REAL-LATE and ZEST-LATE Trials

Dual antiplatelet therapy (aspirin plus clopidogrel) did not appear to be more effective than aspirin alone in reducing the rate of cardiac death or myocardial infarction (MI), according to pooled data from the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated with Drug-Eluting Stent Implantation and Late Coronary Artery Thrombotic Events (REAL-LATE; NCT00484926) and Evaluation of the Long-Term Safety After Zotarolimus-Eluting Stent, Sirolimous-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions Late Coronary Arterial Events (ZEST-LATE; NCT00590174) Trials. The two trials were merged due to their design similarity and slow enrollment, and merged results were presented by Seung-Jung Park, MD, PhD, Asan Medical Center, Seoul, Korea.

Current guidelines recommend the use of clopidogrel 75 mg daily for at least 12 months post-drug-eluting stent (DES) implantation, provided that the patient is not at high risk of bleeding. While early discontinuation of dual antiplatelet therapy is associated with a higher risk of late stent thrombosis in patients with DES, there is no consistent data regarding the appropriate treatment duration and the long-term outcomes that are associated with dual antiplatelet therapy in these patients. The merged data analysis by Dr. Park and colleagues sought to compare antiplatelet strategies in patients on dual antiplatelet therapy who were free of major adverse cardiovascular events (MACEs) and major bleeding for at least 12 months post-DES implantation.

Patients in these two open-label trials were randomized to receive either clopidogrel 75 mg daily plus low-dose aspirin (100 to 200 mg daily; n=1357) or low-dose aspirin alone (n=1344). Patients were well matched at baseline. However,

the REAL-LATE participants included a broader population that did not limit clinical or lesion characteristics. Exclusion criteria across the studies included contraindications to antiplatelet drugs, concomitant vascular disease or other indications that required the long-term use of clopidogrel, noncardiac comorbidities that limited life expectancy to <1 year, and participation in another drug or coronary device study. Follow-up evaluations were performed every 6 months, and the median duration of follow-up was 19.2 months. The primary endpoint was the first occurrence of MI or death from cardiac causes postrandomization. The secondary endpoints included major bleeding, as defined by Thrombolysis in Myocardial infarction (MI) criteria; a composite of death or MI; a composite of death, MI, or stroke; a composite of cardiac death, MI, or stroke; or individual components, including death, MI, stroke of any cause, definite stent thrombosis, or repeat revascularization.

The risk of cardiac death or MI was similar for both groups (1.8% for dual therapy vs 1.2% for monotherapy; p=0.17). The composite risk of MI, stroke, or death from any cause was slightly higher in the dual therapy group (HR, 1.73; 95% CI, 0.99 to 3.00; p=0.051), as was the composite risk of MI, stroke, or death from cardiac causes (HR, 1.84; 95% CI, 0.99 to 3.45; p=0.06). However, neither of these increases reached statistical significance. The risks that were associated with the individual components of the secondary endpoint were similar in both groups. Overall, the use of dual antiplatelet therapy beyond 12 months post-DES implantation did not significantly reduce the risk of MI or death from cardiac causes compared with aspirin monotherapy.

Dr. Park concluded that this study had insufficient statistical power to determine the safety of clopidogrel discontinuation after 12 months. Therefore, larger clinical trials with a longer-term follow-up are needed to evaluate the risk of clopidogrel discontinuation.

Further Reading: Park S-J et al. Duration of Dual Antiplatelet Therapy after Implantation of Drug-Eluting Stents. *N Eng J Med* 15 Apr 2010;362(15):1374-1382.

Diuretic Optimization Strategies Evaluation in Acute Heart Failure

There is no evidence of benefit for various initial administration or dosing strategies of furosemide therapy in patients with acute decompensated heart failure (ADHF). However, the high-intensification (2.5 x chronic daily oral dose) dosing strategy was associated with improvements or trends toward improvement in multiple areas. Findings from the Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF; NCT00577135) Study were presented by G. Michael Felker, MD, Duke Clinical Research Institute, Durham, NC.

Intravenous (IV) loop diuretics are commonly prescribed for patients with ADHF. However, there is some debate concerning the risk, benefit, and appropriate use of higher-dose diuretics. There is also an absence of prospective studies and trial evidence to provide clinicians with consistent guidelines for diuretic management. In light of current uncertainty pertaining to the appropriate administration and dosing of diuretics, DOSE-AHF investigators set out to evaluate the safety and efficacy of two administration (bolus Q 12 hours vs continuous infusion) and two dosing (low intensification of 1 x chronic daily oral dose furosemide vs high intensification of 2.5 x chronic daily oral dose furosemide) strategies.

DOSE-AHF was a double-blind, randomized trial with a 2x2 factorial design that included 308 patients with prior clinical diagnosis of acute heart failure (AHF; defined by at least one symptom and one sign) who were identified within 24 hours of hospital admission. All patients were taking oral furosemide 80 mg to 240 mg daily with an anticipated need for IV loop diuretics for at least 48 hours. Patients were excluded from participation if they received or planned to receive IV vasoactive therapy or ultrafiltration therapy for HF; had acute coronary syndrome within 4 weeks; and had systolic blood pressure <90 mmHg, serum creatinine>3.0 mg/dL at baseline, B-type natriuretic peptide (BNP) <250 pg/mL, or N-terminal pro-BNP (NT-proBNP) <1000 pg/mL.

The coprimary endpoints were the efficacy endpoint of patient global assessment by visual analog scale (VAS) over 72 hours using area under the curve (AUC) and the safety endpoint of renal function assessment, defined as change in creatinine from baseline to 72 hours. The study was 88% powered for detecting a creatinine difference of 0.2 mg/dL and a 600-point difference in VAS. Statistical significance for the two primary endpoints was p≤0.25. VAS was assessed at 6, 12, 24, 48, and 72 hours. The secondary endpoints are contained in Table 1.

The difference in global symptom relief and renal function was not statistically significant at 72 hours with regard to administration method (bolus vs continuous infusion) or dose (low vs high intensification). Additionally, results for all secondary endpoints were similar, regardless of the method of furosemide administration. Though transient changes in renal function occurred in patients who received high-intensification therapy prior to 60 days, the difference between the two groups dissipated by Day 60. High-intensification therapy was associated with improvements or trends toward improvement in multiple

domains, including dyspnea, change in weight, change in NT-proBNP, and net volume loss (Table 1).

It is important to note that this study evaluated only patients with a history of chronic HF and moderate to high diuretic requirements. Therefore, these results may not apply to *de novo* HF patients, concluded Dr. Felker. DOSE protocol also allowed for changes in therapeutic strategy at 48 hours, based on clinical response. This and the study's limited power to detect differences in clinical events may have influenced results with regard to observed differences between the groups.

Table 1. Secondary Endpoints.

Secondary Endpoint	Low Intensification (1 x oral dose/d)	High Intensification (2.5 x oral dose/d)	p value
Dyspnea VAS AUC at 72 hours	4478	4668	0.041
% free from congestion at 72 hours	11%	18%	0.091
Change in weight at 72 hours	-6.1 lbs	-8.7 lbs	0.011
Net volume loss at 72 hours	3575 mL	4899 mL	0.001
Change in NT-proBNP at 72 hours	-1194 pg/mL	-1882 pg/mL	0.06
% Treatment failure (persistent HF, worsening renal failure, or death)	37%	40%	0.56
% with creatinine increase >0.3 mg/dL within 72 hours	14%	23%	0.041
Length of stay, days (median)	6	5	0.55

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Results from the JETSTENT Trial

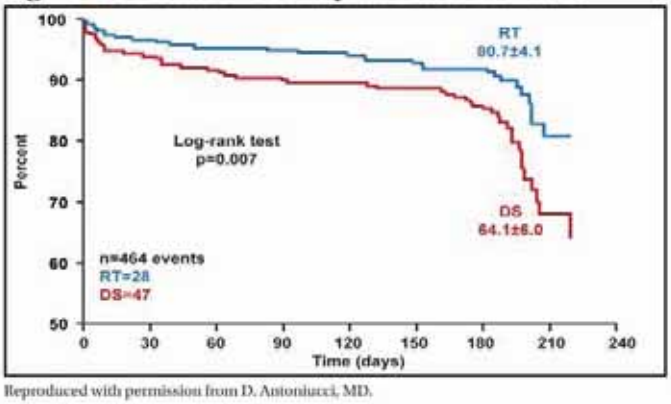
Rheolytic thrombectomy plus stenting is associated with better 6-month outcomes and improved myocardial reperfusion compared with direct stenting alone in patients with ST-elevation myocardial infarction (STEMI). While procedure time was higher in the thrombectomy group (60 minutes) than in the direct stenting group (46 minutes; p<0.001), this did not appear to impact the rate of procedural complications, such as the need for pacing to vessel perforation. David Antoniucci, MD, Careggi Hospital, Florence, Italy, discussed results from the Comparison of Angiojet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting to Direct Stenting Alone in Patients with Acute Myocardial Infarction (JETSTENT; NCT00275990) Trial.

The JETSTENT study included 500 patients with STEMI within 12 hours of symptom onset, at least moderate thrombus burden, and infarct artery vessel diameter ≥2.5 mm. Patients were randomized to either rheolytic thrombectomy (RT) plus stenting (n=256) or direct stenting (DS) alone (n=245). The use of a temporary pacemaker and balloon predilation was strongly discouraged. Patients with recent stroke (≤30 days), recent surgery (≤6 weeks), a prestented infarct-related artery, or lysis were excluded from participation in the study. However, cardiogenic shock was not grounds for exclusion and accounted for 2.7% of patients in the RT group and 5.3% of patients in the DS group. The mean follow-up was 6 months, and the mean age was 63 years. Patients were well matched at baseline.

The primary surrogate endpoints were early ST-segment resolution, defined as ≥50% reduction in ST-segment elevation at 30 minutes, and final infarct size at one month, determined by scintigraphy. Clinical endpoints were major adverse cardiac events (MACEs) at 1, 6, and 12 months and death or readmission for congestive heart failure at 12 months. The secondary surrogate endpoints included Thrombolysis in Myocardial Infarction (TIMI) flow, corrected TIMI frame count, and TIMI blush grade.

There was no significant difference in final infarct size between RT and DS (p=0.40). However, ST-segment resolution at 30 minutes was significantly improved in patients who underwent RT compared with DS (p=0.04). However, anterior acute MI appeared to be a predictor of ST-segment resolution (p<0.001). At one month, there was a 2-fold increase in MACEs in patients who received DS compared with RT (6.9% vs 3.1% for RT; p=0.05). DS was also associated with higher rates of death, MI, total vessel revascularization, and stroke compared with RT at one month. This trend continued at 6 months, with the exception of stroke incidence, which was identical in both groups (0.4% for both). TIMI major bleeding occurred in 3.9% of RT patients versus 1.6% of DS patients (p=0.12). However, this difference did not reach statistical significance. Total MACE rate at 6 months was 20.7% for the DS group versus 12.0% for the RT group (p=0.01). Randomization to RT, age, and bleeding appeared to be predictors of MACEs at 6 months (Figure 1).

Figure 1. 6-Month MACE Kaplan-Meier Estimate.



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The JETSTENT trial demonstrated benefit for RT use in patients with STEMI. This strategy is associated with higher rates of early ST-segment resolution and improved clinical outcomes at 6 months. These improvements occurred without any apparent increase in stroke or major bleeding. Further evaluation is required to confirm the long-term safety and efficacy of this strategy.

Long-Term Results of the DEDICATION Trial Favor the Use of DES Over BMS

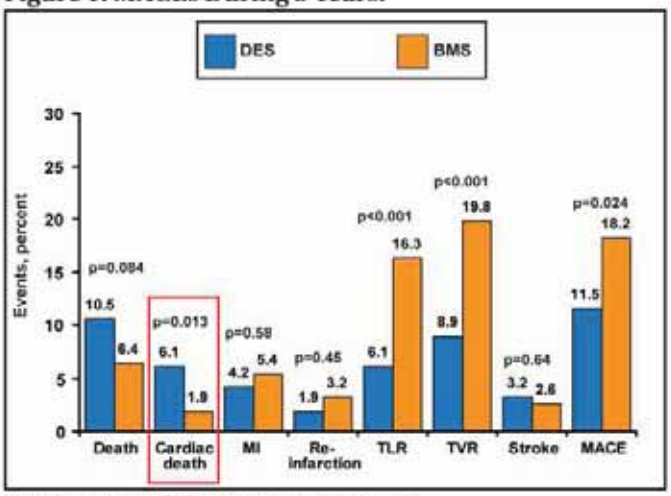
According to long-term follow-up results from the Drug Elution and Distal Protection During Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction (DEDICATION; NCT00192868) trial, drug-eluting stents (DES) reduced the rate of major adverse cardiac events (MACEs) and were not associated with an increased rate of myocardial infarction (MI) or stent thrombosis compared with bare-metal stents (BMS). However, an increased incidence of cardiac death was observed in the DES group. Three-year data from the DEDICATION study was presented by Peter Clemmensen, MD, PhD, Copenhagen University Hospital, Copenhagen, Denmark.

Thus far, DES have demonstrated favorable results with regard to safety and efficacy compared with BMS in patients with coronary artery disease, particularly among those with stable conditions. However, there is limited long-term data available regarding DES use in patients with ST-elevation myocardial infarction (STEMI) who have undergone percutaneous coronary intervention (PCI). Early results from DEDICATION favored DES, but higher mortality rates were associated with DES at 8 months (overall mortality 5.1% for DES vs 2.6% for BMS at 8 months; p=0.14). Therefore, long-term evaluation was warranted in order to confirm the impact of DES on mortality and MACE rates over time.

The 3-year follow-up included 573 patients from the DEDICATION trial who presented with signs and symptoms of a first-time large STEMI, chest pain ≤12 hours duration, and ST-elevation >4 mm in contiguous leads and had high-grade stenosis/occlusion of a native coronary artery that could be crossed with a guidewire. Patients with a history of MI, left main stem stenosis, recent gastrointestinal bleeding (≤1 month), comorbidities with expected survival of <1 year, and linguistic difficulties that required the use of an interpreter were excluded from study participation. Patients were well matched at baseline, and ~65% of patients in both groups had one vessel disease and Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 to 1 at baseline.

The endpoints were MACEs (defined as a composite of cardiac death, reinfarction, and total lesion revascularization), cardiac death, total mortality, MI, total lesion revascularization (TLR), total vessel revascularization (TVR), and stroke at 3 years. Overall, MACEs were less frequent in the DES group (11.5%) than in the BMS group (18.2%) at 3 years (p=0.024). However, the rate of cardiac death (6.1% vs 1.9% for BMS) and all-cause death (10.5% vs 6.4% for BMS) was higher in the DES group. The rates of TLR and TVR were significantly lower for DES compared with BMS (p<0.001 for both). There was no significant difference in the rates of MI or reinfarction between the two groups at 3 years (Figure 1).

Figure 1. MACEs During 3 Years.



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It is important to note that the incidence of stroke was similar between the two groups at 3 years. Though the general theory has been that DES lead to more stent thromboses, this was not the case in the DEDICATION trial, Prof. Clemmensen concluded. DES effectively reduced the rate of MACEs and the need for repeat revascularization in STEMI patients without associated increases in the incidence of MI or stent thrombosis. The increased risk of cardiac death that was associated with DES merits further investigation and should be considered before choosing a treatment strategy.

Long-Term Follow-Up of the PASSION Trial

Rates of cardiac death, myocardial infarction (MI), or target lesion revascularization (TLR) in patients with acute ST-elevation MI (STEMI) who were treated with paclitaxel-eluting stents (PES) were similar in those who were treated with bare-metal stents (BMS) at 5 years. However, there was a trend toward a higher rate of late stent thrombosis

(30 days to 5 years) after treatment with PES. Maarten A. Vink, MD, OLVG Hospital, Amsterdam, The Netherlands, presented findings from the 5-year clinical follow-up of the PASSION (Paclitaxel-Eluting Stent versus Bare-Metal Stent in Acute ST-Elevation Myocardial Infarction) Trial.

Many current guidelines do not consistently support the use of DES in primary percutaneous coronary intervention (PCI) for STEMI due to the lack of long-term outcome trial data. The prospective, randomized, single-blind PASSION trial set out to address the concern of late and very late stent thrombosis that is related to DES use over a 5-year follow-up period. It is the first large-scale randomized study that compared PES with BMS in an exclusively STEMI population.

PASSION included 619 consecutive patients with STEMI who were eligible for primary PCI with stenting. In the interest of focusing on a real-world population, trial exclusion was limited to cardiogenic shock prior to randomization, failed fibrinolysis, expected mortality of <6 months, and mechanical ventilation at presentation. Clinical follow-up occurred at 6, 12, 24, and 60 months. Routine angiographic follow-up was not performed. Patients were randomized to receive either PES (n=310) or BMS (n=309), and all patients received concomitant clopidogrel (300-mg loading dose followed by 75 mg daily for ≥6 months) and aspirin (100- to 500-mgmg loading dose followed by 80 to 100 mg daily indefinitely) postprocedure. GP IIb/IIIa receptor blockers were administered at the discretion of the treating physician, as were thrombus aspiration and direct stenting. The groups were well matched at baseline. The mean age was 61 years, and follow-up of all patients was obtained at 5 years.

The primary endpoint was the composite of death, reinfarction, or TLR (within 5 mm of stent edges) at 5 years. The secondary endpoints included major adverse cardiac events (MACE) at 5 years, individual components of MACE, and stent thrombosis. There was no significant difference in the occurrence of the composite primary endpoint at 5 years, nor was there any difference in the individual components (cardiac death, recurrent MI, or TLR) of the primary endpoint between the two groups. Additionally, there was no significant difference in the occurrence of individual MACE between the two groups. However, there was a slightly higher risk of very late stent thrombosis (1 to 5 years) that was associated with PES (2.5% for PES vs 0.7% for BMS). The rate of definite stent thrombosis at 5 years was 2-fold higher in the PES group (HR, 1.98; 95% CI, 0.67 to 5.79; p=0.20).

Results from the PASSION trial indicate that the long-term risk of cardiac death, MI, or TLR is similar for PES and BMS. The risk of late stent thrombosis is increased slightly with PES, and this risk appears to persist over time. Therefore, clinicians may want to consider the risk versus benefit of PES when choosing a treatment strategy for patients with acute STEMI.

Ticagrelor May Be an Effective Alternative to Clopidogrel in Patients with ACS Who Subsequently Undergo CABG

In patients with acute coronary syndrome (ACS) who are undergoing coronary artery bypass grafting (CABG), treatment with ticagrelor within 7 days prior to surgery is associated with lower rates of mortality after CABG and comparable rates of CABG-related bleeding compared with clopidogrel. The oral, reversibly binding $P2Y_{12}$ antagonist ticagrelor provides greater inhibition of platelet aggregation and a faster offset than clopidogrel, which is an irreversible platelet inhibitor. Findings from a retrospective analysis of the nonrandomized subgroup of patients who required CABG (n=1261) within 7 days of last intake of study drug from the Platelet Inhibition and Patient Outcomes (PLATO; NCT00391872) study, comparing ticagrelor and clopidogrel, were presented by Claes Held, MD, PhD, Uppsala Clinical Research Center, Uppsala, Sweden.

Current ACS guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel for at least 12 months and that clopidogrel be withheld for at least 5 days prior to CABG. However, this is not always possible, as urgent situations may necessitate surgery prior to 5 days after treatment cessation.

The PLATO-CABG analysis included 1261 patients with ACS, of whom 632 were treated with ticagrelor and 629 were treated with clopidogrel. The median age was 64 years, and 81% was male. Approximately 90% of patients underwent coronary angiography at study entry, and approximately 19% underwent percutaneous coronary intervention (PCI) within 24 hours of randomization. The primary efficacy endpoint was the composite of cardiovascular (CV) death, myocardial infraction (MI), or stroke at 12 months post-CABG. The primary safety endpoint was total major bleeding (as defined according to the Global Use of Strategies to Open (GUSTO) occluded coronary arteries guidelines) from time of CABG. The secondary endpoints included the individual components of the primary efficacy endpoint (CV death, MI, and stroke) as well as all-cause mortality and non-CV death.

There was no significant difference between ticagrelor and clopidogrel therapy with regard to the composite primary efficacy endpoint (10.5% vs 12.6%; HR, 0.84; 95% CI 0.60 to 1.16; p=0.29). However, the rate of CV death was significantly lower in the ticagrelor group (4.1% vs

7.9% in the clopidogrel group; p<0.01), with most deaths occurring shortly after CABG and within the first month postprocedure (HR, 0.52; 95% CI, 0.32 to 0.85; p<0.01). The incidence of all-cause mortality was also lower in the ticagrelor group (HR, 0.49; 95% CI, 0.32 to 0.77; p=0.002). There was no reduction in the risk of MI (HR, 1.06; 95% CI, 0.66 to 1.68; p=0.82) or stroke (HR, 1.17; 95% CI, 0.53 to 2.62; p=0.70) with ticagrelor.

Overall, rates of CABG-related bleeding were high in PLATO, which Prof. Claes attributes to the bleeding definitions that were applied in the study, but these rates were not different between ticagrelor and clopidogrel (CABG-Related Major Bleeding 81.2% vs 80.1%; HR, 1.07; 95% CI, 0.80 to 1.43; p=0.67). In addition, there was no significant difference in bleeding when broken down by subtype (ie, major bleeding, life-threatening bleeding, fatal bleeding, TIMI major bleeding, TIMI minor bleeding, and GUSTO severe bleeding).

While these results suggest a reduction in CV death and all-cause mortality in ACS patients who are in need of urgent CABG, the study is a retrospective analysis of a nonrandomized post hoc subgroup, and as such, they are not conclusive, as the findings may have been affected by bias and confounding. The use of ticagrelor in these patients is not associated with an increase in major bleeding, as measured by PLATO definitions, compared with clopidogrel. The findings in the CABG cohort are consistent with the main study outcomes in terms of mortality; however, the reason for the lack of reduction in MI is unclear. A retrospective central review of the causes of post-CABG death are ongoing, as the PLATO-CABG study distinguished between vascular and nonvascular causes but did not investigate further subcategories.

RA Versus SV Grafts in CABG: Is There a Preferred Strategy?

Arterial conduits (particularly the left internal mammary artery [LIMA]) have been shown to be superior to saphenous vein (SV) grafts in terms of long-term patency in patients with coronary artery disease (CAD) who are undergoing coronary artery bypass grafting (CABG). Although the LIMA is the arterial conduit of choice, patients who require more than one bypass must receive either a second arterial graft or a vein graft. While the radial artery is the most frequently used arterial graft in this setting—because it is the easiest to harvest—there is little data concerning its long-term graft patency.

The CABG arm of the prospective, randomized Veterans Administration (VA) Cooperative Study, also known as CSP-474, included 733 patients with stable CAD who were undergoing elective CABG with a LIMA and needed at least one other graft. Findings from CSP-474 were presented by Steven Goldman, MD, Tucson VA Hospital, Tucson, AZ.

Patients were randomized to either radial artery graft (RA; n=366) or SV graft (SV; n=367) to the best recipient vessel. Angiographic assessment was performed at one week and one year post-CABG (completed in 73%) in order to monitor disease progression. There was 89% power to detect a difference in the primary endpoint of angiographic patency at one year. The secondary endpoints included difference in selective graft patency (distal anastomosis to the left anterior descending, circumflex, or right coronary artery) between RA and SV at one year, high-grade disease (string sign) in the graft, and endoscopic harvesting. Other analyses included patency data on cardiopulmonary bypass pump versus "off pump," cost analyses, and quality-of-life assessment at 3 months and one year.

There was no difference in angiographic patency at one year between RA and SV (89% for both). One-week patency rates were also similar (99% for RA vs 97% for SV). There was no difference between RA and SV in the secondary endpoint of selective graft patency at any target. More high-grade disease (defined as a string sign) was observed in the RA group (8%) compared with the SV group (1%; p<0.001), though these rates remained quite low. Endoscopic harvest of SV was associated with lower patency rates compared with traditional harvest of the SV (78% vs 91%; p=0.009), but there was no significant difference in RA patency rates (100% vs 89%) that were dependent on mode of harvest. Additionally, complication rates that were associated with RA and SV were low compared with similar cohorts. At one year, the rate of stroke was 2.0%, the rate of death was 2.0%, and the rate of MI was 1.0%. Operative mortality occurred in 0.7% of patients.

Use of cardiopulmonary bypass (ie, "on" versus "off pump") did not appear to impact RA patency (89% for both). However, higher patency was observed in SV patients who were on pump (90% vs 78%). It is important to note that these data are based on a small number of participants (off-pump patients n=41 for RA and n=48 for SV) and may not be reflective of outcomes that are expected from a real-world population. Quality-of-life assessments for both study groups were comparable at 3 months and one year. While overall hospital costs were similar for the two groups, surgical costs were higher for RA compared with SV ($13,629 vs $12,484 for SV; p<0.001).

In patients with stable CAD who are undergoing CABG with a LIMA and are in need of at least one other graft, RA is not superior to SV in terms of patency at one year. The CSP-424 study is ongoing, and angiographic data will be evaluated during a planned 5-year angiographic follow-up.

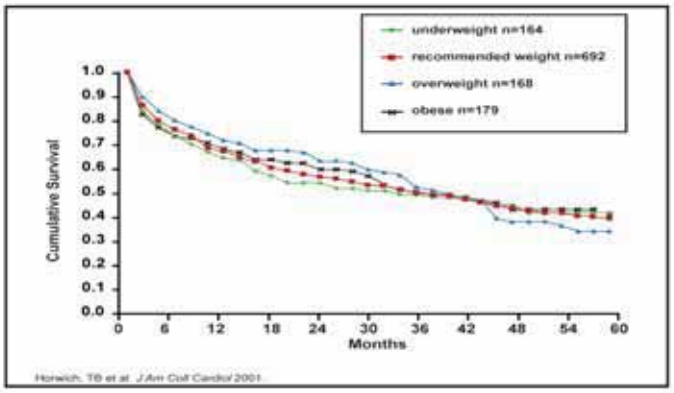
Surviving Heart Failure: The Fatter the Better?

Written by Maria Vinall

The 1999 consensus recommendations for heart failure (HF) stated that obese patients should lose weight [*Am J Cardiol* 1999], and according to data from the Framingham Heart Study, even being overweight poses an increased risk for HF (5% for men and 7% for women for each increment of 1 in body mass index [BMI]) [Kenchaiah S et al. *N Engl J Med* 2002]. However, the current American College of Cardiology/American Heart Association Heart Failure Guidelines [Hunt SA et al. *J Am Col Cardiol* 2005; Jessup M et al. *Circulation* 2009] contain no mention of weight loss for HF patients. Why? According to Tamara Horwich, MD, UCLA, Los Angeles, CA, fatter is better in heart failure.

The relationship between weight and HF was first investigated more than 10 years ago in a study that included 1203 patients with advanced systolic HF. The results of that study showed that obesity is not associated with increased mortality and, in fact, may confer a more favorable prognosis, despite the fact that the obese and overweight patient groups had significantly higher rates of hypertension and diabetes, as well as higher levels of cholesterol, triglycerides, and low-density lipoprotein cholesterol (Figure 1) [Horwich TB et al. *J Am Coll Cardiol* 2001]. These results were recently confirmed in a meta-analysis of nine observational studies (n=28,209) in which both obesity and being overweight were associated with lower all-cause and cardiovascular mortality rates compared with normal weight patients with CHF and were not associated with increased mortality in any study [Oreopoulos A et al. *Am Heart J* 2008].

Figure 1. Adjusted Survival Analysis: Overweight and Obese Fair Better.

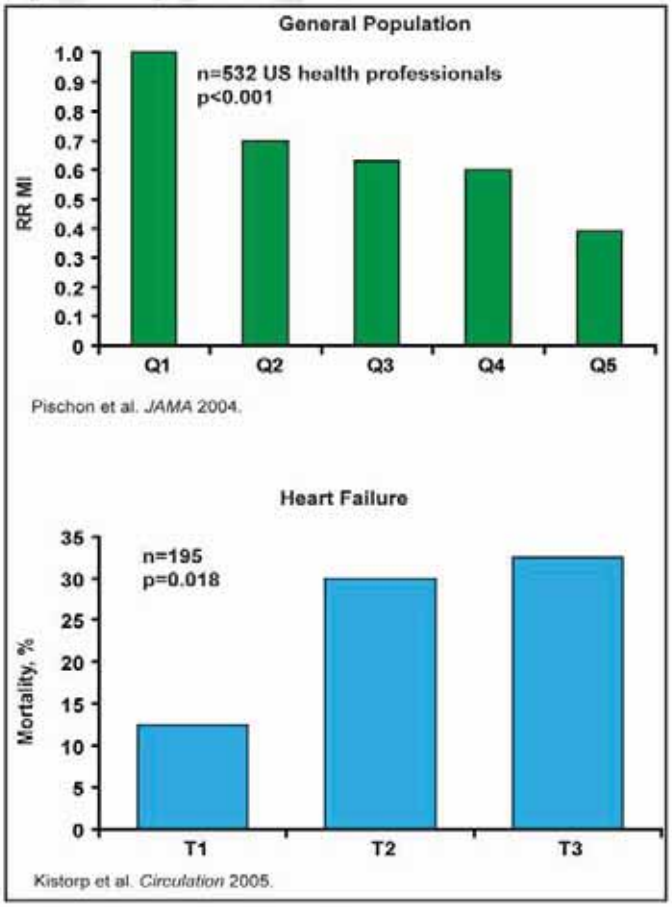


Paradoxically, low body mass index (BMI) may be associated with poorer survival in patients with chronic heart failure (CHF). In the Candesartan in Heart failure: Reduction in Mortality and Morbidity (CHARM) study, CHF patients with ≥5% weight loss in 6 months had more than a 50% increase in mortality compared with those with stable weight. The risk increased more than four-fold for patients whose last recorded annual weight loss exceeded 10%. Weight loss accelerated in the year prior to death [Pocock SJ et al. *Eurt Heart J* 2008]. This reversal has been termed the "obesity paradox."

Several explanations for the obesity paradox in HF patients have been offered: obese HF patients are simply less sick because they present at an earlier stage of disease; high BMI represents greater metabolic reserve in HF; and/or obesity (increased fat or increased lean mass) is protective in terms of altering neurohormonal, inflammatory cytokine, and adipokine physiology [Von Haehling S et al. *Circulation* 2007].

The neurohormonal connection has been evaluated in several studies. Obese individuals tend to have low levels of adiponectin, an adipocyte-derived peptide with insulin-desensitizing and anti-inflammatory properties. In the general population, low levels of adiponectin are associated with a higher risk of MI; however, in HF, the opposite is true—low levels of adiponectin are associated with decreased mortality (Figure 2) [Pischon T et al. *JAMA* 2004]. Another neurohormone that is altered with respect to BMI is brain natriuretic peptide (BNP). HF patients with a BMI <25 have higher levels of BNP compared with overweight (BMI 25 to 29.9) and obese HF patients (BMI ≥30) [Horwich T et al. *J Am Coll Cardiol* 2006]. However, in the general population, low BNP levels are generally associated with lean body mass [DAS SR et al. *Circulation* 2006]. This leads to the question of whether it is lean body mass that is offering cardiovascular protection in overweight and obese HF patients. The answer is important, because almost all of the studies of obesity and HF use BMI as a measure, and while BMI does correlate with fat mass, it can not discriminate between lean mass and fat mass [Romero-Corral A et al. *Int J Obesity* 2008].

Figure 2. Adiponectin Levels.



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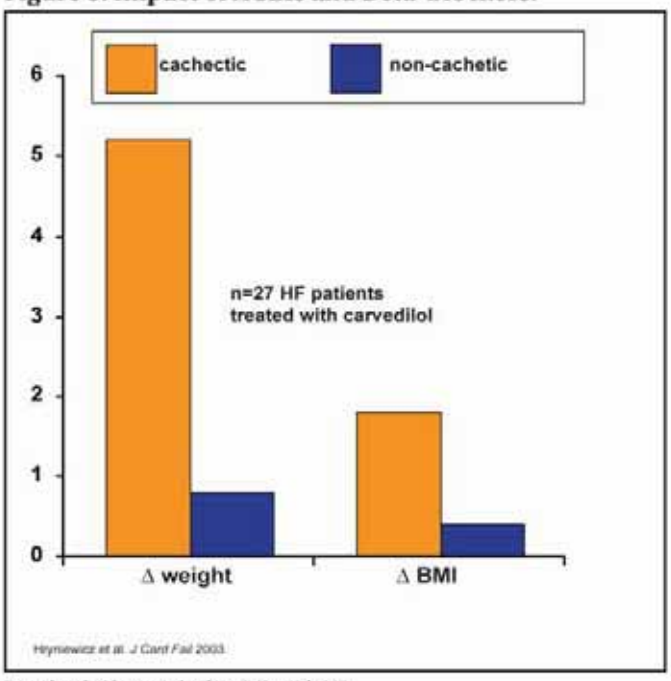
If the paradox implies that being overweight or obese is associated with improved outcomes and if unintentional weight loss portends poor prognosis in HF patients, what are the clinical implications? Dr. Horwich suggests that currently used HF medications, such as ACE inhibitors and beta-blockers, prevent weight loss (Figure 3), and traditional dietary advice that includes the restriction of fluids, salt, alcohol, high K foods, and sugar if the patient is also a diabetic, but not weight reduction. More specifically, for HF individuals with a BMI:

- <30 kg/m^2 – do not encourage weight loss
- >40 kg/m^2 – lose weight to BMI <40
- 30 to 40 kg/m^2 – inconclusive evidence to make recommendation

The best survival has been found for patients with a BMI of 30 to 32 kg/m^2 [Riegel B et al. *Circulation* 2009].

Figure 3. Impact of ACEIs and Beta-Blockers.



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The findings of the obesity paradox extend beyond HF to other chronic conditions, such as end-stage renal disease, rheumatoid arthritis, chronic obstructive pulmonary disease, AIDS, malignancy, and coronary artery disease, as well as in the elderly in general. More studies are needed to determine whether weight loss promotion in patients with HF is a worthwhile goal or may even be harmful. In addition, we need studies to determine what impact intentional weight gain, exercise to increase muscle mass, and nutritional therapy have in HF patients with low BMI.

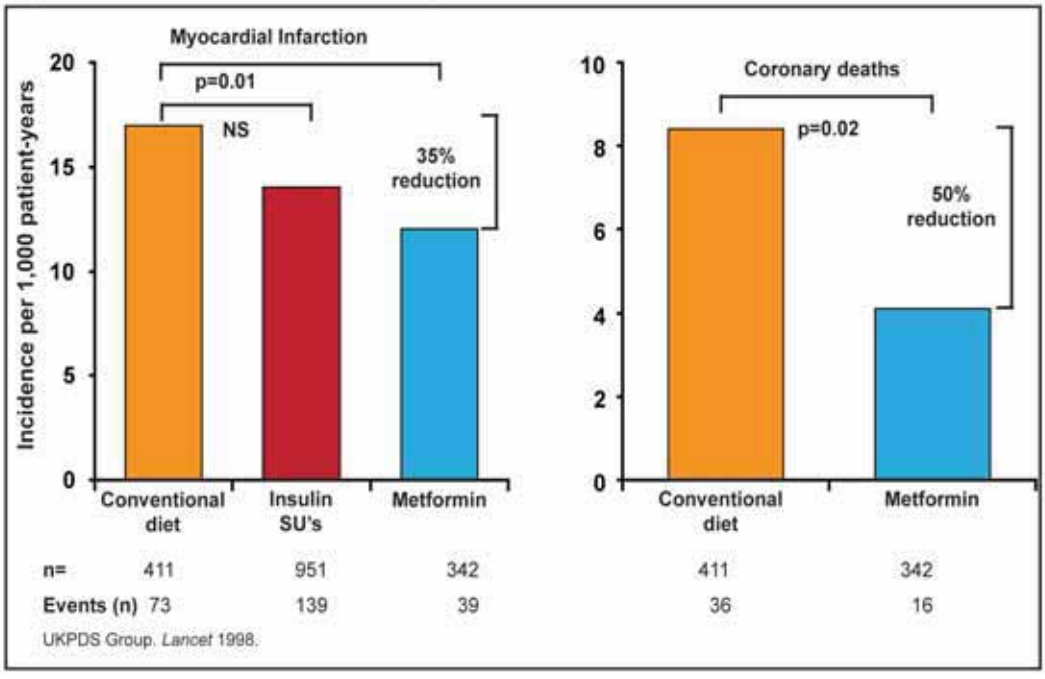
Optimizing Diabetes Management

Written by Maria Vinall

Cardiovascular disease (CVD) is one of the primary clinical risks that are associated with type 2 diabetes. While a clear graded association of CVD risk has been noted with hyperglycemia, the role of glucose control in CVD risk mitigation remains uncertain. This issue was addressed by Darren K. McGuire, MD, University of Texas Southwestern Medical Center, Dallas, TX. Referencing data from the UK Prospective Diabetes Study (UKPDS) Group, Dr. McGuire noted that intensive blood glucose control by either sulphonylureas or insulin substantially decreased the risk of microvascular complications, but not macrovascular disease, in patients with type 2 diabetes [UKPDS Group. *Lancet* 1998].

Another study from this same group investigated whether intensive glucose control with metformin attenuated the risk of heart attacks [UKPDS Group. *Lancet* 1998]. Compared with the conventional treatment group, patients who were allocated to metformin had risk reductions of 32% (95% CI, 13 to 47; p=0.002) for any diabetes-related endpoint (need to list components), 42% for diabetes-related death (p=0.017), and 36% for all-cause mortality (p=0.011). Among patients who were allocated to intensive blood glucose control, metformin showed a greater effect than chlorpropamide, glibenclamide, or insulin for any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021), and stroke (p=0.032) [UKPDS Group. *Lancet* 1998]. A meta-analysis of five trials confirmed these findings. Intensive glycemic control resulted in a 17% reduction in events of nonfatal myocardial infarction (OR, 0.83; 95% CI, 0.75 to 0.93) and a 15% reduction in coronary heart disease events (OR, 0.85; 95% CI, 0.77 to 0.93) but no significant effect on events of stroke or all-cause mortality [Ray KK et al. *Lancet* 2009].

Figure 1. UKPDS Metformin Substudy: CHD Events.



Highlights from the

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As the prevalence of diabetes approaches 10% of the population of the United States and the number of antihyperglycemic medications on the market increases, there are converging pressures for regulatory changes. In part, this has been driven by concerns that some of these therapies may be associated with increased cardiovascular risk. Guidance from the US FDA to the industry states that "sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

Atherosclerotic disease is prevalent in diabetic patients and accounts for significant morbidity and mortality. Danielle Duffy, MD, Thomas Jefferson University, Philadelphia, PA, discussed the appropriate lipids goals for diabetic patients and how to achieve them.

The Adult Treatment Panel III of the National Cholesterol Education Program issued an evidence-based set of guidelines on cholesterol management in 2001 that confirmed the benefit of cholesterol-lowering therapy in diabetic patients. The guidelines support a treatment goal of low-density lipoprotein cholesterol (LDL-C) <100 mg/dL in this population, as this population are felt to be at equivalent risk to patients with known cardiovascular disease.

Large-scale clinical trials and a meta-analysis [Sattar N et al. *Lancet* 2010] confirmed the benefits of statin use in diabetic patients to lower lipids. In one study, 40 mg simvastatin daily reduced the rate of first major vascular events by about 25% in a wide range of diabetic patients [Collins R et al. *Lancet* 2004]. Niacin treatment, added to statin monotherapy to further modify the lipid profile (raise HDL, further reduce triglycerides and LDL), caused a significant regression of carotid intima-media thickness in the ARBITER 6-HALTS trial [Taylor AJ et al. *N Engl J Med* 2009].

In summary, Dr. Duffy noted that a target LDL-C <70 mg/dL remains the primary lipid goal for patients with diabetes, with statins the first-line choice for lipid lowering.

A target-driven, long-term, intensified intervention that is aimed at multiple risk factors in patients with type 2 diabetes and microalbuminuria has been shown to reduce the risk of cardiovascular and microvascular events by about 50% [Gaede P et al. *N Engl J Med* 2003]. Donna M. Polk, MD, University of California, Los Angeles, CA, outlined such an intervention strategy, known as the ABCs of care for providers of diabetic patients.

Table 1. ABCs of Care for Providers of Diabetic Patients.

A	A1c target: glucose lowering to achieve normal to near-normal plasma glucose: HbA1c<7%; Aspirin Daily (75 to 162 mg)
B	Blood pressure control; BP ≤130/85 mm Hg or therapy for hypertension
C	Cholesterol management: first achieve LDL goal of <100 mg/dL; optional LDL goal <70 mg/dL; After achieving LDL goal, then target non-HDL if TG >200 mg/dL.Cigarette smoking cessation
D	Diabetes and prediabetes management; treat metabolic syndrome with lifestyle intervention and metformin.
E	Exercise: for weight loss and maintenance
F	Food choices: patients with prediabetes should receive individualized medical nutrition therapy; Weight loss recommended for all overweight or obese individuals; Fiber 14 g/1000 kcal intake; Saturated fat 7% with minimal trans-fat; Mediterranean style diet effective

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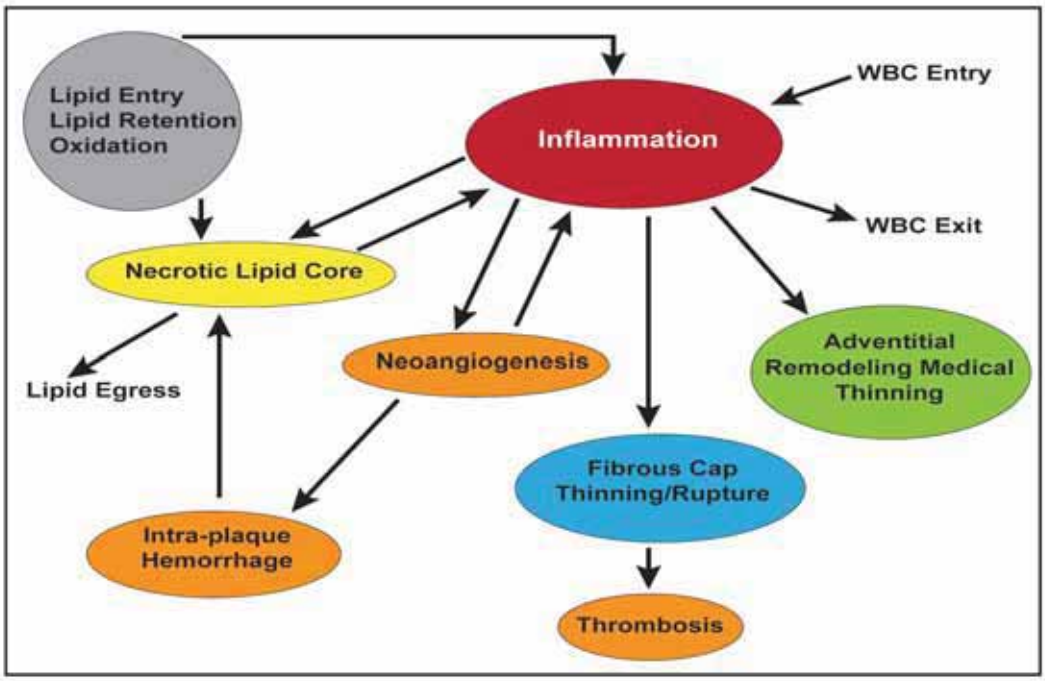
Atherosclerosis Update: Development, Prevention/Stabilization, and Risk

Written by Maria Vinall

Inflammation plays a critical role in all phases of atherosclerosis, and it is triggered in part by lipid entry and retention and subsequent oxidation in the vessel walls (Figure 1). However, while lipids are essential, they are not sufficient to stimulate atherosclerosis. Lipids induce inflammation, in part, by activating the innate immune signaling pathway, involving toll-like receptor (TLR) 4 and myeloid differentiation primary response gene 88 (MyD88) [Michelson KS et al. *Proc Nat Acad Sci* 2004].

Figure 1. Inflammation: A Key Determinant of Plaque Development and Progression/ Stability.



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Most of the factors that contribute to plaque instability (eg, increased necrotic lipid core, reduced collagen content, increased cap-inflammation, etc.) are related to lipid accumulation and subsequent inflammatory pathway activation. Changing the phenotype of the atherosclerotic lesions could increase plaque stability and reduce clinical events. Prediman K. Shah, MD, Cedars Sinai Heart Institute, Los Angeles, CA, suggested several interventions to alter the phenotype and thus reduce inflammation: low-density lipoprotein (LDL) lowering, increasing high-density lipoprotein (HDL)-based interventions, and anti-inflammatory and immunomodulatory interventions.

Carotid plaque in patients with symptomatic carotid artery stenosis who received 40 mg/day pravastatin (n=11) versus no lipid-lowering therapy (n=13) for 3 months before scheduled carotid endarterectomy displayed decreased lipids, lipid oxidation, inflammation, metalloproteinase activity, and cell death and increased tissue inhibitor of metalloproteinase 1 and collagen [Crisby M et al. *Circulation* 2001]. These data show that statins can change human plaque phenotype in a favorable way.

Having low HDL is also proinflammatory. Compared with normal individuals, individuals with familial hypoalphalipoproteinemia have increased levels of inflammation, as evidenced by higher hs-CRP levels, particularly if they also have coronary artery disease [Sampietro T et al. *Circulation* 2002]. Animal studies have shown that plaque lipid content can be dramatically reduced with injections of recombinant HDL (Apo A-I Milano) [Shah PK et al. *Circulation* 2001] or through gene transfer [Wang L et al. *J Am Col Cardiol* 2006]. In humans, infusion with human plasma-derived HDL has been shown to reduce plaque lipid and markers of plaque inflammation in plaques that have been removed from lower extremities and improve the cholesterol efflux-promoting capacity of serum [Shaw J et al. *Circ Res* 2008].

The feasibility of immunomodulating therapy for atherosclerosis has been shown in animal models. Immunization with homologous LDL [Ameli S and Shah PK et al. *Arterioscler Thromb Vasc Biol* 1996; Nilsson J and Shah PK et al. *J Am Col Cardiol* 1997] or Apo B-100-related peptide sequence [Chyu KY et al. *Biochem Biophys Res Commun* 2005] has been shown to reduce aortic atherosclerosis. Human studies of Apo B-100-related peptide vaccine are expected to begin in the summer of 2010, pending investigational new drug approval by the United States Food and Drug Administration. Other novel approaches under investigation include inhibition of Lp-PLA2 with darapladib or sPLA2 using varespladib. Both of these compounds are in early human trials.

Poor control of cardiovascular risk factors, especially hyperlipidemia, diabetes mellitus, smoking, and the metabolic profile, alter the Virchow triad (rheology, substrate, and blood), a primary driver of arterial thrombosis. Their effects include worsening vasoconstriction that causes high shear force and increased platelet deposition; increased tissue factor, which leads to thrombin generation; and increased blood coagulability. James H. Chesebro, MD, University of Massachusetts Medical Center, Worcester, MA, provided data from selected studies, showing that the effect of controlling for even a single risk factor can be significant for reducing arterial thrombus formation.

Reductions in low-density LDL-C levels dilate coronary arteries and microvessels and reduce endothelial dysfunction, platelet deposition, thrombin generation, arterial thrombus, and macrophage adhesion. Studies that used a Badimon perfusion chamber have shown that the use of statins to lower LDL-C is associated with a significant ($p<0.05$) reduction in arterial blood thrombogenicity and arterial thrombus formation. Lowering LDL-C from a median of 140 mg/dL to 105 mg/dL results in a 20% decrease in arterial thrombus formation [Rauch U et al. *Atherosclerosis* 2000]. These results are similar to those that were achieved by adding clopidogrel to aspirin (23% decrease in arterial thrombus formation; $p<0.05$) [Helft G et al. *Arterioscler Thromb Vasc Biol* 2000].

As shown in the ARMYDA-ACS [Patti G et al. *J Am Col Cardiol* 2007] and NAPLES II [Briguori et al *J Am Col Cardiol* 2009] trials, acute treatment with statins just prior to percutaneous coronary intervention (PCI) can reduce 30-day major adverse cardiac events. High-dose statin therapy is also associated with a reduction of coronary events, even in patients who are treated only medically (16% MIRACL; 25% A to Z, and 28% PROVE-IT). In the SAGE (Study Assessing Goals in the Elderly) study, which comprised older subjects (aged 65 to 85 years) with acute coronary syndromes, intensive statin therapy was associated with a significant reduction in all-cause death (HR, 0.33; 95% CI, 0.13 to 0.83; $p=0.014$) compared with moderate therapy, in addition to the reductions in ischemia that were observed with both therapies [Deedwania P et al. *Circulation* 2007].

Controlling diabetes is also an important factor in decreasing thrombotic events. The CD-40 ligand is a mediator and risk marker for inflammation and thrombosis that is increased in individuals with diabetes. The use of insulin-sensitizing thiazolidinediones for controlling diabetes results in a decrease in CD-40 plasma levels and a 29% decrease in thrombotic events [Varo N et al. *Circulation* 2003].

As shown by the results of the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study, intensive diabetes therapy has long-term beneficial effects on the risk of cardiovascular disease (CVD) in patients with type 1 diabetes. In this study, in which patients were followed for a mean of 17 years, intensive treatment reduced the risk of any CVD event by 42% (95% CI, 0.09 to 0.63; $p=0.02$) and the risk of nonfatal myocardial infarction (MI), stroke, or death from CVD by 57% (95% CI, 0.12 to 0.79; $p=0.02$). The decrease in glycosylated hemoglobin values during the DCCT was significantly associated with most of the positive effects of intensive treatment on the risk of CVD [Nathan DM et al. *N Engl J Med* 2005].

Many patients aged under 60 years who present with acute MI are smokers. Smoking is associated with vasoconstriction, increases in TF in the arterial wall, and increases arterial (platelet-rich) thrombus formation. Just stopping smoking can be very beneficial in reducing future cardiovascular events.

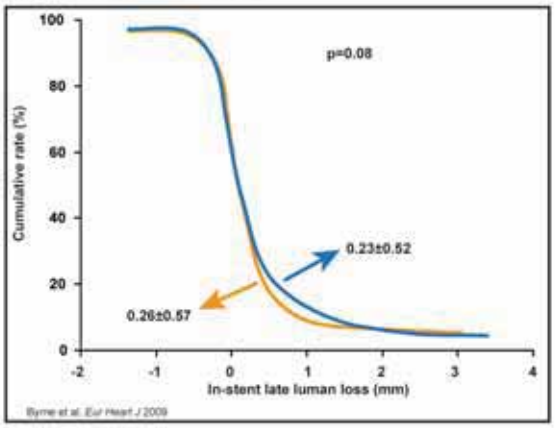
"Aggressive risk factor reduction reduces the thrombotic factors of the Virchow triad and clinical events," said Dr. Chesebro.

DES Update 2010

Written by Maria Vinall

David J. Moliterno, MD, University of Kentucky, Lexington, KY, provided an overview of some of the latest results from clinical trials of drug-eluting stents (DES). The latest data from the Sirolimus-Eluting Stent [SES] Compared With Paclitaxel-Eluting Stent [PES] for Coronary Revascularization-Late (SIRTAX-LATE) study, presented by Lorenz Räber at TCT 2009, showed a narrowing of event curves between PES and SES by 5 years, primarily driven by target lesion revascularizations (TLRs), which were lower for SES up to Year 1 (HR, 0.54; 95% CI, 0.34 to 0.84; p<0.01) but similar between SES and PES at Year 5 (HR, 0.80; 95% CI, 0.59 to 1.52; p=0.16). One-year data from the ISAR-TEST-4 trial show similar results in terms of the outcomes of death, myocardial infarction (MI), TLR, or stent thrombosis between the everolimus-eluting stent (EES) and the SES but a trend toward fewer target vessel revascularizations (TVRs) and a somewhat lower rate of binary restenosis with EES (Figure 1) [Byrne RA et al. *Eur Heart J* 2009]. Unlike the initial one-year results that showed no difference, recently published 2-year data from the SPIRIT-III trial show significantly (p=0.04) fewer ischemic events with EES versus PES (10.7% vs 15.4%; HR, 0.68; 95% CI, 0.48 to 0.98) [Stone GW et al. *Circulation* 2009]. Similar results, in terms of fewer ischemic events with EES (vs PES) were also shown in both the SPIRIT-IV [Stone GW. TCT 2009] and COMPARE [Kehdi E et al. *Lancet* 2010] studies. Finally, 3-year results, presented at TCT 2009 and updated at ACC 2010, for the ENDEAVOR-IV study showed similar early events between zotarolimus-eluting stents (ZES) and PES but fewer later events with ZES. In closing, Dr. Moliterno noted that in addition to increased safety and efficacy, reduced cost has been an important advance in stent technology. Further, the advances have allowed clinicians to take on increasingly difficult cases.

Figure 1. ISAR-TEST 4.



DES are a major advance in the area of interventional cardiology, and most of the time, they work well; however, on occasion they do fail. Debabrata Mukherjee, MD, University of Kentucky, Lexington, KY, discussed the mechanisms of DES failure.

DES failure manifests as restenosis or stent thrombosis. Predictors of DES restenosis include female gender, prior coronary bypass surgery, minimal lumen diameter, lesion length >30 to 40 mm, and vessel and target lesion size [Lee CW et al. *Am J Cardiol* 2006; Kastrati A et al *Circulation* 2006; Berenguer A et al. *Am Heart J* 2005]. Potential mechanisms of restenosis include nonuniform drug delivery (eg, stent underexpansion, incomplete apposition, strut fracture, polymer disruption) and drug resistance or drug failure [Cowley MJ. *J Interven Cardiol* 2006]. Repeat PCI with another DES is currently the accepted treatment for DES restenosis.

Stent thrombosis likely also results from a combination of factors, including procedure- and patient-related factors and lesion characteristics. Predictors of stent thrombosis include stent malapposition and/or underexpansion, the number of implanted stents, stent length, persistent coronary blood flow, dissections, and premature cessation of antiplatelet therapy. In addition, some drugs that are loaded onto the stent may exert prothrombotic effects

[Lüscher TF et al. *Circulation* 2007] and thus may increase the risk for stent thrombosis beyond that seen with BMS.

Preliminary data suggest that second-generation DES are safe and effective. Compared with BMS, they are associated with a similar long-term incidence of death and MI but provide a clinically important decrease in the rate of restenosis among high-risk patients.

The mechanisms of stent restenosis fall into three categories: biological (drug resistance, hypersensitivity), mechanical (stent fractures, polymer peeling, nonuniform stent strut distribution of drug deposition), and technical (incomplete stent expansion, gaps [uncovered lesion sections], and barotraumas to unstented segments). A tentative correlation has been established between these mechanisms and the site of DES restenosis [Costa MA et al. *Circulation* 2005] and between the pattern of restenosis and prognosis [Cosgrave J et al. *J Am Clin Cardiol* 2006]. Currently, results from only one randomized controlled trial in the treatment of DES restenosis have been presented [ISAR-DESIRE 2. Byrne R. TCT 2009]. Other trials that are currently enrolling include GISE-CROSS and CRISTAL.

"Understanding the mechanism of restenosis at time of treatment may impact the way you treat," said George D. Dangas, MD, Columbia University, New York, NY. The treatment of DES restenosis should be based on appreciation of underlying mechanisms and can vary from simple balloon angioplasty to DES, when appropriate, to CABG (coronary artery bypass graft) in the most extreme cases (Table 1).

Table 1. Current Therapeutic Options According to Potential Mechanisms of DES Restenosis.

Type of restenosis	Potential mechanisms	Treatment options
Focal in-stent	• Underexpansion • Fracture • Local vessel biology • Heterofeneous drug distribution	• BA • DES, BA • DES, BA, atherectomy • DES, BA, atherectomy
Focal at stent edge	• Geographic miss • Plaque progression	• DES • DES
Diffuse in-stent	• Vessel biology/Drug resistance	• Different DES, CABG
Proliferative	• Vessel biology/Drug resistance	• Different DES, CABG

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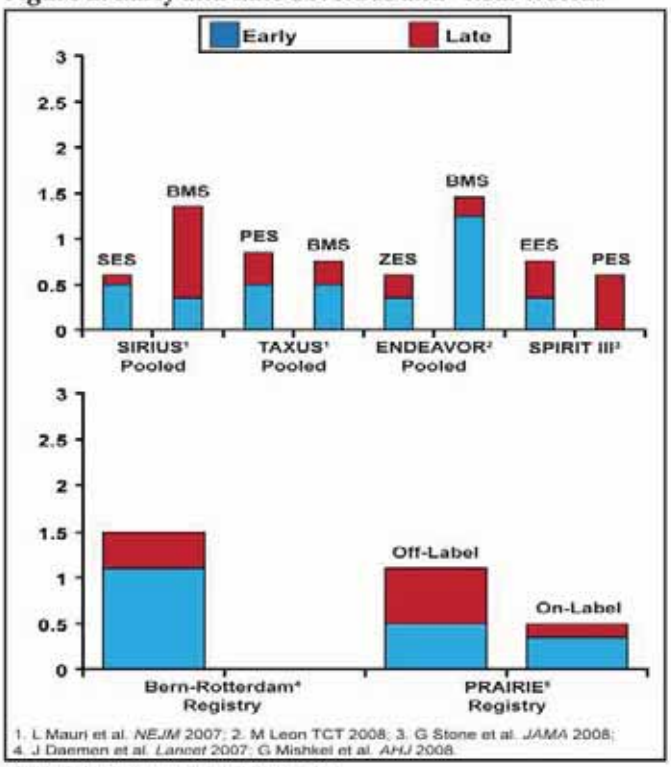
Donald E. Cutlip, MD, Harvard Medical School, Boston, MA, closed this session with a discussion of some of the issues concerning stent thrombosis.

Data from randomized clinical trials indicate that the event rate for early (postprocedure to 30 days) and late (31 days to 1 year) stent thrombosis for both BMS and DES is between 0.5% and 1%, with the highest number being early stent thrombosis (Figure 2). The rate in clinical practice, which includes more complex or "off-label" cases, is just slightly higher, at between 1% and 1.5%, but still with the highest density of events within the first 30 days (Figure 2). Very late (>1 year) stent thrombosis in DES is infrequent (0.2% to 0.6% per year), with the newer stents appearing to have a slightly lower rate. "It's interesting to note that very late stent thrombosis occurs with BMS at just about the same rate as DES," said Dr. Cutlip, "a fact that appears to have been missed in the early BMS clinical trials."

Figure 2. Early and Late ST: RCTs and "Real World."



1. L Mauri et al. *NEJM* 2007; 2. M Leon TCT 2008; 3. G Stone et al. *JAMA* 2008; 4. J Daemen et al. *Lancet* 2007; 5. Mishkel et al. *AHJ* 2008.

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Stent thrombosis is predicted mostly by lesion and technical factors for up to about 1 year, with delayed healing the major factor thereafter. The risk factors are the same for both BMS and DES in the early and late periods, and although the risk factors for very late stent thrombosis are more biological, lesion factors still account for some instances. Several trials have indicated that there are differences in the occurrence of very late stent thrombosis among DES [Stone G; Smits P; Leon M. TCT 2009].

Patients who fail to have adequate response to clopidogrel after the loading dose have a 3-fold higher risk of stent thrombosis [Buonamici P et al. *J Am Col Cardiol* 2007], possibly due to the effect of the polymorphisms of the cytochrome P450 C219 allele on platelet activity [Mega JL et al. *N Engl J Med* 2009]. Although the optimal duration for dual antiplatelet therapy remains uncertain, discontinuation of dual antiplatelet therapy, particularly within the first 30 days and at least out to 6 months is a highly significant risk factor for thrombosis, with odds ratios approaching 50.

Clinical Applications of Three-Dimensional Echocardiography

Nathalie De Michelis, University of California, Irvine, CA, considers real-time 3D echocardiography (RT3DE) a safe, noninvasive imaging modality that is superior to 2D imaging. It can be used to assess left ventricular (LV) volume, mitral valve area, and cardiovascular function in patients with mitral stenosis, a use that is supported by the American Society of Echocardiography [Hung J et al. *J Am Soc Echocardiogr* 2007]. With improvements in automated contouring and its use of a correction factor of 1 mm, it is now possible to use RT3DE in individuals with reduced ejection fraction, atrial fibrillation, and abnormal cardiac rhythms to obtain accurate LV volumes.

"With the recent availability of right ventricular (RV) quantitation software that is practical and validated, RT3DE offers potential advantages over MRI in assessing the right heart, as it allows rapid acquisition of data with the ability to slice a 3D dataset from any angle," stated Judy Hung, MD, Harvard Medical School, Boston, MA. By assessing RV function, it is possible to obtain new information regarding the prognosis of cardiomyopathy, confirm RV volume overload, provide additional risk stratification in patients with shock postmyocardial infarction, and evaluate ventricular structure and function in congenital heart disease. This imaging modality may become a time- and cost-saving alternative to MRI for the quantitative assessment of RV size and function [Leibundgut G et al. *J Am Soc Echocardiogy* 2010].

3D imaging also may be useful for evaluating tumors of the heart and great vessels and selecting optimal surgical approaches prior to the removal of intracardiac masses, concluded Juan Carlos Plana, MD, FACC, University of Texas, MD Anderson Cancer Center, Houston, TX.

The size of an intracardiac mass (vegetation, tumor, or thrombus) is an important predictor of embolic events and response to treatment. 2D echocardiography (transthoracic) underestimates the size of cardiac masses by as much as 24.6% ($p<0.001$) compared with RT3DE, suggesting that RT3DE may be a better choice for the noninvasive evaluation of intracardiac mass size [Asch FM et al. *Echocardiography* 2006]. In addition, 3D imaging offers the advances of unlimited slicing and cropping, spatial manipulation and optimal visualization, and a single, easy acquisition approach that provides multiple points of information. Though evidence suggests that RT3DE offers the ability to improve and expand the diagnostic capabilities of cardiac ultrasonography, as with any new emerging technology, Dr. Plana cautions, "The enthusiasm to embrace a new technology must be tempered by a critical appraisal of the evidence supporting its use."

Leopoldo Perez de Isla, MD, Hospital clinic San Carlos, Madrid, Spain, discussed the use of RT3DE before, during, and after mitral valve stenosis intervention. RT3DE is a novel technique that allows the visualization of mitral valvular anatomy in any desired plane orientation. Compared with all other echo-Doppler methods, RT3DE has the best agreement with the invasively determined mitral value area [Zamorano J et al. *J Am Coll Cardiol* 2004] and can provide not only the anatomical structure of mitral valve apparatus but also the optimal plane of the smallest mitral valve orifice in patients with mitral stenosis [Xie M-X et al. *Am J Cardiol* 2005] and those who are undergoing percutaneous mitral valvuloplasty [Anwar AM et al. *J Am Soc Echocardiogr* 2010].

When used during intervention to determine annular dimension and, thus, guide correct device sizing, RT3DE may help optimize the outcome of percutaneous aortic valve implantation. In one study, RT3DE was able to successfully guide device implantation in 97% of patients (33 of 34) in whom the native valve was crossed with the percutaneous heart valve. Thus, 3D echocardiography may play an important role in determining case selection, in guiding device placement, and in detecting complications of percutaneous aortic valve implantation [Moss RR et al. *JACC Cardiovasc Imaging* 2008].

With more asymptomatic patients with MR being considered for surgery, accurate definition of the functional anatomy of the mitral valve is of paramount importance to aid clinical decision-making. Sunil V. Mankad, MD, Mayo Clinic, Rochester, MN, discussed the role of RT3D echocardiography for viewing the mitral valve in relation to MR repair. RT3D transesophageal echocardiography allows visualization of the mitral valve leaflets, orifice, and submitral apparatus in a manner that is not possible using conventional 2D echo. Mitral valve replacement or repair may be complicated by postoperative dehiscence of the valve or annuloplasty rings that result in clinically significant MR or hemolysis. In mitral valve dehiscence, RT3D transesophageal echocardiography provides additional information about the exact anatomical characteristics of the dehiscence that are not obtainable using conventional 2D echo, which may be helpful in planning the most appropriate corrective intervention [Kronzon I et al. *J Am Coll Cardiol* 2009]. Besides aiding in the surgical repair of MR, it also shows great promise in percutaneous periprosthetic leak closure.

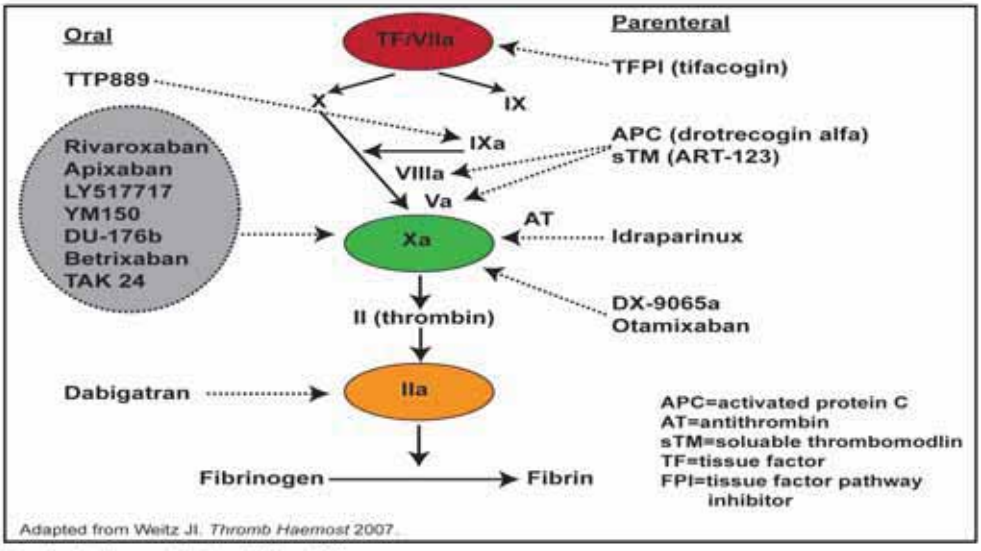
Novel Oral Anticoagulants

Jonathan L. Halperin, MD, Mount Sinai School of Medicine, New York, NY, discussed some of the novel targets for anticoagulants, the two most immediate of which are Factor Xa and Factor IIa (thrombin).

There are several potential targets for novel anticoagulants. "Factor IIa (thrombin) was the first target addressed, because it is the last step in the cascade before the formation of fibrin," said Dr. Halperin (Figure 1). It also has the advantage of potentially interfering with platelet-thrombin interactions, since thrombin is a potent activator of platelets. These platelet-thrombin interactions may be important not only in acute coronary syndromes (ACS) but also in the mechanism of stroke in atrial fibrillation (AF). Hepatoxicity led to the demise of the first oral thrombin inhibitor (ximelagatran) that was developed; however, an excess in hepatotoxicity was not observed in the clinical trial development with the second agent in this class, dabigatran.

Factor Xa, which acts more proximally in the coagulation cascade than Factor IIa, is also a logical target because of its amplification effect and the potential for a reversible action, which is not available at the level of thrombin. The major safety question for the development of the Factor Xa inhibitors is the potential for bleeding. While there is tremendous promise for excellent efficacy with a very low risk of bleeding with the Factor IX and XI inhibitors, they remain in very early development. Tissue factor (TF/VIIa) is also a very appealing target that is particularly attractive to those who deal with patients in the acute surgical setting, but no trials are currently ongoing in patients with AF or ACS.

Figure 1. Investigational Anticoagulant Targets.



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Robert P. Giugliano, MD, SM, Brigham & Women's Hospital, Boston, MA, presented an overview of the characteristics of five new anticoagulant agents and current studies that involve these agents (Table 1) and commented on how each might fit the definition of the "ideal anticoagulant" (Table 2).

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Table 1. Trial and Publication Status.

Ongoing Trials	Important Publications
Dabigatran Trial Status: Completed 11 Phase 2 or 3 trials. Results have been reported for VTE prevention and treatment and for AF; ACS trial is recruiting.	
NCT00329238 Phase 3 VTE secondary prevention NCT00558259 Phase 3 VTE long-term prevention NCT00808067 Phase 3 AF (RELY-ABLE) NCT00818753 Phase 2 elective PCI NCT00844415 Phase 2 VTE adolescents NCT00846807 * VTE post TKR or THR NCT00847301 * TKR/THR mod. renal impairment NCT01083732 Phase 2 VTE children	RE-NOVATE [Eriksson BL et al. *Lancet* 2007] RE-MODEL [Eriksson BL et al. *J Thromb Haemost* 2007] RE-MOBILIZE [*J Arthroplasty* 2009] RE-COVER [Schulman S et al. *N Engl J Med* 2009] RE-LY [Connolly SJ et al. *N Engl J Med* 2009] RE-DEEM [Oldgren J. AHA 2009]
Rivaroxaban Trial Status: Completed 20 Phase 2 or 3 trials. Results have been reported for VTE prevention and treatment; AF study enrollment is complete. ACS trial is recruiting.	
NCT00403767 Phase 3 AF (ROCKET-AF) NCT00439777 Phase 3 PE NCT00440193 Phase 3 DVT NCT00571649 Phase 3 medically ill patients NCT00786422 Phase 2 DVT CYP3A4 NCT00809965 Phase 3 ACS	RECORD [Eriksson BL et al. *N Engl J Med* 2008; Kakkar AK et al. *Lancet* 2008; Lassen MR et al. *N Engl J Med* 2008; Turpie AG et al. *Lancet* 2009]
Apixaban Trial Status: Completed 9 Phase 2 or 3 trials. Results have been reported for VTE prevention. VTE treatment and ACS treatment studies are recruiting. AF study has completed enrollment.	
NCT00412984 Phase 3 Stroke in AF (ARISTOTLE) NCT00457002 Phase 3 Acutely ill patients NCT00496769 Phase 3 AF NCT00633893 Phase 3 Long-term VTE/PE NCT00643201 Phase 3 DVT/PE NCT00831441 Phase 3 ACS NCT00852397 Phase 2 ACS	ADVANCE-1 [Lassen MR et al. *N Engl J Med* 2009] APPRAISE [*Circulation* 2009] ADVANCE-2 [Lassen MR et al. *Lancet* 2010]
Edoxaban (DU-176b) Trial Status: Completed 5 Phase 2 or 3 trials. Phase 2 VTE prevention study has completed enrollment; Phase 3 VTE treatment and AF studies are recruiting. No ACS studies announced.	
NCT00781391 Phase 3 AF (ENGAGE AF-TIMI 48) NCT00986154 Phase 3 VTE	Fuji T et al. *Blood* 2008;112 ASH Abstract 34 Raskob Get al. *Eur Heart J* 2008 (ESC Suppl p 609) Weitz JL et al. *Blood* 2008; 112 ASH Abstract 33
Betrixiban Trial Status: Completed 2 Phase 2 trials. VTE Prevention study completed (not yet reported); VTE treatment study is planned. Phase 2 study in AF reported results March 2010 at ACC. A secondary preventions study is planned in ACS.	
NCT00999336 Phase 2 PK/PD degrees of renal impairment	EXPERT [Turpie AG et al. *Thromb Haemost* 2009] EXPLORE-Xa [Ezekowitz M. ACC 2010]

ACS = acute coronary syndrome; AF=atrial fibrillation; DVT = deep vein thrombosis; PCI = percutaneous coronary intervention; PE = pulmonary embolism; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism; * Observational study

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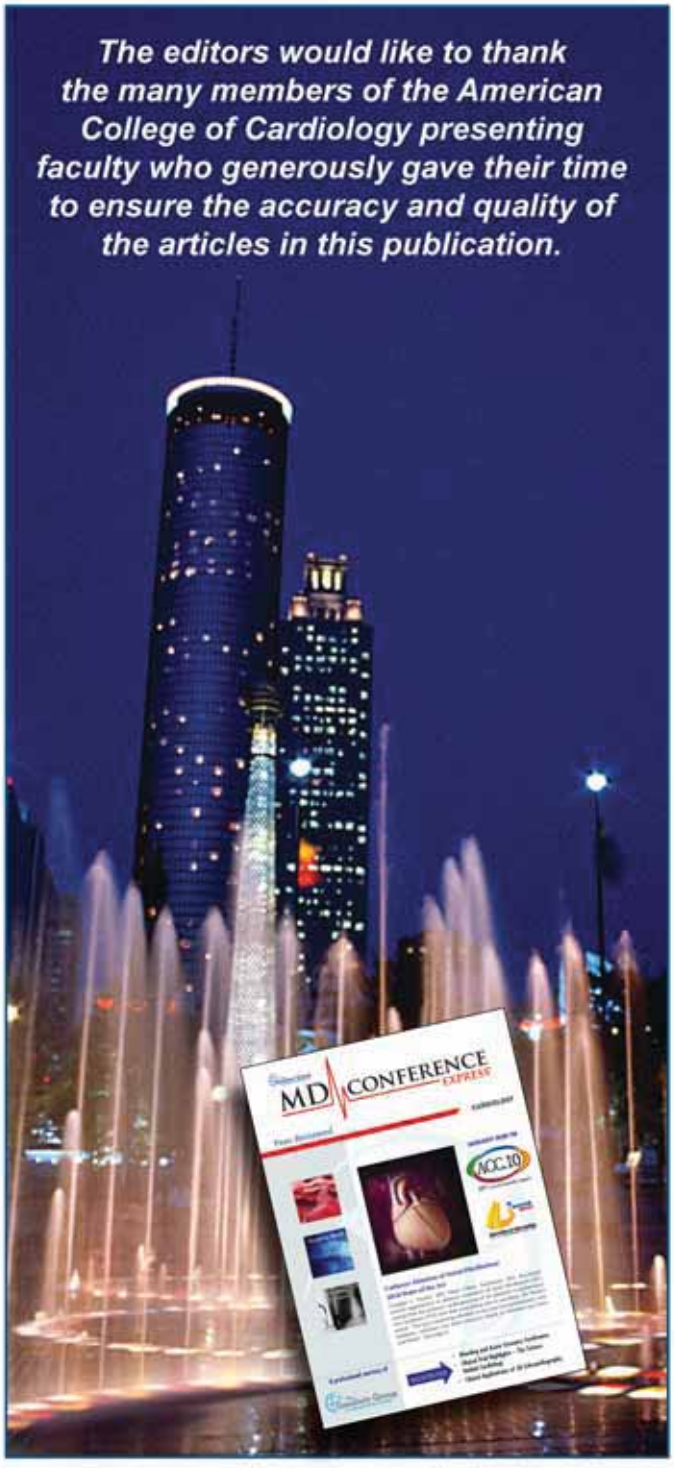
Table 2. PK/PD Properties of an Ideal Long-Term Oral Anticoagulant.

Property	Benefit	Agents in Development
Oral, once daily	Ease of administration	rivaroxaban, edoxaban, betrixaban
Rapid onset of action	No need for overlapping parenteral anticoagulant	All Factor IIa and Xa inhibitors
No food/drug interactions	Simplified dosing	All
Predictable anticoagulant effect	No routine coagulation monitoring	All Factor IIa and Xa inhibitors
Extrarenal clearance	Safe in patients with renal insufficiency	Betrixaban, apixaban, edoxaban (in order of most to least)
Rapid offset of action	Simplifies management in case of bleeding or intervention	All (betrixaban has the longest half-life at 19-20 hours)
Safe antidote	…in case of major bleeding	Potentially all Factor Xa inhibitors

"Compared with warfarin," said Dr. Giugliano, "the new anticoagulant therapies have more stable PK/PD profiles, no diet interaction, and fewer drug-drug interactions. They do not require monitoring of their anticoagulant effect and, so far, do not appear to be associated with off-target adverse events." Dabigatran is the only thrombin inhibitor among the new group. The time to action is short (1 to 4 hours) for those agents for which this information has been reported (all but betrixaban). The only agent that appears to have substantial interaction with the CYP 450 system is rivaroxaban. Bioavailability is good for all of the agents, with the exception of dabigatran, where it is rather low (7%). Protein binding is variable across the group, with rivaroxaban having the highest (>90%). This could be a disadvantage in patients with different levels of plasma proteins, a high state of acute phase reactance, or malnutrition. It could also mean that rivaroxaban is less likely to be successfully removed by dialysis. The half-life of the drugs varies 2-fold or more. Edoxaban has the shortest half-life (8 to 10 hours). Betrixaban has the longest (19 to 20 hours); thus, it would be suitable for once-daily dosing. Renal elimination varies markedly—80% for dabigatran and <5% for betrixaban—which means that there could be roles for more than one agent in this class in clinical practice to accommodate patients with varying renal and hepatic function.

Many excellent alternatives to vitamin K antagonists are on the horizon, and there are meaningful differences in the PK/PD properties of these agents. Trial results so far indicate that dose selection is a critical area for this class of drugs to identify the optimal balance of thrombotic protection and bleeding risk. It also appears advantageous to bring multiple doses forward from Phase II into Phase III testing (rather than the typical single dose that is selected for Phase III) to more thoroughly evaluate these novel agents.



CPD Questionnaire for:

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Indicate whether the following statements are true or false:

1. Current guidelines recommend that all patients who undergo ablation for atrial fibrillation should receive oral anticoagulation therapy with warfarin for at least 2 months after the procedure, unless the CHADS score is □2, in which case the warfarin should not be discontinued.

   T F

2. The CRUSADE score takes into consideration a history of previous bleeding and bleeding diathesis and allows a clinician to calculate the risk of bleeding in patients with non-ST elevation myocardial infarction.

   T F

3. Female gender is associated with an increased risk of bleeding in patients with non-ST elevation myocardial infarction.

   T F

4. Compared to the femoral approach to percutaneous interventions, the radial approach is associated with a similar rate of procedural success, but is associated with a lower rate of bleeding complications, especially in patients undergoing a procedure for acute coronary syndromes.

   T F

5. In the ACCORD Lipid study, there was a higher rate of major CV events in women treated with fenofibrate plus simvastatin than in women treated with placebo.

   T F

6. In patients with type 2 diabetes, intensive therapy to reduce blood pressure was not associated with any increase in adverse events compared with standard therapy.

   T F

7. In patients with impaired glucose tolerance, treatment with nateglinide reduces the risk of developing diabetes.

   T F

8. In patients with impaired glucose tolerance, treatment with valsartan in combination with lifestyle modification reduced the incidence of diabetes in patients with cardiovascular disease (CVD) or risk factors for CVD.

   T F

9. Patients with mitral regurgitation who underwent surgical repair or replacement of their mitral valve were almost 6 times more likely to experience a major adverse event compared with those who underwent a procedure with the MitraClip.

   T F

10. The dose of betrixaban does not need to be reduced in patients with renal insufficiency and it has a low potential for drug interactions, because it is excreted unchanged through the bile and it does not interact with the cytochrome P450 enzymes.

    T F

11. Compared to using aspirin alone, a combination of clopidogrel with low dose aspirin in patients who have had a drug-eluting-stent inserted was associated with a higher risk of myocardial infarction, stroke or death from cardiac causes.

    T F

12. In patients with ST-elevation myocardial infarction, compared to direct stenting alone, rheolytic thrombectomy plus stenting is associated with higher rates of early ST segment resolution and improved clinical outcomes at 6 months.

    T F

13. At 3 years follow-up in the DEDICATION study, the rates of cardiac death and all-cause death were higher in patients receiving a bare metal stent than those receiving a drug-eluting stent.

    T F

14. In patients with acute ST-elevation MI, paclitaxel-eluting stents were associated with a higher incidence of late stent thrombosis than bare metal stents.

    T F

15. In patients with acute coronary syndromes who underwent a coronary artery bypass graft, treatment with ticagrelow was associated with a significantly lower risk of myocardial infarction.

    T F

16. In patients with stable coronary artery disease who are undergoing coronary artery bypass grafting with a left internal mammary artery, and who are in need of at least one other graft, a radial artery graft is not superior to a saphenous vein graft in terms of patency after 1 year.

    T F

17. In patients with heart failure, being obese may be associated with a lower all-cause mortality than being normal weight.

    T F

18. In the DCCT study, intensive glucose control in patients with diabetes reduced the risk of any cardiovascular disease event by 57%.

    T F

19. Predictors of drug-eluting stent restenosis include lesion length <30 mm.

    T F

20. Betrixaban does not require routine coagulation monitoring.

    T F

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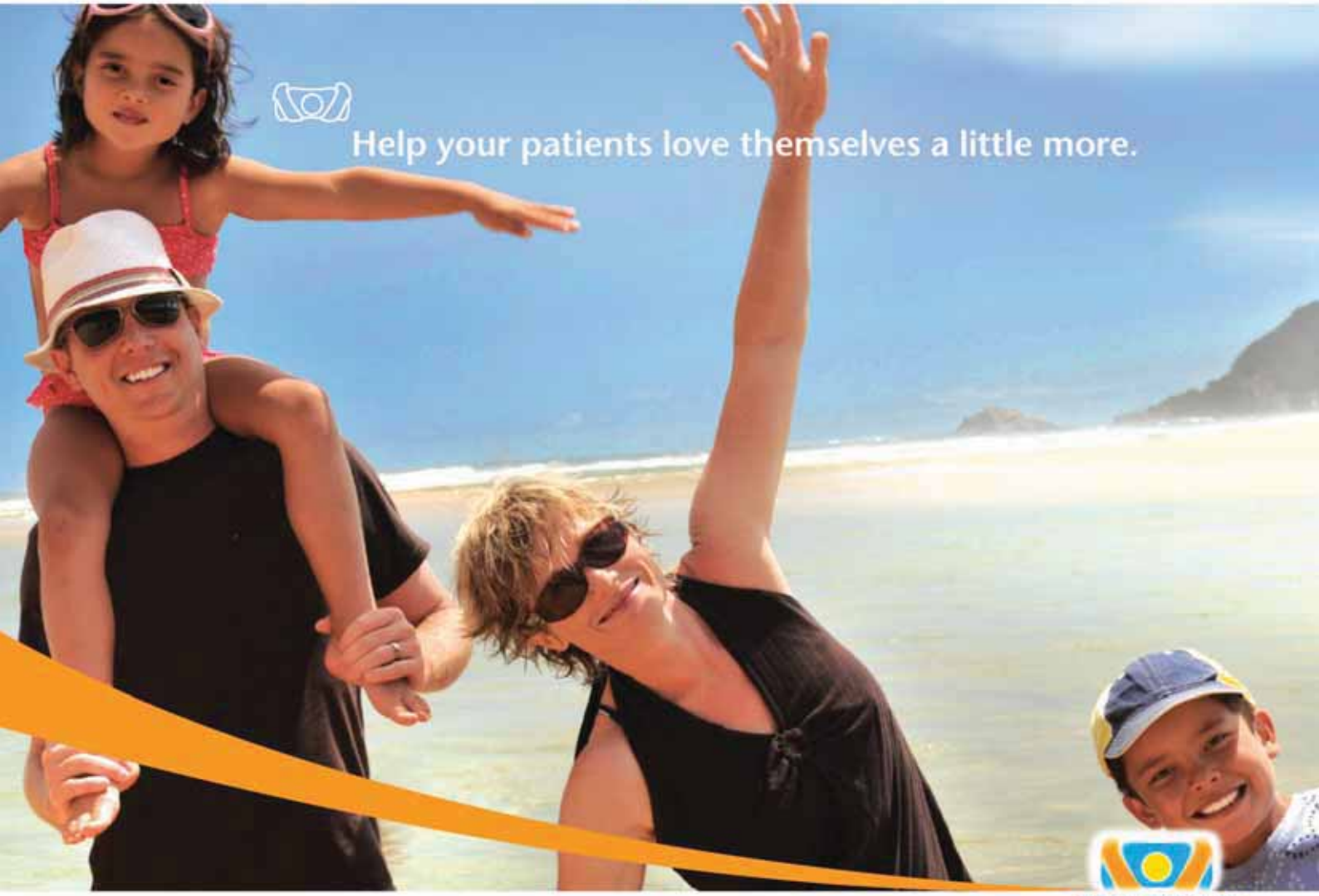

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CRESTOR® 10 mg will get most patients to LDL-C goal[1,3]

CRESTOR® is well-tolerated and has a favourable benefit-risk profile[4,5]

S4 **CRESTOR® 5 (Tablet)** Each CRESTOR® 5 tablet contains 5 mg of rosuvastatin as rosuvastatin calcium. S4 **CRESTOR® 10 (Tablet)** Each CRESTOR® 10 tablet contains 10 mg of rosuvastatin as rosuvastatin calcium. S4 **CRESTOR® 20 (Tablet)** Each CRESTOR® 20 tablet contains 20 mg of rosuvastatin as rosuvastatin calcium. S4 **CRESTOR® 40 (Tablet)** Each CRESTOR® 40 tablet contains 40 mg of rosuvastatin as rosuvastatin calcium. **PHARMACOLOGICAL CLASSIFICATION:** A. 7.5 Serum-cholesterol reducers **INDICATIONS:** Primary hypercholesterolaemia, mixed dyslipidaemia and isolated hypertriglyceridaemia (including Fredrickson Type IIa, IIb and IV; and heterozygous familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate. Indicated in patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments. CRESTOR® 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of CRESTOR® or alternative therapy. Specialist supervision is recommended when the 40 mg dose is initiated. **REGISTRATION NUMBERS:** CRESTOR® 5: 41/7.5/0298, CRESTOR® 10: 36/7.5/0349, CRESTOR® 20: 36/7.5/0350, CRESTOR® 40: 36/7.5/0351. **DETAILS OF THE REGISTERED LICENCE HOLDER:** AstraZeneca Pharmaceuticals (Pty) Ltd Reg No. 1992/005854/07. No. 5 Leeuwkop Road, Sunninghill, 2157, South Africa. Tel: 011 797 6000. Fax: 011 797 6001. www.astrazeneca.co.za. For full details relating to any information mentioned above please refer to the package insert of CRESTOR® 5 mg, 10 mg, 20 mg and 40 mg. CRESTOR® is a registered trademark of AstraZeneca group. Licensed from Shionogi & Co Ltd, Osaka, Japan. EPI Date: 13/05/2008. Date compiled: March 2010.

References: 1. CRESTOR® package insert **2.** Jones P, Davidson MH, Stein EA, *et al.* Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR* Trial). *Am J Cardiol* 2003;**92**:152-160. **3.** Schuster H, Barter PJ, Stender S, *et al.* Effects of switching statins on achievement of lipid goals. Measuring Effective Reduction in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *Am Heart J* 2004;**147**:705-712. **4.** Rosenson RS. Statins: can the new generationn make an impresssion? *Expert Opin Emerg Drugs* 2004;**9**(2):269-279. **5.** Shepherd J, Hunninghake DB, Stein EA, *et al.* Safety of rosuvaststin. *Am J Cardiol* 2004;**94**:882-888.

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