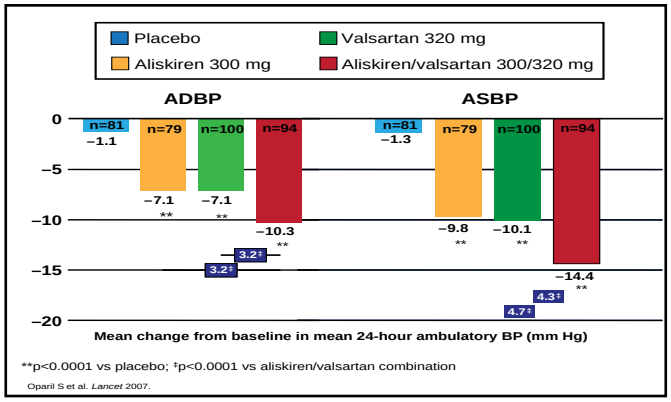
inhibition in patients with hypertension, diabetes, and other CV risk factors. These studies may show whether combining a renin inhibitor with other RAAS blockers provides additional incremental benefits in blood pressure control and CV risk reduction.

Figure 1. Combination Therapy with Aliskiren and Valsartan Improves Blood Pressure Control Compared with Either Component as Monotherapy.



Reprinted from *The Lancet*, Vol. 370, Issue 9538, Oparil S et al, Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial, Pages 221-229, Copyright 2007, with permission from Elsevier.

A New Focus on Genetics and Individualized Management Approaches for CAD

There are many factors that increase the risk of developing coronary artery disease (CAD), including hypertension, dyslipidemia, inflammation, health behaviors, and genetics. Robert Chilton, DO, FACC, Professor of Medicine, University of Texas Health Science Center, San Antonio, Texas, USA, highlighted recent evidence concerning CAD treatment and described the clinical shift in therapeutic concentration from vulnerable plaque to genomics and metabolomics to improve drug risk benefit.

Recent studies have revealed an association between certain genetic phenotypes and CAD risk. In a meta-analysis by Schunkert and colleagues, genetic variants at chromosome 9p21.3 were associated with a 30% increase in CAD per copy of the 9p21.3 risk allele for heterozygote mutation [Schunkert H et al. *Circulation* 2008]. This study supported previous findings that mutations within this genetic locus conveyed a higher risk of CAD [Nilesh J et al. *N Engl J Med* 2007]. Additionally, a Trp719Arg polymorphism within the KIF6 gene, which encodes for a kinesin, also predicts development of CAD [Iakoubova OA et al. *J Am Coll Cardiol* 2008]. These results begin to elucidate the role of genetics in the risk of developing CAD and may prove to be useful predictive markers in the future.

In a population-based study, reductions in short-term fatality rates from myocardial infarction (MI) between 1999 and 2008 were associated, in part, with the use of effective therapeutics, such as statins, renin angiotensin aldosterone system (RAAS) blockers, and β-blockers [Yeh RW et al. *N Engl J Med* 2010]. However, genes also play a role in treatment response, and more individualized strategies may be warranted, based on varying gene polymorphisms and therapeutic interactions. In the PROVE IT-TIMI 22 trial, carriers of 719Arg demonstrated significantly greater benefit from intensive statin therapy compared with noncarriers (41% relative risk reduction [RRR] in death/MI; p=0.018) [Iakoubova OA et al. *J Am Coll Cardiol* 2008]. Similar evaluations that were performed in the CARE and WOSCOPS trials also showed that pravastatin therapy effectively reduced the risk of coronary events in KIF6 719Arg carriers, with a 54% RRR in coronary heart disease and a 41% RRR in acute MI [Iakoubova OA et al. *J Am Coll Cardiol* 2008]. Alternatively, variants that were identified within SLCO1B1 (rs4363657) were strongly associated with an increased risk of statin-induced myopathy [SEARCH Collaborative Group. *N Engl J Med* 2008]. Thus, the need to consider genetics when determining an appropriate treatment strategy has become more apparent.

There has been increasing evidence of interactions between gene polymorphisms and therapies that are associated with variability in coronary risk. Pharmacogenomics and variable therapeutic responses have altered views on treatment approaches and may lead to more emphasis on genetic predictors of risk and therapeutic response moving forward. While previous strategies have focused on factors, such as inflammation, lipids, glucose, and other risk measurements, future approaches may incorporate additional factors, such as individual risk profile, genomics, and biomarkers.

Stroke Prevention in Atrial Fibrillation: Novel Agents Versus the Gold Standard

Stroke prevention is a priority for clinicians who treat patients with atrial fibrillation (AF). Warfarin has been the gold standard therapy for patients with AF who are at moderate or high risk of stroke. However, there are concerns about the limitations of warfarin, such as adherence issues, bleeding risk, narrow therapeutic window, vigilant monitoring requirements, and drug-drug/food-drug interactions that make it difficult to

manage in a clinical setting. Novel strategies for stroke prevention may replace the widespread use of warfarin in the future. One new therapy was shown to be superior to warfarin in a large clinical trial, while three others are in late-stage testing. Stephen La Haye, MD, Kingston General Hospital, Kingston, Ontario, Canada, discussed various approaches to stroke prevention in AF and their relevance to clinical practice.

In high-risk patients with AF, most strokes occur either after warfarin discontinuation in the absence of warfarin or in the presence of suboptimal international normalized ratio (INR) levels, suggesting that anticoagulation therapy should be continued in this cohort [The AFFIRM Investigators. *N Engl J Med* 2002; Gladstone DJ et al. *Stroke* 2009]. While this therapy may be indicated from an efficacy standpoint, the issue of nonadherence and other limitations must be considered, and alternative approaches are warranted. In the ACTIVE studies, investigators assessed the safety and efficacy of other agents (ie, clopidogrel plus aspirin combination therapy and irbesartan) on stroke prevention in patients with AF. In the ACTIVE-W study, comparing clopidogrel + aspirin with warfarin, oral anticoagulation therapy was found to be superior to clopidogrel + aspirin for the prevention of vascular events in high-risk patients with AF (p=0.0003) [The ACTIVE Investigators. *Lancet* 2006]. The ACTIVE-A study, which included patients with contraindications to warfarin or who were unwilling to take warfarin, compared clopidogrel + aspirin combination therapy with aspirin alone. Those who received combination therapy had a significantly lower rate of stroke compared with aspirin alone (RR, 0.72; 95% CI, 0.62 to 0.83; p<0.001). However, the risk of major hemorrhage was significantly higher among those who were taking clopidogrel (RR, 1.57; 95% CI, 1.29 to 1.92; p<0.001) [The ACTIVE Investigators. *N Engl J Med* 2009].

Dr. La Haye put these data into perspective by explaining the risk versus benefit of clopidogrel combination therapy compared with warfarin. Over the course of 3 years, 28 strokes would be prevented for every 1000 patients on clopidogrel + aspirin therapy, but 20 major nonstroke bleeds (3 fatal) would also occur (Table 1).

Dabigatran, a reversible oral direct thrombin inhibitor, shows promise for stroke prevention in AF. Dabigatran has a rapid onset of action and predictable and consistent anticoagulant effects without the drug-drug/drug-food interactions or cumbersome monitoring requirements that are found with warfarin. In the RE-LY study, comparing dabigatran twice daily 110 mg (D110) and dabigatran 150 mg (D150) with warfarin, D110 was associated with lower rates of major hemorrhage but similar rates of stroke and systemic embolism compared with warfarin. Meanwhile, D150 had *similar* rates of major hemorrhage but *lower* rates of stroke (including both ischemic and hemorrhagic) and systemic embolism versus warfarin [Connolly SJ et al. *N Engl J Med* 2009]. As the balance between stroke and bleeding prevention continues to be evaluated, the favorable results with this new agent represent the first major advance in decades (Figure 1). Of note, dabigatran is currently available in selected countries in the 110-mg formulation only. The relatively short half-life of 12 to 17 hours is an important consideration in patients for whom compliance with a twice-daily regimen is a major issue.

Table 1. Risk Versus Benefit of ASA + Clopidogrel Versus Warfarin: The ACTIVE Study.

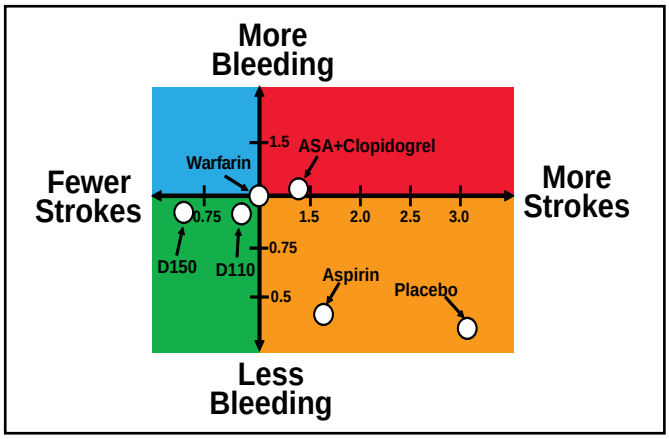
	Meta-analysis OAC vs ASA	ACTIVE A Clopidogrel + ASA vs ASA
Benefit		
Relative reduction in stroke	38%	28%
Risk		
Relative increase in major extracranial bleeding	70%	51%
Relative increase in intracranial bleeding	128%	87%

If 1000 patients were treated with clopidogrel plus ASA over the course of 3 years, this would prevent 28 strokes, 17 of which would be fatal or disabling as well as 6 MIs

This would occur at a cost of 20 major (non-stroke) bleeds, including 3 fatal bleeds

Ann Intern Med 2007; *N Engl J Med* 2009.

Figure 1. Antithrombotic Therapy in Perspective.



Reproduced with permission from S. La Haye, MD.

Dronedarone, a novel multichannel-blocking antiarrhythmic drug, may also be an option for stroke prevention in AF. Dronedarone has been found to reduce the incidence of hospitalization due to cardiovascular events or death in patients with AF (p<0.001) [Hohnloser SH et al. *N Engl J Med* 2009]. A post hoc analysis of this therapy demonstrated that dronedarone reduced the risk of stroke in this cohort,

and this benefit was stronger among those with higher baseline $CHADS_2$ scores [Connolly SJ et al. *Circulation* 2009]. Further evaluation of this strategy is merited to establish the effect of dronedarone on stroke prevention.

Though warfarin may be efficacious for stroke prevention in AF, it does have some shortcomings, including adherence issues, high bleeding rates, and management challenges. Novel therapies, such as combination anticoagulant regimens and newer oral anticoagulants, may provide a safe and effective alternative to warfarin treatment. Antiarrhythmic medications may also offer practical solutions to stroke risk reduction and AF management. However, it is important to balance the options carefully to ensure that the therapeutic benefit outweighs the cost.

CV Health in the Caribbean

Risk factors that contribute to the development of cardiovascular disease (CVD) include smoking, hypertension, dyslipidemia, obesity, and impaired glucose tolerance. Many of these risks can be reduced with lifestyle modification (eg, improved diet and exercise); yet, the burden of disease remains high, particularly in the developing world. In an effort to address the global health challenge of CVD, the US National Institute of Medicine (IoM) released a report, illustrating the global evolution of this epidemic and offering recommendations to manage this growing problem.

C. James Hospedales, MD, MPH, Pan American/World Health Organization, discussed these preventive measures and policy approaches, suggested by the IoM, as well as potential barriers. Limited knowledge concerning the feasibility and effectiveness of CVD prevention policies and programs represents a challenge in this area. The lack of financial resources and infrastructure in low and middle income countries poses other obstacles that must be addressed. Competing health and development priorities also hinder regional and global support for these initiatives. Therefore, the IoM recommends building the knowledge base, creating local solutions that can benefit from global support, organizing resources, and forming collaborations to meet resource needs to overcome these challenges. The ultimate goal of the IoM report is to implement successful CVD programs and policies that will lead to a 2% annual reduction in death rates that are related to major chronic diseases.

Dr. Hospedales challenged the Caribbean Cardiac Society to help with this initiative as a leadership organization to advocate for cost-effective national and local policies that promote health (ie, tobacco taxes and dietary salt reduction programs). Clinicians may strengthen the quality and breadth of these programs by educating clinical staff, joining national committees that promote CVD prevention (ie, Healthy Caribbean Coalition), and supporting local hospital initiatives. Concentration on a healthy workplace and the implementation of preventative models within individual practices may also encourage community support. Details regarding the IoM global CVD report are available at www. iom.edu/globalcvd.

In Barbados, CVD has been a leading cause of illness and death since 2003, with heart attack and stroke responsible for one-third of all deaths on the island. The economic burden of chronic noncommunicable diseases (CNCDs), such as CVD, compounds the problem and with CNCDs, treatment often does not result in a cure. Angela Rose, MSc, University of the West Indies Chronic Disease Research Centre (CDRC), Cave Hill, Barbados, discussed the impact of CVD on health in Barbados.

There are poor outcomes from CNCDs in Barbados. For example, one-third of patients who suffer an acute myocardial infarction (MI) die within 2 weeks. One-third of patients following an acute stroke die within 4 weeks. Additionally, CNCDs account for ~50% of disability-adjusted life-years in the Caribbean, resulting in a large reduction in labor supply and productivity, as most of those affected are of working age. The poorest people are at highest risk for CNCDs. Unfortunately, they are also less financially able to manage the burden of disease. The good news is that 80% of CNCDs are preventable with lifestyle and diet modifications. Therefore, prevention is crucial to ease the treatment issues that are currently faced in the Caribbean.

The Barbados National Registry (BNR) for CNCDs is an initiative of the Barbados Ministry of Health (MoH). The recently launched BNR is a national surveillance system comprising three population-based surveys and registries that are focused on stroke, acute MI, and cancer. Preliminary data have revealed an unmet need for preventative action and standardized interventions to disrupt the spiraling burden of CNCD in this region.

Another MoH funded initiative being implemented by the CDRC is the "Health of the Nation" study, a population-based survey which will evaluate the impact of acute MI and stroke on quality of life and the economy in the hopes of formulating a plan for future health care programs. MI and stroke survivors will be followed in order to evaluate regional access to rehabilitation services and improve diagnostic approaches. Medication compliance and the sources of risk factors will also be assessed to assist in the development of future intervention protocols. Ms. Rose