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SCANNING THE LITERATURE

Summaries of Key Journal Articles

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Arrhythmias

Catheter Ablation of Ventricular Tachycardia in Ischaemic and Non-Ischaemic Cardiomyopathy: Where Are We Today? A Clinical Review

Wissner E, Stevenson WG, Kuck KH.
***Eur Heart J* 2012;Mar 11:[Epub ahead of print].**

Perspective: The following are 10 points to remember from this review of catheter ablation of ventricular tachycardia (VT) in patients with structural heart disease (SHD):

1: Most patients with SHD and monomorphic VT have ventricular scar caused by prior infarction in patients with ischemic cardiomyopathy (ICM) or fibrosis in patients with nonischemic cardiomyopathy (NICM).

2: Because nonclinical VTs often are inducible in patients with VT, a 12-lead electrocardiogram of the spontaneous VT is helpful for identifying clinical VTs in the electrophysiology laboratory.

3: In patients with an implantable cardioverter-defibrillator, the morphology of the stored electrograms of an episode of VT can be a useful template for recognizing clinical VTs in the electrophysiology laboratory.

4: Epicardial ablation is more likely to be necessary in patients with NICM and arrhythmogenic right ventricular cardiomyopathy/dysplasia than in patients with ICM.

5: Activation and entrainment mapping are useful for identifying critical sites for ablation of VTs that are hemodynamically tolerated.

6: When VT is not tolerated, a combination of scar and pace mapping can be used to identify ablation sites.

7: The rate of procedure-related death is reported to be 0-3%, with the most common cause of death being uncontrolled VT.

8: The most common complications are stroke, cardiac tamponade, valve injury, and atrioventricular block.

9: The rate of recurrent VT post-ablation is reported to be 25-50%.

10: There is no evidence that catheter ablation of VT improves survival.

Summary written by: Fred Morady, MD

2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design: A Report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation

Calkins H, Kuck KH, Cappato R, et al.
***Heart Rhythm* 2012;Mar 1:[Epub ahead of print].**

Perspective: The following are 10 points to remember from this extensive consensus statement dealing with ablation of atrial fibrillation (AF):

1: The only Class I indication for catheter ablation (CA) of AF is symptomatic paroxysmal AF refractory to ≥1 rhythm-

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control medication.

2: Symptomatic persistent AF refractory to ≥1 rhythm-control medication is a Class IIa indication for CA.

3: Symptomatic longstanding persistent AF refractory to ≥1 rhythm-control medication is a Class IIb indication for CA.

4: Symptomatic paroxysmal AF prior to drug therapy is a Class IIa indication for CA.

5: Symptomatic persistent and longstanding persistent AF are Class IIb indications for CA.

6: Symptomatic paroxysmal, persistent, and longstanding persistent AF are Class IIa indications for concomitant surgical ablation (SA) in patients undergoing surgery for another indication.

7: Symptomatic paroxysmal and persistent AF prior to drug therapy are Class IIa indications for concomitant SA.

8: Longstanding persistent AF prior to drug therapy is a Class IIb indication for concomitant SA.

9: All types of symptomatic AF refractory to drug therapy are Class IIb indications for stand-alone SA, regardless of whether CA was previously attempted.

10: Stand-alone SA is not recommended for paroxysmal, persistent, or longstanding persistent AF prior to drug therapy.

Summary written by: Fred Morady, MD

Prehospital Epinephrine Use and Survival Among Patients With Out-of-Hospital Cardiac Arrest

Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S.
***JAMA* 2012;307:1161-1168.**

Study Question: Does the use of epinephrine during cardiopulmonary resuscitation (CPR) affect outcomes in patients with out-of-hospital cardiac arrest (OHCA)?

Methods: The data for this observational study were obtained from a registry of 417,188 patients (mean age 72 years) with OHCA. Epinephrine was administered during CPR in 15,030 patients and not administered in the remaining 402,158 patients. A propensity score for epinephrine administration was used to control for potential confounding variables.

Results: Return of spontaneous circulation (ROSC) before hospitalization occurred significantly more often in the epinephrine group (18.3%) than in the propensity-matched nonepinephrine group (10.5%). One-month survival without severe cerebral dysfunction was significantly lower in the epinephrine (1.3%) than the nonepinephrine group (3.1%).

Conclusions: Administration of epinephrine during CPR in patients with OHCA is associated with a higher probability of ROSC before hospitalization, but a lower 1-month rate of survival without severe cerebral dysfunction.

Perspective: By redirecting peripheral blood flow, epinephrine increases coronary and cerebral perfusion. This could explain why epinephrine improved the probability of ROSC before hospitalization in this study. The reasons that epinephrine compromises 1-month survival could include increased myocardial dysfunction, impaired cerebral microcirculation, and/or an increased risk of ventricular tachycardia/ventricular fibrillation after resuscitation.

Summary written by: Fred Morady, MD

Cardiac Biomarkers Are Associated With an Increased Risk of Stroke and Death in Patients With Atrial Fibrillation: A RELY Substudy

Hijazi Z, Oldgren J, Andersson U, et al.
***Circulation* 2012;Feb 28:[Epub ahead of print].**

Study Question: Are plasma levels of troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) predictive of stroke and vascular mortality in patients with atrial fibrillation?

Methods: Biomarkers were analyzed in 6,189 patients at randomization in the RELY study. Outcomes were evaluated after adjusting for established cardiovascular risk factors and the $CHADS_2$ and CHA_2DS_2-VASc risk scores. Patients were stratified based on troponin I concentration quartiles: <0.010; 0.010-0.019; 0.020-0.039; ≥0.040 μg/L; and on NT-proBNP concentration quartiles: <387; 387-800; 801-1402; >1402 ng/L.

Results: Rates of stroke were independently related to levels of troponin I with 2.09%/year in the highest and 0.84%/year in the lowest troponin I group (hazard ratio [HR], 1.99), and to NT-proBNP with 2.30%/year versus 0.92% in the highest versus lowest NT-proBNP quartile groups (HR, 2.40). Vascular mortality was also independently related to biomarker levels with 6.56%/year in the highest and 1.04%/year the lowest troponin I group (HR, 4.38), and 5.00%/year in the highest and 0.61%/year in the lowest NT-proBNP quartile groups (HR, 6.73). Biomarkers increased the C-statistic from 0.68 to 0.72, $p < 0.0001$, for a composite of thromboembolic events.

Conclusions: Elevations of troponin I and NT-proBNP are common in patients with atrial fibrillation and are independently related to increased risks of stroke and mortality.

Perspective: The finding that these biomarkers also predict stroke in the setting of atrial fibrillation is novel and important since they improve risk stratification when added to commonly used clinical scoring methods. This may have important implications in guiding antithrombotic and other therapies, especially in atrial fibrillation subgroups otherwise deemed low risk. Since all patients in this study had at least one stroke risk

factor and were treated with oral anticoagulants, this approach will need to be tested in other atrial fibrillation populations.

Summary written by: Daniel T. Eitzman, MD

Congenital Heart Disease

Functional Health Status in Adult Survivors of Operative Repair of Tetralogy of Fallot

Hickey EJ, Veldtman G, Bradley TJ, et al.
***Am J Cardiol* 2012;109:873-880.**

Study Question: What is the long-term functional health status of adults with repaired tetralogy of Fallot?

Methods: A single study of 840 patients was performed at a single center. A phone interview was performed, and review of charts and echo reports was performed when possible. The Short Form-36 (SF-36) was used to assess patient-reported functional status.

Results: The median age at follow-up was 29.5 years. Telephone interview, review of echocardiograms, and SF-36 surveys were performed in 706,339 and 396 patients, respectively. Moderate or greater pulmonary valve insufficiency occurred in 54%, whereas right ventricular outflow tract stenosis was present in one third of patients. Cardiac symptoms were common, occurring in 45% of patients. Specifically, palpitations occurred in 27%, dyspnea in 21%, and chest pain in 17% of patients. Compared with age- and gender-matched normal controls, subjects with tetralogy of Fallot had significantly abnormal functional status in all physical functioning domains of the SF-36. Decreased physical functioning and echocardiographic abnormalities were more common in older patients ($p < 0.0001$).

Conclusions: Physical limitations are common in adults with repaired tetralogy of Fallot. Efforts to limit ventricular and outflow tract obstruction may result in improved late functional status.

Perspective: The primary concern raised by this study is that functional status seems to worsen with age out of proportion to what is seen in the general population. Whether changes in the early surgical approach (single-stage surgery without initial systemic to pulmonary shunt and avoidance of right ventriculotomy) will lead to improved long-term outcomes in future patients is unclear. It is also not known whether a strategy of earlier pulmonary valve replacement may prevent this progressive decline in functional status.

Summary written by: Timothy B. Cotts, MD

General Cardiology

Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients

Daugherty SL, Powers JD, Magid DJ, et al.
***Circulation* 2012;Feb 29:[Epub ahead of print].**

Study Question: What is the incidence and importance of resistant hypertension in new-onset hypertension?

Methods: A retrospective cohort study was conducted in two integrated health plans that included patients with incident hypertension started on treatment from 2002-2006. Patients were followed for the development of resistant hypertension based on American Heart Association criteria of uncontrolled blood pressure (BP) (defined by Joint National Committee [JNC]-7 thresholds of systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg with lower cut-offs for those with diabetes or chronic kidney disease) despite use of three or more antihypertensive medications using medication fill and BP measurement data. Primary outcome was incident cardiovascular events (CVEs = death or incident myocardial infarction, heart failure, stroke, or chronic kidney disease) in patients with and without resistant hypertension adjusting for patient and clinical characteristics.

Results: Among 205,750 patients with incident hypertension, 21% were on three or more antihypertensive medications for at least 1 month. 1.9% developed resistant hypertension within a median 1.5 years from initial treatment, or 0.7 cases per 100 person-years of follow-up. Variables associated with resistant hypertension included men, older, higher baseline BP, diabetes, chronic kidney disease, and previous stroke and heart failure. Over 3.8 years of median follow-up, CVEs were significantly higher in those with resistant hypertension (unadjusted: 18.0% vs. 13.5%, $p < 0.001$). After adjusting for patient and clinical characteristics, resistant hypertension was associated with a higher risk of CVEs (hazard ratio, 1.47; 95% confidence interval, 1.33-1.62).

Conclusions: Among patients with incident hypertension started on treatment, 1 in 50 patients developed resistant hypertension. Resistant hypertension patients had an increased risk of CVEs, supporting the need for greater efforts toward improving hypertension outcomes in this population.

Perspective: Resistant hypertension in this large cohort study is likely overestimated considering that the BPs were office- rather than home-based or 24-hour ambulatory. Also, the definition based on the JNC-7 criteria may be considered too rigid by some. Nevertheless, the 50% increase in CVEs in patients with resistant hypertension despite four drugs, strongly supports a focus on diet and exercise, which have been shown to reduce BP and reduce CVEs and mortality.

Summary written by: Melvyn Rubenfire, MD

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A Randomized Trial of Tenecteplase Versus Alteplase for Acute Ischemic Stroke

Parsons M, Spratt N, Bivard A, et al.
***N Engl J Med* 2012;366:1099-1107.**

Study Question: What is the comparative efficacy of the standard dose of alteplase with two different doses of tenecteplase?

Methods: In this phase 2B trial, the investigators randomly assigned 75 patients to receive alteplase (0.9 mg/kg of body weight) or tenecteplase (0.1 mg/kg or 0.25 mg/kg) less than 6 hours after the onset of ischemic stroke. To favor the selection of patients most likely to benefit from thrombolytic therapy, the eligibility criteria were a perfusion lesion at least 20% greater than the infarct core on computed tomographic (CT) perfusion imaging at baseline and an associated vessel occlusion on CT angiography. The coprimary endpoints were the proportion of the perfusion lesion that was reperfused at 24 hours on perfusion-weighted magnetic resonance imaging and the extent of clinical improvement at 24 hours, as assessed on the National Institutes of Health Stroke Scale (NIHSS, a 42-point scale; higher scores indicate more severe neurologic deficits).

Results: The three treatment groups each comprised 25 patients. The mean NIHSS score at baseline for all patients was 14.4, and the time to treatment was 2.9 hours. Together, the two tenecteplase groups had greater reperfusion ($p = 0.004$) and clinical improvement ($p < 0.001$) at 24 hours than the alteplase group. There were no significant between-group differences in intracranial bleeding or other serious adverse events. The higher dose of tenecteplase (0.25 mg/kg) was superior to the lower dose and to alteplase for all efficacy outcomes, including absence of serious disability at 90 days (in 72% of patients, vs. 40% with alteplase; $p = 0.02$).

Conclusions: Tenecteplase was associated with significantly better reperfusion and clinical outcomes than alteplase in patients with stroke.

Perspective: The current study reports that, using CT perfusion and angiographic imaging to select patients for thrombolytic treatment of acute ischemic stroke, tenecteplase was superior to alteplase with respect to reperfusion and clinical improvement at 24 hours, and did not increase intracranial hemorrhage. These positive findings should be considered preliminary, due to the small sample size.

Summary written by: Debabrata Mukherjee, MD

Association of Hospital Spending Intensity With Mortality and Readmission Rates in Ontario Hospitals

Stukel TA, Fisher ES, Alter DA, et al.
***JAMA* 2012;307:1037-1045.**

Study Question: What is the association between higher spending in hospitals with mortality and readmissions?

Methods: The study population was comprised of adults (>18 years) in Ontario, Canada, with a first admission for acute myocardial infarction (AMI) (n = 179,139), congestive heart failure (CHF) (n = 92,377), hip fracture (n = 90,046), or colon cancer (n = 26,195) during 1998-2008, with follow-up to 1 year. The exposure measure was the index hospital's end-of-life expenditure index for hospital, physician, and emergency department services. The primary outcomes were 30-day and 1-year mortality, and readmissions and major cardiac events (readmissions for AMI, angina, CHF, or death) for AMI and CHF.

Results: Patients' baseline health status was similar across hospital expenditure groups. Patients admitted to hospitals in the highest- versus lowest-spending intensity terciles had lower rates of all adverse outcomes. In the highest- versus lowest-spending hospitals, respectively, the age- and sex-adjusted 30-day mortality rate was 12.7% versus 12.8% for AMI, 10.2% versus 12.4% for CHF, 7.7% versus 9.7% for hip fracture, and 3.3% versus 3.9% for CHF. Results for 1-year mortality, readmissions, and major cardiac events were similar. Higher spending hospitals had higher nursing staff ratios, and their patients received more inpatient medical specialist visits, interventional and medical cardiac therapies, preoperative specialty care, and post-discharge collaborative care with a cardiologist and primary care physician.

Conclusions: Among Ontario hospitals, higher spending intensity was associated with lower mortality, readmissions, and cardiac event rates.

Perspective: It would be simplistic to interpret this study as suggesting that higher spending is causally related to better outcomes and that providing more money to lower-spending hospitals would automatically improve their outcomes. Higher spending hospitals differed in many ways, such as greater use of evidence-based care, skilled nursing and critical care staff, more intensive inpatient specialist services, and high technology, all of which are more expensive. It is critical to understand not only how much money is spent, but whether it is spent on effective procedures and services.

Summary written by: Debabrata Mukherjee, MD

Cardiac Complications in Patients With Community-Acquired Pneumonia: Incidence, Timing, Risk Factors, and Association With Short-Term Mortality

Corrales-Medina VF, Musher DM, Wells GA, Chirinos JA, Chen L, Fine MJ.
***Circulation* 2012;125:773-781.**

Study Question: What are the type, frequency, and timing of incident cardiac complications; their risk factors; and associations with short-term mortality in patients with community-acquired pneumonia (CAP)?

Methods: A total of 1,343 inpatients and 944 outpatients with CAP were followed up prospectively for 30 days after presentation. Incident cardiac complications (new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction) were diagnosed in 358 inpatients (26.7%) and 20 outpatients (2.1%). For the univariable analysis of baseline factors and incident cardiac complications, the authors used unpaired *t* tests or Wilcoxon rank-sum tests for continuous variables and χ^2 or Fisher exact tests for categorical variables, as appropriate.

Results: Although most events (89.1% in inpatients, 75% in outpatients) were diagnosed within the first week, more than half of them were recognized in the first 24 hours. Factors associated with their diagnosis included older age (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.02-1.04), nursing home residence (OR, 1.8; 95% CI, 1.2-2.9), history of heart failure (OR, 4.3; 95% CI, 3.0-6.3), prior cardiac arrhythmias (OR, 1.8; 95% CI, 1.2-2.7), previously diagnosed coronary artery disease (OR, 1.5; 95% CI, 1.04-2.0), arterial hypertension (OR, 1.5; 95% CI, 1.1-2.1), respiratory rate ≥30 breaths per minute (OR, 1.6; 95% CI, 1.1-2.3), blood pH <7.35 (OR, 3.2; 95% CI, 1.8-5.7), blood urea nitrogen ≥30 mg/dl (OR, 1.5; 95% CI, 1.1-2.2), serum sodium <130 mmol/L (OR, 1.8; 95% CI, 1.02-3.1), hematocrit <30% (OR, 2.0; 95% CI, 1.3-3.2), pleural effusion on presenting chest X-ray (OR, 1.6; 95% CI, 1.1-2.4), and inpatient care (OR, 4.8; 95% CI, 2.8-8.3). Incident cardiac complications were associated with increased risk of death at 30 days after adjustment for baseline Pneumonia Severity Index score (OR, 1.6; 95% CI, 1.04-2.5).

Conclusions: Incident cardiac complications are common in patients with CAP and are associated with increased short-term mortality.

Perspective: This study suggests that incident cardiac complications occur in a substantial proportion of patients with CAP, affecting more than one quarter of those hospitalized for this infection; that the great majority of CAP patients who develop incident cardiac complications have their primary cardiac event within 7 days of presentation, with >50% occurring the same day of CAP diagnosis; and the development of incident cardiac complications is independently associated with a 60% increase in the risk of short-term mortality in patients with CAP. The study findings provide support for increasing efforts to reduce the incidence of pneumonia in high-risk populations through influenza and pneumococcal vaccination.

Summary written by: Debabrata Mukherjee, MD

Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol

Stein EA, Mellis S, Yancopoulos GD, et al.
***N Engl J Med* 2012;366:1108-1118.**

Study Question: What is the effect of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibition on levels of low-density lipoprotein (LDL) cholesterol?

Methods: In healthy volunteers, two randomized studies of an antibody to PCSK9 (REGN727) given intravenously (40 subjects) or subcutaneously (32 subjects) was compared with placebo. These studies were followed by a randomized, placebo-controlled, multiple-dose trial in adults with heterozygous familial hypercholesterolemia who were receiving atorvastatin (21 subjects) and in nonfamilial hypercholesterolemia subjects on atorvastatin (30 subjects) (baseline LDL >100 mg/dl) or a modified diet alone (10 subjects) (baseline LDL >130 mg/dl). The primary outcome for all studies was safety; secondary outcome was the lipid profile.

Results: Among subjects receiving REGN727, there were no discontinuations because of adverse events, and REGN727 lowered LDL in all the studies. In a multiple-dose study, REGN727 doses of 50, 100, and 150 mg reduced LDL levels in the combined atorvastatin-treated populations to 77.5, 61.3, and 53.8 mg/dl, for a difference in the change from baseline of −39.2, −53.7, and −61.0%, respectively, as compared with placebo ($p < 0.001$ for all comparisons).

Conclusions: In three phase 1 trials, REGN727 significantly reduced LDL cholesterol levels in healthy volunteers and in subjects with familial or nonfamilial hypercholesterolemia.

Perspective: The PCSK9 protease is a promising therapeutic target that when blocked, should lead to reduced LDL and reduced coronary artery disease risk. This study demonstrates that a monoclonal antibody to PCSK9 leads to dose-dependent, prolonged reductions in LDL, and this effect is additive to statins in a diverse hyperlipidemic population. This therapy may be useful in statin-intolerant patients and in combination with statins in high-risk populations to achieve extreme lowering of LDL. The effects of REGN727 on vascular events and the long-term safety profile will require further study.

Summary written by: Daniel T. Eitzman, MD

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Heart Failure/Transplant

Decision Making in Advanced Heart Failure: A Scientific Statement From the American Heart Association

Allen LA, Stevenson LW, Grady KL, et al.
***Circulation* 2012;Mar 5:[Epub ahead of print].**

Perspective: The following are 10 points to remember about this Scientific Statement:

1: There are complex trade-offs in the management of patients with several comorbidities that compel clinicians to come up with an optimal management plan that incorporates patient goals, values, and preferences.

2: It is important that the clinician recognizes the natural history of heart failure in the individual patient, especially the critical transition into advanced heart failure, because this is often accompanied by a transition in goals of care from the patient and family perspective, wherein palliative therapies may become the dominant treatment paradigm when transplantation and mechanical circulatory support are not an option.

3: Frequent reappraisal of the clinical course helps manage expectations, improve communication, and inform rational decisions. A comprehensive discussion of prognosis includes the potential impact of worsening symptoms, limited functional capacity, loss of independence, reduced social functioning, decreased quality of life, and increased caregiver commitment in addition to the risk of death.

4: It is important for the physician to define the range of options that are medically appropriate.

5: An annual heart failure review with patients should include discussion of current and potential therapies for both anticipated and unanticipated events, as well as responding to clinical milestones.

6: It is important for the clinician to initiate the development of a comprehensive plan for end-of-life care consistent with patient values, preferences, and goals. ICD deactivation is desirable to avoid unnecessary pain and distress for patients and families at the end of life. Active discontinuation of mechanical circulatory support is often appropriate and necessary at the end of life.

7: Although family units may have discussed end-of-life preferences, important barriers to such discussions include fear of death, trust in others to make decisions, family dynamics, uncertainty about preferences, and psychological burdens associated with surrogate decision making.

8: The decision-making process and communication are described in detail in this statement.

9: The expert panel opined that future research is needed in a variety of areas related to shared decision making (including effective communication training, decision support interventions, group visits, health-related quality-of-life measures, and caregiver burden, needs, and outcomes).

10: Changes in organizational and reimbursement structure will be required to reward and integrate decision making into the delivery of patient-centered health care.

Summary written by: Ragavendra R. Baliga, MBBS

Impact of Progression of Diastolic Dysfunction on Mortality in Patients With Normal Ejection Fraction

Aljaroudi W, Alraies MC, Halley C, et al.
***Circulation* 2012;125:782-788.**

Study Question: What is the impact of progression of diastolic dysfunction (DD) on all-cause mortality in patients initially evaluated as ambulatory outpatients?

Methods: Clinical records and echocardiograms of 1,065 consecutive patients who underwent a baseline echocardiogram between January 1, 2005, and December 31, 2009, and who also had a follow-up echocardiogram within 6-24 months were reviewed. All-cause mortality was assessed by use of the Social Security Death Index. Diastolic function was labeled as normal, mild, moderate, or severe dysfunction corresponding to normal, and grade 1, 2, and 3 diastolic function.

Results: Average patient age was 67.9 years and 58% were male. Baseline DD was noted in 770 patients (72.3%), and was mild in 65.9% and moderate or severe in 7.4%. Clinical association with baseline DD included increasing age and hypertension. For the whole group, average time between echocardiograms was 1.1 ± 0.4 years; average follow-up was 1.6 ± 0.8 years. At baseline, all patients had normal left ventricular (LV) systolic function. Diastolic function remained stable in 783 patients, worsened in 168, and improved in 14. A decrease in LVEF to <55% was noted in 88 patients of whom 60 had stable, 19 worsening, and 9 improved diastolic function. On follow-up, all-cause mortality was reported in 142 patients, including 20 with normal diastolic function, 102 with mild DD, and 20 with at least moderate DD.

Conclusions: In patients with normal baseline LV systolic function, development of DD or worsening of pre-existing DD independently predicts all-cause mortality.

Perspective: This large study nicely demonstrated an independent impact of subsequent development of DD on all-cause mortality in these patients with preserved LV systolic function. The mechanism by which diastolic function relates to adverse outcomes probably relates to progression of underlying disease whether it is ischemic heart disease, hypertensive cardiovascular disease, or other clinical entities.

Whether more aggressive therapy in patients noted to have progression of DD on echocardiography would have an impact on prognosis remains conjectural.

Summary written by: William F. Armstrong, MD

Interventional Cardiology

Intracoronary Versus Intravenous Bolus Abciximab During Primary Percutaneous Coronary Intervention in Patients With Acute ST-Elevation Myocardial Infarction: A Randomised Trial

Thiele H, Wöhrle J, Hambrecht R, et al.
***Lancet* 2012;379:923-931.**

Study Question: What is the safety and efficacy of intracoronary versus intravenous abciximab in patients undergoing primary percutaneous coronary intervention (PCI)?

Methods: AIDA STEMI was a randomized, open-label, multicenter trial in which patients undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI) were randomly assigned in a 1:1 ratio to intracoronary versus intravenous abciximab bolus (0.25 mg/kg bodyweight) during PCI with a subsequent 12-hour intravenous infusion 0.125 μg/kg/min. The primary endpoint was a composite of all-cause mortality, recurrent infarction, or new congestive heart failure (CHF) within 90 days of randomization.

Results: A total of 2,065 patients were randomly assigned to intracoronary (n = 1,032) or intravenous abciximab (n = 1,033). There was no difference in the primary composite clinical endpoint at 90 days (7.0% vs. 7.6%; odds ratio, 0.91; 95% confidence interval, 0.64-1.28; p = 0.58). There was no difference in the incidence of death (4.5% vs. 3.6%; 1.24; 0.78-1.97; p = 0.36) or reinfarction (1.8% vs. 1.8%; 1.0; 0.51-1.96; p = 0.99) between the treatment groups. New-onset CHF was less commonly seen in the intracoronary group (2.4% vs. 4.1%; 0.57; 0.33-0.97; p = 0.04).

Conclusions: In patients with STEMI undergoing primary PCI, intracoronary as compared to intravenous abciximab did not result in a difference in the combined endpoint of death, reinfarction, or CHF.

Perspective: This study did find a reduction in CHF with intracoronary abciximab, although this may be a chance finding since there was no difference in ST resolution or final left ventricular ejection fraction between the two groups. However, there is no downside to intracoronary abciximab (over intravenous use), and in the rare circumstance when abciximab is used, it may be reasonable to administer it directly to the infarct vessel.

Summary written by: Hitinder S. Gurm, MBBS

Prevention/Vascular

Comparison of the Framingham and Reynolds Risk Scores for Global Cardiovascular Risk Prediction in the Multiethnic Women's Health Initiative

Cook NR, Paynter NP, Eaton CB, et al.
***Circulation* 2012;Mar 7:[Epub ahead of print].**

Study Question: How does the Reynolds Risk Score compare with Framingham-based risk scores in the prediction of cardiovascular disease (CVD) risk?

Methods: A case-cohort sample from the Women's Health Initiative (WHI) Observational Cohort was used for the present study. Incident cases included myocardial infarction (MI), ischemic stroke, and CVD death. The control group comprised a random sample of women from the WHI without prior CVD. CVD risk was calculated using the ATP-III score, Reynolds Risk Score, and Framingham CVD model, reweighting to reflect cohort frequencies.

Results: Major CVD cases (n = 1,722) included 752 MIs, 754 ischemic strokes, and 216 CVD deaths. The sample of controls was comprised of 1,994 without prior CVD. Cases included more smokers and diabetics, and generally higher risk factor levels. Blacks were slightly younger than whites, but had higher proportions of smokers and diabetics. The predicted 10-year risk varied widely between models, with 10% or higher risk in 6%, 10%, and 41% of women using the ATP-III, Reynolds, and Framingham CVD models, respectively. The ATP-III and Framingham CVD models overestimated risk for CHD and major CVD. After recalibration, the Reynolds model demonstrated improved discrimination over the ATP-III model through a higher c-statistic (0.765 vs. 0.757), positive net reclassification improvement (NRI) (4.9%), and positive integrated discrimination improvement (IDI) (4.1%) overall, excluding diabetics (NRI = 4.2%), and in white (NRI = 4.3%) and black (NRI = 11.4) women. The Reynolds (NRI = 12.9) and ATP-III (NRI = 5.9%) models demonstrated better discrimination than the Framingham CVD model.

Conclusions: The Reynolds Risk Score was better calibrated than the Framingham-based models in this large external validation cohort. The Reynolds score demonstrated improved discrimination among both black and white women.

Perspective: This well written paper suggests that the Reynolds Risk Score has significant clinical utility for addressing risk among women, and has significant implications for management of CVD risk factors.

Summary written by: Elizabeth A. Jackson, MD

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A Randomized Trial of Nicotine-Replacement Therapy Patches in Pregnancy

Coleman T, Cooper S, Thornton JG, et al., on behalf of the Smoking, Nicotine, and Pregnancy (SNAP) Trial Team.
***N Engl J Med* 2012;366:808-818.**

Study Question: Are nicotine-replacement therapies safe and effective for smoking cessation during pregnancy?

Methods: Participants (16-50 years old) were recruited from seven hospitals in England between May 2007 and February 2010. All women were between 12 and 24 weeks' gestation and had smoked 10 or more cigarettes daily before pregnancy, were currently smoking five or more cigarettes per day, and had an exhaled carbon monoxide concentration of at least 8 ppm. All participants received behavioral cessation support and were also randomly assigned to 8 weeks of treatment with active nicotine patches (15 mg per 16 hours) or matched placebo patches. The primary outcome was abstinence from the date of smoking cessation until delivery, validated by exhaled carbon monoxide measurement. Safety outcomes included adverse events related to pregnancy and birth.

Results: A total of 1,050 women were enrolled, of which 521 were randomly assigned to nicotine replacement therapy and 529 to placebo. No difference was observed in the abstinence rate (from quit date to delivery date) between the two groups (nicotine patch vs. placebo patch) with an unadjusted odds ratio for the nicotine replacement group of 1.26 for smoking abstinence. However, during the first month, the abstinence rate was higher among the nicotine replacement group compared to placebo (21.3% vs. 11.7%). Compliance was low for both groups, with 7.2% of women assigned to the nicotine replacement group and 2.8% of women assigned to placebo using patches for more than 1 month. Rates of adverse pregnancy and adverse birth outcomes were similar between the two groups.

Conclusions: Adding a nicotine patch to behavior support for smoking cessation during pregnancy did not significantly increase the rate of abstinence or the risk for adverse events during pregnancy or with birth. However, low compliance significantly limited the assessment of safety.

Perspective: These data suggest that nicotine replacement may be safe during pregnancy; however, as the investigators note, the low compliance limits this finding. Additional research regarding the factors that are associated with low compliance for smoking cessation will provide information on the design of future interventions for women who smoke during pregnancy.

Summary written by: Elizabeth A. Jackson, MD

The Interleukin-6 Receptor as a Target for Prevention of Coronary Heart Disease: A Mendelian Randomisation Analysis

The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium.
***Lancet* 2012;Mar 14:[Epub ahead of print].**

Study Question: What is the effect of interleukin-6 receptor (IL6R) signaling on coronary heart disease (CHD)?

Methods: Single nucleotide polymorphisms (SNPs) in the IL6R were determined to evaluate the likely efficacy and safety of IL6R inhibition for primary prevention of CHD. Genetic findings were compared with the effects of the IL6 antibody, tocilizumab, reported in trials involving patients with rheumatoid arthritis.

Results: In 133,449 individuals, an IL6R SNP (rs7529229) marking a nonsynonymous IL6R variant (rs8192284; p.Asp358Ala) was associated with increased IL6 concentrations (9.45% per allele) as well as reduced C-reactive protein (decrease 8.35% per allele) and fibrinogen concentrations (0.85% decrease per allele). This pattern was consistent with IL6R blockade from infusions of tocilizumab in patients with rheumatoid arthritis studied in randomized trials. In 25,458 CHD cases and 100,740 controls, the IL6R rs7529229 SNP was associated with reduced odds of CHD events (per allele odds ratio 0.95, $p = 1.53 \times 10^{-5}$).

Conclusions: IL6R signaling seems to have a causal role in the development of CHD.

Perspective: Although associations with IL6 and CHD have been previously demonstrated, causality between CHD and IL6R signaling has been unclear. By showing that a functional IL6R gene variant is associated with reduced CHD risk, this study provides strong support for IL6R as a valid therapeutic target for the prevention of CHD. Since tocilizumab is already in use in patients with rheumatoid arthritis, and leads to similar changes in biomarkers as the gene variant, one might predict that this drug will have beneficial vascular effects. The safety and magnitude of benefit of this drug (or other IL6R antagonists) will need to be tested in further trials.

Summary written by: Daniel T. Eitzman, MD