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SCANNING THE LITERATURE

Summaries of Key Journal Articles

Kim A. Eagle, MD, Editor-in-Chief, Journal Scan, *Ann Arbor, MI*

Christopher P. Cannon, MD, Editor-in-Chief, Cardiosource, *Boston, MA*

William F. Armstrong, MD, *Ann Arbor, MI*, David S. Bach, MD, *Ann Arbor, MI*, Ragavendra R. Baliga, MBBS, *Columbus, OH*, Anna M. Booher, MD, *Ann Arbor, MI*, Timothy B. Cotts, MD, *Ann Arbor, MI*, Jennifer Cowger, MD, *Ann Arbor, MI*, Daniel T. Eitzman, MD, *Ann Arbor, MI*, James B. Froehlich, MD, *Ann Arbor, MI*, Caren S. Goldberg, MD, *Ann Arbor, MI*, Hitinder S. Gurm, MBBS, *Ann Arbor, MI*, Jennifer C. Hirsch, MD, *Ann Arbor, MI*, Elizabeth Anne Jackson, MD, *Ann Arbor, MI*, Fred Morady, MD, *Ann Arbor, MI*, Debabrata Mukherjee, MD, *El Paso, TX*, Himanshu J. Patel, MD, *Ann Arbor, MI*, Melvyn Rubenfire, MD, *Ann Arbor, MI*, Gilbert R. Upchurch, Jr., MD, *Ann Arbor, MI*, Associate Editors, Cardiosource

Arrhythmias

A Multimarker Approach to Assess the Influence of Inflammation on the Incidence of Atrial Fibrillation in Women

Conen D, Ridker PM, Everett BM, et al.
***Eur Heart J* 2010;May 25:[Epub ahead of print].**

Study Question: Does inflammation promote atrial fibrillation (AF) in women?

Methods: Study subjects were 24,734 women (median age 53 years) free of cardiovascular disease and AF at entry followed for a median of 14.4 years. Blood samples at entry were analyzed for three biomarkers of inflammation: C-reactive protein, soluble intercellular adhesion molecule-1, and fibrinogen. An inflammation score of 0-3 was used to indicate the number of biomarkers in the highest tertile per individual.

Results: A first episode of AF occurred in 3% of women. Each biomarker was associated with the occurrence of AF (hazard ratio [HR], 1.10-1.11). Inflammatory scores of 1, 2, and 3 were independently associated with a progressively higher risk of AF (HRs 1.37, 1.49, and 1.68, respectively).

Conclusions: Biomarkers of inflammation are independently associated with the onset of AF in women.

Perspective: There is mounting evidence that inflammation plays a role in new-onset AF, AF after open-heart surgery, and recurrent AF after cardioversion or catheter ablation. A proarrhythmic effect of inflammation may explain why non-antiarrhythmic agents that have anti-inflammatory effects, including statins and fish oil, have been shown to prevent AF in some studies.

Summary written by: Fred Morady, MD

Periprocedural Stroke and Management of Major Bleeding Complications in Patients Undergoing Catheter Ablation of Atrial Fibrillation. The Impact of Periprocedural Therapeutic International Normalized Ratio

Di Biase L, Burkhardt JD, Mohanty P, et al.
***Circulation* 2010;121:2550-2556.**

Study Question: What is the impact of a therapeutic international normalized ratio (INR) on stroke and bleeding complications during radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF)?

Methods: A total of 6,454 patients (mean age 57 years) underwent RFCA of AF at nine centers. The patients were classified as: group I: 8-mm-tip ablation catheter, off warfarin (n = 2,488); group II: open irrigated-tip catheter, off warfarin (n = 1,348); and group III: open irrigated-tip catheter, on warfarin with INR >2 (n = 2,618). Heparin was used in all groups to maintain an activated clotting time >350 seconds.

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Results: The incidence of stroke and transient ischemic attack was significantly lower in group III (0%) than in groups I (1.1%) or II (0.9%). There was no significant difference in the risk of cardiac tamponade between the patients on or off warfarin (0.3% and 0.2%, respectively) or in the risk of major bleeding complication between the three groups (0.4, 0.8, and 0.4%, respectively). The mean amount of pericardial drainage was significantly higher in patients on warfarin (1,200 cc) than off warfarin (700 cc).

Conclusions: A therapeutic INR during RFCA of AF reduces the risk of cerebral thromboembolic complications without increasing the risk of cardiac tamponade or major bleeding complications.

Perspective: This important study demonstrates that maintaining a therapeutic INR with warfarin during RFCA of AF improves the safety profile of the procedure. The impact of warfarin on the amount of pericardial drainage can be minimized by emergent infusion of factor VII (not used in this study).

Summary written by: Fred Morady, MD

Continuing Warfarin Therapy Is Superior to Interrupting Warfarin With or Without Bridging Anticoagulation Therapy in Patients Undergoing Pacemaker and Defibrillator Implantation

Ahmed I, Gertner E, Nelson WB, et al.
***Heart Rhythm* 2010;7:745–749.**

Study Question: Is therapy with warfarin safer than heparin in patients undergoing device implantation?

Methods: This was a retrospective analysis of 459 patients (mean age 71 years) being treated with warfarin who were referred for device implantation. Patients were managed in one of three ways: group I, warfarin not withheld and international normalized ratio (INR) 2-3.5 during the perioperative period; group II, warfarin discontinued 3-5 days before implantation and heparin bridging therapy used; group III, warfarin discontinued 3-5 days before implantation and no bridging therapy used. Warfarin therapy was restarted in groups II-III the evening of implantation.

Results: The mean INRs during device implantation were 2.6, 1.3, and 1.4 in groups I, II, and III, respectively. Pocket hematomas occurred more frequently in group II (5.7%) than group I (0.4%) or III (1.8%). Transient ischemic attacks occurred more often in group III (3.5%) than group I (0%) or II (0.8%). Hospitalization was significantly longer in group II (2.3 days) than group I or II (1.2 days each).

Conclusions: Device implantation in the setting of a therapeutic INR is safer than withholding warfarin, either with or without bridging therapy.

Perspective: This study adds to the literature indicating than heparin is more likely than warfarin to cause bleeding complications after device implantation. Uninterrupted warfarin therapy is associated with a lower risk of thromboembolic complications after both device implantation and radiofrequency catheter ablation of atrial fibrillation. Therefore, there is little rationale for interrupting warfarin therapy in at-risk patients undergoing an electrophysiologic procedure.

Summary written by: Fred Morady, MD

Cardiovascular Surgery

Outcomes in Patients With De Novo Left Main Disease Treated With Either Percutaneous Coronary Intervention Using Paclitaxel-Eluting Stents or CABG Treatment in the Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery (SYNTAX) Trial

Morice MC, Serruys PW, Kappetein AP, et al.
***Circulation* 2010;121:2645–2653.**

Study Question: What are the outcomes in the prespecified subgroup of patients with left main (LM) disease in the SYNTAX trial?

Methods: This observational hypothesis-generating analysis reports the results of a prespecified powered subgroup of 705 randomized patients who had LM disease among the 1,800 patients with de novo three-vessel disease and/or LM disease randomized to percutaneous coronary intervention (PCI) with paclitaxel-eluting stents or coronary artery bypass grafting (CABG) in the SYNTAX trial.

Results: Major adverse cardiac and cerebrovascular event rates at 1 year in LM patients were similar for CABG and PCI (13.7% vs. 15.8%; p = 0.44). At 1 year, stroke was significantly higher in the CABG arm (2.7% vs. 0.3%; p = 0.009), whereas repeat revascularization was significantly higher in the PCI arm (6.5% vs. 11.8%; p = 0.02); there was no difference between groups for other endpoints. For anatomic complexity, those with higher baseline SYNTAX scores had significantly worse outcomes with PCI than patients with low or intermediate SYNTAX scores; outcomes for patients with CABG did not correlate with baseline SYNTAX score, but baseline EuroSCORE significantly predicted outcomes for both treatments.

Conclusions: Patients with LM disease who had revascularization with PCI had safety and efficacy outcomes comparable to CABG at 1 year.

Perspective: These results are consistent with findings of the only other randomized LM trial to compare PCI to CABG, the LE MANS Study (*J Am Coll Cardiol* 2008;51:538–45). Note that follow-up in this study was available only through 1 year and it is possible that, with time, differences in outcomes between patients treated with CABG versus PCI may begin to emerge. Longer term follow-up and additional prospective studies are required to determine whether these two revascularization strategies offer comparable outcomes.

Summary written by: Debabrata Mukherjee, MD

Transcatheter Aortic Valve Implantation for High-Risk Patients With Severe Aortic Stenosis: A Systematic Review

Yan TD, Cao C, Martens-Nielsen J, et al.
***J Thorac Cardiovasc Surg* 2010;139:1519–1528.**

Study Question: What is the safety and clinical effectiveness of transcatheter aortic valve implantation for patients at high surgical risk with severe aortic stenosis?

Methods: Electronic searches were performed in six databases from January 2000 to March 2009. Endpoints included feasibility, safety, efficacy, and durability. Clinical effectiveness was synthesized through a narrative review with full tabulation of results of all included studies.

Results: The current evidence on transcatheter aortic valve implantation for aortic stenosis is limited to short-term observational studies. The overall procedural success rates ranged from 74% to 100%. The incidence of major adverse events included 30-day mortality (0-25%), myocardial infarction (0-15%), cardiac tamponade (2-10%), stroke (0-10%), conversion to surgery (0-8%), moderate to major paravalvular leak (4-35%), vascular complication (8-17%), and valve-in-valve procedure (2-12%). The overall 30-day major adverse cardiovascular and cerebral events ranged from 3% to 35%. The mean aortic valve area ranged from 0.5 to 0.8 cm^2 before and 1.3 to 2.0 cm^2 after transcatheter aortic valve implantation. The mean pressure gradient ranged from 34 to 58 mm Hg before and 3 to 12 mm Hg after transcatheter aortic valve implantation. Death rate at 6 months postprocedure ranged from 18% to 48%.

Conclusions: Use of transcatheter aortic valve implantation should be considered only within the boundaries of clinical trials.

Perspective: This review demonstrated that although transcatheter aortic valve implantation success rate is high, there is a potential for serious complications. Note that the procedural and short-term outcomes appeared to be improving in more recent studies with an accumulating number of patients. At this time, transcatheter aortic valve implantation should be considered only within the boundaries of clinical trials with special arrangements for clinical governance, consent, and audit.

Summary written by: Debabrata Mukherjee, MD

Surgical Management of Descending Thoracic Aortic Disease: Open and Endovascular Approaches. A Scientific Statement From the American Heart Association

Coady MA, Ikonomidis JS, Cheung AT, et al., on behalf of the American Heart Association Council on Cardiovascular Surgery and Anesthesia and Council on Peripheral Vascular Disease.
***Circulation* 2010;121:2780–2804.**

Perspective: The following are 10 points to remember from the American Heart Association (AHA) Scientific Statement on surgical management of descending thoracic aortic disease (TAD).

1. Descending TAD is increasingly recognized, composed of distinct etiologies with predictable and well defined clinical behaviors.

2. Historically, surgical intervention for descending TAD has been associated with high rates of paraplegia and mortality. However, in recent years, mortality (4-9%) and paraplegia (<3%) rates have improved.

3. Endovascular thoracic aortic stent grafts are an attractive treatment option in descending TAD due to lower published risks of mortality and paraplegia, particularly in the high surgical risk groups.

4. Though technically feasible in a variety of clinical settings, some considerations for the broad application of stent grafting in descending TAD include:

- Lack of long-term data on durability (>5 years).
- Lack of prospective randomized trials to directly compare open and endovascular therapy.
- Re-intervention rates, primarily for endoleak, are not insignificant.
- Risk of stroke approaches 4%.

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- Frequent need for left subclavian bypass procedures to secure adequate landing zones.

5. Patients with the Marfan syndrome or other connective tissue diseases were excluded from stent-graft trials and are not ideal candidates for stent grafting.

6. Stent graft therapy of thoracic aortic aneurysm should not be performed at aortic sizes smaller than what is recommended for traditional surgery. Patient selection should be based on lack of candidacy for open surgery, life expectancy, and anatomic suitability.

7. Traditional surgery for complicated acute type B dissection carries significant morbidity and mortality. Endovascular therapy is emerging as an alternative with high technical success, false lumen thrombosis, and low complication rates.

8. Prophylactic stent grafting to prevent complications of chronic type B dissection is compared to medical management in the INSTEAD and ABSORB trials, but long-term data are not yet available.

9. Stent grafting can be performed as an alternative to high-risk surgery in intramural hematoma and penetrating atherosclerotic ulcers (PAUs) in the descending aorta. Stent grafting of PAU is associated with higher complication rates and risk of endoleak is higher.

10. Treatment of traumatic aortic transaction with stent grafts is an alternative to surgery in high-risk cases. However, in this younger population, questions remain regarding graft durability, impact of frequent imaging, radiation exposure, and long-term consequences of left subclavian coverage.

Summary written by: Anna M. Booher, MD

General Cardiology

Bleeding Complications With Dual Antiplatelet Therapy Among Patients With Stable Vascular Disease or Risk Factors for Vascular Disease. Results From the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) Trial

Berger PB, Bhatt DL, Fuster V, et al., on behalf of the CHARISMA Investigators.
***Circulation* 2010;121:2575–2583.**

Study Question: What are the incidence, implication, and outcomes associated with dual antiplatelet therapy (DAPT)?

Methods: The authors analyzed the outcome of patients enrolled in the CHARISMA trial who were randomized to DAPT. CHARISMA randomized patients with established stable vascular disease or multiple risk factors for vascular disease without established disease, to either aspirin or aspirin plus clopidogrel. Severe bleeding was defined by the GUSTO trial criteria, and comprised of fatal bleeding and intracranial hemorrhage, or bleeding causing hemodynamic compromise requiring blood or fluid replacement, inotropes, or surgery. Moderate bleeding was defined as bleeding requiring transfusion, but not meeting any of the severe bleeding criterion.

Results: Randomization to clopidogrel was associated with an increase in bleeding with severe bleeding occurring in 1.7% of the clopidogrel group versus 1.3% on placebo ($p = 0.087$), and moderate bleeding in 2.1% versus 1.3%, respectively ($p < 0.001$). The most common site of bleeding was gastrointestinal, followed by intracranial and bleeding related to surgical procedures. The risk of bleeding was greatest in the first year and patients who did not suffer moderate or severe bleeding during the first year were no more likely than placebo-treated patients to have bleeding subsequently. Moderate bleeding was a strong predictor of subsequent all-cause mortality (hazard ratio, 2.55; $p < 0.0001$).

Conclusions: Use of DAPT is associated with an increased risk of bleeding, with the incremental risk associated with DAPT being concentrated in the first year.

Perspective: This important paper provides key data on long-term bleeding risk in patients on DAPT. The incremental risk of severe bleeding with DAPT versus aspirin alone was 0.4% and 0.8% with respect to moderate bleeding. Further, the additive risk of bleeding was concentrated in the first year. These data should be of immense help to physicians and patients weighing the risk–benefit ratio of DAPT.

Summary written by: Hitinder S. Gurm, MBBS

Population Trends in the Incidence and Outcomes of Acute Myocardial Infarction

Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS.
***N Engl J Med* 2010;362:2155–2165.**

Study Question: Have trends in the incidences and outcomes related to acute myocardial infarction (AMI) changed in recent times?

Methods: Data from Kaiser Permanente Northern California, a large, community-based population of patients hospitalized for AMI, were used for the analysis. Patients were included if they were 30 years or older and experienced an AMI between 1999 and 2008. Patient characteristics, outpatient medications, and cardiac biomarker levels were identified from health plan databases. Outcomes of interest were age- and sex-adjusted

incident rates of AMI, ST-elevation myocardial infarction (STEMI), and non-STEMI (NSTEMI).

Results: A total of 46,086 hospitalizations for AMI over 18,691,131 person-years of follow-up were included. The majority of AMIs were NSTEMIs (66.9%) and 33.1% were STEMIs. The proportion of STEMIs decreased over time, from 47% to 22.9%. Age- and sex-adjusted incidence of MI increased from 274 cases per 100,000 person-years in 1999 to 287 cases per 100,000 person-years in 2000, after which a decline was observed to 208 cases per 100,000 person-years in 2008, representing a 24% relative decrease. For STEMI, both age- and sex-adjusted incident rate decreased from 133 cases per 100,000 person-years in 1999 to 50 cases per 100,000 person-years in 2008. The incidence of NSTEMI increased from 155 cases per 100,000 person-years in 1999 to 202 cases per 100,000 person-years in 2004, after which rates decreased. In more recent years, patients hospitalized with AMI were more likely to be older, female, and have coexisting illness. The number of patients who underwent revascularization procedures within 30 days after AMI increased from 40.7% in 1999 to 47.2% in 2008. For STEMI, the revascularization increased from 49.4% to 69.6%. For NSTEMI, revascularization increased from 33.4% to 41.3%. Age- and sex-adjusted 30-day mortality decreased from 10.5 in 1999 to 7.8% in 2008.

Conclusions: In this population, the incidence of AMI has decreased over time with a significant reduction in the incidence of STEMI as well as a lower death rate after NSTEMI. Potential factors related to the decline in AMI rates include smoking bans, and improved management of blood pressure and lipids.

Perspective: These data demonstrated an encouraging trend in the reduction of AMI. However, continued efforts to prevent AMI, in particular NSTEMI, are warranted. Given the prevalence of obesity and related cardiac risk factors such as hypertension and diabetes mellitus, continued aggressive prevention measures combined with monitoring of population trends are needed.

Summary written by: Elizabeth A. Jackson, MD

Effect of High-Dose Allopurinol on Exercise in Patients With Chronic Stable Angina: A Randomised, Placebo Controlled Crossover Trial

Noman A, Ang DS, Ogston S, et al.
***Lancet* 2010;375:2161–2167.**

Study Question: Does high-dose allopurinol prolong exercise capability in patients with chronic stable angina?

Methods: A total of 65 patients (ages 18-85 years) with coronary artery disease, a positive exercise tolerance test, and stable chronic angina pectoris were recruited into a double-blind, randomized, placebo-controlled, crossover study conducted in the United Kingdom. Patients were assigned to allopurinol (week 1, 100 mg/d; week 2, 300 mg/d; then 300 mg twice daily) or placebo for 6 weeks before crossover.

Results: Mean age was 64 years and 83% were men; 70% were Canadian Cardiovascular Society (CCS) angina class II, and 15% CCS I and III; 84% had ≥2-vessel disease and 85% had normal left ventricular ejection fraction. Concomitant antianginal treatment: 87% beta-blockers, 58% nitrates, 22% calcium channel blockers, and 22% nicorandil. Allopurinol increased the median time to ST depression to 298 s from a baseline of 232 s, and placebo increased it to 249 s ($p = 0.0002$). The point estimate (absolute difference between allopurinol and placebo) was 43 s. Allopurinol increased median total exercise time to 393 s from a baseline of 301 s, and placebo increased it to 307 s ($p = 0.0003$); the point estimate was 58 s. Allopurinol increased the time to chest pain from a baseline of 234 s to 304 s, and placebo increased it to 272 s ($p = 0.001$); the point estimate was 38 s. No adverse effects of treatment were reported.

Conclusions: Allopurinol seems to be a useful, inexpensive, well-tolerated, and safe anti-ischemic drug for patients with angina.

Perspective: The absolute increase in median time to ST depression with allopurinol of 43 s (10% increase) is similar to classic antianginal drugs. Inhibiting xanthine oxidase with allopurinol has been shown to decrease myocardial oxygen demand per unit of cardiac output, improve endothelial function, and reduce afterload. The results are impressive in light of the use of beta-blockers in 87%. The safety and efficacy of allopurinol need to be assessed in a much larger cohort. This very inexpensive generic drug could reduce the need for revascularization, improve quality of life, and reduce coronary events.

Summary written by: Melvyn Rubenfire, MD, FACC

Interventional Cardiology

Radiation Safety Among Cardiology Fellows

Kim C, Vasaiwala S, Haque F, Pratap K, Vidovich MI.
***Am J Cardiol* 2010;May 17:2010;106:125–128.**

Study Question: What is the current level of fellow training with respect to radiation exposure minimization and management?

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Methods: The authors invited 2,545 general and subspecialty cardiology fellows to participate in a survey on knowledge and practice of radiation safety.

Results: Of the 267 respondents (10.5% return rate), 82% had undergone formal radiation safety training. Approximately 60% of the fellows were aware of their hospital's pregnancy radiation policy and knew how to contact the hospital's radiation safety officer. Over half (52%) of the fellows always wore a dosimeter, yet most (81%) did not know their level of radiation exposure in the previous year. Formal training was associated with a greater awareness of institutional radiation pregnancy policy, knowledge of contact information of the radiation safety officer, awareness of safe levels of radiation exposure, and consistent use of dosimeters and RadPads.

Conclusions: There are significant lacunae in the education of cardiology fellows with respect to radiation safety.

Perspective: This survey, despite its small sample, raises real concerns. Lack of fellow education likely results in increased radiation exposure to the fellows, patients, and others involved in the procedure. Hopefully this paper will lead to fellowship programs across the country examining their radiation safety education and rectifying the shortcomings that may exist therein.

Summary written by: Hitinder S. Gurm, MBBS

Interventional Cardiology

Association Between Use of Bleeding Avoidance Strategies and Risk of Periprocedural Bleeding Among Patients Undergoing Percutaneous Coronary Intervention

Marso SP, Amin AP, House JA, et al.
***JAMA* 2010;303:2156–2164.**

Study Question: What is the association between the use of two bleeding avoidance strategies, vascular closure devices and bivalirudin, and post–percutaneous coronary intervention (PCI) bleeding rates in a nationally representative PCI population?

Methods: This was an analysis of data from 1,522,935 patients undergoing PCI procedures performed at 955 US hospitals participating in the National Cardiovascular Data Registry (NCDR) CathPCI Registry from January 1, 2004, through September 30, 2008. This registry is jointly sponsored by the American College of Cardiology (ACC) and the Society for Cardiovascular Angiography and Interventions. The primary outcome was periprocedural bleeding.

Results: Bleeding occurred in 30,654 patients (2%). Manual compression, vascular closure devices, bivalirudin, or vascular closure devices plus bivalirudin were used in 35%, 24%, 23%, and 18% of patients, respectively. Bleeding events were reported in 2.8% of patients who received manual compression, compared with 2.1%, 1.6%, and 0.9% of patients receiving vascular closure devices, bivalirudin, and both strategies, respectively ($p < 0.001$). Bleeding rates differed by preprocedural risk assessed with the NCDR bleeding risk model (low risk, 0.72%; intermediate risk, 1.73%; high risk, 4.69%). In high-risk patients, use of both strategies was associated with lower bleeding rates (manual compression, 6.1%; vascular closure devices, 4.6%; bivalirudin, 3.8%; vascular closure devices plus bivalirudin, 2.3%; $p < 0.001$). Both strategies were used least often in high-risk patients (14.4% vs. 21.0% in low-risk patients, $p < 0.001$).

Conclusions: Vascular closure devices and bivalirudin were associated with significantly lower bleeding rates, particularly among patients at greatest risk for bleeding.

Perspective: These findings emphasize the need for additional research to better understand why higher-risk patients are least likely to receive bleeding avoidance strategies but also suggest the need to test interventions to overcome the risk-treatment paradox, such as directing bleeding avoidance strategies to high-risk patients by providing preprocedural estimates of post-PCI bleeding. Quality improvement tools developed by the ACC NCDR are already helping with rapid adoption of bleeding avoidance and other quality initiative strategies by the cardiovascular community.

Summary written by: Debabrata Mukherjee, MD

Prevention/Vascular

Effects of Fibrates on Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

Jun M, Foote C, Lv J, et al.
***Lancet* 2010;375:1875–1884.**

Study Question: What is the effect of fibrates on major cardiovascular outcomes?

Methods: A systematic review and meta-analysis was used to investigate the effects of fibrates on major clinical outcomes. Eighteen trials provided data for 45,058 participants, includ-

ing 2,870 major cardiovascular events, 4,552 coronary events, and 3,880 deaths. Eight studies enrolled only men, and six were undertaken in diabetics. Secondary prevention was the goal of 11 studies, primary prevention in four, and the remainder included patients with and without a previous history of cardiovascular disease. Eight studies had specific lipid profile requirements for trial entry.

Results: Data for the effects of fibrate therapy on major cardiovascular events were available from five trials, including 19,944 participants and 2,870 cardiovascular events. The mean age ranged between 46 and 68 years. Overall, fibrate therapy produced a 10% relative risk (RR) reduction (95% confidence interval, 0-18) for major cardiovascular events ($p = 0.048$) and a 13% RR reduction (7-19) for coronary events ($p < 0.0001$), but had no benefit on stroke ($p = 0.69$). There was no effect of fibrate therapy on the risk of all-cause mortality ($p = 0.92$), cardiovascular mortality ($p = 0.59$), sudden death ($p = 0.19$), or nonvascular mortality ($p = 0.063$). Fibrates significantly reduced the risk of albuminuria progression and retinopathy. Serious drug-related adverse events were not significantly increased by fibrates, although increases in serum creatinine concentrations were common ($p < 0.0001$).

Conclusions: Fibrates can reduce the risk of major cardiovascular events predominantly by prevention of coronary events, and might have a role in individuals at high risk of cardiovascular events and in those with combined dyslipidemia.

Perspective: The role of fibrates, specifically fenofibrate, in diabetics and nondiabetics with and without coronary disease is not much clearer because of this meta-analysis. Statins are the drug of choice regardless of the lipid phenotype. It is reasonable to consider fibrates for primary and secondary prevention in persons with statin intolerance, preferably in combination with nonstatin lipid-lowering agents that lower the low-density lipoprotein cholesterol.

Summary written by: Melvyn Rubenfire, MD

Diabetes Mellitus, Fasting Blood Glucose Concentration, and Risk of Vascular Disease: A Collaborative Meta-Analysis of 102 Prospective Studies

The Emerging Risk Factors Collaboration.
***Lancet* 2010;375:2215–2222.**

Study Question: What are the risks associated with diabetes and blood glucose concentrations associated with vascular disease?

Methods: This was a meta-analysis using records of diabetes, fasting blood glucose concentration, and other risk factors in people without initial vascular disease. All studies were from the Emerging Risk Factors Collaboration. Combined within-study regressions adjusted for age, sex, smoking, systolic blood pressure, and body mass index were used to calculate hazard ratios for vascular disease.

Results: A total of 698,782 people from 102 prospective studies were included. The mean age of the study population was 52 years and 43% were women. Nonfatal and fatal vascular outcomes occurred in 52,765 subjects over 8.49 million person-years of risk. The adjusted risk of diabetes was 2.00 for coronary heart disease; 2.27 for ischemic stroke; 1.56 for hemorrhagic stroke; 1.84 for unclassified stroke; and 1.73 for the aggregate of other vascular deaths. Risk was higher among women compared to men, and for fatal versus nonfatal events. The adult population-wide prevalence of 10% diabetes was estimated to account for 11% of vascular deaths. Fasting glucose was associated with vascular risk in a nonlinear fashion. For higher levels of fasting glucose, increased risk of vascular disease was observed; for fasting glucose between 5.60 mmol/L and 6.09 mmol/L, the hazard ratio (HR) was 1.11; and for a fasting glucose between 6.10 mmol/L and 6.99 mmol/L, the HR was 1.17.

Conclusions: Diabetes increases risk for vascular disease approximately twofold, independent of other risk factors. Among subjects without diabetes, fasting blood glucose is modestly and nonlinearly associated with risk of vascular disease.

Perspective: These findings from a large set of prospective studies support the understanding that diabetes significantly increases a patient's risk for vascular events. It is interesting that fasting glucose among diabetics does not add prognostic information beyond traditional risk factors. Prevention of diabetes and higher fasting glucose levels to prevent vascular disease is likely more effective than glucose control once diabetes has developed.

Summary written by: Elizabeth A. Jackson, MD

White Rice, Brown Rice, and Risk of Type 2 Diabetes in US Men and Women

Sun Q, Spiegelman D, van Dam RM, et al.
***Arch Intern Med* 2010;170:961–969.**

Study Question: Is rice consumption associated with risk of type 2 diabetes?

Methods: Subjects enrolled in three prospective cohorts were used for the analysis. Men from the Health Professionals

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Follow-up Study (age range, 32-87 years) were included, in addition to women from the Nurses' Health Study (age range, 26-45 years) and Nurses' Health Study II (age range, 26-45 years). Five categories of white rice intake were created, ranging from <1 serving per month, to ≥5 servings per week. Three categories of brown rice were created, ranging from <1 serving per month to ≥2 servings per week.

Results: A total of 39,765 men and 157,463 women were included. Over 20 years of follow-up, 2,648 cases of type 2 diabetes were observed in the Health Professionals Follow-up Study cohort. In the original Nurses' Health Study cohort, 5,550 cases were observed over 22 years of follow-up, and in the Nurses' Health Study II cohort, 2,359 cases were observed during 14 years of follow-up. After adjustment for age, diet, and lifestyle factors such as physical activity, intake of white rice (≥5 servings per week vs. <1 per month) was associated with a higher risk for type 2 diabetes. The pooled relative risk was 1.7. In contrast, intake of brown rice appeared protective, with a relative risk of 0.89 for high intake (≥2 servings per week) compared to low intake (<1 serving per month). Replacing 50 g/day of white rice in the diet with the same amount of brown rice was estimated to lower the risk of type 2 diabetes by 16%. The same replacement of whole grains as a group was estimated to be associated with a 36% lower risk for type 2 diabetes.

Conclusions: Substitution of whole grains, including brown rice for white rice, lowers risk of type 2 diabetes.

Perspective: These findings provide further evidence for recommending whole grains (including brown rice) to patients at risk for diabetes. Dietary changes can have a significant impact on cardiovascular disease prevention; health care providers can use findings from studies such as this to educate their patients regarding healthy dietary practices.

Summary written by: Elizabeth A. Jackson, MD

Effects of Homocysteine-Lowering With Folic Acid Plus Vitamin B_{12} vs. Placebo on Mortality and Major Morbidity in Myocardial Infarction Survivors: A Randomized Trial

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group.
***JAMA* 2010;303:2486–2494.**

Study Question: Does supplementation with folic acid and vitamin B_{12} reduce homocysteine levels and improve mortality and morbidity among patients after myocardial infarction (MI)?

Methods: Mailed invitations to 83,237 men and women (ages 18-80 years) who were survivors of an MI resulted in 34,780 potential subjects attending screening exams. A total of 12,064 participants were enrolled in the study between September 1998 and October 2001. The intervention group received 2 mg of folic acid plus 1 mg of vitamin B_{12}, whereas the control group received matching placebo. Primary outcomes of interest were first major vascular event, defined as major coronary events (coronary death, MI, or coronary revascularization), fatal or nonfatal stroke, or noncoronary revascularization.

Results: Homocysteine levels were reduced by an average of 3.9 μmol/L (28%). During the 6.7 years of follow-up, major vascular events occurred in 1,537 participants who were randomized to folic acid and vitamin B_{12}, and 1,493 of participants randomized to placebo (25.5% vs. 24.8%). The relative risk (RR) of intervention was not significantly different from placebo (RR, 1.04). No significant effects of folic acid and vitamin B_{12} were observed for major coronary events (RR, 1.05), stroke (RR, 1.02), or noncoronary revascularization (RR, 1.18). No significant differences were observed between the two groups for vascular death, nonvascular deaths, or incident cancers.

Conclusions: Folic acid with vitamin B_{12} reduced homocysteine levels, but did not reduce vascular outcomes. Supplementation was not associated with increased cancer incidence.

Perspective: Given the billion dollar supplement industry, these data suggest that folic acid with vitamin B_{12} does not provide protection against vascular events for secondary events. These data add to other data that suggest patients may avoid increasing health care costs by not buying such supplements.

Summary written by: Elizabeth A. Jackson, MD

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