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SCANNING THE LITERATURE

Summaries of Key Journal Articles

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Arrhythmias

Comparing the 2010 North American and European Atrial Fibrillation Guidelines

Gillis AM, Skanes AC.
***Can J Cardiol* 2011;27:7-13.**

Perspective: Nine differences in recommendations for management of atrial fibrillation between the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS), the Canadian Cardiovascular Society (CCS), and the European Society of Cardiology (ESC) are:

1: The CCS emphasizes treatment of comorbidities such as hypertension and sleep apnea.

2: The ESC recommends a resting heart rate target of <110 bpm for heart rate control, the ACCF/AHA/HRS recommends this only if the ejection fraction is >40%, and the CCS recommends <100 bpm.

3: The CCS recommends atrioventricular junction ablation (AVJA) for symptomatic patients with uncontrolled rates despite drug therapy; ESC recommends AVJA for patients with permanent AF who are candidates for cardiac resynchronization therapy.

4: The ACCF/AHA/HRS and ECS recommend avoidance of class IC antiarrhythmic drugs and sotalol in patients with left ventricular hypertrophy, while the CCS recommends avoidance if there are repolarization abnormalities.

5: The ACCF/AHA/HRS and ECS recommend dronedarone to decrease the risk of hospitalization for cardiovascular causes; CCS does not.

6: The ESC recommends angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers for AF prevention; ACCF/AHA/HRS and CCS do not.

7: The ACCF/AHA/HRS makes a class I recommendation for catheter ablation in patients with paroxysmal AF who fail a single antiarrhythmic drug; CCS and ESC make this a class IIA recommendation.

8: The ACCF/AHA/HRS and ECS recommend clopidogrel plus aspirin for patients who refuse warfarin therapy; CCS recommends dabigatran.

9: The ACCF/AHA/HRS and CCS recommend the $CHADS_2$ score as a guide for stroke prevention; ESC recommends the CHA_2DS_2-VASc score.

Summary written by: Fred Morady, MD

Irbesartan in Patients With Atrial Fibrillation

The ACTIVE I Investigators.
***N Engl J Med* 2011;364:928-938.**

Study Question: What are the effects of irbesartan on the risk of cardiovascular events and maintenance of sinus rhythm in patients with atrial fibrillation?

Methods: The investigators randomly assigned patients with a history of risk factors for stroke and a systolic blood pressure

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of at least 110 mm Hg to receive either irbesartan at a target dose of 300 mg once daily or double-blind placebo. These patients were already enrolled in one of two trials (of clopidogrel plus aspirin vs. aspirin alone or vs. oral anticoagulants). The first coprimary outcome was stroke, myocardial infarction, or death from vascular causes; the second was the composite outcome plus hospitalization for heart failure.

Results: A total of 9,016 patients were enrolled and followed for a mean of 4.1 years. The mean reduction in systolic blood pressure was 2.9 mm Hg greater in the irbesartan group than placebo; the mean reduction in diastolic blood pressure was 1.9 mm Hg greater. The first coprimary outcome occurred at a rate of 5.4% per 100 person-years in both groups (hazard ratio [HR] with irbesartan, 0.99). The second coprimary outcome occurred at a rate of 7.3% per 100 person-years among patients receiving irbesartan and 7.7% for placebo (HR, 0.94). The rates of first hospitalization for heart failure (a prespecified secondary outcome) were 2.7% per 100 person-years with irbesartan, and 3.2% with placebo (HR, 0.86). Among patients who were in sinus rhythm at baseline, there was no benefit of irbesartan in preventing hospitalization for atrial fibrillation. More patients in the irbesartan group versus placebo had symptomatic hypotension (127 vs. 64) and renal dysfunction (43 vs. 24).

Conclusions: Irbesartan did not reduce cardiovascular events in patients with atrial fibrillation.

Perspective: The study suggests that among patients with atrial fibrillation, irbesartan does not reduce the risk of death from cardiovascular causes or this outcome plus hospitalization for heart failure. Among patients in sinus rhythm at randomization, there appears to be no effect on recurrence of atrial fibrillation. Based on this, irbesartan should not be routinely prescribed to patients with atrial fibrillation and well-controlled hypertension.

Summary written by: Debabrata Mukherjee, MD

Cardiovascular Surgery

Quality of Life After PCI With Drug-Eluting Stents or Coronary-Artery Bypass Surgery

Cohen DJ, Van Hout B, Serruys PW, et al., on behalf of the SYNTAX Investigators.
***N Engl J Med* 2011;364:1016-1026.**

Study Question: What is the relative improvement in quality of life of patients undergoing coronary artery bypass surgery (CABG) versus percutaneous coronary intervention (PCI) with drug-eluting stents (DES)?

Methods: The authors reported the quality of life data for the SYNTAX study. In this large multicentric trial, 1,800 patients with three-vessel or left main coronary artery disease were randomized to undergo CABG or PCI with paclitaxel-eluting stent. The Seattle Angina Questionnaire (SAQ) and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) were used to assess health-related quality of life at baseline and at 1, 6, and 12 months. The primary endpoint was the score on the angina-frequency subscale of the SAQ, with higher scores corresponding to better health status.

Results: Both revascularization strategies were associated with significant improvement in quality of life at 6 and 12 months. There was no difference in freedom from angina at 1 month between PCI and CABG groups, whereas it was slightly higher with CABG at 12 months (76.3% vs. 71.6%, $p = 0.05$). CABG was associated with a greater increase in the score on the angina-frequency subscale of the SAQ at 6 ($p = 0.04$) and 12 months (and $p = 0.03$), but this was driven by small differences between the two groups (mean treatment effect of 1.7 points at both time points). Scores on almost all other SAQ and SF-36 subscales were higher with PCI at 1 month and were similar at 6 months and beyond.

Conclusions: Compared with PCI, CABG is associated with greater relief from angina in patients with three-vessel or left main coronary artery disease at 6 and 12 months.

Perspective: The 3-year follow-up from the SYNTAX trial suggests that there is no difference in outcome with PCI or CABG in patients with low SYNTAX score, while the outcome is better with CABG in those with intermediate or high SYNTAX scores (http://www.syntaxscore.com). Also, both revascularization strategies are associated with an improvement in quality of life.

Summary written by: Hitinder S. Gurm, MBBS

General Cardiology

Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death

The Emerging Risk Factors Collaboration.
***N Engl J Med* 2011;364:829-841.**

Study Question: What are the associations of baseline diabetes and fasting blood glucose level with the risk of cause-specific death?

Methods: The investigators calculated hazard ratios for cause-specific death, according to baseline diabetes status or fasting glucose level, from individual participant data on 123,205 deaths among 820,900 people in 97 prospective studies.

Results: After adjustment for age, sex, smoking status, and body mass index, hazard ratios among persons with diabetes versus without were: 1.80 (for death from any cause, 1.25 for

death from cancer, 2.32 for death from vascular causes, and 1.73 for death from other causes. Diabetes (vs. no diabetes) was moderately associated with death from cancers of the liver, pancreas, ovary, colorectum, lung, bladder, and breast. Diabetes (vs. no diabetes) was also associated with death from renal disease, liver disease, pneumonia, and other infectious diseases; mental disorders; nonhepatic digestive diseases; external causes; intentional self-harm; nervous system disorders; and chronic obstructive pulmonary disease. Hazard ratios were appreciably reduced after further adjustment for glycemia measures, but not after adjustment for systolic blood pressure, lipid levels, inflammation, or renal markers. Fasting glucose levels exceeding 100 mg/dl, but not levels of 70-100 mg/dl, were associated with death. A 50-year-old with diabetes died, on average, 6 years earlier than a counterpart without diabetes, with about 40% of the difference in survival attributable to excess nonvascular deaths.

Conclusions: Diabetes is associated with substantial premature death from several cancers, infectious diseases, external causes, intentional self-harm, and degenerative disorders.

Perspective: These data show that diabetes is associated with substantial premature mortality, independent of several major risk factors. About 40% of the years of life lost from diabetes can be attributed to nonvascular conditions, including about 10% attributable to cancer. These findings highlight the need to better understand and prevent the multisystem consequences of diabetes.

Summary written by: Debabrata Mukherjee, MD

Estimated Glomerular Filtration Rate and Albuminuria as Predictors of Outcomes in Patients With High Cardiovascular Risk: A Cohort Study

Clase CM, Gao P, Tobe SW, et al.
***Ann Intern Med* 2011;154:310-318.**

Study Question: What is the contribution of estimated glomerular filtration rate (eGFR) and urinary albumin–creatinine ratio beyond that of traditional cardiovascular risk factors to classification of patient risk for cardiovascular and renal outcomes?

Methods: Lower eGFRs and higher urinary albumin–creatinine ratios were associated with the primary cardiovascular composite outcome (for example, an adjusted hazard ratio of 2.53 for an eGFR <30 ml/min per 1.73 m^2 and a very high urinary albumin–creatinine ratio). However, adding information about eGFR and urinary albumin–creatinine ratio to the risk reclassification analyses led to no meaningful decrease in the proportion of patients assigned to the intermediate-risk category. In contrast, eGFR and urinary albumin–creatinine ratio were strongly associated with risk for long-term dialysis, and greatly improved both model calibration and risk stratification capacity when added to traditional cardiovascular risk factors (65% assigned to intermediate-risk categories without renal information vs. 18% with renal information).

Conclusions: In patients with high vascular risk, eGFR and urinary albumin–creatinine ratio do not add much to traditional cardiovascular risk factors, but greatly improve risk stratification for renal outcomes.

Perspective: The utility of information on renal function for predicting the study outcomes may differ in the general population or in persons with renal disease, however. Further research is needed on which patients at high risk for cardiovascular events might benefit from screening for low eGFR and albuminuria and how their clinical management should be modified on the basis of the results.

Summary written by: Debabrata Mukherjee, MD

Heart Failure/Transplant

Diuretic Strategies in Patients With Acute Decompensated Heart Failure

Felker GM, Lee KL, Bull DA, et al., on behalf of the NHLBI Heart Failure Clinical Research Network.
***N Engl J Med* 2011;364:797-805.**

Study Question: How does intravenous furosemide given as a bolus every 12 hours compare with continuous infusion and at either a low or high dose in acute decompensated heart failure (ADHF)?

Methods: This was a prospective, double-blind, randomized trial, where 308 patients with ADHF received furosemide administered intravenously by means of either a bolus every 12 hours or continuous infusion and at either a low dose (equivalent to patient's previous oral dose) or high dose (2.5 times previous oral dose). Specified dose adjustments were allowed after 48 hours. The patients' global assessment of symptoms (quantified as area under the curve [AUC] of the score on a visual-analogue scale over 72 hours), and change in the serum creatinine level from baseline to 72 hours were coprimary endpoints.

Results: When bolus administration was compared with continuous infusion, there was no significant difference in patients' global assessment of symptoms (mean AUC, 4236 ± 1440 and 4373 ± 1404, respectively) or in the mean change in the creatinine level (0.05 ± 0.3 mg/dl and 0.07 ± 0.3 mg/dl, respectively). When comparing the high-dose with the low-dose strategy, there was a nonsignificant trend toward greater improvement in patients' global assessment of symptoms in the high-dose group (mean AUC, 4430 ± 1401 vs. 4171 ± 1436). There was no significant difference between these groups in the mean change in the creatinine level (0.08 ± 0.3 mg/dl with the high-dose and 0.04 ± 0.3 mg/dl with the low-dose strategy). The high-dose strategy

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was associated with greater diuresis and more favorable outcomes in some secondary measures, but also with transient worsening of renal function.

Conclusions: There were no significant differences in symptoms or in the change in renal function when intravenous furosemide therapy was administered by bolus compared with continuous infusion, or at a high dose compared with a low dose in patients with ADHF.

Perspective: This study is important because it suggests that the diuretic regimen or dose has little impact on symptoms or renal function in ADHF. Evaluating the impact of any therapy in ADHF is challenging because heart failure is often accompanied by altered renal function. Further studies are required to determine whether identifying the subtype of cardiorenal syndrome in ADHF has better predictive value in determining the response to the type of diuretic regimen.

Summary written by: Ragavendra R. Baliga, MBBS

Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT)

Zareba W, Klein H, Cygankiewicz I, et al.
***Circulation* 2011;123:1061-1072.**

Study Question: Is the response to cardiac resynchronization therapy (CRT) affected by QRS morphology in patients enrolled in the MADIT-CRT trial?

Methods: The baseline electrocardiogram was analyzed in 1,817 patients (mean age 65 years) with cardiomyopathy, an ejection fraction (EF) ≤30%, New York Heart Association class I-II symptoms, and QRS duration ≥130 ms. Sixty percent were randomly assigned to receive an implantable cardioverter-defibrillator (ICD) with CRT (CRT-D), and the remainder received an ICD. The mean follow-up was 29 months. The primary endpoint was a heart failure event or death.

Results: Seventy percent of patients had a left bundle branch block (LBBB) and the remainder had a non-LBBB (right bundle branch block [RBBB] in 13% and nonspecific interventricular conduction delay [IVCD] in 17%). In the LBBB group, CRT-D therapy was associated with a 53% reduction in the primary endpoint compared to ICD. There was not a significant reduction in the primary endpoint with CRT-D in the non-LBBB group. CRT was associated with a greater reduction in left ventricular end-diastolic volume in patients with LBBB (23%) than with non-LBBB (16%), and a greater absolute improvement in EF (12% vs. 9%, respectively).

Conclusions: CRT-D therapy is associated with a significant reduction in the risk of a heart failure event or death in patients with an EF ≤30% and class I-II heart failure who have an LBBB, but not in those who have a non-LBBB QRS morphology.

Perspective: The greater benefit of CRT in patients with LBBB most likely reflects the greater degree of left ventricular dyssynchrony associated with LBBB than with RBBB or nonspecific IVCD.

Summary written by: Fred Morady, MD

Left Ventricular Lead Position and Clinical Outcome in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) Trial

Singh JP, Klein HU, Huang DT, et al.
***Circulation* 2011;123:1159-1166.**

Study Question: How important is the position of the left ventricular (LV) lead in patients undergoing cardiac resynchronization therapy (CRT)?

Methods: This was a post-hoc analysis of 799 patients with cardiomyopathy, ejection fraction ≤30%, New York Heart Association class I-II heart failure (HF), and QRS ≥130 ms who received CRT in the MADIT-CRT trial. The position of the LV lead was documented by pre-implantation coronary venous angiography and post-implantation chest X-rays. The primary endpoint was death or HF.

Results: In the short axis, the LV lead was positioned on the lateral wall in 59%, the posterior wall in 22%, and the anterior wall in 19% of patients. There were no significant differences in HF or death between these lead positions. In the long axis, the LV lead was midventricular in 63%, basal in 23%, and apical in 14%. The prevalence of HF or death was significantly higher when the lead was apical (21.8%) than nonapical (13.3%).

Conclusions: LV leads that are apical are associated with a higher risk of HF or death in patients with mild HF undergoing CRT.

Perspective: In patients with a left bundle branch block, the LV apex often is activated earlier than basal regions. Placement of an LV lead for CRT in a region with the least amount of delayed activation is expected to be less clinically useful than when placed in basal regions of latest activation. This probably explains why the apical lead position was associated with worse outcomes in this study.

Summary written by: Fred Morady, MD

Interventional

Permanent Pacemaker Insertion After CoreValve Transcatheter Aortic Valve Implantation: Incidence and Contributing Factors (the UK CoreValve Collaborative)

Khawaja MZ, Rajani R, Cook A, et al.
***Circulation* 2011;123:951-960.**

Study Question: What are the incidence and determinants of permanent pacemaker (PPM) need in patients undergoing transcatheter aortic valve implantation (TAVI) using CoreValve?

Methods: The authors evaluated the use of PPM in 270 patients undergoing CoreValve-based TAVI at 10 centers in the United Kingdom.

Results: The study population consisted of 243 patients after excluding those with pre-existing pacemaker (n = 25) or those with incomplete data (n = 2). QRS duration increased from 105 ± 23 to 135 ± 29 ms ($p < 0.01$), and a new left bundle branch block developed in 56.8%. A PPM was required in one third of patients in the first 30 days. Need for a pacemaker varied based on pre-existing electrocardiogram (ECG) abnormalities, with 65% of patients with a right bundle branch block and 43% with a left bundle branch block needing a PPM compared with 27% of those with a normal baseline ECG. The median time to insertion was 4.0 days, with nine patients undergoing PPM on the day of TAVI. Independent predictors of PPM need were periprocedural atrioventricular block (odds ratio [OR], 6.29), balloon predilatation (OR, 2.68), use of the larger (29 mm) CoreValve prosthesis (OR, 2.50), interventricular septum diameter (OR, 1.18), and prolonged QRS duration (OR, 3.45; 95% CI, 1.61-7.40).

Conclusions: PPM implantation is common in patients undergoing TAVI, especially in patients with pre-existing conduction abnormalities.

Perspective: The need for PPM is so common in patients undergoing CoreValve TAVI that it should be considered a consequence rather than a complication of the procedure. This is likely related to the constant outward pressure exerted by the nitinol frame of the valve and the resultant impingement of the conduction system. This study provides an easy tool to identify patients who are at risk for PPM, and may be considered for prolonged observation after TAVI.

Summary written by: Hitinder S. Gurm, MBBS

Standard- vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention: The GRAVITAS Randomized Trial

Price MJ, Berger PB, Teirstein PS, et al., on behalf of the GRAVITAS Investigators.
***JAMA* 2011;305:1097-1105.**

Study Question: Do patients with high on-treatment platelet reactivity after percutaneous coronary intervention (PCI) derive clinical benefit from high-dose clopidogrel?

Methods: GRAVITAS is a randomized, double-blind, active-control trial of 2,214 patients with high on-treatment reactivity 12-24 hours after PCI with drug-eluting stents (DES) receiving high-dose clopidogrel (600 mg initial dose, 150 mg daily thereafter) or standard-dose clopidogrel (no additional loading dose, 75 mg daily) for 6 months. The primary endpoint was 6-month incidence of death from cardiovascular causes, nonfatal myocardial infarction (MI), or stent thrombosis. The key safety endpoint was severe or moderate bleeding.

Results: At 6 months, the primary endpoint had occurred in 2.3% receiving high-dose compared with 2.3% receiving standard-dose clopidogrel (hazard ratio [HR], 1.01; $p = 0.97$). Severe or moderate bleeding was not increased with the high-dose regimen (1.4% vs. 2.3%; HR, 0.59). Compared with standard-dose, high-dose clopidogrel provided a 22% absolute reduction in the rate of high on-treatment reactivity at 30 days (62 vs. 40%).

Conclusions: Among patients with high on-treatment reactivity after PCI with DES, the use of high-dose compared with standard-dose clopidogrel did not reduce the incidence of death from cardiovascular causes, nonfatal MI, or stent thrombosis.

Perspective: Previous studies have demonstrated that high platelet reactivity, while on clopidogrel treatment, is associated with a higher rate of adverse events following revascularization procedures. Even though a higher dose of clopidogrel can reduce this platelet reactivity, it has not been shown that this will lead to a reduction in adverse vascular outcomes. Pending additional clinical trials to test different treatment strategies, the clinical utility of routine platelet function testing after PCI remains dubious.

Summary written by: Daniel T. Eitzman, MD

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Prevention/Vascular

Preventing Weight Gain by Lifestyle Intervention in a General Practice Setting: Three-Year Results of a Randomized Controlled Trial

Ter Bogt NC, Bemelmans WJ, Beltman FW, Broer J, Smit AJ, van der Meer K.
***Arch Intern Med* 2011;171:306-313.**

Study Question: Can an intervention implemented in a general office practice prevent weight gain among adults?

Methods: This was a randomized controlled trial in 11 general practice locations in the Netherlands. All patients included had a body mass index (BMI) between 25 and 40 kg/m^2 and a diagnosis of hypertension and/or dyslipidemia. The intervention group received lifestyle counseling from a nurse practitioner (NP). Those in the control group received usual care from their general practitioner (GP). The primary outcome was body weight, waist circumference, blood pressure, fasting glucose, and lipids after 3 years.

Results: A total of 457 patients were included (mean age 56 years, 52% female). The dropout rate was 24% in the intervention (NP) group and 20% in the usual care (GP) group. In both groups, approximately 60% of participants achieved weight maintenance after 3 years. The change in weight over 3 years was -1.1 in the NP and -0.5 in the GP group. There was no significant difference in mean weight change or change in waist circumference. Fasting glucose was lower among those in the NP (-0.02) compared with the GP group (0.10). No difference between groups was observed for changes in lipids or blood pressure.

Conclusions: Lifestyle counseling by NPs did not result in significant benefits in terms of weight maintained, waist circumference, or other prevention efforts, including lipids and blood pressure. In the majority of patients, lifestyle counseling by providers or NPs resulted in prevention of weight gain.

Perspective: This suggests that lifestyle counseling by GPs can help patients prevent weight gain, and is equivalent to an intervention by NPs. However, the majority of physicians do not routinely counsel patients regarding lifestyle modification.

Summary written by: Elizabeth A. Jackson, MD

Olmesartan for the Delay or Prevention of Microalbuminuria in Type 2 Diabetes

Haller H, Ito S, Izzo JL Jr, et al., on behalf of the ROADMAP Trial Investigators.
***N Engl J Med* 2011;364: 907-917.**

Study Question: What is the effect of treatment with olmesartan on the occurrence of microalbuminuria in patients with type 2 diabetes and normoalbuminuria?

Methods: The investigators randomly assigned 4,447 patients with type 2 diabetes to receive olmesartan (40 mg once daily) or placebo for a median of 3.2 years. Additional antihypertensive drugs (except angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers [ARBs]) were used as needed to lower blood pressure to <130/80 mm Hg. The primary outcome was time to first onset of microalbuminuria. Times to the onset of renal and cardiovascular events were analyzed as secondary endpoints.

Results: The target blood pressure (<130/80 mm Hg) was achieved in nearly 80% of patients taking olmesartan and 71% taking placebo; blood pressure measured in the clinic was lower by 3.1/1.9 mm Hg in the olmesartan group than with placebo. Microalbuminuria developed in 8.2% of the patients in the olmesartan group (178 of 2,160 patients who could be evaluated) and 9.8% with placebo (210 of 2,139); time to the onset of microalbuminuria was increased by 23% with olmesartan (hazard ratio for onset of microalbuminuria, 0.77). The serum creatinine level doubled in 1% of the patients in each group. Slightly fewer patients in the olmesartan group than placebo had nonfatal cardiovascular events—81 of 2,232 (3.6%) compared with 91 of 2,215 patients (4.1%), but a greater number had fatal cardiovascular events—15 compared with 3 patients, a difference that was attributable in part to a higher rate of death from cardiovascular causes in the olmesartan than placebo group among patients with pre-existing coronary heart disease (2.0% vs. 0.2%).

Conclusions: Olmesartan was associated with a delayed onset of microalbuminuria.

Perspective: The primary finding of this study is that ARB-based therapy with olmesartan in patients with type 2 diabetes increased the time to the onset of microalbuminuria by 23%. The overall rates of cardiovascular and cerebrovascular events were low, but there were more deaths from cardiovascular causes in the olmesartan group than placebo. An excessive reduction of blood pressure in some high-risk patients may have conferred a predisposition to an increased risk of death; however, a direct effect of olmesartan cannot be ruled out and requires additional evaluation.

Summary written by: Debabrata Mukherjee, MD

Antihypertensive Treatment and Secondary Prevention of Cardiovascular Disease Events Among Persons Without Hypertension: A Meta-Analysis

Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA.
JAMA 2011;305:913-922.

Study Question: Does treatment with antihypertensive medications among patients with a history of cardiovascular disease (CVD), but not hypertension reduce the risk of death and future CVD events?

Methods: This was a meta-analysis of eligible studies identified from MEDLINE (from 1950 to January 2011), EMBASE, and the Cochrane Collaboration Central Register of Controlled Clinical Trials, and manual examination of references in selected articles. Studies were included if they were randomized controlled trials of antihypertensive treatments including patients with blood pressure <140 mm Hg systolic and/or <90 mm Hg diastolic. A total of 874 papers were identified, from which 25 trials met inclusion/exclusion criteria. Information on participant characteristics, trial design and duration, treatment drug, dose, control, and clinical events was extracted using a standardized protocol. Outcomes included stroke, myocardial infarction (MI), congestive heart failure (CHF), composite CVD outcomes, CVD mortality, and all-cause mortality.

Results: Participants who received antihypertensive medications had a reduced risk for stroke (relative risk [RR], 0.77), MI (RR, 0.80), CHF (RR, 0.71), and composite CVD events (RR, 0.85) compared to controls. Both CVD mortality (RR, 0.83) and all-cause mortality (RR, 0.87) were also lower among participants on antihypertensive medications compared to controls. The corresponding absolute risk reductions per 1,000 persons were −7.7 for stroke, −13.3 for MI, −43.6 for CHF events, −27.1 for composite CVD events, −15.4 for CVD mortality, and −13.7 for all-cause mortality. Results did not differ according to trial characteristics or subgroups defined by clinical history.

Conclusions: Among patients with clinical history of CVD but without hypertension, antihypertensive treatment was associated with decreased risk of stroke, CHF, composite CVD events, and all-cause mortality. Additional randomized trial data are necessary to assess these outcomes in patients without CVD clinical recommendations.

Perspective: This meta-analysis suggests that use of antihypertensive therapies among patients with CVD can further reduce events. As the authors suggest, prior to changes in secondary prevention, randomized trials are warranted, particularly among diabetic patients.

Summary written by: Elizabeth A. Jackson, MD

Long-Term Effects of Intensive Glucose Lowering on Cardiovascular Outcomes

The ACCORD Study Group.
***N Engl J Med* 2011;364:818-828.**

Study Question: What are the 5-year outcomes of intensive glucose lowering on mortality and key cardiovascular events?

Methods: The investigators randomly assigned participants with type 2 diabetes and cardiovascular disease or additional cardiovascular risk factors to receive intensive therapy (targeting a glycated hemoglobin below 6.0%) or standard therapy (targeting a level of 7-7.9%). After termination of the intensive therapy, due to higher mortality in the intensive-therapy group, the target glycated hemoglobin level was 7-7.9% for all participants, who were followed until the planned end of the trial.

Results: Before the intensive therapy was terminated, the intensive-therapy group did not differ significantly from the standard-therapy group in the rate of the primary outcome (composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes) ($p = 0.13$), but had more deaths from any cause (primarily cardiovascular) (hazard ratio [HR], 1.21) and fewer nonfatal myocardial infarctions (HR, 0.79). These trends persisted during the entire follow-up period (HR for death, 1.19; and HR for nonfatal myocardial infarction, 0.82). After the intensive intervention was terminated, the median glycated hemoglobin level in the intensive-therapy group rose from 6.4% to 7.2%, and the use of glucose-lowering medications and rates of severe hypoglycemia and other adverse events were similar in the two groups.

Conclusions: Compared with standard therapy, the use of intensive therapy for 3.7 years to target a glycated hemoglobin level below 6% reduced 5-year nonfatal myocardial infarctions, but increased 5-year mortality.

Perspective: The higher risk of death in the intensive-therapy group would imply that a therapeutic approach that targets glycated hemoglobin levels below 6% should not be generally recommended in this population. Further analyses should explore possible explanations, such as the role of various drugs, drug combinations, or drug interactions; weight gain; the relatively short intervention period; and the observed interaction between the blood pressure and glycemia trials with respect to mortality.

Summary written by: Debabrata Mukherjee, MD

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Association Between Body-Mass Index and Risk of Death in More Than 1 Million Asians

Zheng W, McLerran DF, Rolland B, et al.
***N Engl J Med* 2011;364:719-729.**

Study Question: Is body mass index (BMI) associated with increased mortality risk among Asian men and women?

Methods: Subjects enrolled in 19 studies from Asia were included in this pooled analysis. Subjects with missing data on age, BMI, vital status, and age under 18 years were excluded. Additional exclusion criteria included those with a BMI over 50 kg/m^2. Over 1.1 million adults were followed over a mean follow-up of 9.2 years. Cox regression models were used to adjust for potential confounding factors. A total of 1,141,609 subjects (535,199 men and 606,410 women) were included. The overall mean BMI was 22.9 ± 3.6 (range, 19.8-23.7). Approximately 120,700 deaths were recorded (35.7% from cardiovascular disease, and 29.9% from cancer). The lowest risk of death was observed among persons with a BMI range of 22.6-27.5 kg/m^2. Risk for death was increased for those with a BMI under or over that range. For those with a BMI of 35 kg/m^2 or greater, the increased risk was 50%. For subjects with a BMI of 15 kg/m^2 or less, the risk of death ranged from 2.0-2.8%. A similar U-shaped association was observed between BMI and risk for death from cancer, cardiovascular disease, and other causes. In cohorts comprising Indians and Bangladeshis, the risk of death from any cause and from causes other than cancer or cardiovascular disease was increased among persons with a BMI of 20 kg/m^2 or less, as compared to those with a BMI between 22.6 and 25 kg/m^2. No increased risk of death for this group was noted with a higher BMI.

Conclusions: Underweight was associated with an increased risk of death in all Asian populations, and increase in BMI was associated with an increased risk of death for East Asians, but not for Indians and Bangladeshis.

Perspective: This large-scale study suggests that BMI is an important marker for health; being underweight is a significant indicator of increased all-cause mortality. Factors associated with being underweight may identify opportunities for intervention. Among those populations with increased mortality risk associated with increased BMI, a similar analysis will assist public health efforts in areas of preventive care.

Summary written by: Elizabeth A. Jackson, MD

Public Health Importance of Triggers of Myocardial Infarction: A Comparative Risk Assessment

Nawrot TS, Kunzli N, Munters E, Nemery B.
***Lancet* 2011;377:732-740.**

Study Question: What is the importance and relevance of triggers for myocardial infarction (MI)?

Methods: Literature from PubMed and the Web of Science (January 1960 to January 2010) was examined for studies which identified triggers of nonfatal MI. Data from these studies were used to calculate population-attributable fractions for MI risk. When feasible, the authors completed a meta-regression analysis for studies which examined the same trigger.

Results: Of the 528 references identified, 36 epidemiological studies were included. Exposure prevalence for triggers ranged from 0.04% for cocaine to 100% for air pollution. The odds ratios ranged from 1.05 to 23.7. Trigger risks for MI, from highest to lowest, included cocaine, heavy meal, smoking of marijuana, negative emotions, physical exertion, positive emotions, anger, sexual activity, traffic exposure, respiratory infections, coffee consumption, and air pollution. Air pollution as a trigger was based on a difference of 30 μg/m^3 in particulate matter with a diameter <10 μm (PM10). Accounting for the odds ratio and prevalence of exposure, the highest population-attributable fraction for MI risk was related to traffic exposure (7.4%) followed by physical exertion (6.2%), alcohol (5.0%), coffee (5.0%), negative emotions (3.9%), anger (3.1%), heavy meal (2.7%), positive emotions (2.4%), sexual activity (2.2%), cocaine use (0.9%), marijuana use (0.8%), and respiratory infections (0.6%).

Conclusions: Air pollution is an important risk for MI, given the magnitude of risk and prevalence in the population.

Perspective: This well-done analysis demonstrates that risks which may appear to be small may have significant public health importance if they are present for significant amounts of time. These results suggest that reducing exposure to air pollution could lead to reductions in MI.

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