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Observational Data and Surrogate Endpoints are No Substitute for Randomized Clinical Trial Outcomes

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Observational studies and surrogate endpoints are no substitute for randomized clinical trial outcomes. Numerous observational studies and studies using surrogate endpoints have demonstrated a therapeutic intervention is beneficial with randomized clinical trials showing that this therapeutic intervention increases cardiovascular events. This editorial will discuss a few of these studies.

Many studies have demonstrated that patients with complex ventricular arrhythmias associated with heart disease are at increased risk for new coronary events and for sudden cardiac death [1]. Antiarrhythmic drugs were used in widespread practice to treat ventricular arrhythmias to prevent sudden cardiac death prior to the Cardiac Arrhythmia Suppression Trial 1 (CAST I) [2]. In fact, physicians were reluctant to allow their patients to be randomized in this trial because there was a 50% chance of being randomized to placebo.

CAST I was a prospective, double-blind, randomized study in survivors of myocardial infarction with ventricular arrhythmias in which 730 patients were randomized to encainide or flecainide and 725 patients to placebo [2]. Adequate suppression of ventricular arrhythmias by encainide or flecainide was required before randomization. Despite adequate suppression of ventricular arrhythmias, at 10-month follow-up, encainide and flecainide significantly increased mortality from arrhythmia or cardiac arrest 3.6 times and significantly increased total mortality 2.5 times [2].

The administration of prophylactic lidocaine to patients with acute myocardial infarction to reduce mortality used to be a common practice. However, a meta-analysis of randomized controlled trials of prophylactic use of lidocaine in patients with acute myocardial infarction showed an increased mortality for patients treated with prophylacic lidocaine [3].

Many persons are taking antioxidants to reduce cardiovascular events. However, numerous randomized trials with antioxidant vitamins have shown either no effect on mortality or an adverse effect on mortality. A meta-analysis of 47 randomized trials for primary prevention and secondary prevention showed that the antioxidant supplements significantly increased mortality by 5% [4].

Numerous observational studies have demonstrated that increased homocysteine levels are associated with coronary artery disease, stroke, peripheral arterial disease, and carotid arterial disease [5]. However a meta-analysis of 8 randomized trials of 37,485 patients at increased risk for cardiovascular events showed that lowering of homocysteine levels with folic acid did not reduce cardiovascular events, cancer, or mortality [6].

Numerous studies have found that a low serum high-density lipoprotein (HDL) cholesterol level is a risk factor for coronary artery disease [7]. However, randomized controlled trials have not demonstrated that raising serum HDL cholesterol by drug therapy reduces cardiovascular events.

In a randomized, double-blind study of 15,067 patients at high risk for cardiovascular events, patients were randomized to torcetrapib plus atorvastatin or to atorvastatin [8]. At 12-month follow-up, those treated with torcetrapib had a 72% increase in serum HDL cholesterol but a significant 25% increase in cardiovascular events and a significant 58% increase in mortality [8].

Compared with simvastatin plus placebo, simvastatin plus fenofibrate did not reduce the incidence of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke at 4.7-year follow-up in 5,518 randomized type 2 diabetics at high risk for cardiovascular disease [9].

Niacin is used in clinical practice to decrease cardiovascular events. The Niacin Plus Statins to Prevent Vascular Events (AIM-HIGH) study randomized 3,414 patients with coronary artery disease and a low serum HDL cholesterol treated with simvastatin or simvastatin plus ezetimibe to 1,500 to 2,000 mg daily of extended -release niacin or to placebo [10]. Niacin increased serum HDL cholesterol 25%, decreased serum low-density lipoprotein cholesterol 12%, and decreased serum triglycerides 29%. The National heart, Lung, and Blood Institute data and safety monitoring board stopped this study at 3 years because the primary endpoint of myocardial infarction, ischemic stroke, death due to coronary heart disease, hospitalization for an acute coronary syndrome, or symptom-driven revascularization was 16.4% in patients treated with niacin versus 16.2% in patients treated with placebo and because niacin insignificantly increased stroke by 61% [10].

Numerous observational studies supported use of hormone replacement therapy to prevent cardiovascular disease in postmenopausal women [11]. The Heart Estrogen/Progestin Replacement Study (HERS) randomized 2,763 postmenopausal women with documented coronary artery disease to HRT or placebo [12]. At 4.1-year follow-up, there was no significant difference in cardiovascular events between patients treated with HRT or placebo [12]. However, HRT significantly increased by 52% nonfatal myocardial infarction or death from coronary artery disease during the first year of therapy. HRT also significantly increased at 4.1-year follow-up venous thromboembolic events by 289% and gallbladder disease requiring surgery by 38% [12]. At 6.8-year follow-up of HERS, HRT did not decrease cardiovascular events, insignificantly increased all-cause mortality by 10%, significantly increased venous thromboembolism by 208%, significantly increased biliary tract surgery by 48%, and insignificantly increased any cancer by 19% [13].

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The estrogen plus progestin component of the Women's Health Initiative (WHI) study included 16,608 healthy postmenopausal women aged 50-79 years randomized to estrogen plus progestin or to placebo [14]. At 5.2-year follow-up, this component of the WHI study was prematurely discontinued because the excess risk of events included in the global index was 19 per 10,000 person-years [14]. Absolute excess risks per 10,000 person-years included 7 more coronary events, 8 more strokes, 8 more episodes of pulmonary embolism, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Some physicians recommend percutaneous coronary intervention (PCI) for patients with stable coronary artery disease and myocardial ischemia to decrease mortality and myocardial infarction. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial randomized 2,287 patents with stable coronary artery disease and myocardial ischemia to optimal medical therapy or optimal medical therapy plus PCI [15]. At 4.6-year follow-up, the incidence of all-cause mortality plus nonfatal myocardial infarction was 19.0% in patients randomized to PCI plus optimal medical therapy versus 18.5% to patients randomized to optimal medical therapy alone (p not significant) [15].

The 2011 American College of Cardiology Foundation/American Heart Association expert consensus document on hypertension in the elderly included sections on unanswered questions and future research [16]. Guidelines based on expert medical opinion need to be revised after data from randomized controlled clinical trials are available [17].

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References

1. Aronow WS, Sorbera C (2008) Ventricular arrhythmias in the elderly. In: Aronow WS, Fleg JL, Rich MW, (eds). Cardiovascular Disease in the Elderly, (4thedn), New York: Informa Healthcare: 605-625.
2. (1989) Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. N Engl J Med 321: 406-412.
3. Hine LK, Laird N, Hewitt P, Chalmers TC (1989) Meta-analytic evidence against prophylactic use of lidocaine in acute myocardial infarction. Arch Intern Med 149: 2694-2698.
4. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C (2007) Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 297: 842-857.
5. Aronow WS (2003) Homocysteine. The association with atherosclerotic vascular disease in older persons. Geriatrics 58: 22-24, 27-28.
6. Clarke R, Halsey J, Lewington S, Lonn E, Armitage J, et al. (2010) Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: meta-analysis of 8 randomized trials involving 37,485 individuals. Arch Intern Med 170: 1622-1631.
7. Aronow WS, Ahn C (1996) Risk factors for new coronary events in a large cohort of very elderly patients with and without coronary artery disease. Am J Cardiol 77: 864-866.
8. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, et al. (2007) Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 357: 2109-2122.
9. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, et al. (2010) Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 362: 1563-1574.
10. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, et al. (2011) Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 365: 2255-2267.
11. Stampfer MJ, Colditz GA, Willet WC, Manson JE, Rosner B, et al. (1991) Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the Nurses' Health study. N Engl J Med 325: 756-762.
12. Hulley S, Grady D, Bush T, Furberg C, Herrington D, et al. (1998) Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 280: 605-613.
13. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, et al. (2002) Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study Follow-Up (HERS II). JAMA 288: 49-57.
14. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, et al. (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 288: 321-333.
15. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, et al. (2007) Optimal medical therapy with or without PCI for stable coronary artery disease. N Engl J Med 356: 1503-1516.
16. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, et al. (2011) ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Coll Cardiol 57: 2037-2114.
17. Aronow WS (2011) Hypertension guidelines. Hypertension 58: 347-348.