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CARDIOLOGY

Warfarin Ineffective for HF Without Atrial Fibrillation

In the WARCEF trial, reduced stroke rates were offset by increased bleeding.

The benefits of chronic anticoagulation in patients with heart failure (HF) who do not have atrial fibrillation are controversial. Previous clinical trials were underpowered to generate conclusive evidence, and results of observational studies have conflicted.

In the international WARCEF trial, investigators compared warfarin with aspirin in 2305 patients without a contraindication to anticoagulation (mean age, 61; 80% men). All were in sinus rhythm and had systolic left ventricular ejection fractions less than 35% (mean, 25%). Patients were randomized to receive warfarin (target international normalized ratio [INR], 2.0–3.5; mean, 2.5) or aspirin (325 mg) daily. Sites received sham INR results for patients in the aspirin group.

At a mean follow-up of 3.5 years, the rate of the primary endpoint of ischemic stroke, intracerebral hemorrhage, or all-cause death did not differ significantly between the warfarin and aspirin groups (7.47 and 7.93 per 100 patient-years, respectively). Rates of ischemic stroke were significantly lower with warfarin than with aspirin (0.72 vs. 1.36 per 100 patient-years), but rates of major hemorrhage were twice as high (1.78 vs. 0.87 per 100 patient-years). During follow-up, patients in the warfarin group were within the target INR range 63% of the time.

COMMENT

WARCEF showed no net benefit of warfarin in patients in sinus rhythm with systolic heart failure. Up to now, in the absence of evidence, the use of anticoagulation in this patient population has presumably depended on the instincts of the treating clinician. This well-designed clinical trial injects much-needed evidence into the decision; however, whether clinicians will change their practices based on the results remains to be seen. Furthermore, we don't know whether newer agents, which may provide more reliable anticoagulation than warfarin, might be beneficial in this context.

— Frederick A. Masoudi, MD, MSPH, FACC, FAHA

Homma S et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. **N Engl J Med** *2012 May 17; 366:1859.*

Autologous BMC Therapy for Heart Failure Disappoints in Phase II Trial

Transendocardial cell administration fails to improve left ventricular systolic function, maximal oxygen consumption, or defect size.

Several small studies have suggested that bone marrow mononuclear cell (BMC) therapy for ischemic cardiomyopathy is safe. However, none of these studies were large enough to demonstrate efficacy.

In the randomized, controlled FOCUS-CCTRN trial, investigators studied BMC therapy in 92 patients (mean age, 63; 89% men) with ischemic left ventricular (LV) systolic dysfunction (LV ejection fraction, ≤45%). All were symptomatic (heart failure, angina, or both) and had ischemia on single-photon emission computed tomography (SPECT) and coronary artery disease that was not amenable to revascularization. Patients were assigned 2:1 to receive injections of either 100 million BMCs or placebo into LV epicardial regions identified as viable by electromechanical mapping. Coprimary endpoints were LV end-systolic volume, peak oxygen consumption, and ischemic burden measured by SPECT.

At 6 months, none of the primary outcomes differed significantly between the two groups. There was also no difference in total defect size or in regional wall motion by SPECT. In exploratory analysis, higher CD34 or CD133 cell counts were associated with greater increases in LV ejection fraction.

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COMMENT

FOCUS-CCTRN showed no benefit of bone marrow mononuclear cell therapy on surrogate endpoints. Although the study may inform the design of future trials, whether this approach will ever be useful for patients with heart failure remains entirely unclear. Clinical merit would be credible only if larger trials were to show benefits on meaningful outcomes in this population. ***— Frederick A. Masoudi, MD, MSPH, FACC, FAHA***

Perin EC et al. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: The FOCUS-CCTRN trial. **JAMA** *2012 Apr 25; 307:1717.*

The Factor V Leiden Paradox

Data from a systemic review suggest that pulmonary embolism and deep-vein thrombosis do not necessarily have the same etiology.

The factor V Leiden (FVL) mutation is associated with a greater risk for deep vein thrombosis (DVT) than for pulmonary embolism (PE); this observation is paradoxical because most pulmonary emboli are thought to arise from DVT. However, factors other than FVL might increase the risk for one type of thrombosis versus another.

To explore this possibility, investigators from the Leiden University Medical Center in the Netherlands performed a systematic review of published studies of risk factors for DVT and PE and calculated risk estimates from a large population-based, case-control study. The table shows the risks for DVT and PE associated with several patient factors that are implicated in venous thrombosis, including body mass index, leg injury, oral contraceptive use, pregnancy, puerperium, FVL, black race, chronic obstructive lung disease, and sickle cell trait.

No differences between the risk for DVT and PE were found for many other patient factors, including age, sex, immobilization/stasis, surgery, exercise, smoking, alcohol, cancer, inflammatory bowel disease, kidney disease, hyperthyroidism, blood group, and prothrombin G20210A.

COMMENT

These findings weaken the link between DVT and PE and show that these two manifestations of venous thrombosis have different risk estimates. Furthermore, since most patients have more than one risk factor, the development of DVT or PE might depend on whether a particular combination of risk factors is present. Based on the data from this study, DVT would be more common in pregnant patients with FVL, whereas PE would be more common in blacks with chronic obstructive lung disease. Additional study is needed to confirm these assumptions.

***— David Green, MD, PhD,* Journal Watch Oncology and Hematology**

Risk Factors for DVT and PE

	OR* for DVT	OR for PE
Factors that favor DVT vs. PE		
Increased body-mass index†	2.50	2.21
Minor leg injury	6.3	2.4
Oral contraceptive use (Europe)	4.1–6.6‡	2.5–3.9
Pregnancy	7.8	2.3
Puerperium	7.6	3.5
Factor V Leiden	3.4–10.0	1.3–4.8
Factors that favor PE vs. DVT		
Black race†	0.59	1.4
Chronic obstructive lung disease	1.6–1.7	3.2–3.6
Sickle cell trait	1.1	3.9

** Odds ratio*
† Relative risk
‡ Ranges indicate data from more than one study.

van Langevelde K et al. Broadening the factor V Leiden paradox: Pulmonary embolism and deep-vein thrombosis as two sides of the spectrum. **Blood** *2012 Apr 10; [e-pub ahead of print]. (http://dx.doi.org/10.1182/blood-2012-02-407551)*

What's the Incidence of Venous Thromboembolism After Knee Arthroscopy?

Incidence was 0.40% in this large cohort study.

A million arthroscopic knee procedures are performed annually in the U.S., according to the CDC (http://www.cdc.gov/nchs/data/nhsr/nhsr011.pdf); pharmacologic prophylaxis to prevent venous thromboembolism (VTE) is not administered routinely after this procedure. In a retrospective study from California's Kaiser Permanente health system, researchers calculated the incidence of symptomatic VTE after 21,000 recent elective knee arthroscopies. Patients with histories of VTE and patients who received prophylaxis were excluded; only 2% of patients met these exclusion criteria.

The 90-day incidence of symptomatic VTE was 0.40%, with cases divided roughly evenly between proximal deep venous thrombosis only and pulmonary embolism; only a few cases involved isolated calf-vein thromboses. VTE risk was above average in people 50 or older (odds ratio, 1.5) and in women who had been prescribed oral contraceptives recently (OR, 2.2).

COMMENT

Because the incidence of symptomatic VTE after knee arthroscopy is quite low, these authors endorse the American College of Chest Physicians guideline, which states "For patients undergoing knee arthroscopy without a history of prior VTE, we suggest no thromboprophylaxis rather than prophylaxis" (*Chest* 2012; 141 [Suppl 2]:7S). For patients with histories of VTE (and perhaps patients at high risk for other reasons), pharmacologic prophylaxis seems reasonable. ***— Allan S. Brett, MD, Journal Watch General Medicine***

Maletis GB et al. Incidence of symptomatic venous thromboembolism after elective knee arthroscopy. **J Bone Joint Surg Am** *2012 Apr 18; 94:714.*

Between-Arm Systolic Blood Pressure Differences and Adverse Outcomes

In a prospective cohort study, differences in systolic blood pressure were associated with excess risk for cardiovascular events and death.

A recent meta-analysis showed that a between-arm systolic blood pressure (SBP) difference of ≥15 mm Hg is associated with peripheral vascular disease and increased cardiovascular (CV) and all-cause mortality (*JW Cardiol* Apr 2012, p. 30, and *Lancet* 2012; 379:905). Included in the meta-analysis were the results of a prospective study involving 230 primary care patients with hypertension. Here's a closer look at that study.

After sitting for 5 minutes, patients had BP taken in one arm, then in the other. Bilateral arm BP readings were recorded at three successive clinic visits, and the readings were averaged. At enrollment, 55 patients (24%) had a mean between-arm SBP difference of ≥10 mm Hg and 21 (9%) had a difference of ≥15 mm Hg. After a median follow-up of 9.8 years, adjusted risks for death were significantly increased in patients with a between-arm SBP difference of ≥10 mm Hg (hazard ratio, 3.6) and in those with a difference of ≥15 mm Hg (HR, 3.1). In 183 participants without preexisting CV disease, these risks were also increased (HR, 2.6 and 2.7, respectively). Risks for CV death and combined adverse CV and cerebrovascular events were similar.

COMMENT

In this long-term prospective study, between-arm systolic blood pressure differences in people treated for hypertension were associated with excess risks for all-cause death and adverse cardiovascular outcomes. Notably, JNC 7 (http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf) recommends BP "verification in the contralateral arm" in all patients with hypertension. Identifying patients with between-arm SBP differences is clinically useful, as it alerts clinicians to track BP and the response to treatment consistently in the same arm. Whether evaluating such patients for underlying vascular disease lowers risk for adverse outcomes, however, is unclear.
— Paul S. Mueller, MD, MPH, FACP, Journal Watch General Medicine

Clark CE et al. The difference in blood pressure readings between arms and survival: Primary care cohort study. **BMJ** *2012 Mar 20; 344:e1327.*

Value of Asking About Family History of Heart Disease

Systematically asking primary care patients to report such histories substantially increased the percentage identified as having high CV risk.

Family history of premature heart disease is a recognized cardiovascular (CV) risk factor, yet data on the value of systematically asking patients about it in primary care are scant. Researchers in the U.K. randomized 24 primary care practices to either a usual-care approach, in which patients were stratified into standard Joint British Societies 2 (JBS2) categories of 10-year CV risk (average, <10%; moderate, 10%–19%; high, ≥20%), or an intervention in which patients also completed questionnaires about family history of premature heart disease. If family history was positive (coronary disease in a male first-degree relative aged <55 or a female first-degree relative aged <65), JBS2 risk level was multiplied by 1.5 (a multiplier that is supported by epidemiologic data).

The analysis included 748 patients (age range, 30–65) without previously diagnosed diabetes or heart disease. The percentage of patients classified as high risk was significantly higher in the intervention group than the usual-care group (4.8% vs. 0.3%), even after adjustment for patient and practice characteristics.

COMMENT

Cardiovascular outcomes were not assessed in this trial. However, the findings show that adding information about family history of premature heart disease significantly increases the percentage of patients identified as high risk; for example, an editorialist notes that this approach would identify an additional 400 to 500 high-risk patients in a 10,000-patient practice.
— Jamaluddin Moloo, MD, MPH, Journal Watch General Medicine

Qureshi N et al. Effect of adding systematic family history enquiry to cardiovascular disease risk assessment in primary care: A matched-pair, cluster randomized trial. **Ann Intern Med** *2012 Feb 21; 156:253.*

Berg AO. Family history gets a boost. **Ann Intern Med** *2012 Feb 21; 156:315.*

Fitness and Overweight: How Do They Contribute to Cardiovascular Risk?

Improvements in one measure somewhat — but not completely — offset deteriorations in the other.

Controversy surrounds the relative contributions of changes in weight and fitness to cardiovascular risk. In this longitudinal cohort study, 3148 adults underwent at least three preventive medical examinations over a 27-year period at a single U.S. clinic. Fitness was measured by maximal exercise stress testing; body-mass index and percent body fat were proxies for fatness (a term used by the authors throughout their article). Researchers analyzed the effect of changes in these measures between the first and second examinations on the subsequent development of risk factors.

During a mean follow-up of approximately 6 years after the second examination, 24%, 14%, and 19% of participants developed hypertension, metabolic syndrome, and hypercholesterolemia, respectively. Increasing fatness and decreasing fitness were both associated with increased risks for all three outcomes — even after adjusting for each other and other potential confounders (see table). Stable or increased fitness attenuated, but did not fully compensate for, the detrimental effects of increased fatness; similarly, reduction in fatness attenuated the detrimental effects of loss of fitness.

COMMENT

In this analysis, both increased fatness and reduced fitness were associated with increased risks for hypertension, hypercholesterolemia, and metabolic syndrome, even when accounting for other factors. However, improvements in fitness attenuated the effects of increased body-mass index and percent body fat, and vice versa. The ideal, then, is to motivate our patients to both maintain a normal body weight and improve their fitness level, not just one or the other.

— *Kirsten E. Fleischmann, MD, MPH, Journal Watch General Medicine*

Lee D-C et al. Changes in fitness and fatness on the development of cardiovascular disease risk factors: Hypertension, metabolic syndrome, and hypercholesterolemia. **J Am Coll Cardiol** *2012 Feb 14; 59:665.*

Effects of Fatness and Fitness Changes on Cardiovascular Risk Factors

Risk factor	HR per 1-kg/m^2 increase in BMI	HR per 1-MET increase in fitness
Hypertension	1.16	0.93
Metabolic Syndrome	1.37	0.78
Hypercholesterolemia	1.18	0.88

HR, hazard ratio; BMI, body-mass index; MET, metabolic equivalent

Anticoagulation for Pregnant Women with Mechanical Prosthetic Heart Valves

Encouraging results with low-dose warfarin throughout pregnancy, but the approach must be validated.

Use of mechanical heart valves generally requires anticoagulation with coumarin or heparin derivatives and is associated with higher maternal and fetal complication rates during pregnancy. Because fetal complications may be related to warfarin dose, Italian investigators conducted an observational study of a preoperative counseling protocol for women with valvular heart disease who planned to become pregnant. The protocol included a trial to determine the warfarin dose required to achieve target international normalized ratios (INRs; 1.5–2.5 for aortic valves) for use with newer, presumably less thrombogenic, prosthetic valves. Cesarean delivery was planned to minimize fetal intracranial bleeding.

Of 40 participants, 22 required aortic or mitral valve replacement. Of 17 women who required <5 mg of warfarin daily in the anticoagulation trial, all chose mechanical prosthetic valves; of 5 who required >5 mg warfarin daily, 3 chose bioprostheses. A total of 20 pregnancies occurred. The 3 pregnancies in patients with bioprostheses were uneventful. In the remaining 17 pregnancies, one patient elected to switch to low-molecular-weight heparin and experienced valve thrombosis that was successfully treated, and the other 16 were continued on low-dose warfarin; all 17 delivered healthy babies. More than 90% of weekly INR determinations were within the therapeutic range.

COMMENT

Decision making about anticoagulation in pregnant women with prosthetic heart valves remains problematic because of competing risks (e.g., valve thrombosis, warfarin-associated embryopathy, third-trimester fetal hemorrhage). Although this preoperative counseling strategy yielded encouraging results with low-dose warfarin throughout pregnancy, editorialists warn of the study's limitations (small sample size, applicability only to those who require low-dose anticoagulation, inconsistency with studies showing fetal complications, and limited safety data for the international normalized ratio targets used). Thus, further validation is needed as the search for a safe and effective anticoagulation regimen for pregnant women with mechanical valves continues.

— *Kirsten E. Fleischmann, MD, MPH, Journal Watch Women's Health*

De Santo LS et al. Mechanical aortic valve replacement in young women planning on pregnancy: Maternal and fetal outcomes under low oral anticoagulation, a pilot observational study on a comprehensive pre-operative counseling protocol. **J Am Coll Cardiol** *2012 Mar 20; 59:1110.*

Elkayam U and Goland S. The search for a safe and effective anticoagulation regimen in pregnant women with mechanical prosthetic heart valves. **J Am Coll Cardiol** *2012 Mar 20; 59:1116.*

A Snapshot of Real-World TAVR Results

In a French registry study, outcomes were similar to those in the PARTNER trial.

Recent publication of the PARTNER randomized trial findings (*JW Cardiol* Nov 2010, p. 85, and *N Engl J Med* 2010; 363:1597) led to FDA approval of transcatheter aortic-valve replacement (TAVR) in the U.S. To monitor how TAVR is used in clinical practice, investigators in France established an industry-funded national registry among 34 authorized centers and now report on 3195 patients (mean age, 83; 49% women) who underwent TAVR between January 2010 and October 2011. Median follow-up was 114 days and 99.8% complete.

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References: **(1)** Garrison GD, Dugan SE. Varenicline: A First-Line Treatment Option for Smoking Cessation. *Clin Ther* 2009;**31**(3):463-491. **(2)** Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. *Int J Clin Pract* 2006;**60**(5):571-576. **(3)** Jiménez-Ruiz C, Berlin I, Hering T. Varenicline. A Novel Pharmacotherapy for Smoking Cessation. *Drugs* 2009;**69**(10):1319-1338. **(4)** Kaur K, Kaushal S, Chopra SC. Varenicline for Smoking Cessation: A Review of the Literature. *Curr Ther Res Clin Exp* 2009;**70**:35-54.

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References: 1. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, *et al.* Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension. *N Engl J Med* 2005;**353**(20):2148-2157. 2. Pepke-Zaba J, Gilbert C, Collings L, Brown MCJ. Sildenafil Improves Health-Related Quality of Life in Patients With Pulmonary Arterial Hypertension. *Chest* 2008;**133**:183-189. 3. Croom KF, Curran MP. Sildenafil, A Review of its Use in Pulmonary Arterial Hypertension. *Drugs* 2008;**68**(3):338-397.

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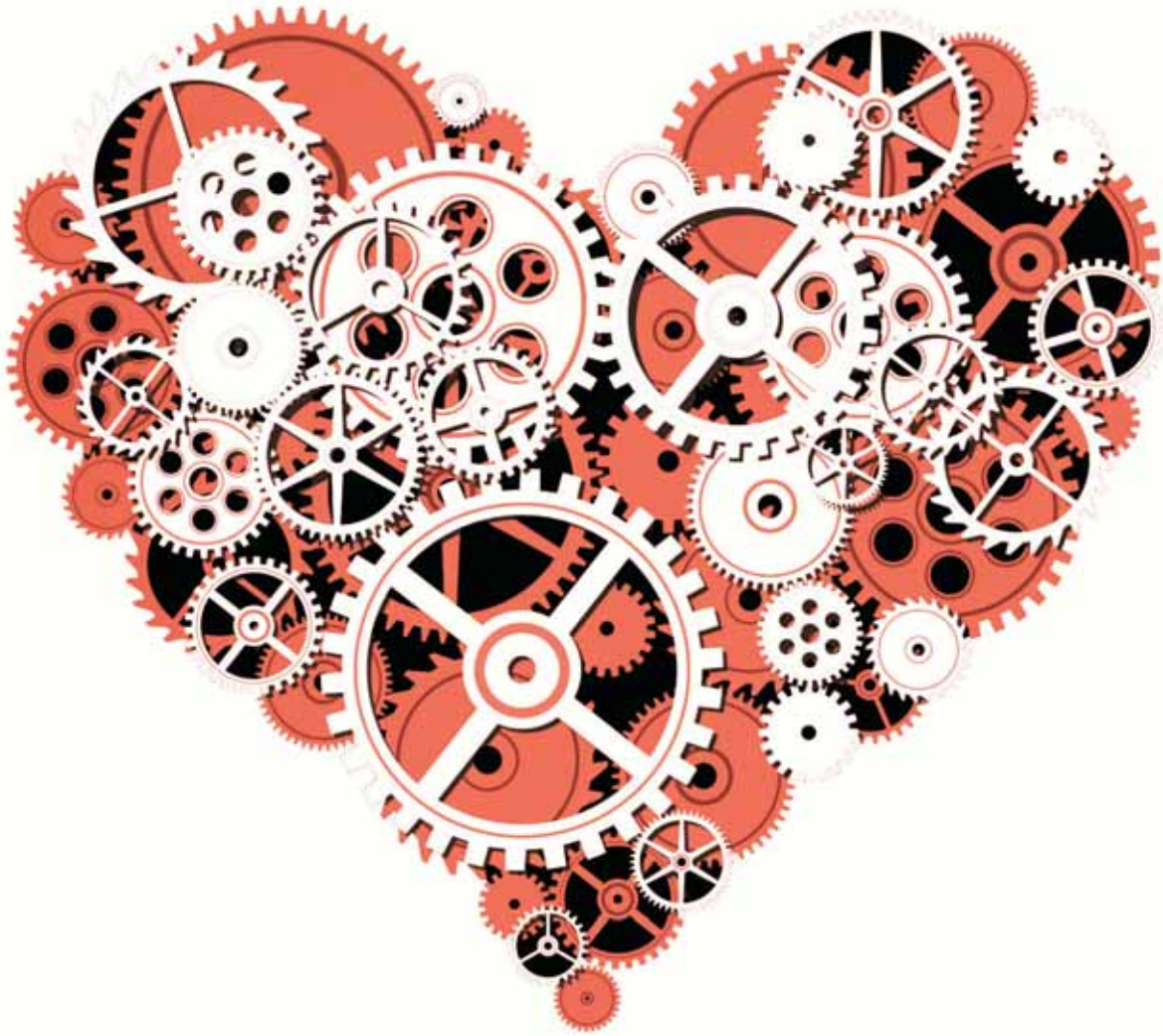

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CASE HISTORY

Anticoagulation Conundrum

This case was originally published on CardioExchange, an online community hosted by the **New England Journal of Medicine** *and* **Journal Watch** *and dedicated to improving cardiac patient care. Membership is free for medical professionals. Register at www.cardioexchange.org to read an expert commentary by James Fang, MD, and join a lively discussion among your peers.*

A 75-year-old woman presents to a general cardiology clinic for the first time. She has a history of atrial fibrillation, sick-sinus syndrome requiring a permanent pacemaker, hypertension, and dyslipidemia. She has no specific complaints other than shortness of breath on exertion. Her medications include aspirin (81 mg daily), carvedilol (25 mg twice daily), lisinopril (5 mg daily), and furosemide (40 mg daily).

The woman has just moved in with her daughter, who lives in the area. She helps take care of her grandchildren and buys the groceries for the entire family.

A transthoracic echocardiogram reveals severe left-ventricular hypertrophy and an LV ejection fraction of 45% (atrial fibrillation is consistently rate-controlled). The patient has mild aortic, mitral, and tricuspid regurgitation. A mass detected in the left atrium does not opacify with contrast, suggesting the possibility of a thrombus.

The patient has brought medical notes from previous physician visits, showing that she was hospitalized 3 years ago with a severe headache. She was found to have a subarachnoid hemorrhage that required embolization. At that time, she had an INR in the 2.0 to 2.4 range on warfarin, which was discontinued in light of the subarachnoid hemorrhage.

A year later, the patient was hospitalized with severe bilateral calf pain. A CT scan revealed thrombotic occlusion of the right common iliac and right external iliac arteries. She underwent bilateral iliac and left profunda thrombectomy, with stent placement in the right common iliac artery. After much discussion between the cardiologists and neurosurgeons, the decision was made to re-initiate anticoagulation with warfarin.

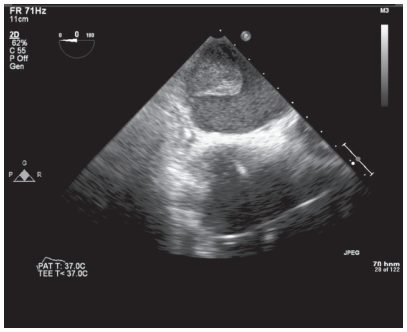
Within 6 months after discharge, the patient was readmitted with a massive GI bleed requiring 8 units of packed red blood cells. At the time of this admission, her INR was 2.2. Subsequently, all anticoagulation was stopped. Six months before the patient's current clinic visit, she had re-initiated aspirin therapy, which she tolerated well.

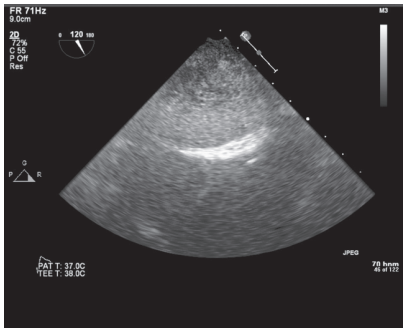
Given this history, the patient is scheduled for an elective transesophageal echocardiogram the day after presenting to the clinic. The images below show the TEE findings: a large 5.5-cm × 2.7-cm heterogeneous multilobulated mass, attached along the posterior wall of the left atrium, which likely represents a thrombus. ***— Tariq Ahmad, MD, MPH***

QUESTIONS

1. Would you anticoagulate this patient? If so, which agent would you use?
2. Would you perform any further diagnostic testing?

Tariq Ahmad, MD, MPH, is a cardiology fellow at Duke University Medical Center.





All patients were high-risk, with a mean Society of Thoracic Surgeons 30-day mortality estimate of 14.4%. Most (75%) procedures were performed in cardiac catheterization laboratories with SAPIEN (67%) or CoreValve (33%) devices inserted via transfemoral (75%), transapical (18%), subclavian (6%), or transaortic/carotid (2%) access. Procedural success was 97%, with a mean hospital stay of 11 days. Mortality was 10% at 30 days and 24% at 1 year, and the 30-day stroke rate was 3.4%. New permanent pacemakers were required in 12% of SAPIEN recipients and 24% of CoreValve recipients. Grade 2 or higher periprosthetic regurgitation at 30 days was observed in 17% of patients and was an independent predictor of 1-year mortality (hazard ratio, 2.5). The proportion of patients who preferred TAVR over conventional surgery increased from 14.4% in 2010 to 17.1% in 2011.

COMMENT

This large, real-world, multicenter experience with transcatheter aortic-valve replacement in a country where devices have been approved for several years yielded outcomes similar to those in the PARTNER trial, although 30-day mortality was higher. The study also highlights some ways in which the European approach differs from the U.S. approach, including less use of hybrid operating rooms, general anesthesia, and nontransfemoral access routes. Increasing patient preference for TAVR requires careful monitoring to ensure that only appropriate inoperable or high-risk patients receive treatment while we await device and technique improvements and long-term durability data.

— Howard C. Herrmann, MD

Gilard M et al. Registry of transcatheter aortic-valve implantation in high-risk patients. **N Engl J Med** *2012 May 3; 366:1705.*

Long-Term Safety of Biodegradable Coronary Stents

Excellent 10-year results in the first cohort of poly-l-lactic–acid stent recipients allay one concern, but the clinical role of this device remains unclear.

The first fully biodegradable (poly-*l*-lactic acid) Igaki-Tamai stent was implanted more than a decade ago, but concerns about inflammatory reactions and the advent of drug-eluting stents (DESs) hampered its development. More recently, biodegradable devices have reentered clinical investigation (*JW Cardiol* Jul 2007, p. 60, and *Lancet* 2007; 369:1869, *JW Cardiol* May 2009, p. 43, and *Lancet* 2009; 373:897), renewing interest in the long-term results of the initial device. In this report, investigators present 10-year results in the first cohort of patients treated with the Igaki-Tamai stent.

A total of 50 patients received 84 stents for de novo (59) or restenotic (4) lesions. Clinical follow-up data were obtained on 96% of participants at 10 years. Rates of freedom from all-cause mortality and cardiac death were 87% and 98%, respectively; only one cardiac death occurred. Including one in-hospital stent thrombosis (on day 5, after discontinuation of antiplatelet therapy), the target-lesion revascularization (TLR) and target-vessel revascularization rates were both 16% per person at 3 years; cumulative rates were 28% and 42%, respectively, at 10 years. One patient experienced very late definite stent thrombosis, in a vessel in which a DES had subsequently been placed. Intravascular ultrasound studies suggested that most stent struts had disappeared by 3 years, although remnants were identified histologically in an atherectomy specimen at 42 months.

COMMENT

This unique follow-up study demonstrated excellent long-term safety of the first biodegradable stent. The device degraded by 3 years, suggesting that later target-lesion revascularizations resulted from atherosclerotic progression. Reassuring as these findings are, the TLR rate with the Igaki-Tamai stent was not as good as with current-generation drug-eluting stents, supporting the case for a biodegradable device that also incorporates an antiproliferative drug. Several such devices have now entered clinical trials, but their use will not be justified without evidence of their long-term safety and superiority to current metallic stents. **— *Howard C. Herrmann, MD***

Nishio S et al. Long-term (>10 years) clinical outcomes of first-in-man biodegradable poly-l-lactic acid coronary stents: Igaki-Tamai stents. **Circulation** *2012 Apr 16; [e-pub ahead of print]. (http://dx.doi.org/10.1161/CIRCULATIONAHA.110.000901)*

Waksman R. The disappearing stent: When plastic replaces metal. **Circulation** *2012 Apr 16; [e-pub ahead of print]. (http://dx.doi.org/10.1161/CIRCULATIONAHA.112.103911)*

Stenting or Medical Therapy for Stable CAD: A Game Changer?

A new meta-analysis convincingly supports optimal medical therapy as an initial approach.

The benefits of percutaneous coronary intervention (PCI) for acute myocardial infarction (MI) are well established, but the procedure's effectiveness for stable coronary artery disease (CAD) has long been questioned. Trials have consistently failed to show that PCI reduces the risk for MI or death compared with an initial strategy of optimal medical therapy (OMT). Previous meta-analyses have been limited by the "moving targets" of evolving approaches to PCI and OMT, and by the conflation of stable CAD with acute coronary syndromes. Now, investigators have conducted a meta-analysis of trials comparing contemporary medical therapy and stent-era PCI in patients with stable ischemic heart disease.

Included were eight trials involving 7229 patients (mean age, 57–64; 68%–100% men). All trials were prospective, randomized comparisons of PCI plus medical therapy versus medical therapy alone and were limited to patients with stable CAD. Stents were implanted during ≥72% of initial PCIs, although drug-eluting stents were used in only a small minority. During a mean weighted follow-up of 4.3 years, no significant differences were found between the PCI and OMT groups in the risks for death (8.9% and 9.1%), nonfatal MI (8.9% and 8.1%), unplanned revascularization (21.4% and 30.7%), or persistent angina (29% and 33%).

COMMENT

Although rates of unplanned revascularization and persistent angina trended lower in the percutaneous coronary intervention group than in the medical therapy group, the differences were not statistically significant, and the rates of death and MI were similar in both groups. The angina differences are particularly difficult to interpret because the trial definitions of this endpoint varied, intermediate (1–2-year) comparisons were not possible, and not all crossovers to PCI were accounted for. Furthermore, whether a preponderance of drug-eluting stents would have altered these results is not known. Regardless, physicians can reasonably conclude (and inform their patients) that PCI for stable CAD will not reduce their risk for death or MI, and that in most cases of persistent angina, a trial of OMT before pursuing PCI is entirely rational, if not prudent.
— *Frederick A. Masoudi, MD, MSPH, FACC, FAHA*

Stergiopoulos K and Brown DL. Initial coronary stent implantation with medial therapy vs medical therapy alone for stable coronary artery disease: Meta-analysis of randomized controlled trials. **Arch Intern Med** *2012 Feb 27; 172:312.*

How Meaningful Are Troponin Elevations After PCI? CME

Registry findings raise questions about the current threshold for MI.

Periprocedural myocardial infarction (MI) is a critical endpoint in percutaneous coronary intervention (PCI) trials. The universal definition of MI is an elevation in either creatine kinase myocardial band (CKMB) or troponin level of 3 times the upper limit of normal. A substantial evidence base supports this threshold for CKMB but is lacking for troponin. To assess the association between CKMB and troponin elevations after PCI and mortality, investigators studied data from an industry-sponsored, multicenter U.S. registry on 4930 consecutive patients (mean age, 65; 69% men) who underwent nonemergent PCI during 2004–2007. Patients with ST-segment-elevation MI, elevated or missing baseline CKMB levels, or missing postprocedural CKMB or troponin levels were excluded.

According to the universal definition, 7.2% of patients experienced an MI by CKMB, 24.3% experienced an MI by troponin, and 74.7% did not experience an MI by either biomarker. When analyzed as continuous variables, both CKMB and troponin elevations were significantly associated with increased 1-year mortality; however, as dichotomous variables using the threefold threshold, the association was

stronger for CKMB (adjusted hazard ratio, 2.5) than for troponin (HR, 1.7). A troponin elevation 20 times the upper limit of normal yielded a frequency of MI and risk for 1-year mortality that were similar to those of a threefold elevation in CKMB.

COMMENT

This study suggests that with respect to mortality, the universal definition of myocardial infarction after percutaneous coronary intervention has markedly different implications depending on the biomarker used: A threefold elevation in creatine kinase myocardial band level is roughly equivalent to a much higher elevation in troponin level. Editorialists express strong reservations about the findings because baseline troponin levels — shown by other studies to be prognostically important — were unavailable. Nonetheless, the study underlines the need for a better understanding of postprocedural troponin elevations, particularly since troponin has largely replaced CKMB in clinical practice. ***— Frederick A. Masoudi, MD, MSPH, FACC, FAHA***

Novack V et al. Troponin criteria for myocardial infarction after percutaneous coronary intervention. **Arch Intern Med** *2012 Mar 26; 172:502.*

Alpert JS and Jaffe AS. Interpreting biomarkers during percutaneous coronary intervention: The need to reevaluate our approach. **Arch Intern Med** *2012 Mar 26; 172:508.*

Optimal Platelet Inhibition for Primary Percutaneous Coronary Intervention

In STEMI patients, prasugrel plus a glycoprotein IIb/IIIa inhibitor produced the best physiologic results during the first 24 hours of treatment.

Adequate platelet inhibition is very important during percutaneous coronary intervention for ST-segment-elevation myocardial infarction. The relative effects of upstream inhibition of platelet activation (IPA) with oral clopidogrel or prasugrel and downstream inhibition of platelet aggregation with glycoprotein IIb/IIIa inhibition is unknown. In this industry-supported study, investigators in Italy compared oral prasugrel and intravenous tirofiban in 100 patients randomized 3:1:1:1 to four groups.

- Prasugrel alone (60 mg)
- Tirofiban (25 µg/kg bolus) and prasugrel
- Tirofiban bolus and clopidogrel
- Tirofiban bolus and infusion (0.15 µg/kg/min for 2 hours) with either prasugrel or clopidogrel (600 mg) at the end of the infusion

IPA was assessed by light aggregometry at baseline and at various time points up to 24 hours.

At 30 minutes, IPA was significantly lower with prasugrel (36%) than with tirofiban (87%). IPA remained higher with tirofiban for the first 2 hours, but then dropped — at 18–24 hours, IPA was higher with prasugrel. Platelet aggregation was generally higher with prasugrel than with clopidogrel, particularly when assessed with a thrombin-receptor agonist peptide. The most consistent platelet inhibition over 24 hours was achieved with the combination of prasugrel and tirofiban (either bolus or with infusion), which resulted in 10 times less variability than either agent alone.

COMMENT

In this small physiologic study, a combination of upstream inhibition of activation with prasugrel and early inhibition of aggregation with tirofiban achieved the most consistent and complete platelet inhibition. Although in many emergency departments, prasugrel is already used instead of clopidogrel for ST-segment-elevation myocardial infarction because of its faster onset of action, these findings suggest that adding a glycoprotein IIb/IIIa inhibitor in the first 2 hours enhances platelet inhibition. This combination warrants further testing, with other agents such as bivalirudin and in studies powered for safety and efficacy. ***— Howard C. Herrmann, MD***

Valgimigli M et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) Trial. **JACC Cardiovasc Interv** *2012 Mar; 5:268.*

North Carolina's Program to Regionalize STEMI Care Is Not Beneficial

Patient outcomes did not differ at participating and nonparticipating hospitals.

Regionalization of trauma care, in which patients are diverted to qualified trauma centers, improves outcomes. The American Heart Association and other groups have advocated similar regionalization of care for ST-segment elevation myocardial infarction (STEMI). The Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) initiative was one of the earliest and most robust programs. Investigators analyzed a statewide hospital discharge database from 2005 to 2007 (spanning the year before and year after implementation of the program) to determine whether patient outcomes were better in RACE-participating hospitals than nonparticipating hospitals. The investigators also analyzed Medicare claims data to determine whether outcomes were better in North Carolina than in the rest of the U.S.

The study included 6565 STEMI patients treated at RACE-participating hospitals and 5850 STEMI patients treated at nonparticipating hospitals. Mortality decreased in the post-RACE year compared with the pre-RACE year both at participating hospitals and nonparticipating hospitals (adjusted odds ratios for mortality, 0.86 and 0.68). The mortality change did not differ significantly between participating and nonparticipating hospitals. Statewide 30-day STEMI mortality among Medicare patients was the same in North Carolina as in the rest of the U.S. (AOR, 0.99).

COMMENT

Editorialists call these results "sobering," because they suggest that the process improvements of the RACE program did not help patients. Together with recent data showing that catheterization is not safer at hospitals able to perform coronary artery bypass grafting (*JAMA* 2011; 306:2487) and that catheterization capability does not necessarily predict better outcomes (*JW Cardiol* Jun 2010, p. 47, and *Arch Intern Med* 2010; 170:433), these results call into question the regionalization of STEMI care. ***— Daniel J. Pallin, MD, MPH, Journal Watch Emergency Medicine***

Glickman SW et al. Assessment of temporal trends in mortality with implementation of a statewide ST-segment elevation myocardial infarction (STEMI) regionalization program. **Ann Emerg Med** *2012 Apr; 59:243.*

Carr BG and Hollander JE. The RACE to where? For what? **Ann Emerg Med** *2012 Apr; 59:253.*

JW ONLINE CME

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This is one of four questions in a recent Journal Watch Online CME exam.

from *"How Meaningful Are Troponin Elevations After PCI?"* (p. 46)

Which of the following statements describes a finding from an analysis of data from a multicenter registry in nonemergent-PCI recipients?

A. The universal definition of MI yielded a higher periprocedural MI rate for CKMB than for troponin.
B. As a continuous variable, either CKMB or troponin elevation was associated with significantly elevated 1-year mortality.
C. By the universal definition of MI, troponin was more strongly associated with 1-year mortality than CKMB was.
D. By the universal definition of MI for troponin, >50% of patients had periprocedural MI.

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Hospital Strategies for Decreasing AMI Mortality

Five specific organizational practices significantly associated with lower risk-standardized mortality rates

In-hospital mortality after acute myocardial infarction (AMI) has decreased significantly over the past several decades but varies considerably among U.S. hospitals. In a quantitative analysis building on previous qualitative research (*JW Cardiol* May 2011, p. 40, and *Ann Intern Med* 2011; 154:384), these investigators sought to identify specific strategies associated with low 30-day risk-standardized mortality rates (RSMRs) after AMI.

Of 590 hospitals surveyed, 537 (91%) responded. The surveyed hospitals had an overall weighted mean RSMR of 15.4% (standard deviation, 1.5; range, 11.5%–21.7%). Multivariate analysis revealed several strategies that were significantly associated with lower-end RSMRs:

- Holding monthly meetings to review AMI cases with hospital clinicians and staff who transport patients to the hospital
- Having an on-site cardiologist at all times
- Cultivating an environment in which clinicians are encouraged to solve problems creatively
- Avoiding cross-training of intensive care unit nurses for cardiac catheterization laboratories
- Having at least one quality-improvement champion who is a physician rather than a nurse

The more of these strategies hospitals employed, the lower their RSMRs tended to be. A secondary analysis, in which having a cardiologist always on site was excluded from the variables, produced essentially the same findings.

COMMENT

All would agree that the best possible care for patients with acute myocardial infarction involves all caregivers working together, reviewing their results, and instituting quality-improvement processes; however, specific approaches for achieving these goals are difficult to evaluate. The strategies identified in this study were associated with lower 30-day risk-standardized mortality and can easily be implemented in most hospitals. ***— Joel M. Gore, MD***

Harlan Krumholz, MD, the Editor-in-Chief of *Journal Watch Cardiology*, is a coauthor of the article summarized but had no role in its selection or the review of this summary.

Bradley EH et al. Hospital strategies for reducing risk-standardized mortality rates in acute myocardial infarction. **Ann Intern Med** *2012 May 1; 156:618.*