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Clinical Cardiology [ALERT]

Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

Has the Benefit of Prophylactic ICDs Been Overestimated Among Those Suffering From Nonischemic Cardiomyopathy?

By Cara Pellegrini, MD

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Dr. Pellegrini reports no financial relationships relevant to this field of study.

SYNOPSIS: Prophylactic implantable cardioverter defibrillator implantation was not associated with an all-cause mortality benefit among patients presenting with nonischemic symptomatic systolic heart failure in DANISH, a randomized, controlled trial in Denmark.

SOURCE: Køber L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016 Aug 27. [Epub ahead of print].

Implantable cardioverter defibrillator (ICD) implantation for primary prevention of sudden cardiac death (SCD) in patients presenting with symptomatic systolic heart failure carries a class Ia recommendation in the American Heart Association guidelines, regardless of heart failure etiology. The rationale for that recommendation extending to the nonischemic heart failure population largely rests on data from SCD-HeFT, a randomized, controlled trial that enrolled 2,521 patients between 1997 and 2001, and was comprised of nonischemic and ischemic heart failure patients in nearly equal proportion. Medical therapy has improved greatly since then, and cardiac resynchronization therapy (CRT) now is used widely in this population, raising the question of whether nonischemic patients truly benefit from the addition of ICD implantation to current standards of clinical care.

The Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality (DANISH) was an investigator-initiated, randomized, unblinded, controlled trial that was conducted at all centers in Denmark that implant ICDs. Patients presenting with symptomatic systolic heart failure with left ventricular ejection fraction ≤ 35% and left ventricular dysfunction out of proportion to coronary artery disease (> 95% of patients

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had undergone a cardiac catheterization; those with one-vessel to two-vessel coronary artery disease could be included, if the extent of disease was not considered sufficient to explain cardiac dysfunction) were eligible for enrollment. Poorly rate-controlled permanent atrial fibrillation or a requirement for dialysis were exclusions. Primary outcome was death from any cause. Secondary outcomes included SCD, cardiovascular death, aborted SCD or sustained ventricular tachycardia, and change from baseline in quality of life.

The authors randomized 1,116 patients to ICD implantation or usual clinic care and followed the patients for a mean of 5.6 years. There was approximately 5% crossover between groups. The average age was 63.5 years, about 25% of patients were female, about 75% presented with an idiopathic etiology of their heart failure, and a slight majority of patients featured New York Heart Association class II symptoms vs. class III symptoms. Medical therapy was excellent, with 92% of patients receiving beta-blocker therapy, 96.5% receiving an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and 58% on a mineralocorticoid-receptor antagonist. More than half the patients presented with a CRT device. Although ICD therapy halved the risk of SCD from 8.2% to 4.3%, the effect on overall mortality was not significant (hazard ratio for death from any cause = 0.87; 95% confidence interval, 0.68-1.12; $P = 0.28$). There was an interaction with age, suggesting ICD implantation may provide survival benefits for younger patients. A similar differential effect was not seen for presence of CRT device. The authors concluded that prophylactic ICD implantation does not provide mortality benefit for nonischemic heart failure patients.

■ COMMENTARY

ICDs are very specific in what they target: prevention of arrhythmic death. Non-cardiovascular death and even non-arrhythmic cardiovascular death are beyond the scope of the ICD, unlike pharmacologic therapy for heart failure, which can affect both arrhythmic mortality and events due to pump failure. Thus, to see a benefit in overall mortality from ICD implantation, the contribution of arrhythmic death to overall death must be sizable in the population studied. This trial provides additional evidence that the competing mortality risks among the nonischemic heart failure population together with the smaller risk of SCD, as compared to that in ischemic heart failure, minimizes the overall mortality benefit from ICD implantation in this population.

There are several potential explanations for the differences in outcome between this study and SCD-HeFT. The much higher use of beta-blockers and other pharmacologic agents for heart failure management in DANISH decreased the overall cardiovascular death rate as well as the contribution of SCD to overall mortality. Additionally, no patients in SCD-HeFT were treated with CRT, which was highly prevalent in the DANISH population. The etiology of the nonischemic cardiomyopathy may have differed as well; certainly, the percentages of patients suffering from hypertension and diabetes were much less in DANISH. Also, DANISH patients were on average 3.5 years older than SCD-HeFT patients, again contributing to a larger competing risk of non-arrhythmic mortality. Finally, it remains possible that DANISH, at half the size of SCD-HeFT, was underpowered to detect a truly present, but small, mortality benefit.

DANISH should prompt cardiologists to consider who among the large nonischemic heart failure population is most likely to benefit from ICD therapy. One consistent message is that younger patients with less competing mortality risk have a greater likelihood of benefit. Whether there is a U-shaped curve similar to that proposed for ischemic cardiomyopathy patients, where not only the sickest, but also the most healthy, are unlikely to benefit from ICD implantation, is as yet unclear. Interestingly, both DANISH and SCD-HeFT showed no benefit of ICDs in women, a population that really deserves greater study. It is really good news that with improving medical therapy, ICDs might not be warranted across the board for heart failure patients. However, it may be premature to conclude that they provide no benefit to the population of nonischemic heart failure patients as a whole. ■

ABSTRACT & COMMENTARY

An Important Update in the Bare-metal vs. Drug-eluting Stent Debate

By Jeffrey Zimmet, MD, PhD

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Dr. Zimmet reports no financial relationships relevant to this field of study.

SYNOPSIS: This randomized trial showed no difference between contemporary drug-eluting stents and bare-metal stents with regard to death and myocardial infarction, while drug-eluting stents demonstrated an advantage in both repeat revascularization and stent thrombosis at six years of follow-up.

SOURCE: Bønaa KH, Mannsverk J, Wiseth R, et al. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016 Aug 29. [Epub ahead of print].

Advances in percutaneous coronary intervention (PCI) devices continue improving the safety and efficacy of this procedure, which clinicians use each year to treat millions of patients. Compared with first-generation drug-eluting stents (DES), second-generation devices not only are more deliverable and easier to use, but also are considered to be safer and more effective, with faster healing and lower rates of stent thrombosis. This has led to wide-ranging speculation about whether these benefits would lead to reductions in hard events, including mortality and non-fatal myocardial infarction (MI). Often lost in the conversation comparing first-generation DES, which no longer are in use, with more modern devices is the fact that its counterpart, the bare-metal stent (BMS), also has improved substantially over time.

The NORSTENT trial was designed as a real-world comparison of long-term outcomes with contemporary DES and BMS. All patients undergoing PCI in Norway between Sept. 15, 2008, and Feb. 14, 2011, were evaluated for enrollment in the trial. Patients were excluded from the trial primarily if they previously had been treated with coronary stents, if they were undergoing treatment of a bifurcation requiring a two-stent technique, or if they had known comorbidities limiting life expectancy to less than five years. Patients with a contraindication to long-term dual antiplatelet therapy (in the case of this trial, nine months of dual antiplatelet therapy) or an ongoing indication for warfarin also were excluded. During this period, out of a total of 20,663 patients undergoing PCI, 12,425 were eligible to participate, and 9,013 actually were randomized. The majority of BMS patients received modern thin-strut stents, while among DES patients, 82.9% received everolimus-eluting stents and 13.1% zotarolimus-eluting stents. In the DES group, 5.1% received older, first-generation stents.

At six years of follow-up, there was no significant difference in the primary composite outcome of all-cause mortality and nonfatal MI between the DES and BMS groups (16.6% vs. 17.1%; $P = 0.66$). Unsurprisingly, rates of target-lesion revascularization were lower in the DES group (5.3 vs. 10.3%; $P < 0.001$), as were rates of all revascularization (16.5 vs. 19.8%; hazard ratio, 0.76; $P < 0.001$). This translates to a number needed to treat of 30 to prevent one revascularization with DES over BMS. The six-year rates of definite stent thrombosis were low in both groups, but were significantly lower in the DES group (0.8% vs. 1.2%; $P = 0.0498$).

The authors concluded that there was no significant difference in death or non-fatal MI between DES and BMS at six years of follow-up, while both restenosis and stent thrombosis were significantly lower with DES.

■ COMMENTARY

In many ways, conclusions from this trial are in the eye of the beholder; however, several points are worth highlighting. First, the lack of a difference between contemporary DES and BMS in all-cause death and MI is unsurprising based on past data, but serves as a useful reminder. The reason to choose DES in the average case is clearly not to prevent these outcomes.

Contrary to the perceptions of many, but in agreement with multiple recent studies, including the EXAMINATION trial and the SCAAR registry, DES as compared with BMS actually showed reduced rates of definite stent thrombosis. This is quite a turnaround from the early days of first-generation DES, which carried higher rates of late ST. That this difference persists out to six years of follow-up provides very solid reassurance about the safety of current DES devices. The observation that this

difference did not translate to lower rates of MI or mortality simply reflects the low overall frequency of stent thrombosis.

What about repeat revascularization? Again, there is no surprise in the revelation that DES leads to lower rates of clinical restenosis and repeat procedures. What might surprise some is that the magnitude of the difference is relatively low (approximately a 5% absolute risk reduction in target lesion revascularization), and that restenosis of the target lesion with BMS was only approximately 10% at six years. Two points are worth mentioning here. First, clinical restenosis requiring repeat intervention is an important outcome, both with regard to healthcare costs and to quality of life. That the NORSTENT study did not demonstrate a coincident improvement in subjective health status most likely reflects, as noted by one editorialist, a failure of the measurement tool rather than a lack of true benefit. On the other hand, the relatively low event rates with BMS means there still is a role for these devices in current practice.

Although the improved safety and efficacy of DES means that these stents will remain the scaffolds of choice in the majority of clinical situations — especially in the context of higher restenosis risk, such as in diabetics, multiple stents, smaller vessels, and chronic total occlusions — BMS remain an attractive option for patients who require noncardiac surgery, who cannot tolerate or adhere to longer-term dual antiplatelet therapy, or for whom cost is an issue. ■

ABSTRACT & COMMENTARY

Optimal Blood Pressure in Patients Presenting with Aortic Stenosis

By Michael Crawford, MD, Editor

SYNOPSIS: A post-hoc analysis of patients suffering from mild to moderate aortic stenosis in a study of low-density lipoprotein cholesterol lowering showed that the optimal blood pressure for the best survival was 130-139/70-90 mmHg.

SOURCES: Nielsen OW, Sajadieh A, Sabbah M, et al. Assessing optimal blood pressure in patients with asymptomatic aortic valve stenosis: The Simvastatin Ezetimibe in Aortic Stenosis Study (SEAS). *Circulation* 2016;134:455-468.

O'Gara PT. Management of hypertension in patients with mild to moderate aortic stenosis: Navigating the SEAS. *Circulation* 2016;134: 469-471.

Systemic hypertension is common in aortic stenosis patients and is associated with worse outcomes. However, little is known about what the optimal blood pressure is in these patients in whom relative hypotension may not be tolerated well. Investigators from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) trial sought to answer this question using the data from this otherwise negative study. The SEAS study excluded patients with heart failure, diabetes, or known atherosclerosis and enrolled patients with aortic flow velocities between 2.5 m/s and 4 m/s with normal ejection fraction and no symptoms.

This report is a post-hoc analysis of the data to correlate blood pressure (BP) with outcomes in 1,767 patients who had adequate measurements of aortic velocity and BP. The primary endpoint for this analysis was all-cause mortality. BP was defined as an average of all measurements during the first four years of follow-up (median 4.3 years). A U-shaped association between systolic BP (SBP) and all-cause mortality was identified with values from 130-139 associated with the best survival with diastolic (DBP) in the range of 60-90 mmHg. SBP > 139 increased the risk of death (hazard ratio [HR] = 1.7 for SBP > 160; $P = 0.033$) as did lower SBPs (HR = 1.6 for SBP 120-129, $P = 0.039$). Low SBP remained harmful in patients suffering from mild and moderate aortic stenosis. A high SBP was associated with myocardial infarction and cardiovascular death in patients with mild but not moderate aortic stenosis. These data were not changed by adjustment for a history of hypertension or antihypertensive treatment. The authors concluded that in patients with asymptomatic aortic stenosis without heart failure, diabetes, and overt atherosclerotic vascular disease, the optimal SBP is 130-139 and the optimal DBP is 70-90 mmHg.

■ COMMENTARY

Guidelines recommend treatment of hypertension in patients presenting with aortic stenosis, but target BPs are not given. This post-hoc observational analysis of the SEAS trial provides some useful information in this regard. SBPs > 160 and < 130 were as-

sociated with increased mortality, but mild systolic hypertension was not (140-159 mmHg). However, the authors suggested that it is reasonable to treat SBP > 140 based on their previous analysis of the SEAS data, which showed that hypertension was associated with worse outcomes in these patients. Interestingly, both the authors and the accompanying editorial provided no explanation for the reason elevated SBP is detrimental in aortic stenosis. Thus, it may be acceptable to tolerate SBPs in the 140-159 range if relative hypotension has been an issue with treatment.

The adverse effect of low DBP is easier to explain, since reducing myocardial perfusion pressure in diastole in patients who probably have high diastolic left ventricular pressures would clearly reduce myocardial oxygen supply, even if the patient had normal coronary arteries. Similar results have been observed in patients with acute coronary syndromes and acute heart failure. The higher mortality risk with high DBPs is harder to explain, but is observed in all studies of BP and outcome. Since BP levels did not influence the time to aortic valve replacement, the effect probably is mediated by augmenting coronary artery disease or other comorbidities.

In SEAS, antihypertension treatment was not regulated, but a previous analysis of this database showed that renin angiotensin aldosterone system blockers generally were safe in aortic stenosis patients. This prompted the editorialist to state that no drugs were off limits if used carefully in these patients. This is probably true for drugs we commonly use now, but may not be for some drugs such as powerful direct vasodilators (e.g., hydralazine). Also, most aortic stenosis patients are elderly and often present with multiple comorbidities that have to be taken into account with drug choice for hypertension. In aortic stenosis in particular, drugs with potent effects on AV conduction may be relatively contraindicated if there are signs of conduction disturbances, such as first-degree AV block.

Another implication of this study is that if patients are on antihypertensive therapy with an SBP < 120 or a DBP < 70 mmHg, one should consider reducing the therapy. In those with BPs in these ranges who are not on antihypertensive medication, seek other causes of relative hypotension and correct them.

The results of this study fit in with the general theme that BP targets for antihypertension treatment likely are different for different patient populations, and one size does not fit all. ■

ABSTRACT & COMMENTARY

Hypothyroidism and PCI Outcomes

By Michael Crawford, MD, Editor

SYNOPSIS: Hypothyroidism is common in patients undergoing percutaneous coronary interventions in a multivariate adjusted observational study was associated with worse long-term outcomes. A subgroup with repeat angiography showed that atherosclerosis progression was the likely reason.

SOURCES: Zhang M, Sara JD, Matsuzawa Y. Clinical outcomes of patients with hypothyroidism undergoing percutaneous coronary intervention. *Eur Heart J* 2016;37:2055-2065.

Gencer B, Rodondi N. Should we screen for hypothyroidism in patients with cardiovascular disease? *Eur Heart J* 2016;37:2066-2068.

Hypothyroidism is common, but missed frequently in clinical settings because the patient often is minimally symptomatic. Optimal results from percutaneous coronary interventions (PCI) involve maximizing coronary artery disease (CAD) risk factor control. Hypothyroidism can accelerate atherosclerosis and depress cardiac function, yet the relationship between hypothyroidism and the outcomes of PCI largely are unknown. Investigators from the Mayo Clinic evaluated their PCI database to determine the relationship between hypothyroidism and major adverse cardiovascular and cerebral events (MACCE) after PCI. Hypothyroidism was defined as a history of hypothyroidism or a thyroid-stimulating hormone (TSH) level > 5.0 mU/mL at the time of PCI. Those with a history of hypothyroidism were subgrouped by whether they were taking thyroid replacement and whether the therapy was adequate (TSH 0.3-5.0) or inadequate (TSH > 5.0). Also, patients were grouped according to their TSH levels euthyroid (0.3-5.0), subclinical hypothyroidism (5.0-10.0), or hypothyroidism (> 10.0). MACCE was defined as cardiac death, myocardial infarction, heart failure, repeat revascularization, or stroke.

From 1994 to 2009, more than 25,000 patients underwent PCI, and after excluding those with no

follow-up angiogram, bypass surgery, a malignancy, no TSH data, or a TSH < 0.3, there were 2,430 patients left in the study, of which 686 had hypothyroidism and 1,744 were euthyroid. Median follow-up was three years. Those with hypothyroidism were older, more likely female, and had more comorbidities such as diabetes. During the hospitalization for PCI, only heart failure was more common in those with hypothyroidism. At 10 years follow-up, after adjusting for covariates, MACCE was significantly higher in hypothyroid patients (hazard ratio [HR], 1.28; 95% confidence interval, 1.13-1.45; $P = 0.0001$) compared to euthyroid patients. Among the components of MACCE, only cardiac death did not reach statistical significance. Also, there was no difference in outcomes between those with subclinical hypothyroidism and hypothyroidism patients. Those who received adequate thyroid replacement therapy experienced similar outcomes to euthyroid patients, and both experienced better outcomes than those with inadequately treated or untreated hypothyroidism. A subgroup of 408 patients were randomly selected to evaluate CAD progression by subsequent angiography. Hypothyroidism exhibited a CAD higher rate of target-lesion progression (HR, 1.43, $P = 0.044$) and downstream progression (HR, 1.90, $P = 0.006$) compared to euthyroidism. The authors concluded that among patients undergoing PCI, hypothyroidism is associated with higher MACCE rates compared to euthyroid patients and that adequate thyroid replacement abrogates this risk.

■ COMMENTARY

As we get more subspecialized in cardiology, it is important to remember the effect of non-cardiac diseases on the progression of cardiovascular disease. This study clearly shows that post-PCI patients with overt or subclinical hypothyroidism have more MACCE and greater angiographic progression of CAD compared to euthyroid patients, even when adjusting for comorbidities such as dyslipidemia exacerbated by hypothyroidism. This suggests the absence of adequate thyroid hormones results in other deleterious effects, such as endothelial dysfunction, enhanced inflammation, and hypercoagulability, all of which have been demonstrated in experimental studies. The detection of hypothyroidism on purely clinical grounds is challenging, especially in the elderly. Thus, routine measurement of TSH in all PCI patients makes sense, and the results of this study appear to justify the small cost.

What to do with an elevated TSH is more controversial. The best approach is probably to obtain a free T4 level. If free T4 is low, then treatment with thyroid replacement seems reasonable. If the free T4 is normal, then by definition the patient has subclinical hypothyroidism (SCH). The authors found SCH in one-third of patients with elevated TSH, but they defined it solely as a TSH level between 5-10. They did not consistently measure free T4 and do not present any data on T4 levels. Other studies suggest that a TSH > 10 (and possibly TSH > 7), regardless of the free T4, should be treated. Despite the lack of a more precise definition of SCH, the patients in this study with SCH experienced better outcomes with therapy. By treating lower levels of TSH (a score between 5-7), the benefits may not counterbalance the risks of thyroid replacement such as atrial fibrillation and bone fractures, not to mention the cost and inconvenience of lifelong replacement therapy.

This study was a prospective cohort investigation, which suffers from the inability to adjust for all confounders, selection bias, and the inability to control testing and treatment. However, this is a fairly large study, with high-quality follow-up, including a subgroup with repeat angiography, and the ability to evaluate the effects of treatment. A large randomized trial of this concept has begun, but until those investigators publish the results, it is prudent to measure TSH in most PCI patients and act on the results as described above. ■

ABSTRACT & COMMENTARY

Heart Failure with Recovered Ejection Fraction: A Distinct Phenotype

By Van Selby, MD

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Dr. Selby reports no financial relationships relevant to this field of study.

SYNOPSIS: Patients suffering from systolic heart failure who subsequently improve their ejection fraction experience a more favorable clinical course compared to those presenting with persistently reduced ejection fraction or heart failure with preserved ejection fraction.

SOURCE: Kalogeropoulos AP, Fonarow GC, Georgiopoulou V, et al. Characteristics and outcomes of adult outpatients with heart failure and improved or recovered ejection fraction. *JAMA Cardiol* 2016;1:510-518.

Patients presenting with chronic heart failure (HF) typically are divided into those with preserved (HFpEF) or reduced left ventricular ejection fraction (HFrEF). Although the management of the two conditions differs significantly, overall prognosis is relatively similar for the two diagnoses. However, it is recognized that some HFpEF patients initially presented with HFrEF and experienced significant improvement in ejection fraction. The characteristics and outcomes of these patients with "recovered" ejection fraction have not been well described.

Kalogeropoulos et al retrospectively evaluated the medical records of all patients who were treated at the Emory University cardiology practice for a diagnosis of chronic heart failure between Jan. 1 and April 30, 2012. Patients were assigned to one of three groups: HFrEF (defined as EF < 40%), HFpEF (defined as current and all previous EF measurements > 40%), or heart failure with recovered ejection fraction (HFrecEF, defined as EF > 40% but any previously documented EF < 40%).

Of 2,166 patients with chronic HF, 350 (16.2%) had HFrecEF, 466 (21.5%) had HFpEF, and 1,350 (62.3%) had HFrEF. Those with recovered EF predominantly were male and featured significantly lower rates of diabetes, coronary artery disease, and hypertension ($P < 0.01$ for all). Over three years of follow-up, age- and sex-adjusted mortality was significantly lower among patients with HFrecEF (4.8%) compared to those with HFrEF or HFpEF (16.3% and 13.2%, respectively; $P < 0.001$). Patients with HFrecEF also experienced significantly fewer all-cause hospitalizations, cardiovascular hospitalizations, and HF-related hospitalizations.

The authors concluded that outpatients with HFrecEF experience a different clinical course than patients with HFpEF or HFrEF, with lower mortality and less frequent hospitalizations, and should be investigated separately in future clinical trials.

■ COMMENTARY

Data from large clinical trials and registries support the concept that appropriate use of evidence-based therapies for systolic HF, such as beta-blockers and ACE inhibitors, leads to improvement in ejection fraction for a significant portion of patients presenting with HFrEF. These patients often are diagnosed with HFpEF. In their single-center cohort, Kalogeropoulos et al found HFrecEF patients represented approximately 43% of all patients with HF and an EF > 40%. The authors also demonstrated fairly convincingly that these patients have different clinical characteristics and substantially better outcomes than those with persistently reduced EF or true HFpEF.

Although it is clear myocardial recovery is possible, the exact underlying mechanisms remain poorly understood. Patients suffering from HFrecEF may experience reverse remodeling, leading to improvements in neurohormonal activation and therefore better outcomes. The lower frequency of coronary artery disease (and presumably myocardial scar) in the HFrecEF group may have improved their ability to reverse remodel. Refining our ability to identify HFrEF patients with potential for remodeling and recovering systolic function would improve risk stratification and guide clinical decision making.

This study has important limitations. As a single-center, academic cohort, the findings may not be generalizable to broader clinical practice. Categorization was based solely on available clinical echocardiographic data, and may have led to misclassification of cases. The authors used a strict EF cutpoint of 40% to differentiate HFpEF and HFrEF, instead of including a "borderline EF" category, as some have recommended. One question that arises frequently in HFrecEF is how long to continue medical therapy for HFrEF once the ejection fraction has recovered. Unfortunately, there is minimal evidence to guide these decisions, and a retrospective study such as this cannot be used to make recommendations regarding clinical management.

From here, prospective studies are needed to determine predictors of improvement in EF, and the optimal treatment strategies for these patients once the EF has recovered. As the authors suggested, patients presenting with HFrecEF may need to be studied as a distinct group in future HF clinical trials. For now, the findings guide the way we categorize patients with HF and are especially useful when discussing prognosis in patients with HFrEF who subsequently recover systolic function. ■

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CME/CE QUESTIONS

1. **Implantable cardioverter defibrillators do not reduce mortality rates in which type of patient?**
   a. Ischemic cardiomyopathy
   b. Non-ischemic cardiomyopathy
   c. Hypertrophic cardiomyopathy
   d. Arrhythmogenic right ventricular cardiomyopathy

2. **Which hypothyroid type patient has the highest adverse outcomes rate post-percutaneous coronary intervention?**
   a. Euthyroid post-treatment cessation
   b. Adequately treated hypothyroid
   c. Inadequately treated hypothyroid
   d. Untreated hypothyroid

3. **An advantage of drug-eluting over bare-metal stents on follow-up is:**
   a. fewer myocardial infarctions.
   b. reduced mortality.
   c. less in-stent restenosis.
   d. All of the above

4. **The optimal systolic blood pressure in patients with mild to moderate aortic stenosis is:**
   a. 130-139 mmHg.
   b. > 140 mmHg.
   c. 140-159 mmHg.
   d. < 130 mmHg.

5. **Which chronic heart failure patients have the best prognosis?**
   a. Reduced ejection fraction
   b. Preserved ejection fraction
   c. Recovered ejection fraction
   d. Worsening ejection fraction