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Causes of death in patients undergoing percutaneous coronary intervention with drug-eluting stents in a real-world setting

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ABSTRACT:

Background. Reports of stent thrombosis and death in patients who have received drug-eluting stents (DES) have provoked debate regarding their long-term safety. We investigated the specific causes of death in patients receiving DES at an academic tertiary-care center. Methods. A retrospective analysis of 1,023 consecutive patients who underwent percutaneous coronary intervention (PCI) with DES from 2003 to 2006 at UCLA Medical Center was performed. Dates and cause of death were obtained by reviewing the patient's medical record, contacting the patient's doctor, or accessing the Social Security Death Index and obtaining copies of death certificates at the Los Angeles County Registrar-Recorder/County Clerk office. If the cause of death could not be determined, it was reported "unknown." Results. At a mean follow up of 2.9 ± 1.3 years, 96 patients who underwent PCI with DES died during the analysis (9.4% mortality). The mean duration between index PCI and death was 331 ± 324 days. The cause of death was unknown in 9 patients, thus the analysis was based upon 87 patients. There were similar number of cardiac (n = 44) and non-cardiac deaths (n = 43). The risk of PCI-related death was 1.3% (13/1023), which included 11 patients (1.1%) who died from stent thrombosis. Fourteen patients (1.4%) who presented with myocardial infarction (MI) and underwent PCI died, and 14 patients (1.4%) died from heart failure. Non-cardiac deaths included cancer, infection, respiratory failure and a cerebrovascular event. Age, chronic renal insufficiency, presentation with MI, chronic obstructive pulmonary disease, history of cerebrovascular event, orthotopic heart transplantation and left ventricular ejection fraction were significantly associated with increased mortality. Conclusions. Cardiac and non-cardiac causes of death contributed similarly to mortality in patients who underwent PCI with DES at a large tertiary care center that manages high-risk patients. Overall PCI-related death and stent thrombosis causing death were low. The majority of deaths occurred in patients after hospital discharge. The majority of patients who died in the hospital presented with acute MI and were in critical condition on presentation.

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Key words: drug-eluting stents, death, stent thrombosis

Drug-eluting stents (DES) have been shown to decrease in-stent restenosis when compared with bare-metal stents (BMS) in relatively simple coronary artery lesions.1–3 DES are used in the

majority of percutaneous coronary interventions (PCI) in the United States. However, the initial enthusiasm of DES was tempered by concerns over long-term safety, especially the increased risk of stent thrombosis, myocardial infarction (MI) and death compared with BMS.4–9

A meta-analysis of 878 patients in the sirolimus-eluting stent trials reported a 3-year mortality rate of 4.1%.10 However, the majority of patients undergo PCI with DES for "off-label" indications. The cause of death in some patients who undergo PCI — including those who present in extremis secondary to acute MI and cardiogenic shock— is not unexpected. There is a paucity of data regarding the exact cause of death in patients who undergo PCI in the "real-world" setting. The purpose of this study was to investigate the specific causes of death in consecutive patients who underwent PCI with DES at an academic tertiary-care center.

Methods

From April 2003 to December 2006, 96 out of 1023 consecutive patients (9.4%) died who underwent PCI with DES—sirolimus-eluting stent (SES) (Cypher™, Cordis Corp., Miami Lakes, Florida) or paclitaxel-eluting stent (PES) (Taxus®, Boston Scientific, Corp., Natick, Massachusetts) — at the UCLA Medical Center. The Institutional Review Board approved the use of the database review for this study.

Percutaneous coronary intervention. Standard techniques were used for PCI. The choice of anticoagulation, use of glycoprotein (GP) IIb/IIIa antagonists, intravascular ultrasound (Boston Scientific), intra-aortic balloon pump counterpulsation, and the decision to use SES or PES was left to the discretion of the operator. High-pressure inflations were performed, and postdilation with noncompliant balloons was performed for optimal stent apposition and expansion to achieve acceptable angiographic results. Aspirin 325 mg/day was continued indefinitely, and clopidogrel was continued for at least 6 months after a loading dose of 300 mg or 600 mg was given.

Definitions. Major adverse cardiac events were defined as death, MI or target vessel revascularization. The cause of death was classified as cardiac or non-cardiac. Cardiac death was further categorized as PCI-related or non-PCI-related. PCI-related death included death secondary to stent thrombosis, vascular complications, contrast-induced nephropathy and infection.11 Non-PCI-related death included patients who presented with acute MI, worsening heart failure and life-threatening arrhythmias. The European Society of Cardiology/American College of Cardiology definition of MI was used.12 Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI: 1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: a) ischemic symptoms; b) development of pathologic Q waves on the electrocardiogram (ECG); c) ECG changes indicative of ischemia (ST-segment elevation or depression); or d) coronary artery intervention. 2) Pathologic findings of an acute myocardial infarction. Target vessel revascularization was defined as a repeat revascularization to treat a vessel. In-stent restenosis was defined as a stenosis of > 50% located within the stent or within 5 mm of the stent edges.

The Academic Research Consortium definition of stent thrombosis was used.13 Definite/confirmed stent thrombosis is defined as acute coronary syndrome and angiographic

confirmation of stent thrombus or occlusion or pathologic confirmation of acute stent thrombosis. Probable stent thrombosis is defined as any unexplained death within 30 days or as target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion. Possible stent thrombosis is defined as unexplained death after 30 days. Acute stent thrombosis occurred within 1 day, early stent thrombosis within 1 month, late stent thrombosis from 1 to 12 months, and very late stent thrombosis after 1 year. If the cause of death was unknown and occurred within 30 days, it was classified as PCI-related cardiac death secondary to probable subacute stent thrombosis. If the cause of death was unknown and occurred between days 31 and 365 days, it was classified as PCI-related cardiac death secondary to possible late stent thrombosis.

Data collection. Baseline demographic data were collected retrospectively on a dedicated PCI database. Long-term data were obtained from medical records or telephone interview with the patient's physician. The Social Security Death Index, which is a reliable indicator of mortality in the United States,14 was used to determine vital status if hospital source documentation was not available. The cause of death in these patients was identified by obtaining copies of death certificates at the Los Angeles County Registrar-Recorder/County Clerk office, which keeps records of anyone who dies in Los Angeles County. Repeat angiography was performed if clinically indicated due to recurrent ischemia or surveillance angiography after unprotected left main coronary artery stenting or PCI in patients with orthotopic heart transplantation.

Statistical analysis. Continuous data are expressed as mean ± standard deviation and were compared by the ANOVA or Kruskal-Wallis test. Categorical variables are presented as frequency and percent and were compared using the chi-square test or Fisher's exact test. A survival curve was generated by the Kaplan-Meier method. A multivariable Cox proportional hazards regression model was created with the use of baseline clinical and angiographic characteristics and procedure-related variables to identify independent predictors of survival. Variables entered into the multivariable models were age, gender, diabetes, hypertension, hypercholesterolemia, left ventricular ejection fraction (LVEF), prior bypass surgery, prior PCI, smoking habit, chronic obstructive pulmonary disease, chronic renal insufficiency (serum creatinine > 1.5 mg/dL), history of cerebrovascular event, history of orthotopic heart transplantation, hematocrit, presentation with MI, peripheral arterial disease, prior mitral or aortic valve surgery, type of DES, restenotic lesions, total stent length, number of diseased vessels and use of GP IIb/IIIa inhibitors. Statistical analyses were performed using SPSS, version 10.0 (SPSS, Inc., Chicago Illinois).

Results

Baseline patient and procedural data. Baseline demographic data are presented in Table 1. The mean follow up was 2.9 ± 1.3 years. The median time of death was 237 days (range: 1–1,139 days). Significant differences between patients who died and those who survived included age (77 ± 12 vs. 66 ± 12 years; p 1.5 mg/dL) (42% vs. 11%; p

Baseline procedural data are presented in Table 2. Significant differences in patients who died and those who survived included number of vessels treated (1.4 ± 0.6 vs. 1.3 ± 0.6; p = 0.05), multivessel PCI (32% vs. 20%; p = 0.02), unprotected left main PCI (11% vs. 1%; p

The causes of death are listed in Table 3. Of the 96 deaths, the cause was unknown in 9 patients, and therefore the analysis was based upon 87 patients. Cardiac death occurred in 44 patients (51%). The risk of PCI-related death was 1.3% (13/1,024): 11 patients (1.1%) died from stent thrombosis, 1 patient from cardiogenic shock secondary to guiding catheter dissection of the left main coronary artery, and 1 patient from a groin complication. Definite stent thrombosis occurred in 7 patients, probable stent thrombosis in 3 (all 3 patients had unexplained death within 30 days of PCI), and possible stent thrombosis in 1 patient (1 patient had unexplained death on day-128 after PCI of the proximal left anterior descending artery). Fourteen patients (1.4%) who presented with MI and underwent PCI died, and 14 patients (1.4%) died from heart failure. Other causes of cardiac death included ventricular arrhythmias (n = 2) and complications during aortic valvuloplasty (n = 1).

Non-cardiac death occurred in 43 patients (49%). Twelve patients (1.2%) died from cancer, 10 from infection, 8 from respiratory failure, 6 from cerebrovascular event, 2 from renal failure, 2 from gastrointestinal bleeding, 1 from liver failure, 1 from Alzheimer's disease, and 1 from trauma.

A Kaplan-Meier survival curve is provided in Figure 1. Two patients died in the cardiac catheterization laboratory (1 due to acute MI with severe cardiogenic shock and another patient died due to complications during aortic valvuloplasty after successful PCI). Twenty-seven patients (2.6%) died within 30 days. If the 9 patients with orthotopic heart transplantation who died were excluded from the analysis, the overall mortality rate was 8.6% (87/1,014).

Age (hazard ratio [HR] 1.07, 95% confidence interval [CI][1.05–1.10]; p

Discussion

Our study systematically details the cause of death in patients treated with PCI with DES in "all-comers." Deaths were similarly distributed between cardiac and non-cardiac causes. The overall incidence of PCI-related death and stent thrombosis causing death was low. The majority of deaths occurred in patients after hospital discharge. The majority of patients who died in the hospital presented with acute MI and were in critical condition on presentation.

Several studies have described the cause of death of patients who underwent PCI. Malenka et al reported on the cause of 121 in-hospital deaths in 12,232 consecutive patients who underwent PCI from the Northern New England Cardiovascular Disease Study Group.15 However, this study was conducted from 1989 to 1993, before the use of stents as well as thienopyridines and GP IIb/IIIa receptor antagonists.

Holmes et al reported on 1,748 patients from the 4 prospective, randomized trials comparing SES and BMS.10 A 1% annual mortality rate was observed in the randomized controlled DES trials and the main cause of death was non-cardiac at a mean of 2.6 years.1–3 Our study differs from the analysis of the randomized clinical trials because we included high-risk patients (those with acute MI, severe left ventricular dysfunction, in-stent restenosis, stent thrombosis and orthotopic heart transplantation, many of whom develop a diffuse and progressive form of coronary artery vasculopathy) and complex lesions (multivessel coronary disease, unprotected left main artery

and saphenous vein grafts), rather than a select group with low or moderate risk. The main cause of death within 30 days was secondary to presentation with acute MI. The main cause of death after 30 days was progressive LV failure. Our study also included patients who underwent multivessel PCI, which may explain the higher overall mortality rate observed in our study (9.4%) compared with the mortality rate observed in the randomized trial (3.7%). An analysis of the New York State database reported lower mortality rates with coronary artery bypass surgery compared with PCI with DES for multivessel coronary artery disease.16

Several studies have reported trends toward increased death with DES compared with BMS. In a 3-year follow up of the RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization) trial, there was a trend toward an increased risk of death in patients treated with SES.17 Similarly, the (SCANDSTENT) (Stenting Coronary Arteries in Non-stress/BENESTENT Disease) trial reported a trend toward increased mortality at long-term follow up in patients treated with SES compared with BMS in complex coronary artery lesions.18 Several studies suggested that DES also were associated with increased risk of late stent thrombosis, MI or death, especially in complex coronary artery lesions.4-6 A meta-analysis of published and presented trials comparing DES and BMS demonstrated increased rates of death or Q-wave MI with SES.8

However, several large pooled analyses of randomized trials that compared DES with BMS demonstrated no difference in mortality at long-term follow up and supported the safety with continued efficacy, particularly the reduction of restenosis and target vessel revascularization.10,19–22 Although the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) reported an increased risk of death in 19,771 patients treated with DES compared with BMS,7 longer-term follow up presented at the 2007 European Society of Cardiology did not confirm these findings.23 The REAL (Registro Angioplastiche dell'Emilia Romagna) Multicenter Registry,24 an analysis from the National Heart, Lung, and Blood Institute Dynamic Registry25 on the on–label versus off-label use of DES and BMS, and an analysis of 67,003 Medicare patients26 also reported no difference in mortality.

On the contrary, some studies have actually demonstrated a survival advantage with DES. Two registries, one from Ontario, Canada27 and another from Wake Forest, North Carolina,28 reported lower mortality rates in patients treated with DES compared with BMS. Similarly, a study of 76,525 Medicare patients reported improved survival associated with DES compared with BMS.29 It is unclear why the various results are disparate, but it may be due to more careful patient selection, prolonged dual antiplatelet therapy and increased use of BMS in patients who may require cessation of dual antiplatelet therapy.30

Acute procedural complications were rare. One patient died secondary to a guiding catheter dissection of the left main artery and another from a groin complication. Only 2 patients died in the cardiac catheterization laboratory (one due to complications from aortic valvuloplasty after undergoing successful PCI and the other who presented with acute MI complicated by cardiogenic shock). Death secondary to stent thrombosis occurred in 1.1%. Newer antiplatelet agents are associated with a lower risk of stent thrombosis and may decrease the mortality rate in patients who undergo PCI with DES.31

Study limitations. This was a nonrandomized retrospective study from a single, tertiary care center and may not be generalized to all patients. The cause of death was unknown in 9 patients. Therefore, the reported cardiac mortality and rate of stent thrombosis may have been underreported. Furthermore, in patients whose death certificates stated MI or sudden death as the cause of death, we were unable to confirm with angiography or autopsy whether these patients died of stent thrombosis. It is also unknown whether patients were on dual antiplatelet therapy at the time of stent thrombosis. In patients who died from stent thrombosis, although there is non-randomized data suggesting that prolonged dual antiplatelet therapy is associated with a reduction in death and MI in patients who underwent PCI,32,33 it is unknown whether longer-term dual antiplatelet therapy would have decreased the rate of stent thrombosis and death. The relationship between death and restenosis was unknown as follow-up angiography was not performed in all patients.

Conclusion

In this analysis of a single tertiary-care center which included high-risk patients and complex lesions, the overall morality rate was 9.4% at a mean follow up of 2.9 years. The cause of death was similar between cardiac and non-cardiac death. Overall, the rate of PCI-related death and stent thrombosis causing death was low. The majority of deaths occurred in patients after hospital discharge. The majority of patients who died in the hospital presented with acute MI and were in critical condition on presentation. Careful selection of patients who are candidates for PCI with DES is needed to optimize clinical outcomes in patients with coronary artery disease.

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