Effectiveness of Implantable Cardioverter-Defibrillators in Patients With Ischemic Heart Disease and Left Ventricular Dysfunction

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Background: Implantable cardioverter-defibrillators (ICDs) have been shown in primary prevention efficacy trials to reduce mortality in patients with ischemic heart disease and left ventricular dysfunction. To investigate the generalizability of this mortality reduction, we examined the effectiveness of ICDs in clinical practice.

Methods: We developed a prospective multicenter cohort of 770 patients with ischemic left ventricular dysfunction (ejection fraction ≤35%) and without a history of ventricular arrhythmia, of whom 395 (52%) received ICDs. Mean ± SD follow-up was 27 ± 12 months. We assessed the degree to which ICDs decreased mortality risk using Cox proportional hazards analyses that controlled for clinical predictors of death, receipt of ICD (a propensity score analysis), and predictors of arrhythmic death (including electrophysiologic variables).

Results: Multivariate Cox analyses showed that those with ICDs had significantly lower all-cause mortality (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.33-0.86). This mortality reduction was mediated through dramatically lower arrhythmia-related mortality (HR, 0.35; 95% CI, 0.17-0.73), with no significant effect on cardiovascular nonarrhythmic (HR, 0.81; 95% CI, 0.34-1.96) and noncardiovascular (HR, 0.76; 95% CI, 0.29-2.05) mortality. No differences were found between the ICD and non-ICD groups for a composite outcome of all-cause mortality, appropriate ICD shocks, or documented symptomatic ventricular arrhythmia, which suggests that the 2 groups had similar baseline risk for life-threatening arrhythmic events (HR, 0.96; 95% CI, 0.63-1.45).

Conclusion: In clinical practice, ICDs appear to reduce all-cause and arrhythmic rates of mortality at levels similar to those found in primary prevention trials.

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compared with medical therapy alone. Because of this potential cost to society, CMS has proposed developing a registry to further examine the benefits of ICD therapy in the nontrial setting. However, such a registry would only include those patients who receive ICDs and would therefore not be able to rigorously examine ICD effectiveness because there would be no control group for comparison.

Given the cost and policy implications of the CMS decision and the need for effectiveness studies to ensure no dilution of benefit from ICD efficacy trials, we undertook an effectiveness study in a nontrial patient population with ischemic heart disease and left ventricular dysfunction to examine the generalizability of the mortality benefit found with prophylactic ICD placement in efficacy trials.

**METHODS**

**PATIENT POPULATION**

A multicenter prospective cohort of consecutive patients with ischemic heart disease and left ventricular dysfunction was developed from 7 cardiology outpatient clinics and coordinated by The Ohio Heart and Vascular Center and the Lindner Clinical Trials Center. The main objective of the cohort was to examine the prognostic utility of microvolt T-wave alternans (MTWA) screening, with a secondary objective of assessing the effectiveness of ICD therapy in the community practice setting. As a result, patients had to be in sinus rhythm (for MTWA screening, with a secondary objective of assessing the effectiveness of ICD therapy in the community practice setting)

Enrollment occurred from March 2001 to June 2004 with follow-up through September 2005. For our study cohort, we included those patients 18 years or older who met the criteria for ischemic heart disease (defined as coronary artery disease on cardiac catheterization with >70% stenosis in >1 coronary artery, history of myocardial infarction, or history of angioplasty or coronary bypass graft surgery) and left ventricular dysfunction (defined as left ventricular ejection fraction [LVEF] ≤ 35% determined via surface echocardiogram [>90%], ventriculogram, or nuclear imaging). Patients with prior coronary revascularization within the past 3 months, a myocardial infarction within the past month, a history of sustained ventricular arrhythmia (≥30 beats), or terminal illnesses such as cancer were excluded.

**BASELINE DATA COLLECTION**

Baseline patient characteristics were collected at initial enrollment and included age, sex, LVEF, QRS duration, and clinical variables (diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic renal insufficiency, peripheral vascular disease, and history of myocardial infarction, stroke, transient ischemic attack, atrial fibrillation, symptomatic heart failure, and unexplained syncope). In addition, baseline medication usage (aspirin, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, β-blocker, spironolactone, statin, digoxin, diuretic, and classes 1 and 3 antiarrhythmic agents), revascularization history (angioplasty or coronary bypass graft surgery), and clinic site data were collected.

During the baseline visit, patients underwent noninvasive screening with both MTWA and Holter studies. All MTWA tests were interpreted according to standard criteria by an expert reader blinded to patient characteristics and clinical outcomes, and results were classified as either negative (33%) or nonnegative (positive [46%] and indeterminate [21%; not retested]). Holter monitoring (24-48 hours) was used for detection of nonsustained ventricular tachycardia (VT), which was defined as more than 100 beats per minute for 3 or more consecutive beats and less than 30 seconds.

Further testing with EPS in the cohort was based on clinical criteria and noninvasive study results. For those patients undergoing invasive EPS, a positive finding was defined as (1) inducible, sustained, monomorphic VT of cycle length 230 milliseconds or longer or (2) inducible ventricular fibrillation, polymorphic VT, or ventricular flutter (monomorphic VT with a cycle length <230 milliseconds) with 2 or fewer ventricular extrastimuli. Because not all patients underwent an EPS, 2 dummy variables were created to reflect 3 levels of EPS status in the cohort: no test, a positive finding, and a negative finding. Finally, ICD implantation in our cohort was performed at the discretion of the attending physician and was primarily (93% of all ICDs implanted) based on a positive EPS result, an abnormal Holter result, or a QRS greater than 120 milliseconds in the post--MADIT-II trial period (after mid-2002).

All patients in the study gave informed consent, and the study was approved by the institutional review board at the Christ Hospital and its affiliated clinics (Cincinnati, Ohio).

**CLINICAL END POINTS AND FOLLOW-UP**

The primary end point was all-cause mortality, which was determined through quarterly clinic visits in 97.5% of cases, routine review of office charts in 100%, telephone contact with patient in 99.4%, and annual query of the US National Death Index (using first and last name, Social Security number, sex, state location, and date of birth) in 100%. Secondary end points included cause-specific mortality, appropriate ICD shock therapy in patients with ICD, and documented symptomatic ventricular arrhythmia not terminated by ICD therapy. Cause-specific mortality was classified as arrhythmic or nonarrhythmic via a modified Hinkle-Thaler system. Arrhythmic deaths included unwitnessed deaths (if the patient’s condition was stable when last observed within 24 hours before death), witnessed instantaneous deaths, and sequelae of cardiac arrest. Nonarrhythmic deaths were further subclassified by cause as cardiovascular nonarrhythmic or noncardiovascular. Cause-specific mortality was adjudicated by an independent panel of 2 investigators blinded to a patient’s clinical characteristics, ICD status, and EPS results. If consensus could not be reached, the decision was referred to a third and senior committee member. Finally, ICDs were evaluated at routine visits, and appropriate ICD shocks were defined as shocks for documented VT or ventricular fibrillation.

The index date for the non-ICD cohort was the date of cohort enrollment. To avoid survival bias against the non-ICD group (since all patients with ICD had to survive until the time of ICD implantation), the index date for the ICD group was the date of ICD implantation, with the median time from cohort enrollment to ICD implantation being 58 days. As survival may not be linear over time, we repeated the analyses such that deaths in the non-ICD group were excluded during the first 58 days (n = 3) and the index date was the enrollment date in the ICD group and found that the results were similar (results not shown).

**STATISTICAL ANALYSIS**

**Unadjusted Analysis**

Baseline characteristics in the ICD and non-ICD groups were compared using t-tests for continuous variables and χ² tests for categorical variables.
categorical variables. Unadjusted all-cause mortality between the ICD and non-ICD groups was assessed with Kaplan-Meier analysis and tested with the log-rank test as well as with Cox proportional hazards analysis. Similar analyses were also performed for cause-specific mortality and for a composite end point of all-cause mortality, appropriate ICD shock therapy, or symptomatic ventricular arrhythmia. 

Adjusted Analysis

Because nonrandomized cohort studies might have significant differences in baseline risk between the compared groups, and because multivariate analyses might not adequately adjust for such differences (ie, the ICD and non-ICD groups might not truly overlap in their mortality risk profiles),5,17 we used a propensity score analysis in our Cox proportional hazards models. A propensity score analysis is a statistical technique that examines factors that influence the likelihood of receiving a particular treatment (in this case, ICD implantation), thereby allowing for comparisons of patients with comparable risk.13,18

To generate the propensity score, multivariate logistic regression was used to model ICD placement (dependent variable) with the 3 independent variables most likely to influence the clinical decision to implant ICDs in our cohort (EPS testing, QRS duration >120 milliseconds, and abnormal Holter findings). The model provides the predicted probability (from 0 to 1) of receiving an ICD for each patient. A C-statistic, representing the area under the receiver operating characteristic curve, indicates how well the propensity score model predicted defibrillator receipt. Next, all study covariates (including clinic site) except the ones used in developing the propensity score were examined for univariate associations with death (P<.10) through Cox proportional hazards analysis. Significant variables in univariate analyses were then systematically evaluated with Cox proportional hazards regression analyses to generate a multivariate model (P<.05) and reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Age, LVEF, and propensity score were kept in the final model, regardless of level of significance.

The same Cox analyses were performed for arrhythmic, nonarrhythmic cardiovascular, and noncardiovascular mortality. Finally, as a sensitivity test to further assess the potential mechanism of benefit with ICD therapy, we equated an appropriate defibrillator shock in ICD patients and symptomatic ventricular arrhythmia in all cohort patients with death, and assessed whether ICD and non-ICD patients were exposed to similar baseline arrhythmic event risks by comparing their risk for a composite outcome of all-cause mortality, ICD shock, or symptomatic ventricular arrhythmia using Cox regression analyses similar to those previously described.

Because other factors beyond EPS testing, QRS duration, and abnormal Holter results may influence decisions for ICD implantation, we also created a full nonparsimonious propensity score model using all study covariates as independent variables to predict ICD placement (C-statistic=0.876).3,19 Cox proportional hazards analyses for each of the aforementioned outcomes with this full propensity score were not found to be substantively different (results not shown).

All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

The study cohort was made up of 770 patients, of whom 395 (52%) received ICDs. Mean ± SD follow-up times were 28 ± 13 months for the non-ICD group and 26 ± 12 months for the ICD group (excluding a median time of 2 months from enrollment to ICD placement). Mortality follow-up was achieved for all cohort patients, and appropriate shock follow-up was achieved for 98% of all ICD patients.

A comparison of baseline characteristics is given in Table 1. An EPS was performed in 48% of the study cohort (376/770). Patients with ICDs had lower LVEFs; were more likely to be male, have a positive EPS finding, a prolonged QRS for more than 120 milliseconds, a nonnegative MTWA finding, an abnormal Holter finding, symptomatic heart failure, and a history of myocardial infarction; and were more likely to be undergoing treatment with a β-blocker, spironolactone, digoxin, or a statin.
In the ICD group, 93% of all subjects had at least 1 of the 3 characteristics used in the propensity score derivation (positive EPS finding, abnormal Holter finding, or QRS >120 milliseconds).

There were a total of 129 deaths (74 in the non-ICD group and 55 in the ICD group), of which 56 were arrhythmic (38 in the non-ICD group and 18 in the ICD group) and 32 were cardiovascular nonarrhythmic (17 in the non-ICD group and 15 in the ICD group) (Table 2). In addition, there were 35 patients with appropriate ICD shocks not associated with death in the ICD group, as well as 4 documented symptomatic ventricular arrhythmias not terminated by ICD therapy.

Univariate Cox models found that there was a nonsignificant trend toward higher survival in the ICD group for the primary end point of all-cause mortality (HR, 0.76; 95% CI, 0.53-1.08), and survival curves constructed with Kaplan-Meier analysis are depicted in the Figure. For cause-specific mortality, ICD therapy was associated with significantly lower arrhythmic mortality (HR, 0.49; 95% CI, 0.28-0.86) but had no significant impact on cardiovascular nonarrhythmic (HR, 0.85; 95% CI, 0.42-1.73) or noncardiovascular (HR, 1.26; 95% CI, 0.65-2.23) mortality.

Our propensity score, derived from the 3 variables most likely to predict ICD placement (EPS, QRS duration, and Holter monitor), showed good discrimination, with a C-statistic of 0.812. The variable most strongly associated with ICD placement was a positive EPS finding (Wald statistic of 0.812. The variable most strongly associated with significantly reduced all-cause mortality (HR, 0.53; 95% CI, 0.33-0.86) (Table 3). These results did not change substantively when the study cohort was limited to patients with LVEF less than 30% (n=538; HR, 0.54; 95% CI, 0.33-0.89) (P = .02). When confining the outcome to arrhythmic deaths only, we found that ICDs were associated with dramatic reductions in arrhythmic mortality (HR, 0.35; 95% CI, 0.17-0.73) (P = .005) (Table 4). However, no significant differences were found with ICD therapy for cardiovascular nonarrhythmic (HR, 0.81; 95% CI, 0.34-1.96) and noncardiovascular mortality (HR, 0.76; 95% CI, 0.29-2.05).

Finally, when a composite outcome of all-cause mortality, appropriate ICD shocks, or symptomatic ventricular arrhythmia was examined, no significant differences were found between the ICD and non-ICD groups, which suggests that the 2 groups were exposed to similar baseline combined rates of mortality and arrhythmic events (HR, 0.96; 95% CI, 0.63-1.43).

**COMMENT**

We found that patients with ischemic heart disease and left ventricular dysfunction had substantially improved survival when they received a prophylactic ICD in clini-

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**Table 2. Summary of Study End Points**

<table>
<thead>
<tr>
<th>End Point</th>
<th>ICD (n = 395)</th>
<th>Non-ICD (n = 375)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up, mean ± SD, mo</td>
<td>26 ± 12</td>
<td>28 ± 13</td>
</tr>
<tr>
<td>Total Deaths</td>
<td>55 (13.9)</td>
<td>74 (19.7)</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>18 (4.5)</td>
<td>38 (10.1)</td>
</tr>
<tr>
<td>Nonarrhythmic CV</td>
<td>15 (3.8)</td>
<td>17 (4.5)</td>
</tr>
<tr>
<td>Non-CV</td>
<td>22 (5.6)</td>
<td>19 (5.1)</td>
</tr>
<tr>
<td>Symptomatic VT/VF</td>
<td>1 (0.3)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>ICD shocks</td>
<td>35 (8.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Clinical Guidelines: CV, cardiovascular; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation.

*Unless otherwise indicated, data are reported as number (percentage) of patients.

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**Table 3. Multivariate Cox Proportional Hazards Model for All-Cause Mortality Adjusted for Propensity Score**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD</td>
<td>0.53 (0.33-0.86)</td>
<td>.01</td>
</tr>
<tr>
<td>PS</td>
<td>1.47 (0.86-2.32)</td>
<td>.35</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.01-1.05)</td>
<td>.003</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.95 (0.93-0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PTCA</td>
<td>0.57 (0.39-0.82)</td>
<td>.003</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.51 (0.36-0.73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>0.65 (0.41-1.02)</td>
<td>.06</td>
</tr>
<tr>
<td>DM</td>
<td>1.42 (0.99-2.03)</td>
<td>.05</td>
</tr>
<tr>
<td>PVD</td>
<td>1.89 (0.96-3.72)</td>
<td>.07</td>
</tr>
<tr>
<td>CHF</td>
<td>2.09 (1.26-3.46)</td>
<td>.004</td>
</tr>
</tbody>
</table>

*Implantable cardioverter-defibrillator therapy, higher LVEF, a history of PTCA or ACE or ARB usage, and aspirin usage were protective for all-cause mortality, whereas a higher PS, older age, DM, PVD, and symptomatic CHF were predictive for all-cause mortality. Age, LVEF, and PS were modeled as continuous variables.

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**Table 4.** Kaplan-Meier curves for the ICD (implantable cardioverter-defibrillator) and non-ICD groups for unadjusted all-cause mortality. Log-rank test statistic = 2.4, P = .12.
cal practice. After adjustment for multiple risk factors, ICD placement was associated with a 47% reduction in all-cause mortality. The magnitude of this mortality benefit was almost entirely mediated through prevention of arrhythmic death, since cardiovascular nonarrhythmic and noncardiovascular mortality were comparable between the 2 groups. Adding further validity to these findings, there was no difference in ICD and non-ICD patients in the combined end point of all-cause mortality, ICD shocks, or symptomatic ventricular arrhythmias, which suggests that ICD patients had better outcomes because ICD shocks protected subjects from sudden cardiac death and that our propensity score analysis compared patients with similar baseline mortality risk. These results suggest that the mortality reduction benefits seen in the MADIT-II and the ischemic SCD-HeFT trial populations can be successfully translated into routine practice without a substantial dilution of benefits.

Recently, CMS expanded ICD coverage to primary prevention patients meeting defined criteria of ischemic heart disease and left ventricular dysfunction, regardless of QRS duration.21 All patients in this cohort were enrolled prior to this coverage expansion decision and publication of the SCD-HeFT trial results, while a significant number were enrolled prior to publication of MADIT-II. At that time, routine prophylactic ICD placement for primary prevention without demonstrated inducibility on EPS was neither standard of care nor reimbursed by CMS. Since the recent CMS decision, however, it may be very difficult to conduct a rigorous prospective effectiveness study similar to that presented here because of broader ICD use and greater selection biases as to who receives an ICD. In a prior effectiveness study of ICDs among high-risk secondary prevention patients with ischemic heart disease and heart failure, we also found that the mortality reduction benefit seen with ICDs remained robust outside of trial settings.5 However, that study evaluated only patients with a history of ventricular arrhythmia (secondary prevention) and was limited by its retrospective design, lack of adjustment for several key variables (LVEF and complete medication data), and its examination of primarily all-cause mortality. In addition, a particular strength of our current study is that electrophysiologic variables such as Holter result, QRS duration, and EPS inducibility were considered in the propensity score models to predict ICD placement.

Adequate control of potential confounders is essential to any cohort study where differences in patient disease severity often exist. In this cohort, patients who received ICDs were sicker at baseline than those who did not. Those who received ICDs were likely to have higher rates of total and sudden cardiac death, since decisions to implant were based on a positive EPS result, an abnormal Holter finding, and a prolonged QRS duration greater than 120 milliseconds, all of which were found to occur at higher frequencies in the ICD group. Moreover, ICD patients were more likely to have had lower baseline LVEF, a nonnegative MtWA study, and a history of symptomatic heart failure, all of which were significant predictors in our final Cox model for all-cause mortality (Table 3). Although ICD patients also had higher utilization rates than non-ICD patients for β-blockers, spironolactone, statins, and digoxin, use of these medications did not significantly predict all-cause mortality in our final Cox model. After adjustment for these baseline differences between the patient groups, we found that ICDs were associated with a significant reduction in total mortality, primarily mediated through prevention of arrhythmic deaths. The good discrimination found with our propensity score model (C-statistic of 0.81) and our result demonstrating that the ICD and non-ICD groups were exposed to similar baseline combined mortality and sudden cardiac death event rates strongly suggest we had adequate case-mix adjustment for our study cohort.

The relative risk reduction (47%) for all-cause mortality found with ICDs in our effectiveness study was greater than that seen for the MADIT-II trial (31%) and among ischemic patients in the SCD-HeFT trial (28%).1,2 A higher risk of arrhythmic death in our study population explains most of this effect size difference. Most (77%) of our ICD population had a positive EPS finding compared with the 36% found with the ICD group in the MADIT-II trial.20 Indeed, risk-adjusted arrhythmia-related mortality in the non-ICD group was higher in our study population (20% at 3 years) than in the MADIT-II trial population (16% at 3 years).21 When only arrhythmia-related mortality was considered, however, both the MADIT-II trial (HR, 0.33) and our study (HR, 0.35) found similar dramatic results with ICD therapy.21

As with most prospective cohort studies, the major limitation is that the treatment groups being compared were not identical in disease severity. Multivariate analyses can reduce, but not eliminate, potential selection bias influencing study results. However, the use of propensity scores with excellent model discrimination is a particular strength of our study. Another limitation is that we did not have complete information on several variables of interest, such as laboratory values (creatinine, sodium, and hemoglobin), New York Heart Association class, and duration of prior ischemic heart disease. Although we equated appropriate ICD shocks and symptomatic ventricular arrhythmias with mortality as part of our sensitivity analysis, we caution that these are not equivalent end points and that ICD detection algo-

### Table 4. Unadjusted and Adjusted Cox Proportional Hazards Model Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.76 (0.53-1.08)</td>
<td>0.53 (0.33-0.86)</td>
<td>.009</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>0.49 (0.28-0.86)</td>
<td>0.35 (0.17-0.73)</td>
<td>.005</td>
</tr>
<tr>
<td>CV nonarrhythmic</td>
<td>0.85 (0.42-1.73)</td>
<td>0.81 (0.34-1.96)</td>
<td>.64</td>
</tr>
<tr>
<td>Non-CV</td>
<td>1.26 (0.65-2.23)</td>
<td>0.76 (0.29-2.05)</td>
<td>.59</td>
</tr>
<tr>
<td>All-cause + ICD shock + VT/VF</td>
<td>1.32 (0.97-1.80)</td>
<td>0.96 (0.63-1.45)</td>
<td>.86</td>
</tr>
</tbody>
</table>

Abbreviations: CV, cardiovascular; ICD, implantable cardioverter-defibrillator; VT, ventricular tachycardia; VF, ventricular fibrillation.

*Unless otherwise indicated, data are reported as hazard ratios (95% confidence interval). Univariate (unadjusted) and multivariate Cox proportional hazards models adjusted for propensity score for all-cause and cause-specific mortality are shown. Implantable cardioverter-defibrillator therapy reduced all-cause mortality through prevention of arrhythmic deaths, with no significant impact on cardiovascular nonarrhythmic and noncardiovascular mortality.
rhythms were not standardized. Therefore, our analyses with this combined end point should be interpreted as a sensitivity analysis only. Because our cohort included only patients in sinus rhythm, our results are not generalizable to the 8% to 15% of patients in atrial fibrillation or paced rhythms.1,2 Finally, our study evaluated the effectiveness of ICDs in a cohort with ischemic heart disease and left ventricular dysfunction and would not be generalizable to patients with nonischemic heart disease.

In conclusion, prophylactic placement of ICDs in routine clinical practice was associated with lower all-cause and arrhythmic rates of mortality in patients with ischemic heart disease and left ventricular dysfunction. These apparent benefits occurred despite excellent medication management, which suggests that the mortality reduction benefits found with ICDs in well-controlled primary prevention efficacy trials can be translated into routine practice without substantial dilution in benefit.

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Author Contributions: Dr Chan had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chan, Chow, Hayward, and Vijdan. Acquisition of data: Chow, Kereiakes, Schloss, and Waller. Analysis and interpretation of data: Chan, Chow, Eagle, Hayward, and Vijan. Drafting of the manuscript: Chan. Critical revision of the manuscript for important intellectual content: Chan, Chow, Eagle, Hayward, and Vijan. Statistical analysis: Chan. Obtained funding: Chan. Study supervision: Chan, Chow, Kereiakes, Schloss, Waller, Eagle, Hayward, and Vijan.

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