Clinical Evaluation of New Heart Valve Prostheses: Update of Objective Performance Criteria

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This article summarizes the long-term clinical results of the Food and Drug Administration–approved heart valves, provides current updates to the objective performance criteria (OPC) used to evaluate new heart valve prostheses, and documents the steps that the International Organization for Standardization Committee used to arrive at the updated OPC. Data were extracted from 19 Food and Drug Administration summaries of safety and effectiveness data reports (31 series) and 56 literature articles (85 series) published from 1999 to 2012. The OPC were calculated for five valve-related complications by valve type (mechanical and bioprosthetic) and valve position (aortic and mitral).

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In 1993, the US Food and Drug Administration (FDA) issued a heart valve guidance document, finalized in 1994, containing objective performance criteria (OPC) defining adversity/complication rates that would be acceptable when new valve prostheses would be considered for approval. These OPC were derived from published heart valve series and augmented with summaries of safety and effectiveness (SSE) data from heart valve premarket approval (PMA) applications [1]. The FDA extracted data from a comprehensive literature review [2], which was then updated to include references published through mid 1993 [3]. From this substrate of more than 60,000 valves and 200,000 valve-years, the FDA extracted a subset of more than 10,000 patients and 45,000 patient-years, including only studies that used FDA-approved devices and that adhered to heart valve guidelines published by American Association for Thoracic Surgery/Society of Thoracic Surgeons (AATS/STS) in 1988 [4]. The FDA then defined the OPC by summarizing complication rates from these studies.

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The FDA included OPC for seven complications for each of two valve types—mechanical and bioprosthetic, with aortic and mitral combined for each type. The OPC, ranging from 0.2 to 3.5 events per 100 patient-years, are shown in Table 1 ("Original OPC" columns). These OPC were meant to approximate the average, expected complication rates. They were implemented using a suggestion from a group of experienced investigators [5] who recommended approval of a new valve only if complication rates observed during preapproval studies for that prosthesis were statistically significantly lower than twice the OPC.

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A hypothesis-testing evaluation was used, with the one-sided null hypothesis that the complication rate of new valve was equal or greater than 2 × OPC, the probability of type 1 error was 5%, and the probability of type 2 error was 20% (80% power). As it was not practical to require that for a lower OPC (eg, 0.6% per year for major paravalvular leak, which would have required 4,860 valve-years), the OPC of 1.2% per patient-year for that OPC was chosen to produce the final minimum sample size requirement for evaluation of all OPC; that was calculated as approximately 800 valve-years [6]. In practice, each complication rate would have a confidence interval computed; the upper 95% one-sided confidence limit would need to be less than 2 × OPC to support approval. Several formulas have been proposed for Poisson confidence limits. The one recommended for assessing valve OPC was suggested by Cox [7].

The International Organization for Standardization (ISO), a federation of national standards bodies spanning the world, adopted these FDA OPC values, located in Annex R of the 2005 published ISO 5840 guidance for substitute heart valves [8]. In 2012, the ISO formed a new committee to update the OPC values; the FDA has expressed interest in adopting the ISO updates (reversing the previous order of adoption). Thus, a task force was formed and met periodically during 2012 and 2013.

The purpose of this article is to provide the updated OPC and to document the steps followed by the ISO committee to arrive at these values. The updated OPC values are published in the 2014 edition of ISO 5840.

Material and Methods

Data Sources

The SSE is a document mandated by the FDA to be publicly available upon issuance of an approval notice for a PMA. The SSE data are provided to FDA by valve

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Abbreviations and Acronyms

AATS = American Association for Thoracic Surgery
BLD = bleeding
FDA = Food and Drug Administration
ISO = International Organization for Standardization
LIT = literature articles
OPC = objective performance criteria
PMA = premarket approval
RCT = randomized controlled trial
SSE = summary of safety and effectiveness
STS = The Society of Thoracic Surgeons
TE = thromboembolism

manufacturers. The SSE data present a reasoned, objective, and balanced evidentiary basis for a FDA decision to approve or deny the PMA.

The majority of the SSE reports were presented in a consistent format. Late events and late patient-years were used to calculate linearized rates. If late patient-years were not given, they were calculated by subtracting 1 month from the total patient-years for each patient. SSE data are considered to have the most complete follow-up and reporting of complications, and most closely reflect the data which will be submitted for future PMAs. Thus, it was hoped that the new OPC could be produced using SSE data alone, but this approach was found to be inadequate, largely because of insufficient SSE data for all valve types of interest. For example, there were only 6 SSE series with 4,660 total patient-years for mitral bioprosthetic valves, so the SSE data were supplemented by data from a current literature (LIT) review.

The LIT review was undertaken with a search using Medline for English language articles published between January 1, 1999, and March 19, 2012. Studies selected for inclusion were those that reported on a FDA-approved valve; claimed adherence to the original 1988 AATS/STS guidelines [4], the 1996 update [9], or the current 2008 guidelines [10]; reported results separately by valve position and valve model.

Series excluded were those that focused on special subsets, such as children, elderly, rheumatic disease, endocarditis, certain sizes of valves, and so forth; contained international-multicenter studies; had fewer than 400 patient-years of follow-up; contained patients who completely or partially overlapped with SSE data; or were updated by a newer or more informative report, which was selected.

From each selected study, information about the following data categories were extracted when available: the report/article—country, institution, author and year of publication; the valve—model, position and total number of valves implanted; the patients—mean age and sex distribution; the follow-up—total patient-years, maximum follow-up years, and completeness of follow-up; and the complications—mortality, thromboembolism, bleeding (all, major, anticoagulant-related, and major anticoagulant-related), valve thrombosis, endocarditis, paravalvular leak (all and major), nonstructural valvular dysfunction, hemolysis, valve explant, and structural valvular dysfunction.

The majority of LIT articles did not clearly state whether they reported all events or late events, nor did they report late patient-years. Therefore, late events (if specified) or events (as reported) and total patient-years were used to calculate linearized rates.

Major Changes

The current FDA heart valve guidance uses OPC, along with safety and effectiveness control data published in articles in the prosthetic heart valve clinical literature, for premarket approval of new prosthetic heart valves. There are two sets of OPC for mechanical valves and bioprosthetic valves, and each contains targets for seven valve-related complications (Table 1): thromboembolism, bleeding (all and major), valve thrombosis, endocarditis, and paravalvular leak (all and major). The original ISO standard for a new heart valve was that complication rates must be statistically significantly lower than twice the OPC for all seven FDA-defined categories. The ISO committee made three major changes to the original OPC.

Table 1. Original and Proposed New Objective Performance Criteria

	Mechanical Valve			Bioprosthetic Valve		
		Proposed New			Proposed New	
Adverse Event	Original OPC	Aortic	Mitral	Original OPC	Aortic	Mitral
Thromboembolism	3.0	1.6	2.2	2.5	1.5	1.3
Valve thrombosis	0.8	0.1	0.2	0.2	0.04	0.03
All hemorrhage	3.5			1.4		
Major hemorrhage	1.5	1.6	1.4	0.9	0.6	0.7
All paravalvular leak	1.2			1.2		
Major paravalvular leak	0.6	0.3	0.5	0.6	0.3	0.2
Endocarditis	1.2	0.3	0.3	1.2	0.5	0.4

OPC = objective performance criteria.

REVIEW