Introduction of Objective Performance Criteria for Transcatheter Aortic Heart Valve Device Approval

Considerations and Recommendations for the Introduction of Objective Performance Criteria for Transcatheter Aortic Heart Valve Device Approval

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ABSTRACT

In the United States, new surgical heart valves can be approved on the basis of objective performance criteria (OPC). In contrast, the US Food and Drug Administration traditionally requires stricter criteria for transcatheter heart valve (THV) approval, including randomized, clinical trials. Recent US Food and Drug Administration approval of new-generation THVs based on single-arm studies has generated interest in alternative study approaches for THV device approval. This review evaluates whether THV device approval could follow a pathway analogous to that of surgical heart valves by incorporating OPC and provides several considerations and recommendations. Factors to be taken into account in the construction of OPC include the maturity of THV technology, variability in transcatheter aortic valve replacement practice, end points included as OPC, follow-up terms for specific OPC, patient populations to which these OPC apply, and (statistical) methods for OPC development. We recommend that approval of THV devices in the United States for low-and intermediate-risk patients or for new indications should provisionally rely on data from randomized, clinical trials. However, it is recommended that formal OPC be applied for approval of new-generation THVs for use in high- and extreme-risk patient populations.

Keywords: aortic valve, aortic valve stenosis, device approval, heart valve prosthesis implantation, transcatheter aortic valve replacement

Since the introduction of prosthetic surgical heart valves in the 1950s, a great number of valve prostheses have been developed for surgical aortic valve replacement (SAVR), with continuous improvement in outcomes by advances in valve design.[1,2] More recently, transcatheter aortic valve replacement (TAVR) has rapidly been adopted as an alternative therapy for high- or extreme-surgical-risk patients with severe aortic stenosis (AS).

In Europe, THV devices and surgical prostheses share a common market approval process. The Conformité Européenne (CE) mark provides authorization for a manufacturer to sell a product in the European Economic Area by affirming that it complies with prespecified legal requirements. Importantly, the level of scientific evidence required to achieve CE mark requires a single-arm demonstration of short-term safety and efficacy in ≈50 patients. In contrast, the approval process for new-generation surgical or transcatheter prostheses in the United States is very different. For surgical prostheses, the development of objective performance criteria (OPC) by the US Food and Drug Administration (FDA) has superseded the requirement to perform randomized, clinical trials (RCTs) because of the maturity of the device field and the minimal changes in new iterations of previously approved valves (predicate devices). Until recently, approval of THVs has required randomized comparisons with standard FDA-approved therapies because the technology is immature, device design is significantly different, and device development is still iterating rapidly. However, similar to the development of surgical prostheses, the established efficacy of TAVR as shown in multiple RCTs of high-risk patients has potentially made the requirement for lengthy RCTs before the introduction of new THV devices unacceptable from societal, patient, and physician standpoints. It may place patients at unnecessary risk by delaying access to improved safer and more efficient technology. Therefore, alternative study approaches should be considered for new THV device approval.

The FDA recently also approved several THVs on the basis of single-arm studies, the first one being the CoreValve device, which was tested in the CoreValve Extreme Risk Pivotal trial.[3] Innovative trial designs, perhaps incorporating OPC, have been proposed but not formally introduced as alternatives to RCTs for new THV device approval.[4] This review provides an overview of OPC, considers the potential role of OPC for THV device approval, and discusses the challenges associated with such an approach. Several recommendations for the future implementation of OPC for THV devices are provided.

OBJECTIVE PERFORMANCE CRITERIA

Traditionally, 2 methods of establishing a comparator for single-arm studies have been used: OPC and performance goals (PGs; Table 1). OPC are linearized event rates of safety end points that are derived from historical controls included in meta-analyses of available data. A PG, on the other hand, represents a single point estimate considered sufficient as a comparator.

In general, the process of developing a PG is less formal than the process of developing OPC. Therefore, compared with PGs, OPC are thought to be superior because of the increased maturity of device technology and the more robust data from which the comparator is developed.[5] For the FDA to allow a device to be considered for approval with OPC, it should fulfill a number of criteria: (1) The device technology should be sufficiently mature; (2) the meta-analysis from which event rates are derived should include an accumulation of studies and all relevant literature from different devices; (3) the OPC should not be developed by companies using only their own data; and (4) the OPC must be contemporary and updated regularly because technology may become obsolete over time, thereby attenuating the rigor and relevance of the OPC.

Table 1 Different Methods Used as Comparators in Single-Arm Studies

	OPC for Heart Valves	PG	OPG in the CoreValve Trial[3]
Comparator	Other similar devices	Other similar devices	Standard nondevice therapy
Development of comparator estimates	Historical controls in a meta-analysis of available data on existing similar devices	Often based on upper or lower confidence limit of efficacy or safety end point of existing similar device(s)	Meta-analysis of standard nondevice therapy, corrected for outcome of nondevice arm in a single randomized trial
Outcome	Linearized rate (%/patient-y)	Point estimate (X% at X [time])	Point estimate (43% at 1 y)
Composition of end point(s)	14 Single-component end points (7 for biological and 7 for mechanical valves)	1 Single-component or composite end point	1 Composite end point of death and major stroke
Nature of end point	Safety	Safety or efficacy	Efficacy
No. of criteria	14	1	1
Statistical comparison	Upper 95% CI of preapproval study should be less than twice the established OPC rate	Upper 1- or 2-sided 95% CI of preapproval study should be less than comparator point estimate	Upper 95% CI of preapproval study should be less than comparator point estimate

CI indicates confidence interval; OPC, objective performance criteria; OPG, objective performance goal; and PG, performance goal.

OPC Development

The OPC for surgical valves were conceived, subsequently developed, and then implemented after 2 major RCTs evaluating mechanical and biological prostheses did not identify significant safety concerns.[1] It was thus recognized that traditional randomized evaluations were not feasible because of the large sample sizes required to identify infrequent events. Such large RCTs would also greatly impede the timely introduction of technological advancements to

the market.[7] In 1993, the FDA convened an expert workshop to consider alternative study designs for regulatory approval of new valves. This forum proposed a strategy of comparing new valves with valve-related adverse event rates of existing valves occurring after the immediate postoperative 30-day period. These rates were to be derived from meta-analyses of historical data.[5,8]

An initial meta-analysis was performed, including >60 000 valve implantations and >200 000 patient-years of follow-up. A subselection of studies was based on previously FDA-approved valves in reports adhering to reporting guidelines.[9] Expert consensus identified 7 procedure-related complications that were to be assessed for new device approval, the so-called OPC (Table 2).[10] Because events occurred at a rate of 0.2% to 3.5% per 100 patient-years, this would demand an unduly large 4860 patient-years of follow-up for approval of each new valve in a study with 80% power and a 1-sided significance level of 0.05. The FDA agreed to evaluate these complication rates in studies with a minimum of 800 patient-years of patient follow-up to allow enough statistical power for events that occur at a rate of 1.2%/y, thus representing at least 9 of 14 OPC end points (eg, 7 for biological and 7 for mechanical prostheses; Table 2).

Table 2 OPC for Surgical Prostheses

	Original OPC				Proposed New OPC			
	Mechanical Valve		Tissue Valve		Mechanical Valve		Tissue Valve	
					Aortic	Mitral	Aortic	Mitral
	OPC*	Patient-Years†	OPC*	Patient-Years†	OPC*		OPC*	
Thromboembolism	3.0	323	2.5	388	1.6	2.2	1.5	1.3
Valve thrombosis	0.8	1,213	0.2	4,850	0.1	0.2	0.04	0.03
All hemorrhage	3.5	277	1.4	693	…	…	…	…
Major hemorrhage	1.5	647	0.9	1,078	1.6	1.4	0.6	0.7
All PVL	1.2	808	1.2	808	…	…	…	…
Major PVL	0.6	1,617	0.6	1,617	0.3	0.5	0.3	0.2
Endocarditis	1.2	808	1.2	808	0.3	0.3	0.5	0.4

OPC indicates objective performance criteria; and PVL, paravalvular leak.

* Events per 100 patient-years (%/y).

† Patient-years required to satisfy the requirement of establishing that the observed rate is <2 times the OPC, with 80% power and α=0.05.

Adopted from Grunkemeier et al[10] and Wu et al.[11]

Requirements for Device Approval Based on OPC

For a new valve to be approved, the upper 95% confidence interval of linearized complication rates should be less than twice the established OPC rate for each of the complications. In addition to these clinical event rates, a new valve must show functional improvement in patients (eg, New York Heart Association classification) and fulfill certain hemodynamic criteria.

Subsequently added criteria include the need to have follow-up of ≥300 patients for ≥1 year, with an equal distribution of included patients over 3 centers.

Newly Developed OPC

Since the introduction of OPC, numerous prosthetic valves have been approved with this approach.[4] However, new OPC based on more contemporary evidence have recently been proposed.[11] With the use of the same study selection criteria, rate estimates were produced from an updated meta-analysis. Improved valve design, contemporary therapeutics, and closer patient follow-up have clearly decreased the expected complication rates (Table 2). In contrast to the original OPC, it has been proposed that separate OPC for valves in the aortic and mitral position be reported.

OPC for Coronary Stents

The process of using OPC for device approval in cardiovascular disease has not been limited to heart valves. New-generation coronary stents may be evaluated and approved with OPC (Table I in the online-only Data Supplement). However, the process of OPC development and the requirements for device approval are very different from those for surgical heart valves (Figure). Important differences that may be adopted for THV device approval include that OPC for coronary stents are based on complex statistical modeling whereas OPC for surgical heart valves include no statistical modeling; that, depending on the treatment indication or degree of design modification, either OPC are used or a randomized equivalence trial is required for approval; and that events are a combination of safety and efficacy whereas OPC for surgical heart valves include only safety end points.[12,13]

COREVALVE EXTREME RISK PIVOTAL TRIAL

The methodology for approving the CoreValve THV for use in extreme-risk patients in the United States has been considered somewhat controversial.[3] The trial did not use OPC in the traditional sense but introduced a new terminology: the objective performance goal (OPG) (Table 1). The OPG was based on outcomes analyzed in a meta-analysis of studies evaluating balloon aortic valvuloplasty as a stand-alone therapy for AS. These were adjusted for the standard treatment arm of the Placement of Aortic Transcatheter Valves (PARTNER) 1B trial, which included medical therapy, and balloon aortic valvuloplasty in 88% of patients.[14] Even though this treatment has been deemed ineffective for severe AS, it formed the statistical basis for the CoreValve Extreme Risk Pivotal trial was to determine whether TAVR with the CoreValve THV was not significantly worse than the lower 95% confidence interval of standard treatment with the objective PG used as a comparator point estimate. However, because its primary goal was therefore to determine the efficacy of the CoreValve THV, the trial reflects a

measure similar to a PG. Its sole purpose was to quantify an improvement in patient outcome (mainly survival in this group) compared with the conservative management of severe AS, which was the standard of care in this patient population. The OPG did not, as is the case for OPC for surgical valve prostheses, derive data from available THV devices and evaluate the safety of the THV device in terms of multiple complication rates. As a result, it cannot be determined whether the CoreValve is comparable to the previously approved SAPIEN valve, particularly in terms of safety end points related to the valve.

HURDLES AND CONSIDERATIONS FOR CURRENT OPC USE FOR THV APPROVAL

SAVR and TAVR are considered to be complementary treatment options for select patients with native severe AS. It would therefore seem reasonable that the quality of both transcatheter and surgical heart valves be measured with the same criteria. However, the nature and rates of complications differ between SAVR and TAVR, complicating the potential application of surgical OPC to THV devices. For example, if OPC for surgical prostheses were applied to the PARTNER or CoreValve trial data, these devices would not have been approved on the basis of significantly increased paravalvular leak (PVL) with the transcatheter devices.[15] Therefore, specific OPC for the approval of THV devices would be more appropriate. A number of factors need to be considered in the development of such OPC.

Maturity of Technology

The maturity of the device technology is one of the most important criteria for the FDA to consider the use of OPC. A great deal of TAVR research has been devoted to refining patient selection, improving procedural safety, and delivering better clinical outcomes. Such information has been instrumental in the development of new-generation THV devices that overcome technical and procedural issues related to first-generation devices. Indeed, direct comparisons between first- and new-generation devices have reported lower complication rates with more contemporary valves.[16] Recent introductions to the European market of new repositionable, recapturable, and retrievable THVs and THVs that often contain sealing cuffs to reduce PVL have similarly shown promising clinical outcomes.[17]

Despite these promising results with new-generation THV, the majority of published TAVR outcome data relate to first-generation THVs that are no longer in use. The rapid evolution of THV technology may have already rendered the initial SAPIEN and CoreValve randomized trial outcome data superseded. A meta-analysis of all relevant data for the development of TAVR OPC would largely include obsolete THV devices and include only limited patient follow-up with new THVs. The inferiority bar that would be set as OPC would be so low that virtually any new device, however flawed, would not have significant trouble meeting

this antiquated bar. These data may thus be unsuitable for determining adverse events rates and treatment goals. A meta-analysis for TAVR OPC development should be up to date and include a variety of new-generation THV devices. It should not be based on a single device type or old-generation devices. Therefore, it is questionable whether TAVR practice and THV devices have matured sufficiently to allow the development of OPC.

Variability in TAVR Practice

The quality of new THV devices is often measured by a comparison of rates of procedural complications.[18] However, whether these complication rates truly reflect an improvement in only the valve design is debatable. Procedural complications may be heavily influenced by operator experience and skill, by variability in TAVR practice, by procedure development, and importantly by variability in patient selection criteria. Compared with a relatively stable SAVR practice, standard practices for TAVR are rapidly changing as a result of new data.

Patient selection is hospital, heart team, and even operator dependent. The selection of lower-risk patients or the exclusion of "futile" patients will be associated with significant outcome improvements.[19,20] Second, the rigor of preoperative assessment and valve sizing is variable. Third, although the majority of centers use a transfemoral-first approach to TAVR, other centers have favored alternative routes.[21] Each access route will be associated with specific procedural complications. Fourth, variability in use of ancillary devices (eg, embolic protection) may have an impact on adverse events.[22] Fifth, increased operator experience has been linked to reductions in procedural complications. Experienced operators can often avoid scenarios in which complications can occur or better manage them if they do occur. Moreover, algorithms for management of complications often differ, which may affect outcomes. For example, thresholds for blood transfusions after access site complications can be highly variable. Lastly, end-point adjudication according to the Valve Academic Research Consortium remains a challenge for some of these end points, resulting in misclassifications and overestimation or underestimations of outcomes.[23,24]

Patient Population

Current large registries and RCTs of TAVR have essentially included high-risk populations with multiple severe comorbidities. Long-term follow-up is limited by the high rates of non-cardiovascular and cardiovascular non–valve-related deaths. Although valve hemodynamic performance is maintained,[25] information on actual valve durability and safety remains scarce.

Data from high-risk patients should not form the basis for the development of OPC for the approval of THV devices that are also to be used in lower-risk patients. Short- and medium-term outcomes are significantly improved in lower-risk patients.[19] Development of OPC based solely on high-risk trial data risks the approval of THV devices that perform unsatis-factorily in lower-risk patient populations.

Therefore, it may be appropriate to develop TAVR OPC for specific patient populations (ie, separate low-, intermediate-, high-, or extreme-risk OPC). Specific procedural complications may have a greater impact in cohorts of high- than low-risk patients. For example, conversion to open surgery should be very low in populations of extreme-risk patients, who are not surgical candidates by default. This is less relevant in low-risk patients, who will have excellent results of SAVR despite the complication. In contrast, the impact of PVL and the requirement for new permanent pacemaker implantation may become more crucial in low-risk patients with a long life expectancy as opposed to high-risk patients in whom prognosis is already severely impaired as a result of comorbidities. Other complications such as coronary obstruction are likely to be of equal importance in all populations.

Follow-Up

Traditionally, OPC for prosthetic valves have focused on long-term events, not on procedural events. Technically, SAVR is relatively straightforward, and the design of the prosthetic valve has minimal impact on the operative technique and procedural outcome. The technical aspect of the procedure itself is considered to be less relevant for the actual safety of the valve. In contrast, design features of the THV delivery system and the THV have a significant impact on the TAVR procedure. Moreover, specific complications that should be considered as OPC may be a result of major differences in design features of THV devices, related to balloon expandability or self-expandability and specifically the height of devices, stent matrixes, presence and length of a skirt, and sealing rings.

OPC for TAVR should be a combination of short-and long-term criteria. To have sufficient statistical power to detect outcome differences, it should be mandatory to have a minimum length of follow-up and a minimum number of patients included in preapproval studies, similar to the practice of surgical OPC.

End Points

OPC for heart valves emphasize the long-term safety of new valves, as measured by events related to the device design: Thrombogenicity and bleeding are intertwined and related to valve design, the need for oral anticoagulation, and the targeted International Normalized Ratio; rates of PVL can be a measure of structural valve deterioration; and endocarditis evaluates the susceptibility of a valve for the colonization of organisms.

The poor prognosis of many high-risk patients has necessitated an end-point focus on death and strokes in TAVR trials rather than device-related safety. Indeed, stroke and PVL have been addressed adequately in numerous studies. However, many other complications have been reported only anecdotally.[26] Studies have just recently scrutinized rates of valve thrombosis, bleeding, and endocarditis during follow-up. [25,27–29] These traditional OPC end points remain clinically relevant because their occurrence is associated with prognosis. [25,28] Considering death as an end point itself, however, should be avoided. Analyses of predictors

of death after TAVR demonstrate that comorbidities are the most important predictors of mortality.[30,31] Procedural complications that are operator dependent such as bleeding and vascular complications have also been shown to predict mortality. Therefore, death as an OPC would not necessarily represent a measure of valve safety (eg, prosthetic inadequacy or design).

Similar to OPC for coronary stents that require collection of 30-day major adverse cardiac events, procedural safety events related to specific valve designs should be considered in OPC. Alternatively, a 30-day early safety PG may also be sufficient for the rapid introduction of new technology. These may include but are not limited to the following events: conversion to open surgery, coronary obstruction, annular rupture, ventricular septal perforation, mitral valve apparatus damage or dysfunction, early valve migration or embolization, PVL, and permanent pacemaker implantation. Other procedural end points related to specific approaches (eg, transapical or transaortic TAVR) should be considered less relevant.

In addition to traditional heart valve OPC that should be required to test the safety of THV devices, long-term evaluation should include hemodynamic performance of THVs and the freedom from structural valve deterioration. These end points are crucial to assess the efficacy of TAVR.

The use of composite end points as OPC should be avoided. Potential risks related to valves will not become apparent because lower and higher event rates of specific complications in the composite will even out.

Statistical Analysis

Multivariate adjustment for OPC in coronary stent approval is performed on the basis of clinical and procedural characteristics (Figure). TAVR outcomes are highly dependent on patient selection, practice variability, and patient comorbidities. For OPC of THVs, it would therefore also be appropriate to provide outcome adjustment based on clinical profiles and procedural characteristics of TAVR patients. A disadvantage of this approach is the lack of clear predictors for surgical OPC end points (eg, endocarditis or valve thrombosis). Little predictability is derived from patient, procedural, or postprocedural characteristics available in the immediate perioperative phase. Similarly, numerous TAVR-specific outcomes that could be considered for OPC occur rarely. Identification of clear predictors is therefore limited, and outcome adjustment would be insufficient.

NON-OPC ALTERNATIVES FOR DEVICE APPROVAL

Propensity score analysis using historical controls has been proposed as an alternative to OPC for device approval. Multivariate analyses have demonstrated TAVR outcomes to be dependent largely on patient baseline characteristics, except for the impact of PVL, different

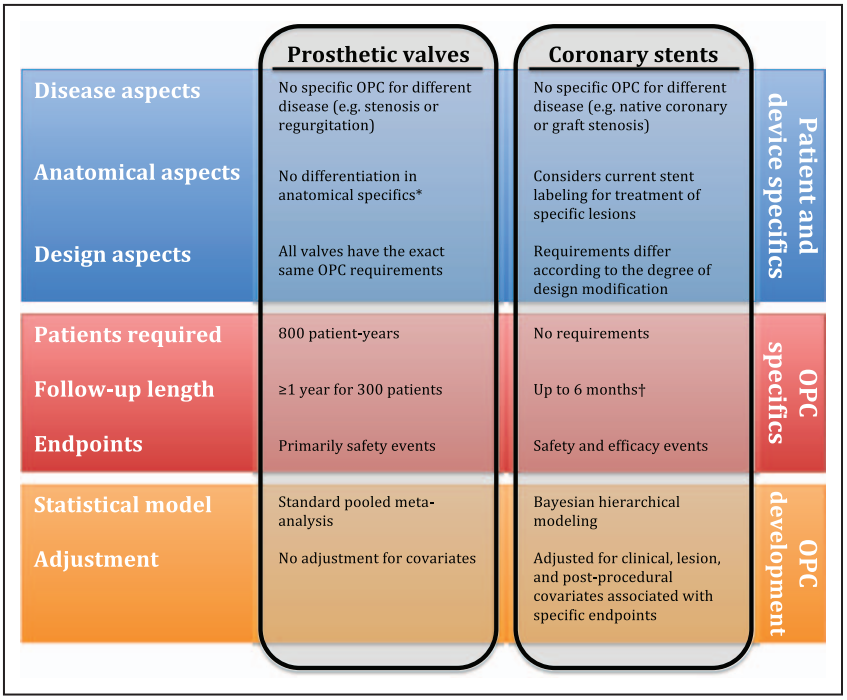

Figure Differences in development and specifics of objective performance criteria (OPC) for prosthetic valves and coronary stents. *Newly developed OPC take into consideration whether a valve is located in the aortic or mitral position, but the US Food and Drug Administration has not yet adopted these. †Depending on the degree of stent device design modifications, with longest follow-up required being 6 months.

access routes, and procedural adverse events.[30,31] These variables would allow for appropriate propensity matching. However, TAVR research has focused largely on evaluating prognostic results of TAVR in a comorbid patient population. Besides hemodynamic performance during follow-up, reports and predictors of valve function and safety have been scarce. Even with propensity score analysis or propensity matching, analyses would focus predominantly on efficacy, not safety. This highlights the need for further maturity of device technology and research to reduce the "noise" in current outcome studies that obscures actual valve safety during follow-up.

Should RCTs be mandatory for specific indications, bayesian and adaptive trial designs over a frequentist's superiority approach may be alternatives that can potentially reduce sample size or trial duration and costs.[32] Such trial designs mandate satisfactory information from previous RCTs and informative large registries, which are available for TAVR. Other RCT designs using composite end points and noninferiority trials have been proposed to reduce sample sizes.[33] However, liberal noninferiority margins to artificially claim noninferiority should be avoided.[34] Furthermore, composite end points pose several limitations, although

they may be overcome by application of hierarchical statistical methodology.[35] The concept of registry-based RCTs has recently been introduced in cardiovascular medicine to ease trial planning and execution.[36] This may certainly be possible in the setting of the many existing large-scale TAVR registries.

CONSIDERATIONS FOR TAVR OPC DEVELOPMENT

Despite the numerous hurdles currently related to developing OPC for THV device approval, it is likely that there will not be an ideal time for introducing OPC. Challenges will remain and new hurdles will arise. OPC for THV device approval will need to be introduced at some point and subsequently optimized. Regular updates when new evidence becomes available will be required.

The causes, interventional techniques, and devices differ significantly between TAVR and transcatheter mitral valve interventions. Therefore, separate OPC for aortic and mitral procedures should be developed.

Important recommendations relate to the risk profile of distinct patient populations because OPC should be patient group specific. New treatment indications for TAVR require data from an RCT on which OPC can subsequently be developed. With robust data from RCTs, approval of new THV devices for use in high- and extreme-risk patients should be made possible by the introduction of formal OPC (Table 3). The use of OPC cannot currently be justified for low- or intermediate-risk patient populations for whom randomized data with a surgical AVR control are scarce; only large, powered RCTs can demonstrate whether TAVR can be recommended for use in intermediate-risk patients.[37] With the ongoing PARTNER II and Surgical Replacement and Transcatheter Aortic Valve Implantation (*SURTAVI*) trials,

Table 3 Proposal for Current THV Device Approval Based on OPC, PGs, and Data From RCTs

Patient Population	Early Safety	Long-Term Safety and Efficacy
Low risk	Similar safety as a propensity-matched surgical cohort, or as determined by a 30-d PG once a THV has been approved for use in these patients	Show both similar results in an RCT comparing TAVR versus SAVR and fulfill surgical OPC
Intermediate risk	Similar safety as a 30-d PG	Through a non-inferiority or superiority THV vs THV RCT if TAVR is superior to SAVR in ongoing TAVR vs SAVR RCTs, or fulfill OPC that can be derived from these ongoing trials
High and extreme risk	Similar safety as a 30-d PG	Through noninferiority or superiority THV vs THV RCT, or fulfill specific THV OPC in a single-arm registry

OPC indicates objective performance criteria; PG, performance goal; RCT, randomized, clinical trial; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and THV, transcatheter heart valve.

contemporary data on the best strategy for intermediate-risk patients will be available shortly. These data can function as new standards and form the basis for the development of OPC for intermediate-risk patients. In the future, the development of 30-day PGs will help rapidly integrated new-generation iterative THVs into clinical practice and will be available on short notice from large national and company databases such as the Transcatheter Valve Therapeutics registry.[31] For low-risk patients, long-term performance of THVs should at least match that of surgical prostheses and fulfill surgical OPC.

Table 4 contains a summary of recommendations for OPC development. Importantly, OPC development should be done in close collaboration with regulatory bodies in charge of device approval.[4]

Table 4 Considerations and Recommendations for OPC Development

Procedure
Separate surgical and transcatheter heart valve OPC
Separate aortic and mitral valve OPC
Uniform for different access approaches
OPC for THV development
Based on TAVR data only
Based on multiple new-generation THVs
Regular updates
May include covariate adjustment
Patient populations
Separate OPC according to risk populations
No OPC for new treatment indications
Follow-up
Specific short- and long-term criteria
A minimum length of follow-up requirement
End points
Avoid composite end points
Composed of valve-related events
Exclude events specifically related to the patient population, access approach, or operator experience
Events may differ according to risk profiles of patient populations
Short term: focus on safety
Long term: combination of safety and efficacy
Identification of valve design features related to specific adverse events

AVR indicates aortic valve replacement; OPC, objective performance criteria; RCT, randomized, controlled trial; TAVR, transcatheter aortic valve replacement; and THV, transcatheter heart valve.

CONCLUSIONS

It is recommended that applying formal OPC for the approval of new-generation THVs for use in high- and extreme-risk patient populations in the United States be considered. For now, approval of THV devices for use in low- and intermediate-risk patients or for new indications should provisionally be considered only with data from RCTs. However, in the near future, data from specific RCTs (PARNTER II and SURTAVI) can form the basis for development of additional OPC for intermediate-risk patients. Development of these and future OPC should include considerations of technology maturity, short- and long-term data, specific events likely to be related to particular THV designs, patient risk profile, and statistical methods to produce OPC.

Supplemental Table 1 Objective Performance Criteria for coronary stents

Engineering evaluation compared to approved conventional stainless steel stents		Patient factors	Lesion factors	Stent factors	New stent: frequentist evaluation technique	Modified stent: Bayesian evaluation technique
Conventional stent design or minimal design deviation		Elective coronary or vein graft	3.0-5.0mm reference	Balloon expandable; stainless steel; slotted tube, welded, coil	Registry: 30-day MACE and acute angiographic predicted restenosis rate compared against OPC	Update prior similar stent experience for direct probability comparison with acute MACE and predicted restenosis OPC
Moderate design deviation		Elective coronary or vein graft	3.0-7.0mm reference	Balloon or self-expandable; stainless steel nitinol, coated, new metal, covered; tube, welded, coil	Registry: 30-day MACE and 6-month angiographic endpoints compared to OPC	Update prior similar stent experience for direct probability comparison to acute MACE and 6-month OPC
New patient population or new untested stent design	Severe design deviation	Elective coronary or vein graft	3.0-7.0mm reference	Balloon or self-expandable; stainless steel nitinol, coated, new metal, covered; tube, welded, coil	Randomized equivalence trial against standard approved stent, 8/9-month angiography and clinical follow-up	
	Conventional design or moderate or severe design deviation	Elective coronary	<2.75mm reference or lesion >35mm	Balloon or self-expandable; stainless steel nitinol, coated, new metal, covered; tube, welded, coil	Randomized superiority trial against balloon angioplasty, 8/9-month angiography and clinical follow-up	

OPC = Objective Performance Criteria; MACE = major adverse cardiac event

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