Door Widening on Potential TAVI Populations

ARTICLES BY
PATRICE WENDLING

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PARIS – In inoperable patients with severe aortic stenosis, their EuroSCORE – a predicted operative mortality from cardiac surgery – consistently predicted outcomes from transcatheter aortic valve implantation in a prospective, single-center study.

Among 177 consecutive patients declined for surgery, the procedural success rate was 100% in patients with a EuroSCORE of less than 20% and 95.7% in those with a EuroSCORE of more than 20%.

Moreover, there were no deaths at 30 days in the low-risk group, but mortality was 11.1% in the high-risk group. This result was maintained at 1 year (5% vs. 25%), and both differences were highly significant, Dr. Matthieu Godin reported at the congress.

"This may be the first step towards a broader assessment of percutaneous techniques in populations at lower surgical risk, but without forgetting that surgery is currently the … standard," he said.

Transcatheter aortic valve implantation (TAVI) is not commercially avaliable in the United States. In Europe, however, TAVI is considered a less invasive therapeutic option for severe aortic stenosis among nonsurgical and high–surgical-risk patients, as defined by a logistic EuroSCORE (European System for Cardiac Operative Risk) of more than 20% or a Society of Thoracic Surgeons risk score of more than 10%.

TAVI is frequently performed, however, in patients with low to intermediate logistic EuroSCOREs and contraindications to conventional valve replacement due to comorbidities not included in the surgical risk models, said Dr. Godin of Rouen (France) University Hospital–Charles Nicolle Hospital, where the first TAVI was performed in 2002 by coinvestigator Dr. Alain Cribier (Circulation 2002;106:3006-8).

In an effort to address this evolution and an eager marketplace, the American College of Cardiology and Society of Thoracic Surgeons released an expert consensus document that explores key components that will be necessary for successful integration of transcatheter valve therapy into clinical practice (J. Am. Coll. Cardiol. 2011;58:445-55. Epub 2011 Jun 28). While praising the "transformational technology," the societies cite limited evidence from only one randomized trial in aortic stenosis (PARTNER) and one in mitral insufficiency (EVEREST II) in stating that "adoption of these techniques to populations beyond those studied in these randomized

CoreValve Shows No Signs of Degeneration After 3 Years

PARIS – Hemodynamic values were sustained up to 3 years after CoreValve transcatheter aortic valve implantation among 393 patients with severe symptomatic aortic stenosis.

Importantly, there were no signs of unexpected early degeneration of the CoreValve prosthesis, lead author Dr. Anke Opitz reported at the congress.

One of the fundamental questions facing transcatheter aortic valve implantation (TAVI) is whether the durability of transcatheter aortic valves is comparable to that of conventional biological aortic valves, which typically start degenerating at about 10-15 years.

"We expect that the duration will be as long as the conventional biological aortic valves, but this is a completely new style of valve," Dr. Opitz said in an interview. "It's very different from the conventional valves because you have to crimp these valves [on to the catheter] and sometimes you do post dilation, so there's a lot more stress on the valves than on the conventional ones," she added.

The CoreValve (Medtronic) and Edwards Sapien (Edwards Lifesciences) transcatheter valves are limited to investigational use in the United States but have been available in Europe since 2007.

U.S. approval of the Edwards Sapien valve is expected, however, following a July 2011 U.S. Food and Drug Administration advisory panel vote in favor of the valve for treatment of certain inoperable patients.

Dr. Opitz reported on 393 consecutive patients implanted from June 2007 to June 2011 at the German Heart Center in Munich with the CoreValve device, which consists of a self-expandable nitinol stent with a porcine pericardium valve. Femoral access was possible in 87% of patients; 63% of patients were implanted with a 29-mm prosthesis and 37% with a 26-mm prosthesis.

The patients' mean age was 80 years, mean EuroSCORE was 19.1%, and their mean Society of Thoracic Surgeons risk score was 5.8%.

We expect the duration to be as long as the conventional valves, but this is a completely new style.

DR. OPITZ

Transthoracic echocardiography revealed that the effective orifice area increased significantly, from 0.7 cm^2 at baseline to 1.55 cm^2 after TAVI, and remained unchanged through 36 months at 1.57 cm^2 in 20 evaluable patients, Dr. Opitz reported.

The peak aortic valve gradient decreased significantly after TAVI (78 mm Hg vs. 21 mm Hg), as did the mean aortic valve gradient. Both gradients remained low through the 36 months. Severity of stenosis rises with the gradients.

Septal wall thickness also decreased significantly, from 14.9 mm preoperatively to 13.1 mm at 36 months follow-up.

Left ventricular end diastolic diameter remained unchanged from baseline at 12-, 24-, and 36-month follow-ups. The percentage of patients with a left ventricular ejection fraction less than 35% decreased significantly, from 19% at baseline to 4% at 12 months, 6% at 24 months, and 7% at 36 months, Dr. Opitz said.

Paravalvular aortic valve regurgitation occurred in 64% of patients after TAVI but was trivial or mild in 65%, mild to moderate in 20%, and moderate in 15%, she noted.

Dr. Opitz reported no conflicts of interest. ■

One-Year Survival Better in Women Than Men After TAVI

PARIS – Although female sex is a risk factor for worse outcomes after conventional cardiac surgery, the opposite appears to be true following transcatheter aortic valve implantation.

Among 260 consecutive patients undergoing TAVI for severe aortic stenosis, female sex was linked with significantly better 1-year survival (76% vs. 65%).

The study, described as the first analysis of sex difference with this emerging technique, also identified female sex as an independent predictor of long-term survival, Dr. Kentaro Hayashida and his colleagues reported at the congress.

The increased survival rate in women treated with TAVI may represent a paradox in the cardiovascular disease gender gap.

"Surgical aortic valve replacement in female patients is technically demanding because of their smaller stature and body surface area, higher body mass index, and smaller aortic root," Dr. Hayashida of the Institut Cardiovasculaire Paris-Sud (ICPS) in Massy, France, said in an interview. "In our study cohort, TAVI was performed with a similar device success rate, compared to males, because of the procedural feasibility inherent in this novel technique."

TAVI was successfully achieved in 91% of women and 88.4% of men, a nonsignificant difference. Similarly, no significant sex differences were observed for 30-day mortality (12% for women and 18% for men).

Longer life expectancy and early detection of aortic stenosis in women may, in part, have contributed to their improved survival, coauthor and colleague Dr. Philippe Garot said. He pointed out that despite both sexes having made gains in cardiovascular disease mortality from 1950 to 1999, an 80-year-old man in France can expect to live 8.3 more years, compared with 10.5 additional years for an 80-year-old French woman.

The average age at the time of surgery was 83 years in both study groups.

At baseline, women had a significantly lower logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation, 22% vs. 26%), higher left ventricular ejection fraction (54% vs. 47%) and less coronary artery disease (49% vs. 79%), peripheral artery disease (27% vs. 40%), and previous cardiac surgery (14% vs. 26.4%) than did men.

Women, however, also had a significantly smaller femoral artery size (7.74 vs. 8.55 mm), annulus size (20.9 vs. 22.9 mm), and valve size (23.9 vs. 26.3 mm) than did men, Dr. Garot said.

Longer life expectancy may partially explain the increased TAVI survival in women.

DR. GAROT

In a multivariate analysis, male sex was identified as an independent predictor of long-term mortality (odds ratio, 1.80), the authors reported. Other significant risk factors were previous cardiac surgery (OR, 2.3), postprocedural aortic regurgitation (OR, 2.3), transfusion of four or more units (OR, 2.5), acute kidney injury (OR, 6.9), and conversion to open surgery (OR, 5.1).

Notably, vascular complications were not associated with mortality in the study, Dr. Garot said.

Data were prospectively collected on 131 women and 129 men with severe aortic stenosis who were treated at the ICPS from September 2006 through December 2010. TAVI was performed using the Edwards Sapien or Sapien XT valves (85%) or the third-generation CoreValve Revalving system (15%), with 65% of valves placed via the transfemoral approach.

Dr. Hayashida and his coauthors report no conflicts. ■

To see an interview with Dr. Garot, scan this QR code using your smartphone.

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trials, therefore, is not appropriate at the current time."

Dr. Godin stressed that his results should not be interpreted to suggest that the indication for TAVI should be expanded to low-risk surgical candidates.

The Placement of Aortic Transcatheter Valves (PARTNER) trial enrolled two distinct cohorts. Cohort A included 699 patients (median age 84 years) who were candidates for conventional surgery but were at high surgical risk based on an STS score of at least 10% or on coexisting conditions that would be associated with at least a 15% predicted risk of death by 30 days after surgery. Cohort B included 358 patients (median age 83 years) who were deemed unsuitable for conventional surgery because of coexisting conditions that would be associated with at least a 50% predicted probability of death by 30 days after surgery or a serious irreversible complication (N. Engl. J. Med. 2010;363:1597-607).

Dr. Godin's analysis included 177 patients who presented during 2006-2011 with degenerative aortic stenosis and were implanted with the Edwards Sapien valve up to October 2009 and the Edwards Sapien-XT prosthesis thereafter. A transfemoral approach was used in 72% and a transapical approach in 28%.

In all, 60 patients had a EuroSCORE of less than 20% (mean 12%) and 117 had a EuroSCORE of at least 20% (mean 32%). Their mean ages were 80 years and 84 years, respectively.

Contraindications to conventional surgery in the low-risk group included porcelain aorta in 15%, chest irradiation in 20%, and chest deformity in 8.3%.

The low- and high-risk groups had similar rates of major stroke (1.7% and 0.9%, respectively), major vascular complications (5% and 6%), and definitive pacemaker implantation (5% and 6%). The low-risk group had significantly less life-threatening bleeding (7% vs. 21%) and significantly shorter mean ICU stays (2 days vs. 3 days) and mean hospital stays (9 days vs. 11 days), Dr. Godin reported.

Dr. Godin reported no conflicts. Dr. Cribier is a consultant for Edwards Lifesciences, and two additional coauthors are proctors for the company. ■

Scan this QR code with your smartphone to see an interview with Dr. Godin.

Pediatric Patients 10 to 17 Years of Age: In an 8-week double-blind, placebo-controlled study boys and post-menarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (heFH) (n=192), were treated with WELCHOL tablets (1.9-3.8 g, daily) or placebo tablets *[See Clinical Studies (14.1) in the full prescribing information]*.

Table 2
Placebo-Controlled Clinical Study of WELCHOL for Primary Hyperlipidemia in heFH Pediatric Patients: Adverse Reactions Reported in ≥2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality

	Number of Patients (%)	
	WELCHOL N = 129	Placebo N = 65
Nasopharyngitis	8 (6.2)	3 (4.6)
Headache	5 (3.9)	2 (3.1)
Fatigue	5 (3.9)	1 (1.5)
Creatine Phosphokinase Increase	3 (2.3)	0 (0.0)
Rhinitis	3 (2.3)	0 (0.0)
Vomiting	3 (2.3)	1 (1.5)

The reported adverse reactions during the additional 18-week open-label treatment period with WELCHOL 3.8 g per day were similar to those during the double-blind period and included headache (7.6%), nasopharyngitis (5.4%), upper respiratory tract infection (4.9%), influenza (3.8%), and nausea (3.8%) *[See Clinical Studies (14.1) in the full prescribing information]*.

Type 2 Diabetes Mellitus: The safety of WELCHOL in patients with type 2 diabetes mellitus was evaluated in 4 double-blind, 12-26 week, placebo-controlled clinical trials. These trials involved 1128 patients (566 patients on WELCHOL; 562 patients on placebo) with inadequate glycemic control on metformin, sulfonylurea, or insulin when these agents were used alone or in combination with other anti-diabetic agents. Upon completion of the pivotal trials, 492 patients entered a 52-week open-label uncontrolled extension study during which all patients received WELCHOL 3.8 g/day while continuing background treatment with metformin, sulfonylurea, or insulin alone or in combination with other anti-diabetic agents.

A total of 6.7% of WELCHOL-treated patients and 3.2% of placebo-treated patients were discontinued from the diabetes trials due to adverse reactions. This difference was driven mostly by gastrointestinal adverse reactions such as abdominal pain and constipation.

One patient in the pivotal trials discontinued due to body rash and mouth blistering that occurred after the first dose of WELCHOL, which may represent a hypersensitivity reaction to WELCHOL.

Table 3
Placebo-Controlled Clinical Studies of WELCHOL Add-on Combination Therapy with Metformin, Insulin, Sulfonylureas: Adverse Reactions Reported in ≥2% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality

	Number of Patients (%)	
	WELCHOL N = 566	Placebo N = 562
Constipation	49 (8.7)	11 (2.0)
Nasopharyngitis	23 (4.1)	20 (3.6)
Dyspepsia	22 (3.9)	8 (1.4)
Hypoglycemia	17 (3.0)	13 (2.3)
Nausea	17 (3.0)	8 (1.4)
Hypertension	16 (2.8)	9 (1.6)

Hypertriglyceridemia: Patients with fasting serum TG levels above 500 mg/dL were excluded from the diabetes clinical trials. In the phase 3 diabetes trials, 637 (63%) patients had baseline fasting serum TG levels less than 200 mg/dL, 261 (25%) had baseline fasting serum TG levels between 200 and 300 mg/dL, 111 (11%) had baseline fasting serum TG levels between 300 and 500 mg/dL, and 9 (1%) had fasting serum TG levels greater than or equal to 500 mg/dL. The median baseline fasting TG concentration for the study population was 172 mg/dL; the median post-treatment fasting TG was 195 mg/dL in the WELCHOL group and 177 mg/dL in the placebo group. WELCHOL therapy resulted in a median placebo-corrected increase in serum TG of 5% (p=0.22), 22% (p<0.001), and 18% (p<0.001) when added to metformin, insulin and sulfonylureas, respectively *[See Warnings and Precautions (5.2) and Clinical Studies (14.2) in the full prescribing information]*. In comparison, WELCHOL resulted in a median increase in serum TG of 5% compared to placebo (p=0.42) in a 24-week monotherapy lipid-lowering trial *[See Clinical Studies (14.1) in the full prescribing information]*.

Treatment-emergent fasting TG concentrations ≥500 mg/dL occurred in 4.1% of WELCHOL-treated patients compared to 2.0% of placebo-treated patients. Among these patients, the TG concentrations with WELCHOL (median 604 mg/dL; interquartile range 538-712 mg/dL) were similar to that observed with placebo (median 644 mg/dL; interquartile range 574-724 mg/dL). Two (0.4%) patients on WELCHOL and 2 (0.4%) patients on placebo developed TG elevations ≥1000 mg/dL. In all WELCHOL clinical trials, including studies in patients with type 2 diabetes and patients with primary hyperlipidemia, there were no reported cases of acute pancreatitis associated with hypertriglyceridemia. It is unknown whether patients with more uncontrolled, baseline hypertriglyceridemia would have greater increases in serum TG levels with WELCHOL *[See Contraindications (4) and Warnings and Precautions (5.2)]*.

Cardiovascular adverse events: During the diabetes clinical trials, the incidence of patients with treatment-emergent serious adverse events involving the cardiovascular system was 3% (17/566) in the WELCHOL group and 2% (10/562) in the placebo group. These overall rates included disparate events (e.g., myocardial infarction, aortic stenosis, and bradycardia); therefore, the significance of this imbalance is unknown.

Hypoglycemia: Adverse events of hypoglycemia were reported based on the clinical judgment of the blinded investigators and did not require confirmation with fingerstick glucose testing. The overall reported incidence of hypoglycemia was 3.0% in patients treated with WELCHOL and 2.3% in patients treated with placebo. No WELCHOL treated patients developed severe hypoglycemia.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of WELCHOL. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Drug Interactions with concomitant WELCHOL administration include:

- Increased seizure activity or decreased phenytoin levels in patients receiving phenytoin. Phenytoin should be administered 4 hours prior to WELCHOL.
- Reduced International Normalized Ratio (INR) in patients receiving warfarin therapy. In warfarin-treated patients, INR should be monitored frequently during WELCHOL initiation then periodically thereafter.
- Elevated thyroid-stimulating hormone (TSH) in patients receiving thyroid hormone replacement therapy. Thyroid hormone replacement should be administered 4 hours prior to WELCHOL *[See Drug Interactions (7)]*.

Gastrointestinal Adverse Reactions

Bowel obstruction (in patients with a history of bowel obstruction or resection), dysphagia or esophageal obstruction (occasionally requiring medical intervention), fecal impaction, pancreatitis, abdominal distension, exacerbation of hemorrhoids, and increased transaminases.

Laboratory Abnormalities

Hypertriglyceridemia

7 DRUG INTERACTIONS

Table 4 lists the drugs that have been tested in *in vitro* binding or *in vivo* drug interaction studies with colesevelam and/or drugs with postmarketing reports consistent with potential drug-drug interactions. Orally administered drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to WELCHOL. Alternatively, the physician should monitor drug levels of the co-administered drug.

Table 4
Drugs Tested in *In Vitro* Binding or *In Vivo* Drug Interaction Testing or With Post-Marketing Reports

Drugs with a known interaction with colesevelam	Cyclosporine[c], glyburide[a], levothyroxine[a], and oral contraceptives containing ethinyl estradiol and norethindrone[a]
Drugs with post-marketing reports consistent with potential drug-drug interactions when coadministered with WELCHOL	phenytoin[a], warfarin[b]
Drugs that do not interact with colesevelam based on *in vitro* or *in vivo* testing	cephalexin, ciprofloxacin, digoxin, warfarin[b], fenofibrate, lovastatin, metformin, metoprolol, pioglitazone, quinidine, repaglinide, valproic acid, verapamil

[a] Should be administered at least 4 hours prior to WELCHOL

[b] No significant alteration of warfarin drug levels with warfarin and WELCHOL coadministration in an *in vivo* study which did not evaluate warfarin pharmacodynamics (INR). *[See Post-marketing Experience (6.2)]*

[c] Cyclosporine levels should be monitored and, based on theoretical grounds, cyclosporine should be administered at least 4 hours prior to WELCHOL.

In an *in vivo* drug interaction study, WELCHOL and warfarin coadministration had no effect on warfarin drug levels. This study did not assess the effect of WELCHOL and warfarin coadministration on INR. In postmarketing reports,