Executive Summary

Medtronic Contegra® Pulmonary Valved Conduit
Models 200 (unsupported) and 200S (supported)

H020003

Prepared by the Center for Devices and Radiological Health
for the September 16, 2015 Pediatric Advisory Committee Meeting

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INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with postmarketing safety information to support its annual review of the Contegra® Pulmonary Valved Conduit ("Contegra"). The purpose of this annual review is to (1) ensure that the Humanitarian Device Exemption (HDE) for this device remains appropriate for the pediatric population for which it was granted, and (2) provide the PAC an opportunity to advise FDA about any new safety concerns it has about the use of this device in pediatric patients.

This document summarizes the safety data the FDA reviewed in the year following our 2014 report to the PAC. It includes data from the manufacturer's annual report, postmarket medical device reports (MDR) of adverse events, and peer-reviewed literature.

BRIEF DEVICE DESCRIPTION

Contegra is a glutaraldehyde-crosslinked, heterologous bovine jugular vein with a competent tri-leaflet venous valve. The device is available in 6 sizes in even increments between 12 and 22 mm inside diameter, measured at the inflow end. The device is available in two models: one without external ring support (Model 200), and one with ring support modification (Model 200S).

INDICATIONS FOR USE

Contegra is indicated for correction or reconstruction of the right ventricular outflow tract (RVOT) in patients aged less than 18 years with any of the following congenital heart malformations:

- Pulmonary Stenosis
- Tetralogy of Fallot
- Truncus Arteriosus
- Transposition with Ventricular Septal Defect (VSD)
- Pulmonary Atresia

Contegra is also indicated for the replacement of previously implanted, but dysfunctional, pulmonary homografts or valved conduits.

REGULATORY HISTORY

April 24, 2002:	Granting of Humanitarian Use Device (HUD) designation for Contegra (HUD #020003)
November 21, 2003:	Approval of Contegra HDE (H020003)
April 11, 2013:	Approval to profit on the sale of Contegra

DEVICE DISTRIBUTION DATA

FDASIA amended section 520(m) of the FD&C Act to allow devices with HDEs indicated for use in pediatric patients or a pediatric subpopulation to be sold for profit; the number of devices distributed in any calendar year cannot exceed the Annual Distribution Number (ADN) for each device. The ADN is defined as the number of devices reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States. The FDA has interpreted this to mean that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual. For Contegra, one device is reasonably necessary to treat an individual, therefore the ADN for this device is 4,000. Annual distribution of Contegra has not yet exceeded the ADN. In 2014, a total of 633 devices were sold in the U.S., and 398 devices were implanted. At least 367 of the devices were implanted in pediatric (<22 years) patients.

MEDICAL DEVICE REPORT REVIEW

Overview of the Manufacturer and User Facility Device Experience (MAUDE) Database

MAUDE is one of several important postmarket surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries, and malfunctions. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (i.e., manufacturers, importers, and device user facilities) and voluntary reporters (e.g., health care professionals, patients, and consumers). The FDA uses the information in MDRs to:

- establish a qualitative snapshot of adverse events for a specific device or device type,
- monitor device performance,
- contribute to benefit-risk assessments, and

- detect actual or potential safety issues or other problems with devices used in "real world" settings, including rare or unexpected adverse events, such as those associated with:
  - long-term device use,
  - vulnerable populations, or
  - user error.

Although MAUDE data provide valuable information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. Other limitations of MAUDE data include the following:

- Under-reporting of events.
- Lack of information about the frequency of device use.
- Reporting bias can occur because of such things as manufacturer reporting practices, increased media attention, and/or FDA's regulatory actions.
- It is not representative of all known safety information for a reported medical device, and therefore should be interpreted in the context of other available information when making device-related or treatment decisions.
- The number of MDR reports cannot be interpreted or used in isolation to reach a conclusion about the existence, severity, or frequency of problems associated with a device.
- MDRs alone cannot be used to determine changes in the rates of events over time or to compare device event rates.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.

MDRs Associated with Contegra

FDA received 79 MDRs regarding Contegra entered into the MAUDE database between 06/01/14 and 05/31/15. Of these, 30 were identified as unique MDRs. The remaining 49 MDRs were excluded from the MDR data set for the following reasons:

- One MDR was a duplicate of another MDR submitted by a different reporter.
- 48 MDRs described events reported in literature that was either presented to the PAC in 2014 or reviewed later in this document.

Therefore, the following MDR analysis is based on data from 30 unique MDRs submitted by the manufacturer.

Patient Demographic Data

Reporting country information is included in 29 of the 30 MDRs; 21 are from the United States (US) and 8 are from outside of the US (OUS). Patient gender information is included in 26 MDRs; 12 involved males and 14 involved females. Patient age is included in 24 MDRs; 22 are pediatric patients and 2 are adults. TABLE 1 summarizes this information.

TABLE 1: Patient Demographic Data (30 MDRs total; 22 involve pediatric patients)

Demographic	Format	Value	Number of MDRs containing the demographic
Reporting Country	US : OUS	72% : 28%	21 : 8 (29 Total)
Patient Gender	Male : Female	46% : 54%	12 : 14 (26 Total)
Patient Age	Pediatric : Adult	83% : 17%	**22** : 2 (24 Total)
	Pediatric & Adult Age Range Average Age	 17 days – 51 years 7.0 ± 10.6 years	
	Pediatric Only Age Range Average Age	 17 days – 13 years 4.4 ± 3.6 years	

Reported Problems

The 30 MDRs were individually reviewed and analyzed for the primary reported problem. Additionally, the "time to event occurrence" (TTEO) was either obtained from MDR event text or calculated as the time period between the Date of Implant and Date of Event. The primary reported problem by patient age group and the TTEO are outlined in TABLE 2.

TABLE 2: Primary Reported Problem by Patient Age and TTEO

Primary Reported Problem	Total MDR Count	Patient Age (years)			TTEO (months)	
		Pediatric (≤21)	Adult (>21)	Age not reported	Range	Mean
Stenosis	12	8	2	2	1 - 110	42
Device size issue	4	2	0	2	0 - 45	11
Increased pressure gradients	2	2	0	0	5 - 79	42
Pulmonary insufficiency / Coaptation issue	2	2	0	0	0.4 - 45	23
Structural deterioration	1	1	0	0	6	--
Thrombus	1	1	0	0	2	--
Bleeding	1	1	0	0	1	--
Infection	1	0	0	1	No info	--
Death	1	0	0	1*	2.7	--
Explant (reason not reported)	5	5	0	0	2 - 134	49
Total	**30**	**22**	**2**	**6**	--	--

** This death was determined to be unrelated to Contegra.*

The 30 MDRs include 1 death report and 29 injury reports. The events are summarized as follows:

Death (n=1 MDR, patient age not reported)

The death report was originally submitted with limited information. A follow-up report noted that the patient became sick 6 weeks post device implant and one side of the patient's heart had stopped functioning. The patient expired 10 weeks post implant and the cause of death was not reported. According to the staff in the hospital, the patient death was unrelated to Contegra.

Injuries (n=29 MDRs, including 22 pediatric patients)

The primary reported problems of the 29 injury reports were categorized and the events are summarized below.

Stenosis (n=12 MDRs, including 8 pediatric patients)

Stenosis was the most frequently reported problem. In these 12 reports, stenosis (e.g., calcification, obstruction, host tissue overgrowth, pannus formation) was identified between 1 and 110 months post implant, and all required interventions. The interventions included device explantation (8 MDRs), stenting (2), balloon dilation (1), and valve-in-valve transcatheter heart valve implantation (1).

Device size issue (n=4 MDRs, including 2 pediatric patients)

There were 4 reports of inadequate device size involving 2 pediatric patients and 2 patients whose ages were not reported. The device size was reported as too large or too small for the patient, or patient-device incompatible. Two patients required device replacement on the same day of implant surgery, one patient required replacement 4 days post implant, and one at 45 months post implant. The root cause of the inadequate device sizes could not be determined. Three of the devices were not available for analysis. The manufacturer investigated the remaining device and concluded that the device met all applicable manufacturing specifications.

The Instructions for Use (IFU) for Contegra include the following statements relevant to the device size: "The Contegra Pulmonary Valved Conduit consists of a heterologous (bovine) jugular vein with a tri-leaflet venous valve and a natural sinus slightly larger in diameter than its lumen." and "The Contegra Pulmonary Valved Conduit is sized in even increments between 12 and 22 mm (inside diameter), measured at the inflow end." The manufacturer modified the IFU to include a statement in the Warnings and Precautions section to further address the device size issue.

Increased pressure gradients (n=2 MDRs, both are pediatric patients)

Two reports noted increased pressure gradients across the RVOT of pediatric patients. One patient required valvuloplasty 5 months post implant and the other required device replacement 79 months post implant.

Pulmonary insufficiency/coaptation issue (n=2 MDRs, both are pediatric patients)

Pulmonary insufficiency or coaptation issue was noted in 2 MDRs. One pediatric patient required balloon dilation 2 weeks post implant and the performance of the device was improved. The other pediatric patient required Contegra replacement 45 months post implant. No subsequent adverse effects were reported in either patient.

Structural deterioration (n=1 MDR, a pediatric patient)

Structural deterioration of Contegra in a pediatric patient occurred 6 months post implant. A pseudo-aneurysm in the conduit and bilateral pulmonary artery stenosis were also observed. During the re-operation, the conduit was found to be deteriorating and having little structural

integrity. The shape of the sinus from the outflow suggested that there may have been some dilation of the conduit wall in the sinus area. Contegra was replaced with a pulmonary homograft. No subsequent adverse effects were reported. The device was not returned to the manufacturer. It could not be confirmed if there were any quality issues with the device.

Thrombus (n=1 MDR, a pediatric patient)

A 21-month-old patient developed thrombosis in the valved conduit and coronary artery 12 days post implant. The patient was treated with medication and a cardiac catheterization for thrombus removal. The device remains implanted with no further reports of adverse effects.

Bleeding (n=1 MDR, a pediatric patient)

A severe intra-pleural hematoma was noted on the day of Contegra implant surgery. The 13-month-old patient required an open chest surgery for removal of the hematoma. The source of bleeding could not be determined. The device remains implanted. No subsequent adverse effects were reported.

Infection (n=1 MDR, patient age not reported)

This report states that Contegra was explanted due to infection. The patient age, implant duration and the details of the event were not available in the report and the explanted device was not returned for the manufacturer's analysis.

Device explanted - reason not reported (n=5 MDRs, all are pediatric patients)

Five reports indicate that Contegra was explanted and replaced in 5 pediatric patients between 2 and 134 months post implant. Limited information is provided in the reports regarding the reason(s) for the device explant. Despite the manufacturer's attempts to collect the devices, the explanted devices were not returned to the manufacturer. No additional information was available for the manufacturer to fully investigate these events.

Conclusions Based on the MDR Review

1. No new safety issues were identified based on the MDR review for this reporting period.
2. As with our last review, FDA continued to receive reports of device size issue in this reporting period. The root causes of these issues could not be determined.

LITERATURE REVIEW

Purpose

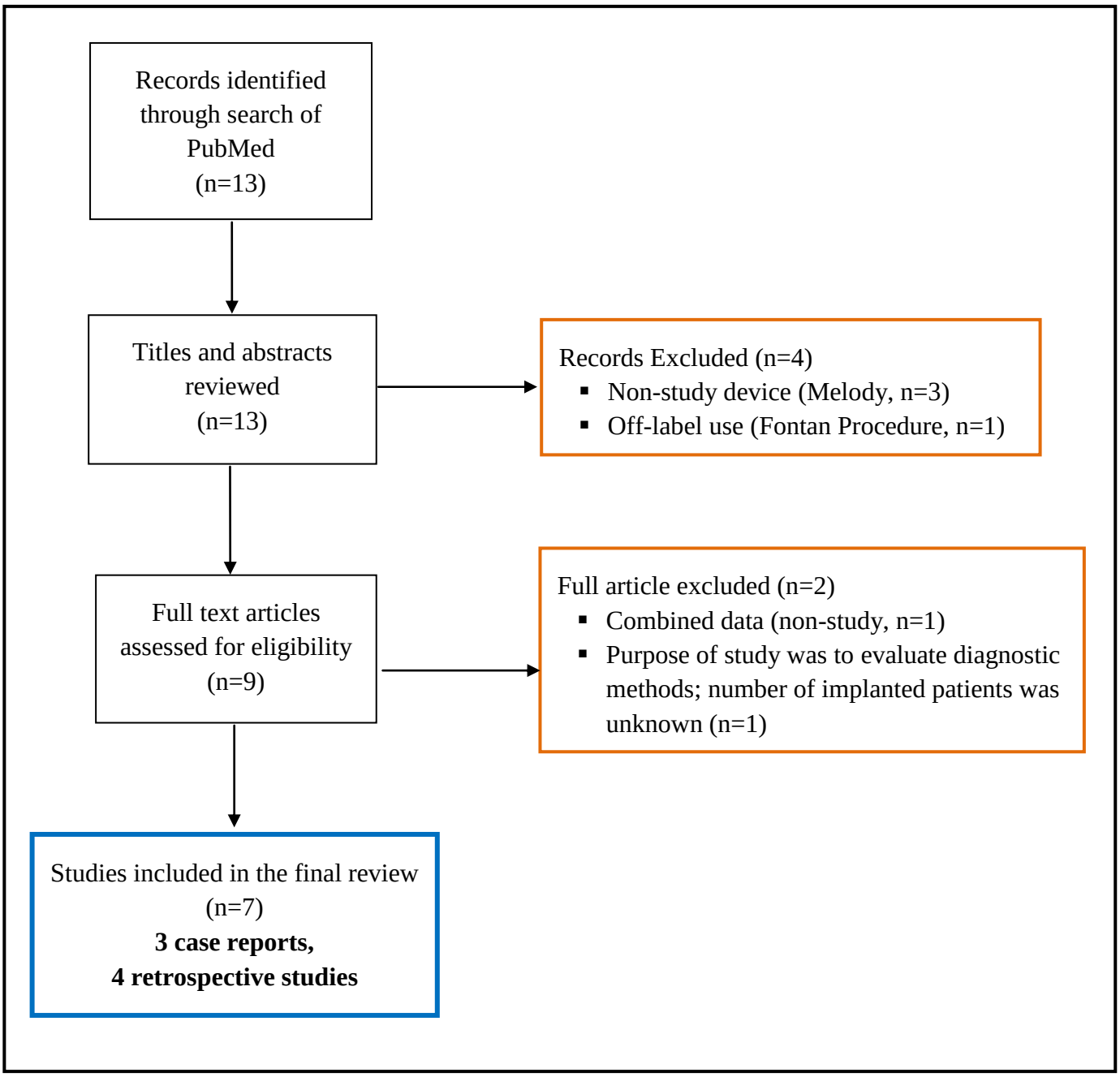
The objective of this systematic literature review is to provide an update of safety events associated with the use of Contegra since last year's literature review.

Methods

A search of the PubMed database was conducted for published peer-reviewed literature. The search was conducted using the same search terms used for last year's literature review: "Contegra" OR "Bovine Jugular vein" OR "Pulmonary valved conduit." The search was limited to articles published in English from 07/01/14 through 05/31/15.

A total of 13 articles were found. The articles were subjected to first pass review of titles and abstracts. Four articles were excluded as follows: non-study device (Melody, n =3), off-label use (Fontan procedure, n= 1). Nine (9) articles were retained for second pass review. Of the 9 articles reviewed for full text during the second pass, 2 articles were excluded. In one article the endpoint results were combined with a non-study device. The other article was excluded because the intent of the study was to evaluate diagnostic methods and the sample size of patients implanted with Contegra was unknown. Thus a total of seven (7) articles were retained for the final review analysis. FIGURE 1 diagrams the article retrieval and selection process, including the criteria for exclusion.

FIGURE 1: Article Retrieval and Selection



Results

The seven articles[1-7] reviewed included 3 case reports[1,5,6] and 4 retrospective studies.[2-4,7] One case report was from Pakistan, one was reported by authors in the United States, and another by authors in Spain. Two retrospective studies were conducted in Europe, one in Canada, and one in Australia. The sample sizes for Contegra-treated patients ranged from 1 to 244 (case reports and articles). The age of

patients at implant ranged from 4 days to 47.4 years. The median age of patients at time of Contegra implant ranged from 4 months to 9.9 years for patients in the retrospective studies. The median follow-up time ranged from 3.2 to 9.3 years.

Case Reports

All three case reports involved pediatric patients. Each report is discussed below.

Hidalgo-Garcia[1]: A 4 year old female had correction of D-transposition of the great arteries, ventricular septal defect, and pulmonary stenosis with Contegra placement at 2 years of age. The child experienced 2 episodes of infective endocarditis caused by pathogens rarely reported in the pediatric age group:

- During the first hospital admission, Aggregatibacter aphrophilus was isolated and antimicrobial management was instituted. Due to the prompt patient response, the prosthetic material was not removed. The child was discharged after an 8-week course of antibiotics (size of vegetation decreased from 4x5 to 2x2 mm).
- Two years later she was readmitted with a 16-day history of fever (39.9^{o}C). Echocardiogram revealed an increase in size of vegetation on the Contegra valve (8x10 mm). Staphylococcus lugdunensis was isolated and the infection responded to an antibiotic regimen. One week after discharge, she was readmitted with fever and respiratory distress. A computed tomography (CT) scan was suggestive of pulmonary embolism. The Contegra device was removed and replaced with a new Contegra device (pulmonary homograft was not available for the patient at that time).

There were no infective complications after implantation of the new Contegra device. However, 9 months after her last admission, the child developed severe left ventricular dysfunction due to compression of the anterior descending right coronary artery by the prosthetic material which required replacement of the second Contegra implant.

Weldin[6]: A 2-year-old child (gender not specified) with congenitally corrected transposition of the great arteries, ventricular septal defect, multilevel RVOT stenosis, and morphologic left ventricle presented for surgical intervention at 19 months of age. After Contegra implantation, the patient received a pacemaker for a third degree heart block and was discharged on post-operative day 14, in stable condition. During a routine outpatient visit at 9 months post implant, echocardiographic examination revealed an increase in interval velocity across the distal Contegra from 2.0 m/s (peak gradient = 16 mm Hg) to 3.7 m/s (peak gradient = 55 mm Hg). Functional diameter of the distal conduit measured by 2 dimensional imaging was 10 mm. Follow-up echocardiographic examination was scheduled for three months later. The patient developed acute hemodynamic insufficiency, collapsed and died two weeks after the last visit. Autopsy revealed acute dissection of a thick neointima extending from the distal conduit anastomosis to the location of the Contegra valve, and significant neointima proliferation in the proximal conduit anastomosis.

Shahid[5]: This report presents a case series (retrospective review) of six patients with Tetralogy of Fallot and absent pulmonary valve syndrome (APVS) who underwent surgical correction. One of the patients, a 5 year old, was implanted with Contegra to treat severe RVOT obstruction and moderate-to-severe pulmonary regurgitation. Post-implant assessment of Contegra showed favorable outcomes with only mild regurgitation and a RVOT gradient of 15 mmHg. The authors reported that no complications were observed.

Retrospective Studies

Two retrospective studies include both adult and pediatric patients[2,7], with ages ranging from 4 days to 30 years and 8 days to 47 years, and the remaining two studies include only pediatric patients[3,4].

Early mortality

Early mortality (i.e., death at ≤30 days post-implant) rate of 0.8-2.7%[2-4] was reported in three studies. In two studies that compared Contegra to homograft, early mortality was comparable[2,4]. In a study involving the use of three different conduits, Vitanova et al reported similar early mortality rates for Contegra 2.7%, homograft 4.8%, and Hancock 2.7% patients (P=0.8)[3].

Late mortality

Late mortality (i.e., death at >30 days post implant) rates of up to 6.1%[2,3] were reported in two studies. In the study that reported late mortality of 6.1%[2], the authors indicated that there were no deaths related to right ventricular-pulmonary artery dysfunction or implantation.

Survival

The all-cause death-free survival rates reported by Kaplan Meier or Actuarial analysis was 94.7%[2] at 1-year, 90-92.8%[2,4] at 5 years, 90%[2] at 7 years, and 88.6- 90%[2,3] at 10 years.

Yong et al[4] compared Contegra and homograft in 113 Contegra patients (mean age 6.5 years) and 136 homograft implanted patients (mean age 7.7 years) and reported no difference in survival rate at 5 years between Contegra 90% (95% CI: 82–94) and homograft 89% (95% CI: 82–93), (P=0.58). In a multivariate analysis, small conduit size (Hazard Ratio (HR) = 0.8, P=0.044) and syndrome diagnosis (HR=2.9, P=0.012) were found to be risk factors for mortality. Ugaki et al[2] found similar rates of survival at 1, 5, 7 and 10 years for Contegra-implanted patients (94.7%, 92.8%, 90.0% and 90.0%, respectively) and homograft-implanted patients (90.4%, 89.5%, 89.5% and 86.8%, respectively) (P = 0.39). Similarly, the 10-year survival for Contegra (88.6%), homograft (85.3%), and Hancock (89.1%) conduits were found to be no different (P=0.9)[3].

Reoperation/Surgical Intervention/Conduit Exchange

Three studies reported freedom from reoperation or conduit exchange[2-4]. The freedom from reoperation in Contegra patients was 96.3% at 1 year[2], 59.4– 79.3% at 5 years[2-4], 64.2% at 7 years[2], and 38% at 10 years[3].

Yong et al[4] reported comparable rates of freedom from reoperation at 5 years for patients implanted with Contegra 75% (95% CI: 59–86) and homograft 85% (95% CI: 77–91). Multivariate analysis showed no difference in reoperation rates between Contegra and homograft (P=0.41). A larger conduit size (HR=0.8, P=0.007) was observed to be a protective factor against reoperation. Small conduit size was associated with higher graft failure. Similarly, Ugaki et al[2] evaluated 244 Contegra patients (median age 56 months) and 135 homograft patients (median age 20 months), and observed comparable rates of freedom from reoperation at 7 years (64.2% vs. 68.6%, P=0.86). Age less than 3 years at operation (Odds Ratio (OR)=5.0, P<0.001) and endocarditis (OR=16.0, P<0.001) were the significant risk factors associated with conduit replacement.

At 5 years, Vitanova et al[3] observed freedom from conduit exchange for Contegra (59.4%), homograft (69.4%), and Hancock (53.8%). The rates of freedom from conduit exchange at 10 years were observed to be: Contegra 38.0%, homograft 38.1%, and Hancock 20.3%. There was no difference in durability between the conduits (Homograft vs. Contegra P=0.4, Contegra vs. Hancock P=0.6).

Endocarditis

Infective endocarditis was reported in 4 studies[2-4]. Survival of infective endocarditis rates at 5 and 10 years were reported as 87.8% and 77.3%[7], respectively.

Van Dijck et al[7] in a study of patients implanted with Contegra (n=53, median age 9.9 years, implanted 2000 to 2012), homograft (n=517, median age 13.3 years, implanted 1989 to 2013), and Melody (n=107, median age 14.3 years, implanted 2006 to 2013) reported infective endocarditis in 11 Contegra patients (20.4%) after 4.8 years, 14 homograft patients (2.4%) after 5.7 years, and 8 Melody patients (7.5%) after 1.3 years. The freedom from endocarditis by Kaplan Meier analysis at 5 and 10 years for Contegra was 87.8% and 77.3%, respectively, for homograft it was 98.7% and 97.3%, respectively, and for Melody at 5 years it was 84.9% (log-rank test; P<0.001). Contegra and Melody patients had significantly higher incidence of endocarditis compared to homograft patients (i.e., both conduits were significantly associated with endocarditis (P<0.001).

Ugaki et al[2] compared 244 Contegra patients (median age 56 months) and 135 homograft patients (median age 20 months) implanted between 2000 and 2012 and also reported higher incidence of endocarditis for the Contegra cohort (9.4%) than for the homograft cohort (0.7%, P<0.001). Patient age older than 3 years at RVOT reconstruction (OR=7.9, P=0.017) and use of Contegra (OR=9.9, P=0.030) were significant risk factors for development of graft endocarditis. Graft endocarditis occurred at a

median time of 44 months (15 days to 10 years) after RVOT reconstruction. The authors of this study also reported that in the 2 months preceding development of endocarditis, 25% of Contegra patients (6 patients) had undergone non-cardiac surgery or had infection, including urinary tract infection, percutaneous gastric tube infection, wound infection, pneumonia, and gastroenteritis.

However, in the study by Yong et al[4], of the 38 patients who required conduit replacement (Contegra n=10, homograft n=28), four patients (11%) required conduit replacement due to endocarditis. There was no significant difference between the two groups in the occurrence of infective endocarditis requiring reoperation (P=0.85).

Vitanova et al[3] reported endocarditis as the reason for conduit exchange in 1 Contegra patient (0.03%) and 1 homograft patient (0.02%) at a median time of 5.3 years in a study of patients treated with Contegra (n=35), homograft (n=62), and Hancock (n=48) conduits.

Conduit Stenosis and Insufficiency/Regurgitation

Three studies reported data on Contegra stenosis or insufficiency[2-4].

Vitanova et al[3] assessed conduit performance in children less than 1 year old at the time of implant with Contegra (n=31), homograft (n=55), or Hancock (n=44), implanted between 1994 and 2011, and reported freedom from at least moderate stenosis of 75.1%, 85.4%, and 69.1% at 5 years and 35.8%, 59.2%, and 49.7% at 10 years, for Contegra, homograft, and Hancock conduits, respectively.

Freedom from at least moderate conduit insufficiency was 74.6%, 91.7%, and 86.9% at 5 years and 44.2%, 64.8%, and 52.1% at 10 years, for Contegra, homograft, and Hancock conduits, respectively. Patients with a Contegra conduit developed moderate conduit stenosis or insufficiency faster than patients with a homograft (P=0.01).

In the study by Ugaki et al[2], the authors reported that graft failure in Contegra was due to stenosis 11.9% (29/244), stenosis plus regurgitation 8.6% (21/244) and regurgitation alone 0.01% (3/244) compared to homograft failure due to stenosis 8.8% (12/135), stenosis plus regurgitation 10.4% (14/135) and regurgitation alone 4.4% (6/135).

Among patients who underwent right ventricular to pulmonary artery conduit implantation with Contegra (n=113, mean age 6.5 years) or homograft (n=136, mean age 7.7 years), Yong et al[4] reported 11 patients developed distal stenosis resulting in graft failure. Distal stenosis occurred more commonly in Contegra (n=7, 64%) than homograft (n=4, 36%) conduit, P=0.004.

Thrombosis

In the study by Vitanova et al[3], thrombosis was observed in 4 patients that resulted in conduit exchange at a median time of 1.3 years. The Hancock conduit was the only conduit associated with a thrombosis (P=0.01). No thrombosis was reported for the Contegra patients.

Discussion of the Literature

The survival rates of patients implanted with the Contegra have been demonstrated to be comparable to that of patients implanted with the homograft in three studies that reported patient survival[2-4]. Smaller conduit size (HR=0.8, P=0.04) was found to be a risk factor for mortality[4]. The risk of mortality is likely not related to the selection or performance of the conduit itself. A smaller conduit size may signify younger age at surgery and neonates undergoing cardiac surgery are at higher risk of death due to their smaller body size. This finding is also consistent with reports from prior studies Fiore et al[8].

Multiple studies reported comparable rates of freedom from reoperation or conduit exchange between the Contegra and pulmonary homografts (Contegra 59-79% vs. homograft 69-85% at 5 years)[2-4]. The freedom from reoperation at 5 years for Contegra (59-79%) is similar to the 5 year rate for the premarket cohort (76%). In the Vitanova et al study, the long term durability of the Contegra was observed to be no different from the latter two (Contegra 38%, homograft 38.1%, Hancock 20.3% at 10 years)[3].

A larger conduit size was found to be protective against reoperation. Conversely, small conduit size was associated with higher graft failure[4]. Age at implant less than 3 years (OR=5.0, P<0.001), and complications of infective endocarditis (OR=16.0, P<0.001) were identified as risk factors associated with conduit exchange or reoperation.

A prior study by Urso et al[9] (n=347; Contegra 54, homograft 293) reported that patients implanted with Contegra conduits were two times more likely to undergo graft replacement than those receiving a homograft and concluded that the use of the Contegra conduit was an independent risk factor for graft replacement (HR=2.5). Niemantsverdriet et al[10] observed similar findings with Contegra conduits as independent risk factor for conduit failure in 194 patients (Contegra 23, homograft 159, synthetic conduit 12) undergoing RVOT reconstruction (Contegra conduits HR=2.80, P=0.02).

The published literature also showed higher rates of graft endocarditis in Contegra than in homograft[2,7] or Melody[7]. The 5- and 10-year rates of freedom from endocarditis was significantly lower for Contegra than homograft (i.e., 87.8% and 77.3% for Contegra vs. 98.7% and 97.3% for homograft at 5 and 10 years, respectively, log-rank test; P<0.001)[7]. In the study by Dijck et al, the endocarditis rate in Contegra patients (20.4%) was 8.5 times greater than the rate in homograft patients (2.4%). Similarly, the Ugaki et al study, reported an endocarditis rate of 9.4% in Contegra patients that was over 10 times the rate in homograft patients (0.7%)[4].

Regarding risk factors, an age at implant of more than 3 years (OR=7.9, P=0.017) and the use of Contegra grafts (OR=9.9, P=0.030) were significant risk factors for development of endocarditis[2]. Graft infection tended to occur at median time 44 months post implant, suggesting endocarditis may be more likely to occur the longer the graft remains in place. In the study by Ugaki et al, the authors indicated that 25% of Contegra patients had undergone non-cardiac surgery or had infection in the 2 months preceding the development of endocarditis.

In patients who were less than 1 year old at implant, moderate stenosis or insufficiency tended to develop faster in Contegra patients than in homograft patients (i.e., freedom from moderate re-stenosis at 5 and 10 years was 75% and 36%, respectively, for Contegra vs. 85% and 59%, respectively, for homograft; freedom from moderate insufficiency at 5 and 10 years was 74.6% and 44%, respectively, for Contegra vs. 92% and 65%, respectively, for homograft). Distal stenosis was also observed to occur more commonly in Contegra patients (64%; P=0.004) than in homograft patients (36%; P=0.004).

Thrombus or thromboembolism related to Contegra was not commonly reported in the recent studies. One case of pulmonary embolism was reported in the patient with recurrent endocarditis in a case report[1].

The case involving acute neointima dissection leading to death in the 2-year old child was the only death directly attributable to Contegra in the current literature search. Acute dissection is a rare complication. The authors recommended that post implant follow-up should include serial echocardiographic evaluation, and for younger patients with rapidly increasing velocity across the conduit, cardiac catheterization or MRI should be considered. They suggested that findings of rapidly progressive conduit stenosis should prompt urgent or emergent surgical reintervention.

The reported case of recurrent infective endocarditis in the 4 year old child adds to the growing knowledge that pediatric endocarditis may be caused by uncommon microorganisms and may result in severe complications. The authors concluded that isolation of S. lugdunensis or A. aphrophilus from blood cultures in febrile children should be considered relevant and cardiac involvement must be ruled out.

Conclusions Based on the Literature Review

Review of literature published from 07/01/14 through 05/31/15 revealed the following observations.

- Published literature shows that patients implanted with Contegra, homografts, or other conduits (e.g., Hancock) have similar long term survival rates through 5 and 10 years.
- One case of late mortality directly related to Contegra due to acute neointima dissection was reported.

- Stenosis or insufficiency tended to develop more commonly in Contegra patients than in homograft patients.
- The freedom from reoperation or conduit exchange rates in Contegra patients are comparable to those in patients with other conduits (i.e., Contegra 59.4-79.3% at 5 years and 38% at 10 years, homograft 69.4–85% at 5 years and 38.1% at 10 years, Hancock 20.3% at 10 years) and freedom from reoperation for the premarket cohort.
- Freedom from endocarditis rates are reported to be lower in Contegra patients (87.8% at 5 years and 77.3% at 10 years) than in patients with other conduits or valves (homograft 98.7% at 5 years and 97.3% at 10 years, or Melody 84.9% at 5 years). One case of recurrent endocarditis caused by pathogens that are rare in pediatric population was reported.

The ability to draw conclusions from this literature review is limited by the following factors.

1. Several of the studies were retrospective or case reports. Thus the studies were not randomized to balance for differences in covariates, especially for one study that compared Contegra to homograft or the Hancock conduit. Thus, the study results may not be as robust as for randomized controlled trials (RCT).
2. In studies that compared Contegra to other conduit(s), the follow-up times tended to vary for the different treatment arms, which could influence observed rates.
3. Although the *median* age or *mean* ages of all patients included in each of the four retrospective studies fell within the pediatric age range (i.e., ≤ 21 years), two studies[2,7] included adult patients and did not differentiate the observations by pediatric/adult age group.
4. The Contegra conduits studied were implanted over a wide time period (1994 to 2012) and patient management or standards of care could have changed over this period of time.

ACTIONS TAKEN BASED ON THE 2014 PAC DISCUSSION

During its initial review of Contegra in 2014, the PAC primarily discussed three types of adverse events (i.e., device size issues, coronary artery compression, and discolored glutaraldehyde solution).In response to the PAC's feedback and FDA's request, the manufacturer provided the following additional information:

- The device Instructions for Use (IFU) was revised to:
  - add statements in the Precautions section about how the Contegra conduit is sized, and the potential risk of coronary artery compression, and
  - include the serious events of coronary artery compression, conduit neointimal dehiscence, and conduit dissection in the Potential Adverse Events section.

- An investigation was conducted on the discolored glutaraldehyde solution event.
  - No discoloration of solution had been noted during manufacturing.
  - Glutaraldehyde under normal storage conditions can react with itself to become highly polymerized, exhibiting a translucent amber color over time.
  - There are other factors that can influence the polymerization of glutaraldehyde, such as temperature, pH, and buffering.
  - The storage conditions for the product are included in the IFU as follows "The Contegra pulmonary valved conduit must be stored between 15°C and 25°C (59°F and 77°F). Refrigeration is not required, and freezing may damage the device. Room temperature storage up to 25°C (77°F) is satisfactory provided the device is not exposed to sunlight or other ultraviolet light sources or placed where significant temperature fluctuations may occur."
  - A 4-year real-time shelf life study was conducted for Contegra and the storage solution. This study showed that the 4-year real-time shelf life had no affect on product performance. The Contegra device has a 3-year shelf life.

  Given the results of the investigation on the discolored solution, no additional actions are planned.

SUMMARY

The FDA did not identify any new safety signals during this review of the Contegra annual report, the MDRs received, and the peer-reviewed literature published since our last report to the PAC. Both Medtronic and the FDA have taken actions to address the topics discussed by the PACs in 2014.

The FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted. The FDA will continue our routine monitoring of the safety and distribution information for this device.

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