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 Fall 2021 Pediatric Advisory Committee Meeting

INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this document provides the Pediatric Advisory Committee (PAC) with post-marketing 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 2020 report to the PAC. It includes data from the manufacturer's annual report, post-market 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 (Figure 1): one without external ring support (Model 200), and one with ring support modification (Model 200S).

Figure 1: Contegra 200 and 200S (ring-supported) Models

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 (HUD # 01-0076)
- November 21, 2003: Approval of HDE (H020003)
- April 11, 2013: Approval to profit on the sale of Contegra

DEVICE DISTRIBUTION DATA

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. However, it is to be noted that unless the sponsor requests to update their ADN based on the 21st Century Cures Act, the ADN will still be based on the previously approved ADN of 4,000. The approved ADN for Contegra is 4000 tests total per year. Since the last PAC review, a total of 403 devices were sold in the U.S., and 245 devices were implanted. At least 234 of the devices were implanted in pediatric (<22 years) patients.

MEDICAL DEVICE REPORT (MDR) REVIEW

Overview of MDR Database

The medical device reports (MDRs) database is one of several important post-market surveillance data sources used by the FDA. Each year, the FDA receives several hundred thousand MDRs suspected device-associated deaths, serious injuries, and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as health care professionals, patients, and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems in a "real world" setting/environment, including:
  - rare, serious, or unexpected adverse events
  - adverse events that occur during long-term device use
  - adverse events associated with vulnerable populations
  - off-label use
  - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important post-market surveillance data sources. Other limitations of MDRs include, but are not necessarily limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- 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.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

There were 81 MDRs regarding Contegra identified in the FDA's MDR database between June 1, 2020 and May 31, 2021. Of the 81 MDRs, 21 MDRs were related to journal articles. The 21 MDRs related to journal articles are excluded from the MDR data analysis for this year's review since these MDRs described events reported in literature that were either presented to the PAC previously (prior years), or are discussed in the Literature Review section of this document. Therefore, the MDR analysis is based on the review of 60 unique MDRs, all submitted by the manufacturer.

Patient Demographic Data

Of the 60 MDRs, 58 (96%) were received from the United States. Patient gender information was included in 60 MDRs; 34 involved males and 26 involved females. Patient age was included in 60 MDRs; 59 were pediatric patients and 1 was an adult. Table 1 summarizes this information.

Table 1: Patient Demographic Data (Total 60 MDRs; involve 59 pediatric patients)

Demographic Data		Percentage	Number of MDRs
Reporting Country	US : OUS	96% : 4%	58 : 2 (60 Total)
Patient Gender	Male : Female	57% : 43%	34 : 26 (60 Total)
Patient Age	Pediatric : Adult	98% : 2%	59 : 1 (60 Total)
Pediatric Only: Age Range: 1 month – 21 years; Average Age: 7.2 ± 5.8 years			

Primary Reported Events

The 60 MDRs were individually reviewed and analyzed to determine the primary reported events. Additionally, the "time to event occurrence" (TTEO) was either obtained from MDR event text or calculated as the period between the Date of Implant and the Date of Event. The primary reported event by patient age

group, as well as the associated TTEO ranges and means are outlined in Table 2 below.

Table 2: Primary Reported Event by Patient Age and TTEO for 2021 PAC Review

Primary Reported Event	Total MDR Count	Patient Age (year)		TTEO (month)*	
		Pediatric (<22)	Adult (≥22)	Range	Mean
Stenosis	**20**	20	0	4.8 - 148	77
Device replaced (reason not provided)	**35**	34	1	0 - 145	47
Arrhythmia	**3**	3	0	0.16 - 0.26	0.21
Endocarditis	**1**	1	0	2	-
Other infection	**1**	1	0	2.7	-
Grand Total	**60**	59	1		

*TTEO: "Time to event occurrence" was obtained from MDR event text or calculated as the period between the Date of Implant and the Date of Event.

A comparison of the primary events reported in the MDRs for the current analysis period with those from 2018, 2019, 2020 and 2021 PAC MDR analyses are shown in Table 3 below. The types of primary reported events are consistent, with "stenosis" and "device replacement" remaining as the most frequently reported events for the past 4 years.

Table 3: Comparison of Primary Reported Events for Contegra in 2018, 2019, 2020, & 2021

Primary Reported Event	2018 PAC	2019 PAC	2020 PAC	2021 PAC
	MDR Count (%)	MDR Count (%)	MDR Count (%)	MDR Count (%)
Stenosis	33 (63%)	51 (48%)	36 (39%)	20 (33.3%)
Device replaced (reason not provided)	12 (23%)	38 (36%)	32 (35%)	35 (58.3%)
Valve regurgitation/ insufficiency	2 (4%)	6 (6%)	7 (8%)	0
Inadequate size for patient	0	4 (4%)	3 (3.3%)	0
Arrhythmia	0	2 (2%)	4 (4.4%)	3 (5%)
Increased pressure gradient	2 (4%)	2 (2%)	2 (2%)	0
Infection/endocarditis/sepsis	1 (2%)	2 (2%)	3 (3.3%)	2 (3.3%)
Conduit dilation/aneurysm	1 (2%)	1 (1%)	2 (2%)	0
Pulmonary edema/ hemorrhage	1 (2%)	0	0	0
Thrombus	0	0	1 (1%)	0
Adhesions	0	0	1 (1%)	0
Unknown	0	0	1 (1%)*	0
Total	**52**	**106**	**92**	**60**

*One MDR indicates that after an unknown duration of time following the implant of the Contegra device, the patient died. The cause of death is unknown.

The primary events reported in the 60 MDRs involving 60 injuries are summarized below.

Stenosis (n=20 MDRs, including 20 pediatric patients)

Stenosis of conduit or pulmonary artery continued to be the most frequently reported event. In these 20 reports, stenosis (in conjunction with calcification, obstruction, pulmonary regurgitation or insufficiency and/or elevated pressure gradients) was identified in patients between 4.8 and 148 months post implant.

Of the 20 stenosis reports, one reflected early and mid-term events (within one-year post Contegra implant) in pediatric patients. In this pediatric patient, the Contegra device was explanted and replaced 4 months and 25 days post implant and replaced with a larger sized conduit due to severe stenosis and severe insufficiency.

Eighteen reports (involving 18 pediatric patients) reflected late events of stenosis (greater than one-year post implant) and the patients required interventions between 2 to 13 years post implant without additional adverse effects reported.

One MDR reported an unknown duration post implant, a transcatheter pulmonary bioprosthetic valve was implanted valve-in-valve due to pulmonary stenosis.

Overall, the interventions required for the 20 patients with stenosis included transcatheter pulmonary valve (TPV) implantations conducted as valve-in-valve (12), surgical replacement of pulmonary valve (7), and implanted stent in conduit (1).

Device replacement[1] – reason for replacement not reported (n=35 MDRs; 34 pediatric patients)

Thirty-five MDRs indicate that Contegra was replaced, including 34 MDRs involving pediatric patients. Although the reasons for the device replacement were not reported in the MDRs, 25 of the 35 reports described that the valved conduit was replaced with a larger size of device between 5 and 98 months post Contegra implant. Three of the reports described that the conduit was replaced with a smaller size device. Two of the reports described that the conduit was replaced with a conduit of the same size and model. In the remaining 5 MDRs, no information was available regarding the reason for device replacement and the device was not returned to the manufacturer for analysis.

Arrhythmia (n=3 MDRs; 3 pediatric patients)

Three pediatric patients developed complete heart block which necessitated permanent pacemaker implantation between 5 and 8 days post implant of the Contegra valved conduit. No additional adverse patient effects were reported. The manufacturer noted that conduction disturbances are known potential adverse effects associated with cardiac or thoracic procedures and can be resolved with medical treatment(s) or a permanent pacemaker.

Endocarditis/Infection (n=2 MDRs; 2 pediatric patients)

Two MDRs described two separate events of endocarditis and infection. During the endocarditis event, the

[1] "Replacement" is defined as the intervention taken to replace or substitute the function of Contegra device, including replacing the Contegra valved conduit surgically or via a transcatheter valve-in-valve procedure, without removing the Contegra device.

patient developed aspergillus fumigatous endocarditis 2 months after implant of Contegra. Vegetation was visible on echocardiogram. Approximately 3 months after implant, the device was explanted and replaced with a larger conduit of the same model.

During the infection event, the Contegra device was implanted in a 3-year-old patient during a complex repair for congenital heart disease. A routine culture was taken during the chest closure procedure and was found positive for pseudomonas aeruginosa. The patient developed sepsis and four days post implant the patient's chest was re-opened showing purulent mediastinitis. The patient was started on a 6-week antibiotic regimen. Urine cultures were also positive for yeast and the patient was started on anti-fungal therapy. The patient's chest was reclosed 21 days post implant after several negative mediastinal swabs. Two months post implant, the patient was found positive for pseudomonas aeruginosa and scans showed metabolically active tissue compression around the truncus pulmonalis. The patient was treated with antibiotics and the valved conduit was explanted and replaced with a homograft 2 months and 22 days post implant.

Conclusions Based on the MDR Review

- The MDRs received in this reporting period reflect peri-operative or late term events which are known complications. These events were likely associated with the procedure or patient underlying conditions and have been addressed in the device IFU.

- No new safety issues were identified based on the MDR review for this reporting period. The rates and types of events identified for this reporting period are similar to those in the previous reporting periods.

CONTEGRA LITERATURE REVIEW

Purpose
The objective of this systematic literature review is to provide an update on the safety of the Contegra bovine jugular vein conduit (BJVC) device when used in pediatric patients.

Methods
A search of the PubMed and EMBASE databases were conducted for published literature using the search terms: "Contegra" OR "Bovine Jugular Vein" OR "Pulmonary Valved Conduit," which were the same terms used in the 2020 literature review. The search was limited to articles published in English from 06/01/2020 through 05/31/2021.

Figure 2 depicts the article retrieval and selection process including the criteria for exclusion. A total of 99 (24 PubMed; 75 EMBASE) articles were retrieved. Twenty-eight (28) articles were duplicates. The remaining 71 articles were subjected to review of titles and abstracts. Thirty-four (34) articles were excluded from full-text review for reasons listed: Eight (8) articles discussed only other conduits or devices, six (6) articles were commentaries or letters to the editor that provided no new data, five (5) articles were animal studies, five (5) articles on animal study**,** five (5) conference abstracts, three (3) articles reviewed for prior PAC meetings, three (3) articles discussed surgical or imaging technique, two (2) non-systematic or non-relevant reviews, one (1) study in a foreign language, and one (1) in-vitro study were excluded.

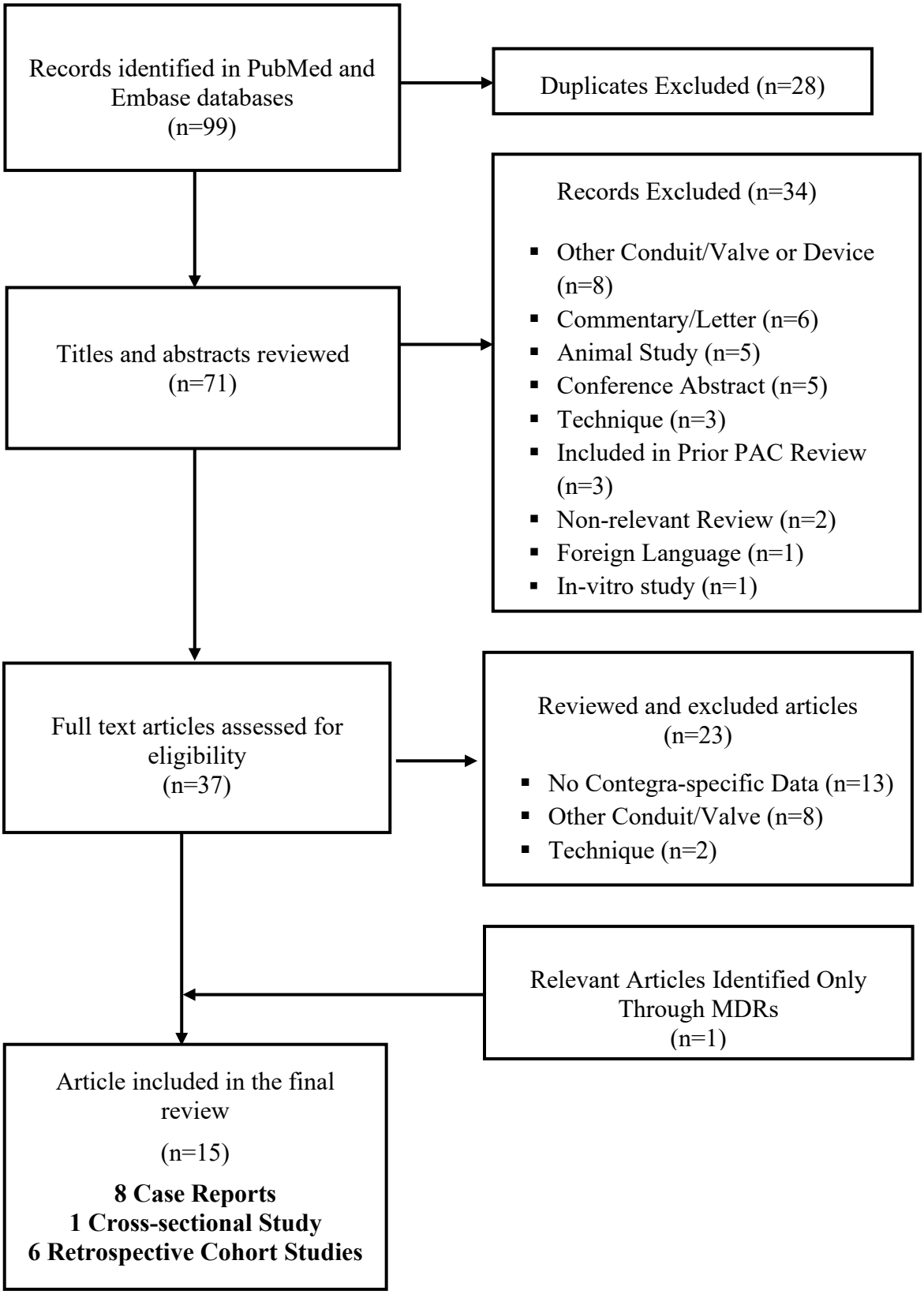
A total of 37 articles were retained for full text review. Of these 37 articles, the 23 were excluded from further review: Thirteen (13) articles did not present any results specific to Contegra bovine jugular vein

conduit (BJVC), eight (8) additional articles provided data only on other conduit or valve types, and two (2) additional articles described surgical techniques and did not provide relevant data for the systematic review.

Of note, in addition to the articles retrieved from PubMed and EMBASE databases, there were 19 publications identified through the review of the device manufacturer's adverse event reports submitted through the MedWatch system (MDR reports). Seven articles were out of this review's search date range, eight of the articles mentioned in the MDRs were also identified during this literature search. The abstracts of the remaining four articles were reviewed to determine if they should be included in the final literature review, three did not fit the inclusion criteria (2 did not provide any outcomes related specifically to Contegra, and one was in Japanese). The remaining case report was added to the final literature review.

A total of 15 articles were included in this systematic literature review.

Figure 2: Article retrieval and selection process



Characteristics of Publications Included in Evidence Assessment

There were six (6) retrospective cohort studies, one (1) cross-sectional study, and eight (8) case reports identified in this literature review. The retrospective cohort and cross-sectional studies were conducted in Australia [1], Austria [2], Japan ([3], [4]), Lebanon [5], Thailand [6], and the United Kingdom [7]. Case Reports were of patients treated in India [8], Iran [9], Italy [10], Japan [11], Malaysia [12], Saudi Arabia [13], Spain [14], and the United States [15].

A total of 442 patients implanted with a Contegra BJVC were involved in the six (6) retrospective cohort studies (please note that there was some overlap in patient population for one of the single center and one of the multicenter retrospective cohort studies ([3] and [4]) one (1) cross-sectional study, and eight (8) case reports. The majority of the retrospective cohort studies did not provide the mean or median age for patients with Contegra BJVC implants or specify if the patient population was solely pediatric. In these studies, the median age at implant for the entire study cohort ranged from six (6) months to 6.5 years, and the maximum reported age at implant for any of the cohorts was 24.6 years ([4], [1], [5], [7]). Age at Contegra implant was provided in two retrospective cohort studies and in the cross-sectional study ([3], [6], [2]). Hirai et al. [3] reported a mean age of 2.3 years (SD: 1.4 years) at time of Contegra BJVC implant in their comparison of outcomes of patients implanted with Contegra BJVC devices (n=20) to those of patients implanted with expanded Polytetrafluoroethylene (ePTFE) devices. In their cross-sectional study of patients surgically treated for infective endocarditis (IE), Gierlinger et al. [2] provided the age at implant for every patient, and age at implant for the five patients with Contegra devices explanted ranged from 0.9 to 13.9 years. Junnil et al.'s [6] retrospective cohort study provided a comparison of long-term outcomes in pediatric patients who received different conduit types for right ventricular outflow tract reconstruction. Of the eight patients who received a Contegra implant, the median age was 0.75 years [interquartile range (IQR): 0.24 – 2.0 years]. Age at Contegra BJVC implant was reported in seven (7) of the eight (8) case reports and ranged from 2 months to 14 years (Alhawri, [9], [15], [11], [12], [10], [14]).

The years of implant for Contegra BJVC devices ranged from 1998 to 2019 across the retrospective cohort studies and the one case report where time of implant was mentioned ([3], [4], [6], [1], [5], [7], and [8]). The maximum implant year range in any study was 20 years [7]. Patient follow-up duration post-Contegra BJVC implant was explicitly discussed in only two of the six retrospective cohort studies and was a mean of 4.9 years post-implant in one study [3] and a median of 3.1 years in the other [4]. The remaining four retrospective cohort studies provided limited to no information on the duration of follow-up for patients implanted with a Contegra BJVC. The cross-sectional study of patients surgically treated for infective endocarditis noted duration of Contegra BJVC implant prior to surgical intervention which ranged from 0.3 to 7.8 years across five patients [2]. While year of Contegra BJVC implant was provided in only one case report (2010[8], duration of implant was noted in all eight case reports and ranged from under one (1) week to ten (10) years ([13], [9], [15], [11], [12], [10], [8], [14]).

Safety Results Discussion

Perioperative Adverse Events and Perioperative Mortality

For the purpose of this summary perioperative adverse events and mortality are defined as adverse events or death noted by the study authors as occurring within 90 days of the procedure. In-hospital mortality was reported in Junnil et al. [6] Perioperative fever was discussed in Shaker et al. [5]. One case report [13] discussed perioperative adverse events and mortality in a patient treated with a Contegra BJVC device.

Junnil et al. [6] evaluated long-term outcomes of pediatric patients who underwent right ventricular outflow tract (RVOT) conduit implantation from 2006 through 2018 (n=143) at their hospital in Thailand. Only

eight (5.6%) of the 143 patients studied received a Contegra BJVC implant during this time period. The remainder received either pulmonic (n=61) or aortic (n=74) homografts. While the focus of this retrospective cohort study was longer-term events, the authors did provide data on perioperative deaths for the entire cohort and by conduit type. Perioperative mortality was 12.6% (18/143) for the entire cohort, 16.4% (10/61) in the group that received pulmonic homografts, 6.8% (5/74) in the group that received aortic homografts, and 37.5% (3/8) in the group that received Contegra BJV conduits. Causes of in-hospital mortality for the Contegra Group were Low Cardiac Output Syndrome and multiorgan failure (n=2) and pneumonia and sepsis (n=1). It should be noted that the authors did not perform any statistical testing of these results to determine significance, and that these comparisons were not adjusted for any potentially confounding factors. The authors did report statistically significant demographic differences between the conduit type groups including age at implant, primary diagnosis, and median graft diameter. Patients who received Contegra BJV conduits were younger and more likely to have been diagnosed with Truncus arteriosus than the aortic homograft group, and they were more likely to have received a small diameter graft than either the pulmonic homograft or aortic homograft group.

Shaker et al. [5] compared the incidence of perioperative fever among patients who either received pulmonary conduits (n=59) at their hospital in Beirut, Lebanon from June of 2009 through December of 2015. Eight different pulmonary conduit types were used during this time period, with the most common being Contegra BJVC (n=34) and Labcor (n=12). Other conduit types included Hancock (n=5), aortic homograft (n=2), pulmonic homograft (n=2), Jotec (n=2), and Darcon (n=1). Postoperative fever occurred in 61% of all patients (n=36), and 38.8% of all subjects had a prolonged fever (fever lasting >7 days). Patients who developed any fever (n=36) were compared to those who had no postoperative fever (n=23). The sponsor conducted multivariable logistic regression analyses to identify potential risk factors for prolonged fever. Age and gender were always in the models and then stepwise regression was used to determine if conduit type, the duration of pacing wires, and/or the intervention duration were independently associated with postoperative fever. The only conduit type independently associated with increased postoperative fever risk was the Labcor conduit. No risk results were specifically presented for patients implanted with Contegra BJVC devices.

Alhawri et al. [13] discussed a 21-month-old patient with a history of recent subaortic membrane repair and repair of a hole in his right coronary cusp. The patient consequently had an aortic mycotic pseudoaneurysm as well as a severe infection (patient's blood culture tested positive for *Streptococcus mitis/Streptococcus oralis)* at the site of the original aortotomy. The authors noted that the initial operation (subaortic membrane and right coronary cusp repair) was done at a different hospital. The authors repaired the pseudoaneurysm successfully with the off-label use of a Contegra BJVC to replace the ascending aorta above the sinotubular junction. They stated that they chose off-label use of the Contegra device because of the small size of the patient and the fact that homografts were not available. The patient developed a persistent fever eight (8) days after the pseudoaneurysm repair despite treatment with multiple antibiotics and antifungals. Within four days of the identification of persistent fever, the patient developed a new aneurysmal dilatation, continued to deteriorate, and died shortly thereafter. The authors attributed the outcome to the aggressiveness of the infection and the type of conduit tissue used.

Longer-term Survival

Three of the retrospective cohort studies provided information on longer-term survival ([6], [3], and [4]) for the cohorts of patients who received the Contegra BJVC device. While each of the case reports. Two of the case reports provided longer-term data on intervention-free survival ([15] and [12]).

Hirai et al. [3] compared the outcomes of pediatric patients implanted either with a Contegra BJVC (n=20)

or an expanded Polytetrafluoroethylene (ePTFE) conduit (n=24) for right ventricular outflow tract (RVOT) construction at their hospital in Japan from 2013 through 2017. Baseline and operative characteristics were similar across both groups. Hirai et al. also noted that any patients who transferred hospitals or were lost to follow-up were excluded from the study. Mean follow-up time were similar between the two groups [4.9 years (SD 1.9 years) for Contegra BJVC group; 4.2 years (SD 1.1 years) ePTFE group]. While survival rates were not presented, Hirai et al. noted that there was one (1) late death, 4.5 years after implant, in the group of patients who received an ePTFE conduit, but no deaths occurred during the follow-up period for the patients in the Contegra BJVC group.

Hoashi et al.'s [4] multicenter retrospective cohort study provided mid-term outcomes for patients who were implanted with a Contegra BJVC (n=178) for reconstruction of the right ventricular outflow tract across five centers in Japan. Median follow-up time for the cohort was reported as 3.1 years (IQR 1.3 -5.1 years). The authors reported that survival at 1, 3, and 5 years post-implant was 91.3% for each time point. The Kaplan-Meier curve for survival after Contegra BJVC implant is shown in Figure 2 (A) from Hoashi et al below. Additionally, the authors noted that while there were 13 cardiac deaths and 2 deaths from other causes during the study period, none of the cardiac deaths were related to the Contegra BJVC implant. The authors performed multivariable Cox proportional-hazard regression to identify risk factors mortality. Based upon this modeling body weight under 6.0 kilograms at the time of implant was (HR: 37.70, 95% CI: 3.38 – 421.80) and not undergoing a subsequent catheter intervention (HR:8.11, 95% CI: 1.03-63.60) were risk factors for mortality at one year post-implant.

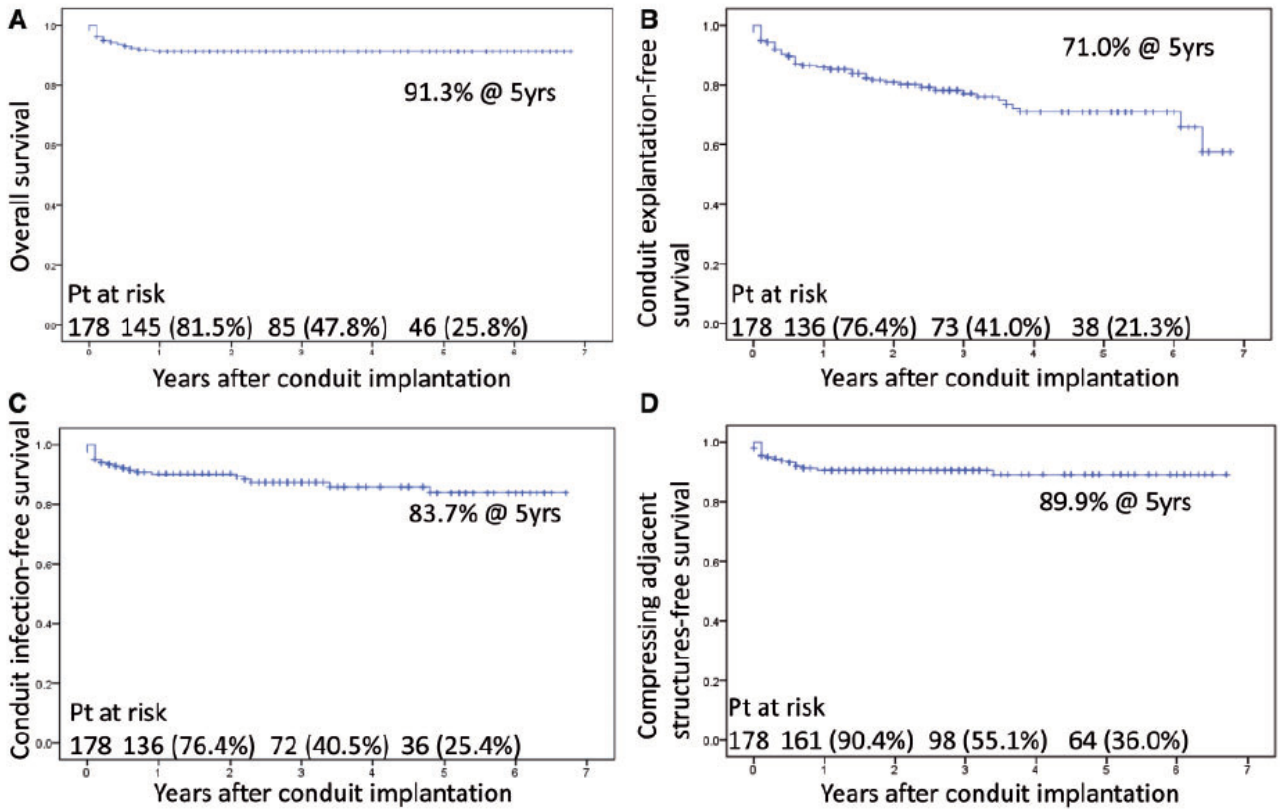


Figure 2: (**A**) Overall survival, (**B**) conduit explantation-free survival, (**C**) conduit infection-free survival and (**D**) compressing adjacent structures-free survival, after Contegra implantation.

Junnil et al. [6] provided Kaplan-Meier estimates of longer-term survival stratified by conduit type (see Figure 2 from the journal article below). Longer-term survival for patients implanted with Contegra BJVC appeared lower than both pulmonic and aortic homografts. This reflects the relatively high rate of early/perioperative mortality (3/8 or 38%) in the patients who received a Contegra BJVC implant (please see Section *"Perioperative Adverse Events and Perioperative Mortality")*. Additionally, the authors noted that while the maximum follow-up time for a patient implanted with a Contegra BJVC was six (6) years, the median follow-up time for the entire cohort was 7.6 years. and as evidenced in Figure 2 from the authors, there were no reported deaths in the limited follow-up duration of the Contegra group after the initial perioperative period. The authors used log-rank tests to determine if there was a statistically significant difference in survival across all conduit types (yes, p=0.01). Additionally, they used the log-rank test to compare survival of patients implanted with a Contegra BJVC to patients implanted with a pulmonic homograft and did not find a statistically significant difference (p = 0.16). However, it should again be noted that (and as discussed in the *"Perioperative Adverse Events and Perioperative Mortality"* Section), these estimates have not been adjusted for potential confounders, and meaningful differences in the baseline characteristics of patients were observed by the conduit type used to treat those patients.

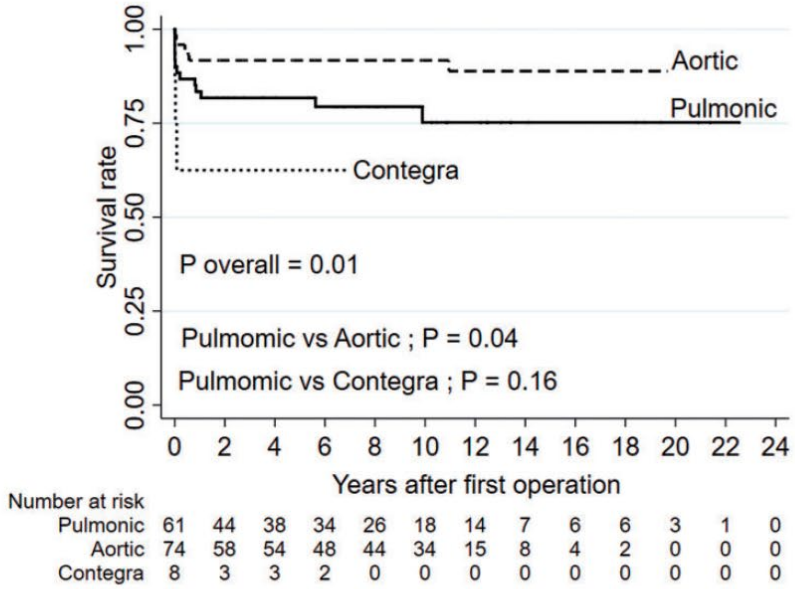


Figure 2. Survival rate of patients after the first operation according to type of graft.

Felmly and Kavarana [15] provided a case report detailing the novel surgical technique they used to treat a six-month-old male patient with truncus arteriosus with an interrupted aortic arch at their hospital in the United States. The patient had ductal stents and bilateral pulmonary artery bands placed as a neonate. The authors noted that the patient also had an aberrant right subclavian artery. The main purpose of the case report was to detail how the authors performed the definitive repair of the patient's truncus arteriosus, when the patient reached six months of age. Felmly and Kavarana used the aberrant right subclavian artery to create a composite flap to reconstruct the back wall of the patient's aorta. Among many other additional repairs, a Contegra BJVC was used to create a right ventricle-to-pulmonary artery conduit. The authors stated that the patient had an uneventful post-operative course, was discharged home 12 days post-operation, and was doing well 3.75 years after surgery. They did not mention any need for reintervention for the Contegra BJVC.

Sharma et al. [12] also provided a case report discussing the staged repair of a male patient with truncus arteriosus with interrupted aortic arch at their hospital in Malaysia. The authors noted that the patient had bilateral pulmonary artery banding performed when he was 11 days old. Sharma et al. stated that the follow-up corrective surgery was delayed because the patient experienced multiple episodes of *Klebsiella pneumoniae* infections. Once the patient reached 13 months of age, he was to weigh enough to have corrective surgical repair. As part of this repair, the authors used a Contegra BJVC to create the right ventricle to pulmonary artery connection. The patient was discharged home on post-operative day seven (7), and Sharma et al. stated that at one (1) year follow-up the patient was doing well.

Infective Endocarditis

Infective endocarditis, and its association with Contegra BJVC implant, was specifically discussed in the cross-sectional study and in four of the six retrospective cohort studies ([2], [3], [4], [1], [7]). The two additional retrospective cohort studies discussed perioperative infection or fever associated with Contegra BJVC implant ([6], [5]), and this information is summarized in the preceding "Short-Term Adverse Events" section. Endocarditis is additionally mentioned in one of the case reports [13], however, as that case was also a mortality, it is summarized in the preceding "Perioperative Adverse Events and Perioperative Mortality" section.

Gierlinger et al. [2] provided a retrospective analysis of all patients admitted to a single facility between March 2013 and July 2020 for treatment of infective endocarditis following interventional or surgical pulmonary valve replacement. The mean time from conduit implant to surgery for Infective Endocarditis was 4.1 years for Contegra 95% CI 0.5-7.7. The authors noted that *"prosthetic pulmonary valves tended to show a shorter time to IE than homografts."* There are significant limitations to this assertion given the nature of this study. A microbial organism was identified in 4 of the five Contegra patients surgically treated for IE: gram-positive cocci, HACEK (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species Group) organism, *Streptococcus salivarius*, and *Staphylococcus epidermidis*.

Hirai et al. [3] compared outcomes in patients treated with either Contegra BJVC or ePTFE conduits at a single center in Japan. The authors reported that one patient who received a Contegra BJV conduit experienced bacteremia, but the infection was medically managed and none of the patient in either group had a conduit replaced due to infection.

Hoashi et al. [4] who's retrospective study provided midterm results for patients implanted with Contegra BJVC across five centers in Japan, noted that conduit infection occurred in 7 (3.9%) of 178 patients. Additionally, they noted that all 7 infections occurred at 2 of the 5 institutions participating in the study. The authors specified that only one of the patients with an infected conduit was successfully treated with antibiotics (IV administered over the course of six weeks). The remaining 6 patients who experienced conduit infection, all required explantation for infection treatment. The infective organisms identified in the patients were methicillin-sensitive *Staphylococcus aureus* (n=2), methicillin-resistant *Staphylococcus lugdunensis* (n=2), *Staphylococcus epidermis* (n=1), *Streptococcus equisimilis* (n=1), and penicillin-susceptible *Streptococcus pneumoniae* (n=1). Conduit infection-free survival rates at 1, 3 and 5 years after the implantation were 90.1%, 87.2% and 83.7%, respectively**.** The Kaplan-Meier curve for infection-free survival is provided in the preceding *"Long-term Survival"* Section (Figure 2 (C) Hoashi et al.). The authors noted that they did not conduct univariable or multivariable analysis of risk factors for conduit infection due to the statistical infeasibility of analysis given very low number of events.

Saxena et al. [1] conducted a retrospective analysis of the outcomes for a cohort of consecutive patients who underwent RVOT conduit placement from 2004 through 2016 at their hospital in Australia. Of the 119 patients identified for this cohort, only 17 received a Contegra BJVC. Patient baseline demographics were not broken down by RVOT conduit type. Saxena et al. defined infective endocarditis by the presence of a conduit vegetation visualized on transthoracic echocardiography and positive blood cultures or by accelerated conduit deterioration with positive blood cultures and clinical findings as defined by the American Heart Association. While identifying infective endocarditis not one of the primary purposes of the study, the authors noted that one subject (1% of all total subjects) required reintervention for infective endocarditis. It was indicated in the paper that this subject initially received a Contegra BJV conduit, which would make the estimated incidence of infective endocarditis in the Contegra BJVC group approximately 5.8% (1/17). The Contegra BJV conduit was replaced with a pulmonary homograft. No other information regarding the patient or infective endocarditis in the remainder of the study population was provided.

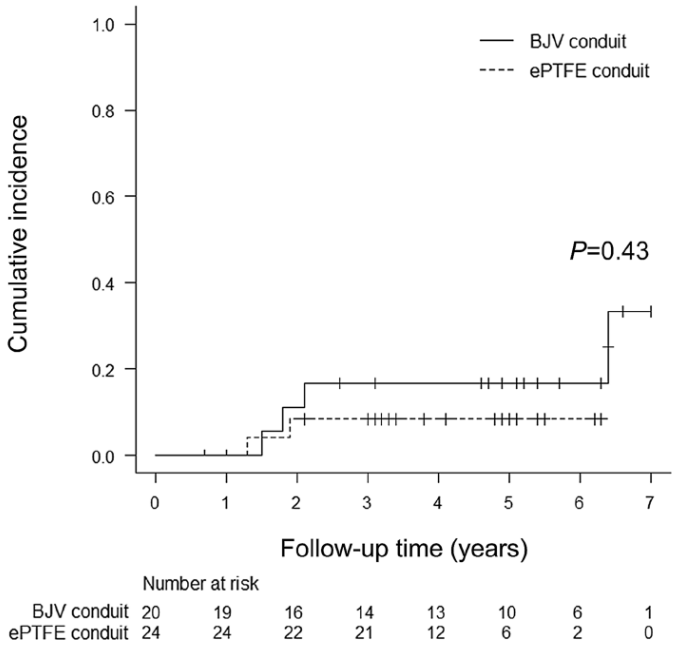
Willetts et al. [7] who compared outcomes between conduit types [pulmonic homograft (PHG), aortic homograft (AHG), Contegra BJVC, and composite porcine valve (CPV)] over a 30-year span at a single center in Australia, reported that the overall proportion of patients who underwent conduit replacement due to infective endocarditis was 4.3% (n = 18). Additionally, they noted that Contegra BJV conduits were more commonly replaced for infective endocarditis than other conduit types (BJVC 4.7% vs: CPV 2.2% , PHG 1.8% and AHG 0.3%) and had an approximately 4-fold greater incidence of replacement for infective endocarditis per patient-year (BJVC 0.45%: vs CPV 0.14%, PHG 0.09%, and AHG 0.01%). However, it did not appear that the authors performed any statistical comparison of these results, and incidence rates should be interpreted with caution given that the authors did not provide information on follow-up rates outside of 90-days post-procedure.

Conduit Deterioration, Reintervention, or Replacement

Five of the six retrospective cohort studies provide analysis on the conduit deterioration, reintervention, or replacement ([3], [4], [6], [1], and [7]) of the Contegra BJVC after implant. Five of the eight case reports discuss reintervention on an implanted Contegra BJVC ([9], [11], [10], [8], and [14]).

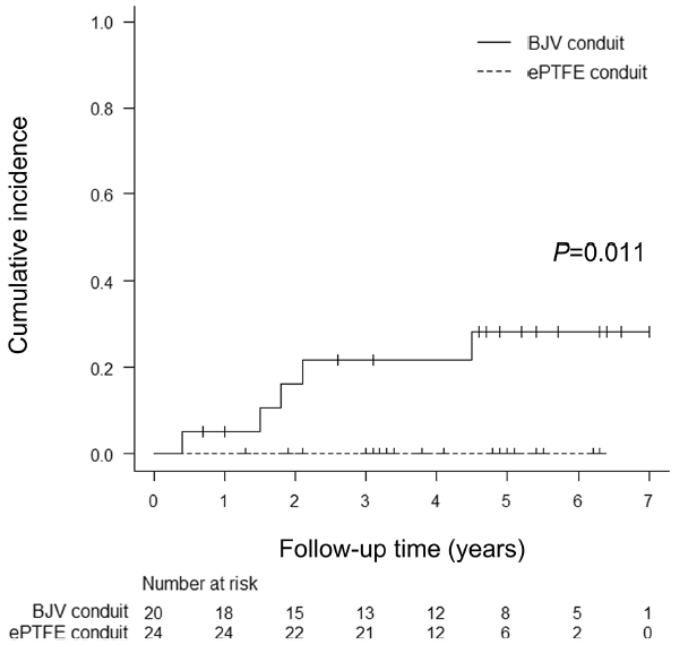
Hirai et al. [3] compared outcomes of pediatric patients who received RVOT reconstruction with either a Contegra BJVC or an ePTFE conduit. Their analyses included the cumulative incidence need for conduit replacement by group. Replacement was needed in 20% (n=4) of Contegra implants and in 8% (n=2) of ePTFE implants. A Kaplan-Meier curve of cumulative incidence of conduit replacement stratified by initial conduit type was provided by the authors (see Figure 5 from journal article that follows). A log-rank test was used to determine if the difference in K-M curves by conduit type was statistically significant. The authors noted that this difference was not (p=0.43). Causes for conduit replacement were aneurysmal conduit dilatation (n=3) and calcific conduit stenosis (n=1) in the Contegra BJVC group.

Fig. 5 Cumulative incidence of conduit replacement



The authors stated that aneurysmal conduit dilatation was identified in 5 (25%) of the 20 patients who received a Contegra BJVC, but no patients in the ePTFE conduit group had aneurysmal conduit dilatation identified. The cumulative incidence of conduit dilatation was statistically significantly higher in the Contegra BJVC group compared to the ePTFE conduit group (see Kaplan-Meier curve provided by the authors as Figure 3 in their journal article that follows) as assessed by log-rank test (p=0.011).

Fig. 3 Cumulative incidence of conduit dilatation



Hirai et al. also analyzed the number of patients who needed reintervention with balloon angioplasty by

initial conduit type and found no statistically significant difference between the two groups (30% of patients with Contegra BJVCs vs. 42% of patients with ePTFE conduits, p=0.42) when analyzed using the Pearson Chi-square test. The authors additionally stated that they did not find a statistically significant association with conduit type and degree of branch pulmonary stenosis (p=0.50) or the degree of pulmonary regurgitation (p=0.44)

Additionally, Hirai et al. performed multivariable logistic regression to identify risk factors for worse than moderate branch pulmonary stenosis and separate multivariable analysis for risk factors associated with the need for replacement of the implanted RVOT conduit. In multivariable analysis, higher pulmonary artery index at baseline was protective in relationship to risk for branch pulmonary stenosis (Odds Ratio: 0.981, 95% CI: 0.969-0.993, p=0.003), and higher numbers of balloon angioplasties needed for branch pulmonary stenosis before the initial RVOT reconstruction was a risk factor for branch pulmonary stenosis after RVOT implant (OR: 4.60, 95% CI (1.39 – 15.18), p=0.012). The authors noted that they did not identify any statistically significant risk factors for need for replacement of the initial implant with their multivariable logistic regression model.

Hoashi et al. [4] who as previously noted, evaluated the mid-term outcomes patients who received Contegra BJVCs (n=178) at five hospitals across Japan provided Kaplan-Meier analyses of conduit explantation-free survival, survival free of adjacent structure compression, and survival free of different types of stenosis. Additionally, they performed multivariable Cox proportional-hazard modeling to identify risk factors for the need for catheter intervention or conduit explant. Median age at implant was 16 months, and median follow-up time post-implant was 3.1 years.

Hoashi et al. reported that survival free from catheter intervention was approximately 53% at five-years post-implant (see Figure (A) from journal article that follows). Additionally, at five-years survival free of: conduit body stenosis was approximately 85% (see Figure 4 (C) that follows), proximal conduit stenosis was approximately 90% (see Figure 4 (B) that follows), distal conduit stenosis was approximately 64% (see Figure 4 (D) that follows), and compression of adjacent structures was approximately 90% (see Figure 2 (D) from Hoashi et al. included in preceding *"Long-term Survival"* Section).

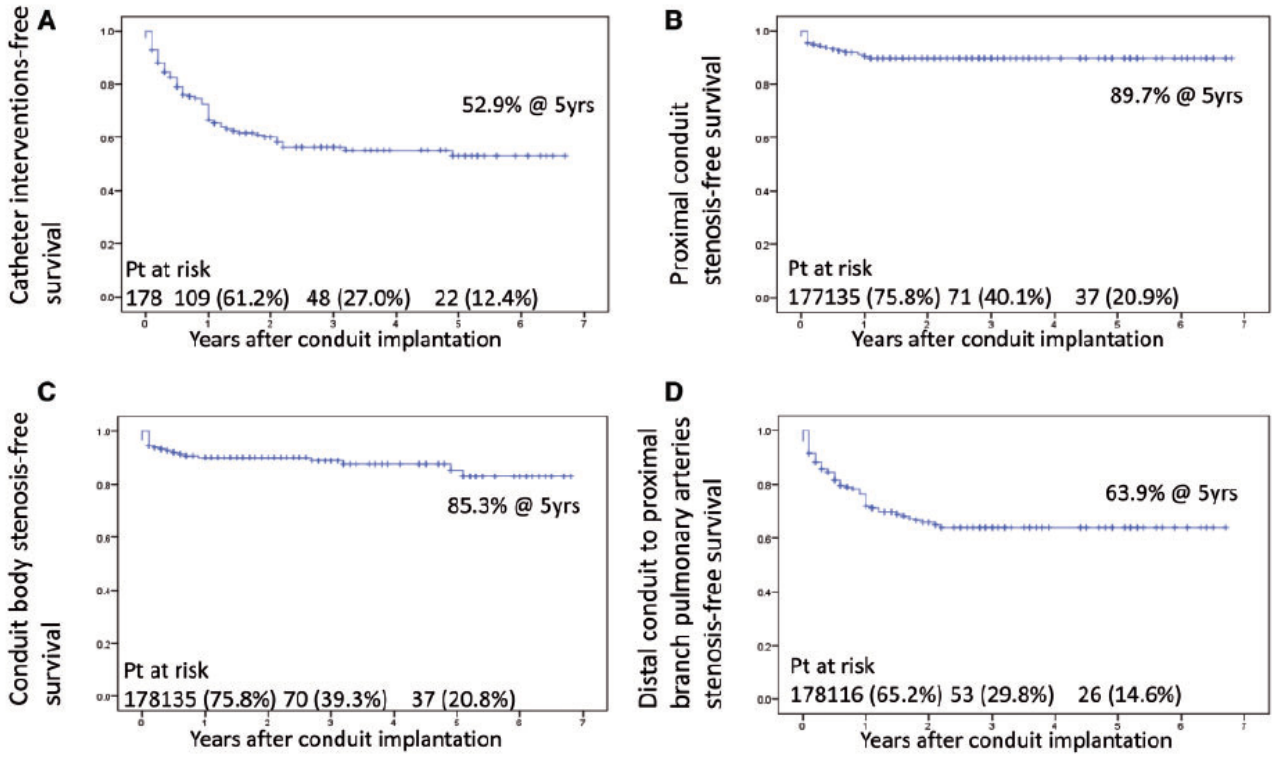
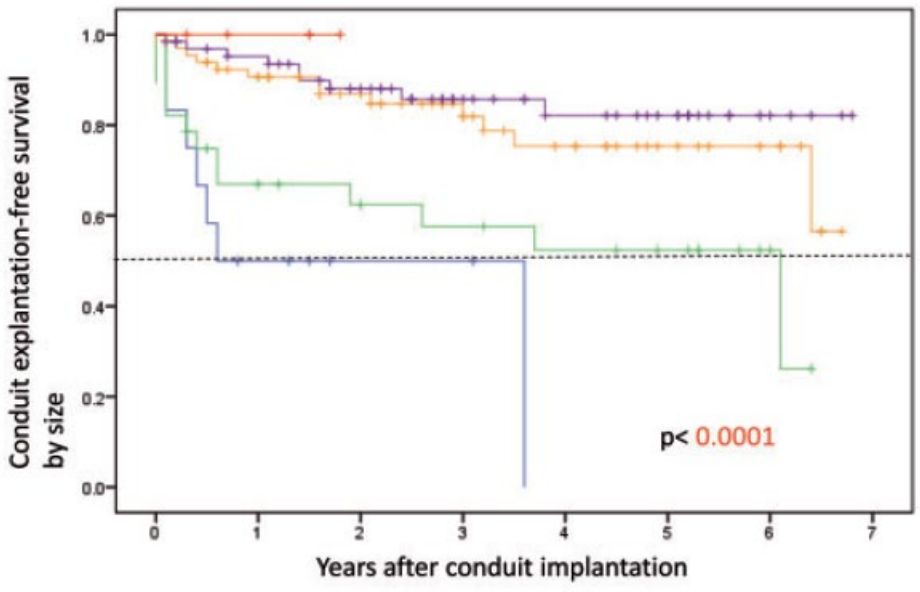


Figure 4: (**A**) Catheter intervention-free survival, (**B**) proximal conduit stenosis-free survival, (**C**) conduit body stenosis-free survival and (**D**) distal conduit and branch pulmonary artery stenosis-free survival, after Contegra implantation.

Hoashi et al. investigated the risk factors associated with need for conduit explantation. To evaluate the association between implanted conduit size and need for conduit explantation, they provided a Kaplan-Meier curve for survival free of conduit explantation stratified by conduit size (see Figure 3 from journal article that follows). This univariable analysis demonstrated a higher need for explantation over time among patients implanted with smaller conduits. Hoashi et al. also provided multivariable Cox proportional-hazard modeling to identify risk factors for catheter intervention and conduit explantation at one-year post-implant. The multivariable modeling for risk factors for need for catheter intervention identified weight under 6.0 kg at the time of Contegra BJVC implant (HR: 1.97, 95% CI: 1.17 – 3.34) and stenosis of distal conduit to branch pulmonary arteries (HR: 13.56, 95% CI: 7.41 – 24.81) as statistically significant risk factors for catheter intervention within the first year after Contegra BJVC implant. Multivariable analysis for conduit explantation risk showed a statistically significant association between conduit infection (HR: 5.8, 95% CI: 1.5 - 19.6) and common arterial trunk (HR: 3.1, 95% CI: 1.2 - 8.2) and the need for conduit explantation within the first year after Contegra BJVC implant.



Pt at risk by conduit size

<12mm*	12	5	2	2			(*downsized)
12mm	28	17	14	12	10	8	3
14mm	67	55	42	30	21	13	8
16mm	66	56	43	29	24	17	5
18mm	5	2					

Figure 3: Conduit explantation-free survivals by implanted conduit size.

Junnil et al. [6] as noted previously, compared outcomes in patients treated with different types of conduits (Contegra BJVC, pulmonary homograft, and aortic homograft) for RVOT replacement at their hospital in Thailand from 2006 through 2018. Of the 143 total patients identified, only eight (8) received Contegra BJVCs, and the maximum follow-up time for Contegra was six (6) years compared to 12 years in the aortic homograft group, and 18 years in the pulmonic homograft group. They compared conduit failure, which they defined as *"the need for reoperation or reintervention for conduit stenosis, external homograft compression, conduit regurgitation, or anatomical dehiscence,"* by conduit type.

The authors used Kaplan-Meier analysis paired with a log-rank test to evaluate if there was a statistically significant difference in conduit failure by conduit type over time (see Figure 3 from journal article that follows). They found no statistically significant difference between the groups based on the log-rank test (p=0.48).

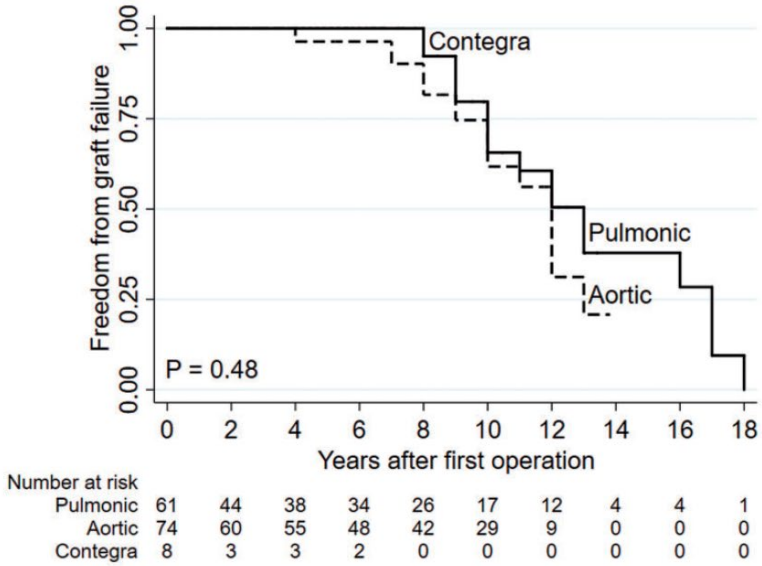


Figure 3. Freedom from graft failure according to type of graft.

Junnil et al. provided a separate analysis of freedom from reoperation over time stratified by conduit type (see Figure 4 (a) from journal article that follows), and they specified that there were no reoperations in the Contegra BJVC group over their maximum of six (6) years of follow-up. Again, a log-rank test was used to evaluate if the differences in survival curves for freedom from reoperation by conduit type were statistically significant, and it was not (p=0.28). The authors also conducted univariable and multivariable Cox proportional-hazard regression to evaluate risk factors associated with time to reoperation. The authors stated that the only statistically significant predictor of reoperation was having a primary conduit diameter less than 18 mm when compared to having a primary conduit diameter of greater than or equal to 18 mm (HR: 3.16, 95% CI: 1.38 – 7.23, p =0.007).

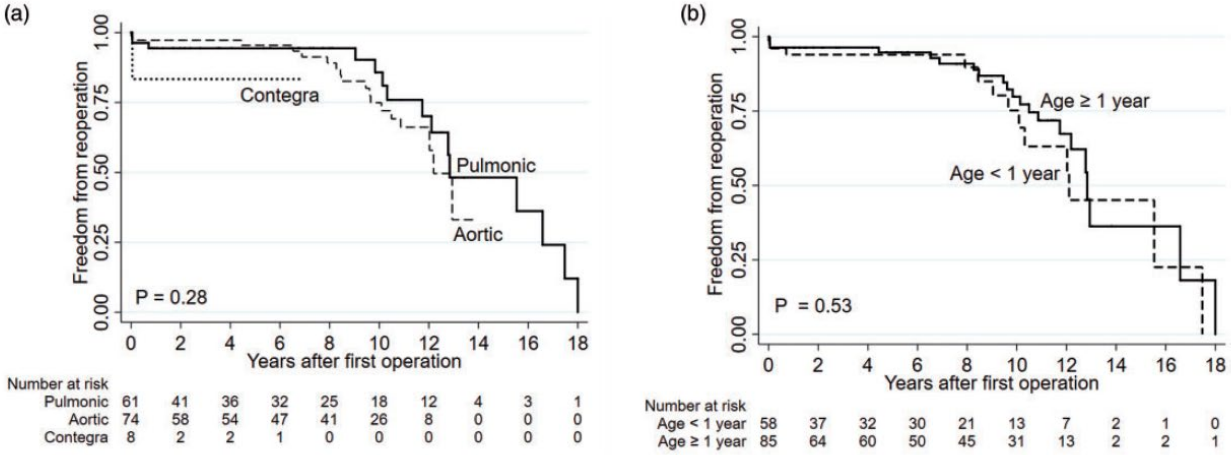
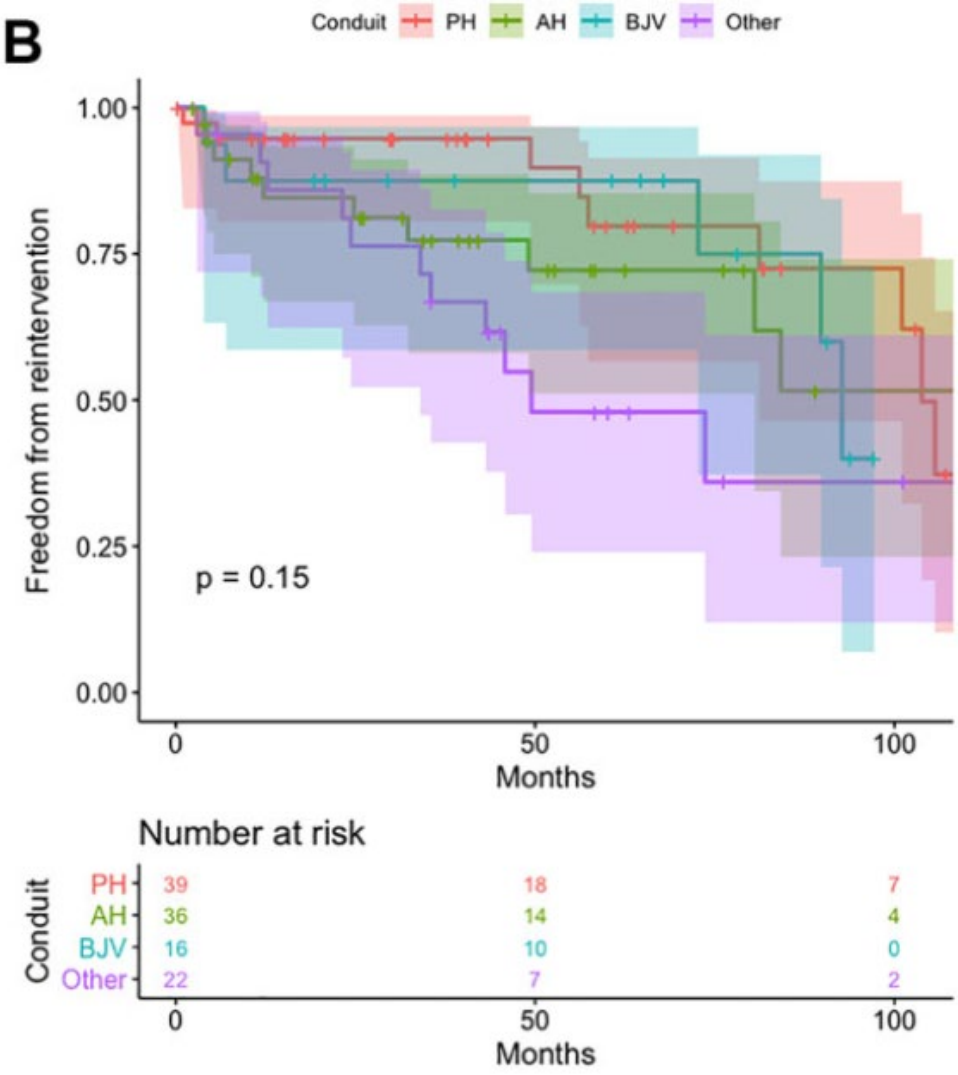


Figure 4. Freedom from reoperation (A) according to type of graft, and (B) according to age at first operation.

Saxena et al. [1] conducted a retrospective analysis of the outcomes for a cohort of consecutive patients who underwent RVOT conduit placement from 2004 through 2016 at their hospital in Australia. Of the 119 patients identified for this cohort, only 17 received a Contegra BJVC. Patient baseline demographics were not broken down by RVOT conduit type. However, the authors did analyze time to reintervention by conduit type. They defined reintervention as the need for either surgical or transcatheter conduit reintervention as indicated by clinical and hemodynamic evaluation.

The median time to conduit replacement across all conduit types was 43.5 months with a ten-year survival free of reintervention of 33%. A Kaplan-Meier analysis (Figure 2B from the journal article which follows) of the freedom from reintervention over time was provided stratified by conduit type (pulmonary homograft, aortic homograft, Contegra BJVC, and Other conduit type). Saxena et al. noted that any perioperative deaths were removed from the analysis. The authors also conducted univariable and multivariable Cox proportional-hazard regression analyses to identify risk factors associated with the need for reintervention. When patients with Contegra BJVC were compared to patients with pulmonary homografts in univariable Cox Proportional-Hazard modeling, and multivariable Cox proportional-hazard modeling, Contegra BJVCs did not appear to be statistically significantly associated with increased risk of reintervention over time in either univariable analysis Contegra BJVC vs. Pulmonic homograft HR 1.29 (95% CI 0.43-3.83, p=0.649), or multivariable analysis Contegra BJVC vs. Pulmonic homograft HR1.68 (95% CI 0.54 -5.17, p=0.368).



Willetts et al. [7] compared outcomes of patients who received one of four conduit types (AHG, Contegra BJVC, CPV, or PHG) for RVOT reconstruction at their hospital in the United Kingdom from 1988 through 2018. The main analysis strategy in this publication was to investigate outcomes stratified by patient's weight at time of implant. The majority of results were broken down by weight category rather than conduit type. However, the authors did present some outcomes related to conduit durability by conduit type.

The authors defined conduit dysfunction *"as a peak conduit velocity 4 m/s or greater, a tricuspid regurgitant velocity 4 m/s or greater where no pulmonary arterial stenoses distal to the conduit insertion were subsequently identified, or a greater than moderate degree of conduit valve regurgitation."* Additionally, the authors noted that no individual echocardiographs were reviewed for this retrospective study, and that conduit dysfunction relied on the medical records from the cardiologist for each patient. Pulmonary homografts (PHGs) and AHGs demonstrated similar freedom from dysfunction, outperforming both BJV conduits (HR, 1.52; CI, 1.12-2.05, p= .007), and CPV conduits (HR, 1.48; CI, 1.11- 1.98, p =.007, Figure E2).

Reintervention was defined as any catheter intervention undertaken that affected any part of the RVOT. This included balloon dilatation or stenting of the conduit but not transcatheter pulmonary valve implantation, which was coded as conduit replacement.

The authors included surgical and transcatheter conduit procedures in their definition of conduit replacement. The authors provided univariable and multivariable Cox proportional-hazard modeling for the risk of conduit replacement. In univariable analysis, conduit type was a significant predictor of freedom from replacement in all patients, with homografts outperforming both BJV and CPV conduits (see Figures 5 that follows from the journal article).

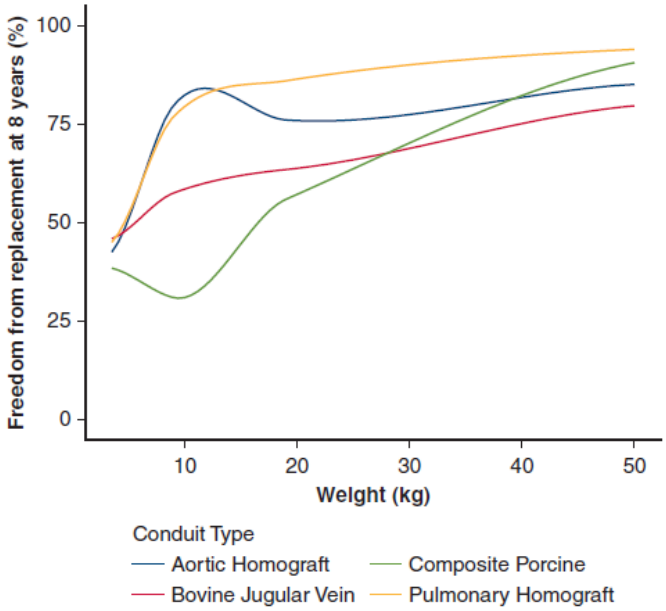


FIGURE 5. Freedom from RVPAC replacement at 8 years postimplantation versus patient weight at implantation for AHGs, Contegra BJV conduits, Hancock composite porcine conduits, and PHGs. *Solid lines* represent locally weighted smoothing regression of point estimates over the range of weights for all patients included in the study.

In multivariable analysis, conduit type was only significant predictor of need for replacement in the group of patients who weighed more than 5 kg but less than 20 kg at initial implant. No difference in Hazard Ratio (HR) was observed between AHGs when compared to PHGs, but an increased HR for both BJV conduits (HR: 1.96, 95% CI: 1.47-2.54, p= .02) and CPV conduits (HR: 3.72, 95% CI: 3.01-4.54, p<.001) was observed in relation to PHGs. The authors provide a Figure (Figure 6 which follows from the journal article) detailing the results of this multivariable analysis.

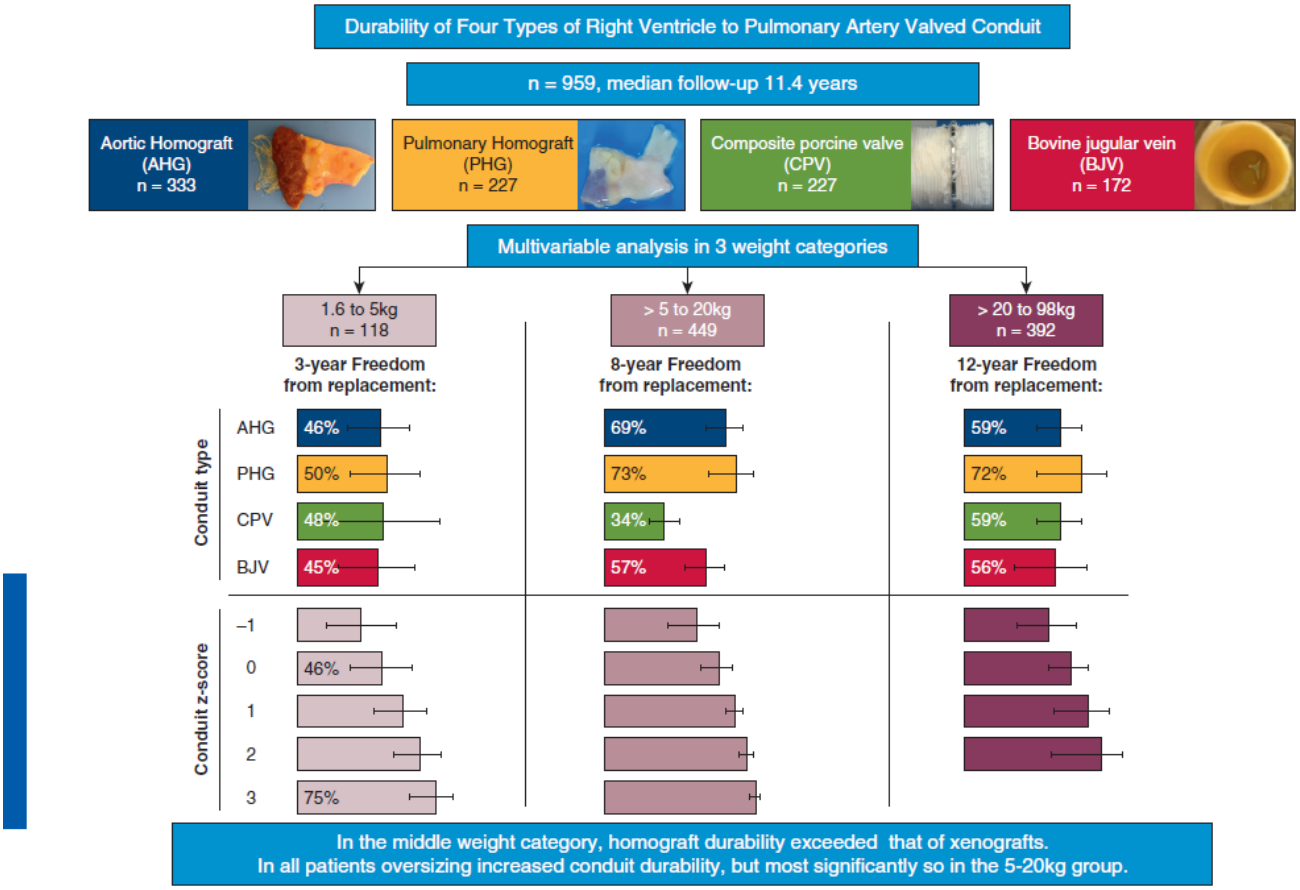


FIGURE 6. Summary of major findings in multivariable analysis of freedom from conduit replacement in 959 RVPACs in patients divided into 3 groups by weight at conduit implantation (≤5 kg, >5-20 kg, >20 kg). *Horizontal bars* denote percentage freedom from replacement at 3, 8, and 12 years respectively for different conduit types and initial conduit z-score in each patient group. *Horizontal capped lines* represent 95% confidence limits. *AHG*, Aortic homograft; *PHG*, pulmonary homograft; *CPV*, composite porcine valve; *BJV*, bovine jugular vein.

Amirghofran et al. [9] provided a case report detailing the use of the autologous innominate vein to create pulmonary arteries in a patient with pulmonary atresia, double outlet right ventricle, ventricular septal defect, and complete absence of major pulmonary arteries in a six-month-old infant at a hospital in Iran. While not the focus of the case report, the authors noted that they later completed total repair of the patient's heart and used a Contegra BJVC *"to establish continuity between the right ventricle and innominate vein."* The Contegra BJVC conduit was bilaterally stented three-years post implant due to stenosis, and balloon angioplasty was performed on the Contegra BJVC one-year after the stenting. The authors stated that the patient was *"in NYHA class I and good condition,"* at the time of writing the manuscript.

Ide et al. [11] also provided a case report detailing the staged repair of an infant with pulmonary atresia at a hospital in Japan. The patient was reportedly extremely low birth weight and had a ventricular septal defect, and major aortopulmonary collateral arteries in addition to the pulmonary atresia. The patient underwent banding to constrict her patent ductus arteriosus 2 days after birth and banding of her collateral artery 9 days after birth. She underwent definitive repair of her heart when she was six months old. Part of this repair was the use of a Contegra BJVC to reconstruct the RVOT. The patient underwent balloon angioplasty of her pulmonary artery due to stenosis six-months after the repair. However, the authors noted that during follow-up for an additional two years, the patient did not need any additional interventions.

Sirico et al. [10] provided a case report detailing the reintervention for a calcified Contegra BJVC six years after its initial implant. The Contegra BJVC implanted as an RVOT conduit, when the patient was two months old, as part of the repair of the patient's heart necessary due to pulmonary atresia. The Contegra BJVC was replaced by a Hancock conduit, at the authors' hospital in Italy. The focus of the case report is the treatment of perioperative adverse events related to the placement of the Hancock conduit. The patient experienced post-surgical myocardial infarction after placement of the new Hancock conduit which required emergency percutaneous coronary intervention and medication typically used for adults. However, the patient survived, recovered, and was discharged home, reportedly in good condition, 16 days post-PCI.

Sivaprakasam et al. [8] provide a case report describing the treatment of a patient for a stenotic Contegra BJV conduit at a hospital in India. The patient received the Contegra BJVC to reconstruct her RVOT after prosthetic pulmonary valve endocarditis. The authors reported that the Contegra BJVC underwent transcatheter stenting seven (7) years after placement. A transcatheter pulmonary valve was implanted within the stented conduit one year later. The patient was discharged one day post-procedure and was reportedly doing well and asymptomatic six-months post-placement of the transcatheter pulmonary valve within the stented conduit.

Valderrama et al. [14] describe, in their case report, the treatment of severe stenosis and regurgitation of both RVOTs (a Contegra BJVC and her native RVOT conduit) for a patient with double RVOT at a hospital in Spain. The patient had a Contegra BJVC implanted when she was 14 years old as part of her repair of tetralogy of Fallot. The authors placed Melody transcatheter pulmonary valves in the Contegra BJVC and in her native RVOT. The authors reported that the patient was followed for an addition seven years post percutaneous pulmonary valve implantation, and she reportedly maintained clinical and functional improvement.

Evidence Assessment

Overall, there were no new safety events identified, and/or change in their incidence or severity. The current systematic literature review reflects the post-market reported safety data of the Contegra device for use in pediatric patients.

The evidence derived from this systematic literature review has limitations that are important to consider when interpreting the findings. The literature search identified eight (8) case reports, six (6) retrospective cohort studies, and one (1) cross-sectional study. Case reports, retrospective cohort, and cross-sectional studies do not randomize patients to a treatment type (e.g. Contegra BJVC or pulmonary homograft) therefore they are subject to potential biases and confounding related to subject selection. Additional sources of potential problems with the internal validity for these studies were: retrospective data collection (which may lead to insufficient or incomplete patient data), differences in length of follow-up or completeness of follow-up after implant by cohort (which is especially problematic in cohorts being compared for time to events), and the combination of different patient populations (e.g. pediatric and adult patients, or patients treated for very different diseases). Even when patients are matched by demographic characteristics or multivariable modeling is completed with the adjustment for known or potential confounders (as was conducted in all six retrospective cohort studies), unmeasured confounding, or lack of/insufficient balance for differences in covariates can cause confounded or biased assessments of outcomes. One example of potentially unmeasured confounding is change in therapy or patient populations over time. These retrospective cohort studies included patients implanted with a Contegra BJVC over long enough time periods (maximum of 20 years) for significant changes in therapy or patient demographics to be probable, and none of these studies considered the impact of treatment period in their analyses.

Additionally, results from single site studies (5 of the 6 retrospective cohort studies found in this search) can also be difficult to generalize to the larger population.

Finally, the search terms used have been consistent for every year of literature update for this PAC. There is the possibility that other descriptive search terms for the device may have resulted in different publications, which could cause unintended missed articles. However, this is in part mitigated by the cross-referencing of our search results with the citations provided identifying adverse events in literature searches conducted by the device manufacturer. These are sent to us as a Medical Device Reports.

Conclusions Based on the Literature Review
Review of the literature published between 06/01/20 and 05/31/21 revealed the following observations:

- In the multi-center retrospective cohort study [4] where longer -term survival was explicitly presented for patients implanted with a Contegra BJVC, five-year survival was 91.3%.

- The incidence of infective endocarditis ranged from 0.0% to 5.8% (where easily calculable or reported) for patients implanted with a Contegra BJVC.

- Freedom from reintervention or reoperation decreases over time regardless of conduit type.

- Comparisons of need for reintervention or reoperation (using multivariable logistic Cox proportional-hazard modeling) for Contegra BJVCs versus other conduit types (homografts or other xenografts), did not show Contegra BJV conduit choice to be a statistically significant predictor of need for earlier reoperation or reintervention compared to other conduit types. One study (Willets et al.) found that Contegra BJVC use relayed a statistically significant increased hazard ratio for need for replacement compared to pulmonary homografts, but only in a subset of patients weighing greater than 5.0 kg and less than 20.0 kg.

SUMMARY

The FDA did not identify any new unexpected risks during this review of the MDRs received and the literature published since our last report to the PAC. The FDA believes that the HDE for this device remains appropriate for the pediatric population for which it was granted.

The FDA recommends continued routine surveillance and will report the following to the PAC in 2022:

- Annual distribution number
- MDR review and
- Literature review

REFERENCES

1. Saxena, A., et al., *Outcomes Following Heterotopic Placement of Right Ventricle to Pulmonary Artery Conduits.* World Journal for Pediatric and Congenital Heart Surgery, 2021. **12**(2): p. 220-229.
2. Gierlinger, G., et al., *Surgical therapy of infective endocarditis following interventional or surgical pulmonary valve replacement.* Eur J Cardiothorac Surg, 2021.

3. Hirai, K., et al., *Outcomes of Right Ventricular Outflow Tract Reconstruction in Children: Retrospective Comparison Between Bovine Jugular Vein and Expanded Polytetrafluoroethylene Conduits.* Pediatric Cardiology, 2021. **42**(1): p. 100-108.
4. Hoashi, T., et al., *Mid-term outcomes of Contegra implantation for the reconstruction of the right ventricular outflow tract to proximal branch pulmonary arteries: Japan multicentre study.* Interactive cardiovascular and thoracic surgery, 2021.
5. Shaker, R., et al., *Placement of Labcor Pulmonary Conduit Results in a High Incidence of Postoperative Fever.* World Journal for Pediatric and Congenital Heart Surgery, 2021. **12**(1): p. 55-60.
6. Junnil, P., et al., *Long-term course after pediatric right ventricular outflow tract reconstruction.* Asian Cardiovascular and Thoracic Annals, 2020.
7. Willetts, R.G., et al., *Four right ventricle to pulmonary artery conduit types.* Journal of Thoracic and Cardiovascular Surgery, 2021.
8. Sivaprakasam, M.C., et al., *First transcatheter pulmonary valve implantation - An Indian made valve.* IHJ Cardiovascular Case Reports (CVCR), 2020. **4**(1): p. 13-16.
9. Amirghofran, A.A., et al., *Using the autologous innominate vein as a substitute for pulmonary arteries in a patient with pulmonary atresia and absent pulmonary arteries.* J Cardiothorac Surg, 2021. **16**(1): p. 89.
10. Sirico, D., et al., *Cangrelor use in a 6-year-old patient undergoing complex percutaneous coronary intervention after post-surgical myocardial infarction.* Platelets, 2020. **31**(8): p. 1090-1093.
11. Ide, Y., et al., *Successful staged repair of pulmonary atresia, ventricular septal defect, and major aortopulmonary collateral arteries in an extremely low birth weight infant.* General Thoracic and Cardiovascular Surgery, 2020. **68**(6): p. 637-640.
12. Sharma, P., et al., *Delayed surgical repair of truncus arteriosus with interrupted aortic arch following bilateral banding of branch pulmonary arteries: a case report.* Cardiothoracic Surgeon, 2021. **29**(1).
13. Alhawri, K., et al., *Lethal recurrent mycotic ascending aortic pseudoaneurysm in a 21-month-old child with repaired subaortic membrane.* Annals of Pediatric Cardiology, 2020. **13**(3): p. 252-255.
14. Valderrama, P., et al., *Melody valve implantation in tetralogy of Fallot with acquired double right ventricular outflow tract.* EuroIntervention, 2020. **16**(7): p. 558-559.
15. Felmly, L.M. and M.N. Kavarana, *Composite Subclavian Artery Flap Repair of Truncus Arteriosus-Interrupted Aortic Arch.* Annals of Thoracic Surgery, 2020. **110**(5): p. e425-e426.