# FDA Executive Summary

Prepared for the
**Fall 2020,** Meeting of the
FDA's Pediatric Advisory Committee

# H020003

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

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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 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 2019 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 for Contegra (HUD #020003)
- November 21, 2003: Approval of Contegra HDE (H020003)
- April 11, 2013: Approval for 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 implants total per year. Since the last PAC review, a total of 605 devices were sold in the U.S., and 209 devices were implanted. At least 206 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 116 MDRs regarding Contegra identified in the FDA’s MDR database between June 1, 2019 and May 31, 2020. Of the 116 MDRs, 19 MDRs were related to journal articles and 5 MDRs were submitted by the manufacturer from information they received through a post market clinical follow-up survey on the Contegra device. The 19 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. The 5 MDRs related to the post market clinical follow-up survey are also excluded. No unique device identifier numbers, patient counts, or patient information were provided in these 5 MDRs, so it cannot be determined whether these observations have been previously reported. Stated adverse events in these 5 MDRs are consistent with known potential adverse events of the Contegra device. Therefore, the MDR analysis is based on the review of 92 unique MDRs, all submitted by the manufacturer.

**Patient Demographic Data**

Of the 92 MDRs, 89 (97%) were received from the United States. Patient gender information was

included in 89 MDRs; 42 involved males and 47 involved females. Patient age was included in 91 MDRs; 86 were pediatric patients and 5 were adults. Table 1 summarizes this information.

**Table 1: Patient Demographic Data (Total 92 MDRs; involve 86 pediatric patients)**

| Demographic Data | | Percentage | Number of MDRs containing the demographic |
|---|---|---|---|
| Reporting Country | US : OUS | 97% : 3% | 89 : 3 (92 Total) |
| Patient Gender | Male : Female | 47% : 53% | 42 : 47 (89 Total) |
| Patient Age | Pediatric : Adult | 95% : 5% | 86 : 5 (91 Total) |
| Pediatric Only: Age Range: 2 months – 21 years; Average Age: 9.7 ± 5.9 years | | | |

**Primary Reported Events**

The 92 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 2020 PAC Review**

| Primary Reported Event | Total MDR Count | Patient Age (year) | | | TTEO (month)* | |
|---|---|---|---|---|---|---|
| | | | | Age not reported | Range | Mean |
| Stenosis | **36** | 33 | 3 | 0 | 4.6 - 204 | 89 |
| Device replaced (reason not provided) | **32** | 30 | 1 | 1 | 0 - 165 | 63 |
| Valve regurgitation/ insufficiency | **7** | 7 | 0 | 0 | 48 - 159 | 87 |
| Arrhythmia | **4** | 4 | 0 | 0 | 0 - 0.4 | 0.2 |
| Inadequate size for patient | **3** | 3 | 0 | 0 | 0.3 - 142 | 63 |
| Endocarditis | **3** | 3 | 0 | 0 | 38 - 76 | 63 |
| Increased pressure gradient | **2** | 1 | 1 | 0 | 84 - 156 | 120 |
| Conduit dilation | **2** | 2 | 0 | 0 | 4 - 27 | 15.5 |
| Adhesions | **1** | 1 | 0 | 0 | 27 | 27 |
| Thrombus | **1** | 1** | 0 | 0 | 0.07 | 0.07 |
| Unknown | **1** | 1** | 0 | 0 | N/A | N/A |
| **Grand Total** | **92** | 86 | 5 | 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.

** Denotes patient death. The remaining 90 MDRs represent injury events.

A comparison of the primary events reported in the MDRs for the current analysis period with

those from 2017, 2018, and 2019 PAC MDR analyses are shown in Table 3 below. The types of primary reported events are consistent, with "stenosis," "device replacement" and "valve regurgitation/insufficiency" remaining as the most frequently reported events for the past 4 years. Although "adhesions" were not reported as a primary reported event in 2017, 2018, and 2019, the event appeared to be related to patient factors which are discussed in the section below.

**Table 3: Comparison of Primary Reported Events for Contegra MDRs in 2017, 2018, 2019, & 2020**

| Primary Reported Event | 2017 PAC MDR Count (%) | 2018 PAC MDR Count (%) | 2019 PAC MDR Count (%) | 2020 PAC MDR Count (%) |
|---|---|---|---|---|
| Stenosis | 37 (44%) | 33 (63%) | 51 (48%) | 36 (39%) |
| Device replaced (reason not provided) | 35 (42%) | 12 (23%) | 38 (36%) | 32 (35%) |
| Valve regurgitation/ insufficiency | 5 (6%) | 2 (4%) | 6 (6%) | 7 (8%) |
| Inadequate size for patient | 0 | 0 | 4 (4%) | 3 (3.3%) |
| Arrhythmia | 2 (2.3%) | 0 | 2 (2%) | 4 (4.4%) |
| Increased pressure gradient | 1 (1.2%) | 2 (4%) | 2 (2%) | 2 (2%) |
| Infection/endocarditis/sepsis | 1 (1.2%) | 1 (2%) | 2 (2%) | 3 (3.3%) |
| Conduit dilation/aneurysm | 2 (2.3%) | 1 (2%) | 1 (1%) | 2 (2%) |
| Pulmonary edema/ hemorrhage | 0 | 1 (2%) | 0 | 0 |
| Thrombus | 1 (1.2%) | 0 | 0 | 1 (1%) |
| Adhesions | 0 | 0 | 0 | 1 (1%) |
| Unknown | 0 | 0 | 0 | 1 (1%)* |
| **Total** | **84** | **52** | **106** | **92** |

*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 92 MDRs involving 2 deaths and 90 injuries are summarized below.

***Stenosis (n=36 MDRs, including 33 pediatric patients)***

Stenosis of conduit or pulmonary artery continued to be the most frequently reported event. In these 36 reports, stenosis (in conjunction with calcification, obstruction, pulmonary regurgitation or insufficiency and/or elevated pressure gradients) was identified in patients between 4.6 and 204 months post implant.

Of the 36 stenosis reports, 5 reflected early and mid-term events (within one year post Contegra implant) in pediatric patients. Two of these 5 pediatric events involved infants whose valves were explanted and replaced with a pulmonary valved conduit of the same size (1 year and 5 months post implant, respectively) due to stenosis of the conduit. In the third pediatric patient,

the Contegra device was explanted surgically 5 months and 9 days post implant and replaced with a larger sized conduit due to stenosis and dilation of the branch pulmonary arteries. In the fourth pediatric patient, the Contegra device was explanted 4 months and 20 days post implant and replaced with a pulmonary homograft due to stenosis of the conduit caused by both intimal growth and interval somatic growth. In the fifth pediatric patient, the Contegra device was explanted 4 months and 3 weeks post implant and replaced with a conduit of the same size due to stenosis and moderate insufficiency.

The other 31 reports (involving 28 pediatric and 3 adult patients) reflected late events of stenosis (greater than one year post implant) and the patients required interventions between 1 to 17 years post implant without additional adverse effects reported.

Overall, the interventions required for the 36 patients with stenosis included transcatheter pulmonary valve (TPV) implantations conducted as valve-in-valve (19), surgical replacement of pulmonary valve (15), and transcatheter balloon angioplasty (1). One patient underwent a diagnostic cardiac catherization where it was determined that the patient was not a candidate for TPV replacement. The patient was referred for surgical replacement of the conduit, but no interventions had been performed.

***Device replacement[1] – reason for replacement not reported (n=32 MDRs; 31 pediatric patients)***

Thirty-two MDRs indicate that Contegra was replaced, including 31 MDRs involving pediatric patients. Although the reasons for the device replacement were not reported in the MDRs, 21 of the 32 reports described that the valved conduit was replaced with a larger size of device between 0 and 165 months post Contegra implant. Three of the reports described that the conduit was replaced with a smaller size device. One MDR stated a Contegra device was explanted and replaced with an unknown device. However, upon manufacturer follow-up, they discovered that the conduit had not been explanted. No further patient or device information was provided. In the remaining 7 MDRs, no information was available regarding the reason for device replacement and the device was not returned to the manufacturer for analysis.

***Valve regurgitation/insufficiency (n=7 MDRs; 7 pediatric patients)***

Seven (7) MDRs reported valve regurgitation or insufficiency between 48 and 159 months post Contegra implant. Five (5) of the 7 pediatric patients required a TPV valve-in-valve implantation. One patient required a pulmonary homograft implantation. Contegra valved conduits remained in the patients and were not explanted. One patient had a Contegra valve explanted and replaced with a larger conduit of the same model. No additional adverse patient effects were reported.

***Inadequate size for the patient (n=3 MDRs; 3 pediatric patients)***

Three (3) reports noted inadequate size of valved conduit for the pediatric patients. In one of the 3 patients, Contegra valved conduit (size 12mm) was explanted 9 days post implant since 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.

surgeon reported the initial implant was too long for the patient and caused the sternum to press on the pulmonary artery. The conduit was replaced with a pulmonary homograft. The other 2 pediatric patients received the Contegra device and one required a surgical replacement with a larger valved conduit 11 years and 10 months post implant. The other patient received a new bioprosthetic valve sutured in the previously implanted conduit 4 years post implant. Both device replacements were due to patient outgrowth.

***Arrhythmia (n=4 MDRs; 4 pediatric patients)***

Three pediatric patients developed various arrhythmias (sinus and atrio-ventricular node dysfunction, complete heart block, and atrio-ventricular block, respectively) which necessitated permanent pacemaker implantation between 0 and 11 days post implant of the Contegra valved conduit. One pediatric patient had a permanent pacemaker implanted 6 days post implant of the Contegra device but the reason for implant was not reported. 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.

***Increased pressure gradients (n=2 MDRs; 1 pediatric patient)***

Two MDRs described increased pressure gradients in 1 pediatric patient and 1 adult. Both the pediatric patient and the adult patient required a TPV valve-in-valve implantation 7 years and 13 years post implant, respectively. The Contegra devices remained implanted in the patients and were not returned for manufacturer analysis. There were no other additional adverse patient effects reported.

***Endocarditis (n=3 MDRs; 3 pediatric patients)***

Two MDRs described two separate events for one pediatric patient. During the first event, the 11-year-old patient developed endocarditis 76 months after implant of Contegra and developed stenosis resulting in explantation of the Contegra valve and replacement with a 22 mm valve. Six years and three months later, the patient (then 17 years old) developed endocarditis resulting in mild insufficiency, valve explantation, and replacement with a 27 mm valve. There were no additional adverse patient effects reported for either event. For both events, the manufacturer reviewed the device history records and the sterility lot records of the valves and no anomalies were noted. Therefore, they stated it was unlikely that the endocarditis originally came from the device and/or manufacturing process. The information received also indicated that the endocarditis occurred over 6 years after implant in both cases. The manufacturer states endocarditis events that occur more than 12 months after the procedure are called late prosthetic-valve endocarditis and are largely community-acquired versus a result of the manufacturing process of the valve.

For the third MDR, it was reported that the endocarditis was from gram-positive cocci, and that there was vegetation on the conduit. It was also reported that the patient had a history of recurrent endocarditis caused by dental hygiene problems.

***Conduit dilation (n=2 MDRs; 2 pediatric patients)***

Two MDRs described conduit dilation in two pediatric patients. The first patient required the Contegra valve to be explanted and replaced 27 months post implant. The second patient required the valve to be explanted and replaced 4 months post implant. Both devices were sent to the manufacturer for analysis. The manufacturer stated device history reviews were performed and there were no issues identified regarding manufacturing. Pannus and calcification were noted on the first device. However, the manufacturer states the pannus and calcification are likely not the root cause of the reported conduit dilation.

For the second device, the condition of the explanted device made it difficult to perform a full assessment of the reported dilation. Upon visual examination, the conduit was segmented into two sections. Incisions were observed on the conduit and appeared to have occurred during explant. The incision lacerated all leaflets; the existing leaflet segments were slightly stiff but flexible. Tissue deterioration was noted on two of the three leaflets. Thrombotic host tissue was noted on the wall of the conduit and the leaflet adjacent to the commissure. In an effort to investigate the potential root cause of the dilation, the manufacturer requested information related to the patient's medical history and imaging prior to conduit explant. No information was obtained. Conduit dilation is a known potential adverse effect of the Contegra device and the rate of MDR-reported conduit dilation events has remained consistent in the last 4 years.

***Adhesions (n=1 MDR; 1 pediatric patient)***

In a 16-year-old patient, the Contegra device was explanted and replaced with a bioprosthetic pulmonary valved conduit of the same size and model 27 months post implant. The reason for replacement was incidental adhesions. The physician noted that the device did not fail. No additional adverse patients effects were reported.

***Thrombus (n=1 MDR; 1 pediatric death)***

> Two days post implant of the Contegra device, a 5-year-old female became hypotensive and experienced cardiac arrest. Resuscitation measures were performed and the patient was placed on venous-arterial extracorporeal membrane oxygenation (ECMO) and underwent mediastinal exploration due to bleeding from the superior and inferior vena cava as a result of torn sutures from cardiac resuscitation. The patient returned to ICU in critical but stable condition. Six days post-implant, cardiac catherization showed conduit thrombosis and was explanted the next day and replaced with another conduit of the same size and model. The conduit was "completely thrombosed" with thrombus also removed from the right ventricle and main pulmonary artery. Two days after conduit replacement, ECMO support was discontinued and twelve days later, the patient was removed from life sustaining therapies due to hypoxic neurological injury. It was reported that the neurological injury was a result of the cardiac arrest 21 days earlier. No autopsy was performed.

***Unknown cause of death (n=1 MDR; 1 pediatric death)***

An 18-year-old female died after an unknown duration of time following implant of the Contegra

device. The cause of death is unknown and the device has not been returned to the manufacturer for product analysis.

**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.

## LITERATURE REVIEW

### Purpose

The objective of this systematic literature review is to provide an update on the safety of the Contegra 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 2019 literature review. The search was limited to articles published in English from June 1, 2019 through May 31, 2020.

Figure 2 depicts the article retrieval and selection process including the criteria for exclusion. A total of 78 (17 PubMed and 61 EMBASE) articles were retrieved. Seventeen (17) articles were duplicates. The remaining 61 articles were subjected to review of titles and abstracts. Forty-six (46) articles were excluded from full-text review, including two (2) on animal studies**,** 19 conference abstracts, 2 letters to the Editor/editorials, 2 on other xenografts/devices, 4 on homografts, 3 on percutaneous pulmonary valve implantation (PPVI), 3 on surgical procedures/techniques, 8 reviewed in past PAC meetings, 2 in a foreign language, and 1 not relevant to Contegra (other study).

A total of 15 articles were retained for full text review. Additionally, one of the 15 articles had an associated erratum which was reviewed in conjunction with the article and was not counted as a separate review or as an exclusion. Of these 15 articles, 8 were excluded from further review, including 4 non-relevant to Contegra bovine jugular vein (non-Contegra), and 2 with combined data (e.g., Contegra results combined with those of other devices), and 2 *in vitro* studies.

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), of which 7 were out of the search date range of this review and 10 were already identified during the literature search. The remaining 2

articles (one case report and one retrospective cohort study) were relevant and added to this systematic literature review.

In all, a total of 9 articles were included in this systematic literature review.

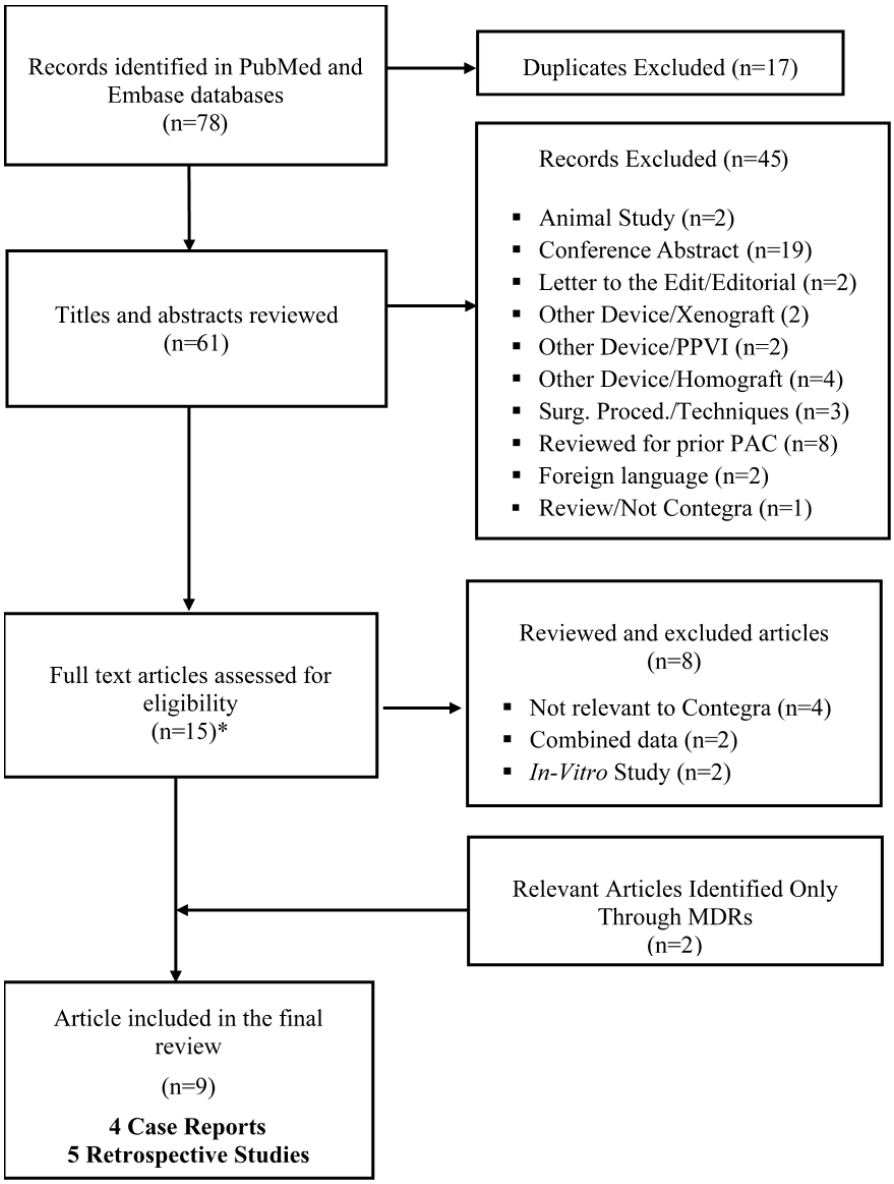


**Figure 2: Article retrieval and selection process**

*One article included in the full text review had an associated erratum, which was reviewed but not counted as a separate article.

## Characteristics of Publications Included in Evidence Assessment

There were five retrospective studies and four case reports identified in this literature review. Three of the retrospective cohort studies were conducted in the U.S. [1-3], one in multiple countries within the European Union [4] , and one in Saudi Arabia [5]. Two (2) of the case reports were from the U.S. [6, 7], one from India [8] and one from Turkey [9, 10].

A total of 1,262 patients were involved in the five retrospective studies and four case reports. There was some overlap in patient population for one of the single center and one of the multicenter studies [1, 2]. While four of the five retrospective cohort studies [1-4] and all of the case reports [6-8, 10] described use of the Contegra valved conduit as a replacement for the right ventricular outflow tract (RVOT), one retrospective cohort study [5] investigated the Contegra conduit for extracardiac total cavopulmonary connection (TCPC).

Seven articles clearly specified that their study populations were pediatric only, with a total of 351 patients, of which 110 were treated with the Contegra valved conduit [1-3, 6-8, 10]. The remaining articles combined pediatric and adult patients. In articles where implant dates were reported, patients were implanted with a Contegra conduit at dates ranging from 1990 to 2018 [1-5].

Information on follow-up duration for Contegra conduits was provided explicitly in only two of the retrospective cohort studies [3, 4]. The median follow-up duration for Contegra conduits in the study by Boethig et al.[4] was approximately 4 years. The study by Patel et al.[3] studied a pediatric only population and reported that the median follow-up duration for Contegra conduits was 1.7 years (IQR 0.5 – 4.9).

## Safety Results Discussion

***Operative/Short-term Mortality/Short-term Adverse Events***

*Operative or short-term mortality was provided broken down by the cohorts of patients who received the Contegra device in 3 of the 5 retrospective cohort studies [2, 3, 5]. One of the 4 case reports discussed short-term mortality after Contegra implant [8]. Adverse events* during *or shortly after Contegra implant were discussed in 3 of the retrospective cohort studies [1, 3, 5].*

Herrmann et al.[2] conducted a retrospective record review and summarized outcomes of interest, including short-term mortality, for all patients who underwent truncus arteriosus repair at their facility between 1981 and 2018. Of the 100 patients reviewed, 36 received a Contegra bovine jugular vein conduit (BJVC). "Early mortality" was defined as death within the first 30 postoperative days. Multivariable Cox proportional-hazard modeling was conducted to determine if any prespecified risk factors, including conduit material (aortic homograft, pulmonary homograft, or Contegra bovine jugular vein conduit), were associated with the risk of early mortality. The other pre-specified covariates of interest were age at operation, weight at operation, whether the patient had truncus arteriosus with an interrupted aortic arch, whether the patient had a coronary artery anomaly, conduit size, and decade of operation. When aortic homograft was compared to the BJVC (after controlling for the other variables), the hazard ratio

(HR) for early mortality was 2.2 (95% confidence interval (CI): 0.6-8.0; p=0.25). When pulmonary homografts were compared to BJVCs (after controlling for the other variables), the HR for early death was 0.6 (95% CI: 0.2-2.2; p=0.40). Additionally, in a multivariable analysis, patients with truncus arteriosus with an interrupted aortic arch (after controlling for the other variables including conduit type) were more likely to die within the first 30 postoperative days compared to patients with truncus arteriosus without an interrupted aortic arch (HR: 5.4, 95% CI: 1.7-17.4), and this difference was statistically significant (p=0.005).

Ismail et al.[5] conducted a retrospective review of the records of all patients who underwent a TCPC procedure at their single facility in Saudi Arabia from 2002 to 2017. Of the 206 patients reviewed, 66 had a Contegra BJVC, 37 had a polyethylene terephthalate (PET) conduit and 103 had a polytetrafluoroethylene (PTFE) conduit. It should be noted that the use of the Contegra BJVC for TCPC is not included as part of the indication for use in the FDA approved labeling. In addition to several other outcomes of interest, the authors provided results on short-term mortality. The study defined "hospital mortality" as death occurring during admission or within 30 days of the initial extracardiac TCPC operation. The overall hospital mortality was 3.4%, with 4 (6.06%) deaths in the Contegra group, one (2.7%) in the PET group and 2 (1.94%) in the PTFE group. The study also compared the incidences of hospital mortality among the groups using Fisher's exact test and found that the differences among the groups were not statistically significant (p=0.339). In addition, the study provided a comparison of "postoperative outcomes" broken down by conduit type, which included stroke, bleeding, chylothorax, and ascites and were found to be not different by a statistically significant margin among the three conduit types. The median ventilation time was statistically significantly lower for the PTFE group (14 hours), compared to the Contegra group (24 hours) and PET group (4 hours) when compared using the Kruskal-Wallis rank test and Dunn's test for *post hoc* analysis (p=0.002).

Mastropietro et al.[1] pooled data from 15 US centers for a multi-center retrospective cohort study. The objective of the study was to identify risk factors for postoperative major adverse cardiac events (MACE) after repair of truncus arteriosus in a pediatric patient population (n=216) treated between 2009 and 2016. Median age at implant (10 days, IQR: 7-24 days) and patient demographics were provided for the full cohort and were not broken down by conduit type. Contegra conduits were implanted in 55 of the patients. The authors noted upon a bivariate analysis that there was a statistically significantly higher proportion of patients who experienced a MACE with Contegra BJVC compared to other conduits (e.g., aortic allograft, pulmonary allograft, other/no conduit) (p=0.04). They stated that the Contegra BJVC diameters "were significantly larger in the 55 patients (median: 54 $mm/m^2$; range: 48-57 $mm/m^2$), compared with 136 patients who received pulmonary or aortic allografts (median: 50 $mm/m^2$; range; 44-54 $mm/m^2$; $p<0.01$)." The authors further conducted bivariate analyses on the relationship between MACE and patient demographic and baseline data, preoperative patient clinical data, and patient operative data (including conduit type), to help determine what variables to include in their multivariate logistic regression models, and they considered any variable with a p-value <.2 in the bivariate analysis for inclusion in the multivariate model. Additionally, they conducted a mixed effects multivariate logistic regression model analysis where they included the treatment center as a random effect. The authors further stated that any variable in the multivariable model with a p-value of <0.05 after multivariable analysis was identified as an independent risk factor for MACE. Three risk factors were identified for MACE after repair of truncus arteriosus, that

is, failure to diagnose before discharge from the nursery, CPB duration >150 min, and RV-PA conduit diameter >50 mm/$m^2$.

Patel et al.[3] conducted a retrospective chart review of all patients 18 years of age or younger who underwent right ventricular outflow tract (RVOT) reconstruction, with either a Contegra BJVC (n=15) or a pulmonary homograft (n=56), as part of the Ross operation at their facility between 1998 and 2016. The authors matched pulmonary homograft patients (n=15) to Contegra BJVC patients (n=15) by age. They compared several outcomes of interest, including "early mortality" by conduit type. They reported that there were no cases of "early mortality" in either the Contegra BJVC cohort or the pulmonary homograft cohort. It should be noted that the authors did not explicitly define "early mortality" in this article. The study also compared "early complications" by conduit type using the chi square test. No statistically significant differences were observed in early complications (need for mediastinal exploration, need for postoperative extracorporeal membranous oxygenation (ECMO), or need for permanent pacemaker implant) for BJVC recipients compared to pulmonary homograft recipients. The authors did not specify the timeframe after RVOT replacement for early complications.

Talwar et al.[8] provided a summary of a pediatric patient (1 month of age at time of surgery) who needed surgical treatment for hypoplasia of the ascending aorta and aortic arch interruption with a common arterial trunk, classified as Type 4 per Van Praagh classification. As part of the surgical treatment, a Contegra BJVC was used to create the right ventricular-pulmonary artery (RV-PA) continuity. There was unrestricted left ventricle to aorta communication and an unobstructed RV-PA observed via intraoperative transesophageal echocardiography. Additionally, the authors noted no blood pressure difference between the upper and lower patient extremities which indicated satisfactory repair of the arch interruption. Despite the immediate operative success, the patient experienced sudden bradycardia and hypotension approximately 8 hours after surgery. Cardiopulmonary resuscitation was performed, and he was placed on ECMO support. The patient reportedly died of sepsis 7 days post-surgery.

***Longer-term Survival***

*Four of the retrospective cohort studies provided some information on longer-term survival [2-5] for the cohorts of patients who received the Contegra device. However, the duration of follow-up by conduit type varied by cohort within and among studies. Three of the four case report patients who received a Contegra BJVC were alive at the time of the writing of the report, which ranged from 3-11 years after initial Contegra Implant [6, 7, 10]. As these case reports described adverse events potentially associated with the Contegra device, they are summarized in the section corresponding to those adverse events for this systematic literature review.*

Boethig et al.[4] compared longer-term survival among three cohorts of subjects who received different types of conduits (i.e., Contegra BJVC, decellularized pulmonary homograft or DPH, and cryopreserved homograft or CH) for pulmonary valve replacement at various European institutions. These cohorts were matched by age at implantation, diagnosis, and number of previous pulmonary valve replacements. Mean follow-up was approximately 4 years for the Contegra BJVC cohort, approximately 5 years for the CH cohort, and approximately 2 and 6 years for the DPH subcohorts (depending on whether the DPH data were collected as part of the ESPOIR Trial or the ESPOIR Registry). The follow-up rate for the patients in the DPH cohorts

were “100%,” while the follow-up rates for the BJVC and CH cohorts were not specified. The long-rank test was utilized to compare the Kaplan-Meier survival curves for the three cohorts, which found no statistically significant difference in survival at 10 years after initial implant among the Contegra BJVC cohort (96.6%), the CH cohort (92.6%), or the DPH cohort (98.9%), as shown in Figure 3.

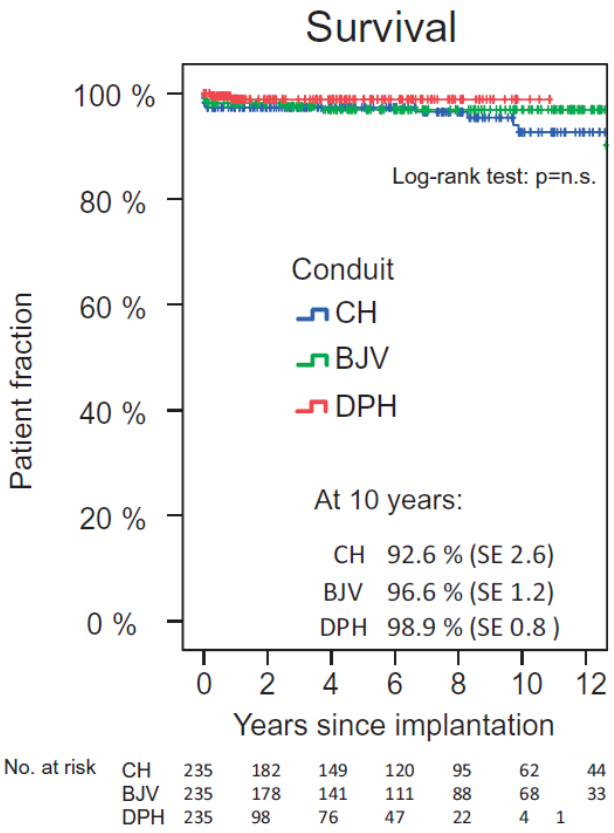


**Figure 3: Survival for DPH, CH and BJV cohorts (Boethig et al.[4]). BJV: bovine jugular vein; CH: cryopreserved homografts; DPH: decellularized pulmonary homografts.**

Herrmann et al.[2] reported that 14 (14%) out of the 100 patients who received conduits for truncus arteriosis repair at their facility experienced late mortality, and that causes of late morality included apneic event, acute respiratory distress syndrome, and sepsis. These late deaths occurred more than 30-days post-implant (10 occurred within the first 2 years after implant and the remaining four occurred between 3 and 17 years post-implant). While the authors did not break down deaths by conduit type nor provide a statistical assessment of the association between conduit type and late mortality, they stated that none of the late mortality events “appeared to be related to the type of implanted cardiac material.”

Ismail et al.[5] compared longer-term survival among cohorts who received a Contegra BJVC, a PET conduit, or a PTFE conduit for TCPC at their single center. It should be noted that no data was explicitly provided on the follow-up rates after discharge, and BJVC implants were no longer implanted at this facility for this condition as of the end of 2013. Additionally, while the maximum duration of follow-up after extracardiac TCPC was reported as 15 years for this study, no data were presented on follow-up time per cohort. Kaplan-Meier curves (right censored) were

utilized to compare survival times among the three cohorts. There was no statistically significant difference among the three cohorts using the log-rank test (p=0.221), as shown in Figure 4. The authors also conducted multivariate Cox proportional-hazard modeling to analyze if conduit type had a statistically significant association with survival time while controlling for other potential confounders. Conduit type was not associated with survival in this model (HR: 0.98, 95% CI: 0.44-2.2; p=.97). The authors did not discuss what variables were included in this modelling or how they were selected.

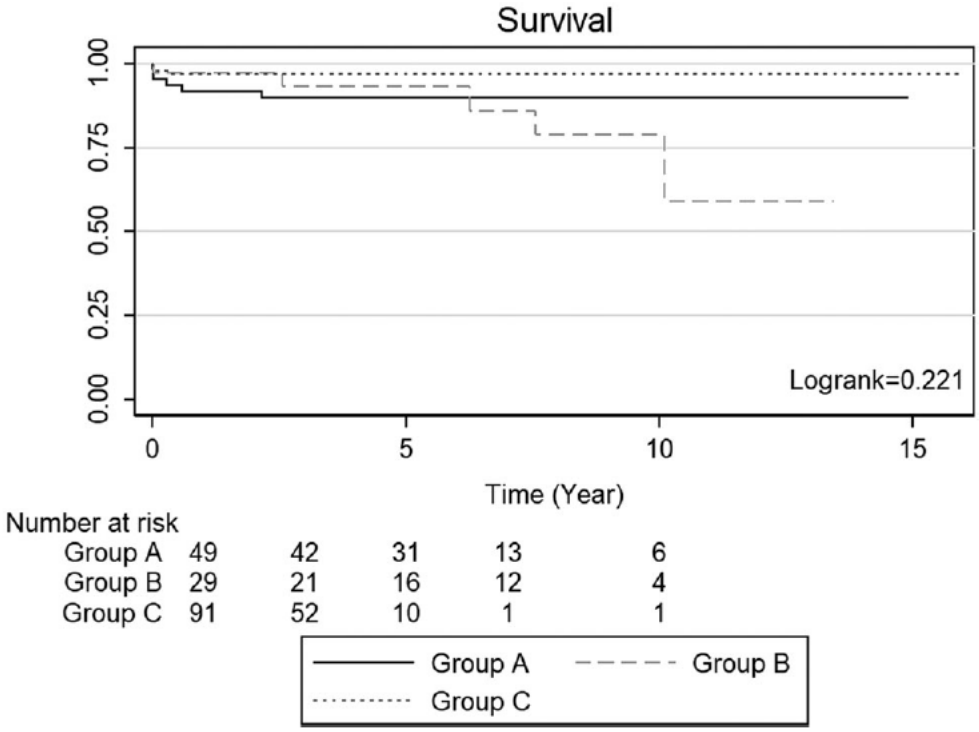


**Figure 4: Kaplan-Meier survival estimates in the three groups (Ismail et al.[5]). Group A (bovine jugular vein patients); group B (polyethylene terephthalate non-valved conduit patients) and group C (polytetrafluoroethylene non-valved conduit patients)**

Patel et al.[3] provided "late mortality" results for their 30 patient cohort. There were no "late" deaths in the Contegra BJVC cohort and there were 3 deaths in the pulmonary homograft cohort (p=0.07). However, mean follow-up time in the Contegra BJVC cohort was statistically significantly shorter than the pulmonary homograft cohort (n=15; mean: 1.7 years; IQR: 0.5-4.9 years vs. n=15; mean: 6.8 years; IQR: 1.9-13.4 years, respectively; p=0.03). The authors did not explicitly define "late mortality" in this article.

***Endocarditis***

*Endocarditis, and its association with Contegra BJVC implant, was discussed in four of the retrospective cohort studies [2-5]. Two of the retrospective cohort studies also provided a statistical comparison of endocarditis incidence or rates by conduit type [3, 4]. Endocarditis is additionally mentioned in one of the case reports [7].*

In their comparison of matched cohorts of patients receiving different conduit types for

pulmonary valve replacement, Boethig et al.[4] noted that the rate of freedom from endocarditis at 10 years was different and statistically significantly lower for the BJVC cohort (90.4%, standard error (SE): 2.25) when compared to the DPH (96.2%, SE: 2.1) and CH (97.4%, SE: 1.2) cohorts when analyzed using the long-rank test (p=0.03), as shown in Figure 5. As mentioned previously, the authors indicated a 100% follow-up rate for the DPH cohorts but did not indicate the follow-up rate for the BJVC or CH cohorts, and there were differences in the mean follow-up time between the DPH cohorts and the BJVC and CH cohorts.

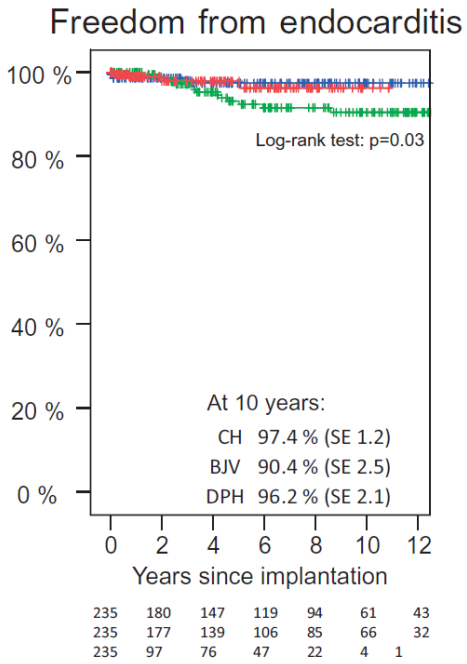


**Figure 5: Freedom from endocarditis for DPH, CH and BJV cohorts (Boethig et al.[4]). BJV: bovine jugular vein; CH: cryopreserved homografts; DPH: decellularized pulmonary homografts.**

Herrmann et al.[2] reported one case (2.8%) of infective endocarditis among the 36 truncus arteriosus patients at their facility who received a BJVC during the study period (1981-2018). Details of this patient's treatment or outcome after endocarditis were not reported. The authors noted that this rate of endocarditis is lower than that of the larger population of patients receiving RVOT reconstruction at their facility, which they had reported on in previous studies. The authors hypothesized that this might be attributable to the younger patient age at the time of initial repair in the truncus arteriosus population.

Ismail et al.[5] stated that there were no reported reinterventions due to infection in the BJVC cohort of patients who received a conduit as part of their extracardiac TCPC treatment. No comparison of infection rates between cohorts was provided.

Patel et al.[3] compared complications by conduit type among patients who received a BJVC and age-matched patients who received a pulmonary homograft as part of the Ross operation at their facility. Endocarditis was reported as a "late complication" in one of the age-matched pulmonary homograft patients, but no cases of endocarditis were reported in the BJVC patients.

The difference in late endocarditis was compared using a chi square test and no statistically significant difference was found (p=0.31).

Chau et al.[7] provided a case report describing the treatment of an 11-year-old female who was born with Tetralogy of Fallot and pulmonary atresia who was admitted to the hospital with a fever that had lasted one week. As a newborn, the patient had a palliative aortopulmonary shunt placed. At one year of age she received a complete repair which included closure of the ventricular septal defect and placement of an unspecified conduit between the right ventricle and the pulmonary artery. Due to subsequent severe conduit stenosis, the original conduit was replaced with a Contegra BJVC when she was three years of age. At seven years of age she received a percutaneous pulmonary valve implant (Medtronic Melody valve) due to progressive homograft stenosis. Four years later, at age 11, she presented to the hospital with fever. Infective endocarditis was suspected and confirmed via echocardiogram and chest computed tomography angiography. Intravenous antibiotic treatment was attempted but was unsuccessful. The Contegra conduit and Melody valve were surgically removed, and a pulmonary homograft was used in their place.

***Explantation, Reintervention, Regurgitation, Stenosis, and Thrombosis***

*Four of the retrospective cohort studies provided an analysis of the association between reintervention or explantation with conduit type [2-5]. Boethig et al.[4] provided an analysis of the relationship between conduit type, the development of stenosis, regurgitation, or stenosis and regurgitation with explantation. Ismail et al.[5] investigated the relationship between thrombosis, conduit type, and need for reintervention. Patel et al.[3]discussed reintervention and reoperation in Contegra patients and provided a comparison of pulmonary valve replacement rate by initial conduit type. One case report discussed stenosis, regurgitation, and catheter-based reintervention associated with a Contegra device [6]. Two case reports discussed explantation of the Contegra device [7, 10], one of which was summarized in the preceding Endocarditis Section [7] and the other of which is summarized below [10].*

Boethig et al.[4] noted that the rate of explantation (over the full study period) was higher for the BJVC cohort compared to the DPH cohort. Freedom from explantation at 10 years was 96.7% (SE: 2.1) in the DPH cohort, 82.7% (SE: 3.2) in the BJVC cohort, and 84.4% (SE:3.2) in the CH cohort, as shown in Figure 6. The authors also compared freedom from stenosis in cohorts receiving either a BJVC (Contegra), CH, or DPH for pulmonary valve replacement. The rate of freedom from stenosis (defined as >50 mmHg peak gradient) was statistically significantly lower for the BJVC cohort (57.1% ; SE: 4.2%) compared to the DPH cohort (73.9%; SE: 6.1%) at 10 years. However, it should be noted that the mean follow-up time for the DPH cohort was shorter than that for the BJV conduit cohort.

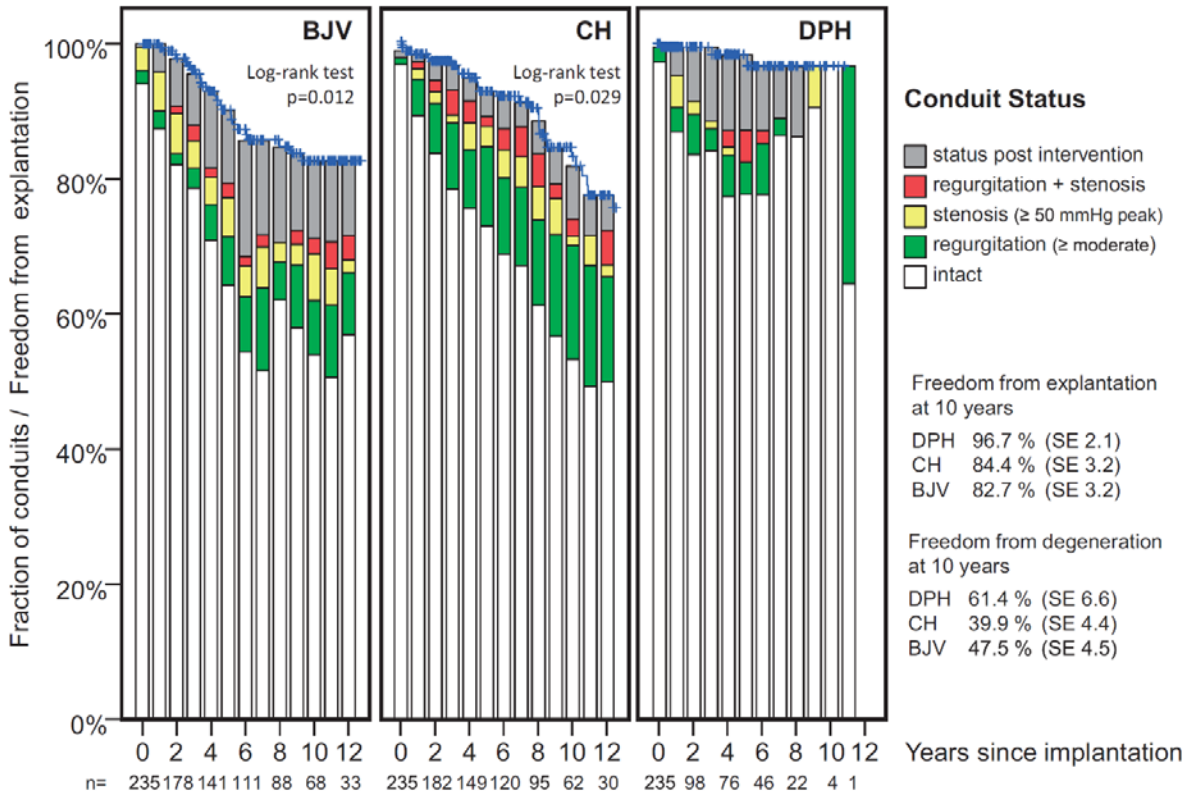


**Figure 6: Freedom from explantation and functional conduit status for DPH, CH and BJV cohorts (Boethig et al.[4]). BJV: bovine jugular vein conduits; CH: cryopreserved conventional homografts; DPH: decellularized pulmonary homografts.**

Herrmann et al.[2] analyzed the relationship between conduit material and freedom from reoperation. Using Kaplan-Meier analysis, as shown in Figure 7, patients who received a BJVC (Contegra) after initial truncus arteriosis repair experienced a longer period of freedom from reoperation when compared to patients who received homografts (aortic or pulmonary) (p=0.05). Additionally, the authors conducted Cox proportional-hazard modelling to evaluate the relationship between conduit material and time to reoperation. Patients who received an aortic homograft were more likely to have a shorter time to reoperation than those implanted with a BJVC (HR: 3.1; 95% CI: 1.37-7.7; p=0.02). However, no statistically significant difference in time to reoperation was observed when patients implanted with a pulmonary homograft were compared to patients implanted with a BJVC (HR, 2.1; 95% CI:0.8-5.8, p=0.15). Variables included in the Cox proportional-hazard models were the same as those mentioned in the section summarizing early mortality results. In addition to conduit type, conduit size had a statistically significant association with time to reoperation in the multivariate model. Larger conduits were associated with decreased risk of reoperation over time compared to smaller conduits (HR: 0.7, 95% CI: 0.6-0.9; p<0.001). The authors also analyzed the association between need for catheter-based reintervention and conduit type. They found no statistically significant association between conduit type and need for (or time to) catheter-based reintervention in a univariate analysis, or in multivariate Cox proportional-hazard modelling. This was true when aortic homografts were compared to BJVC (HR: 0.4, 95% CI: 0.1-2.0; p=0.29) and when pulmonary homografts were compared to BJVC (HR: 0.6, 95% CI: 0.2-1.3; p=0.18).

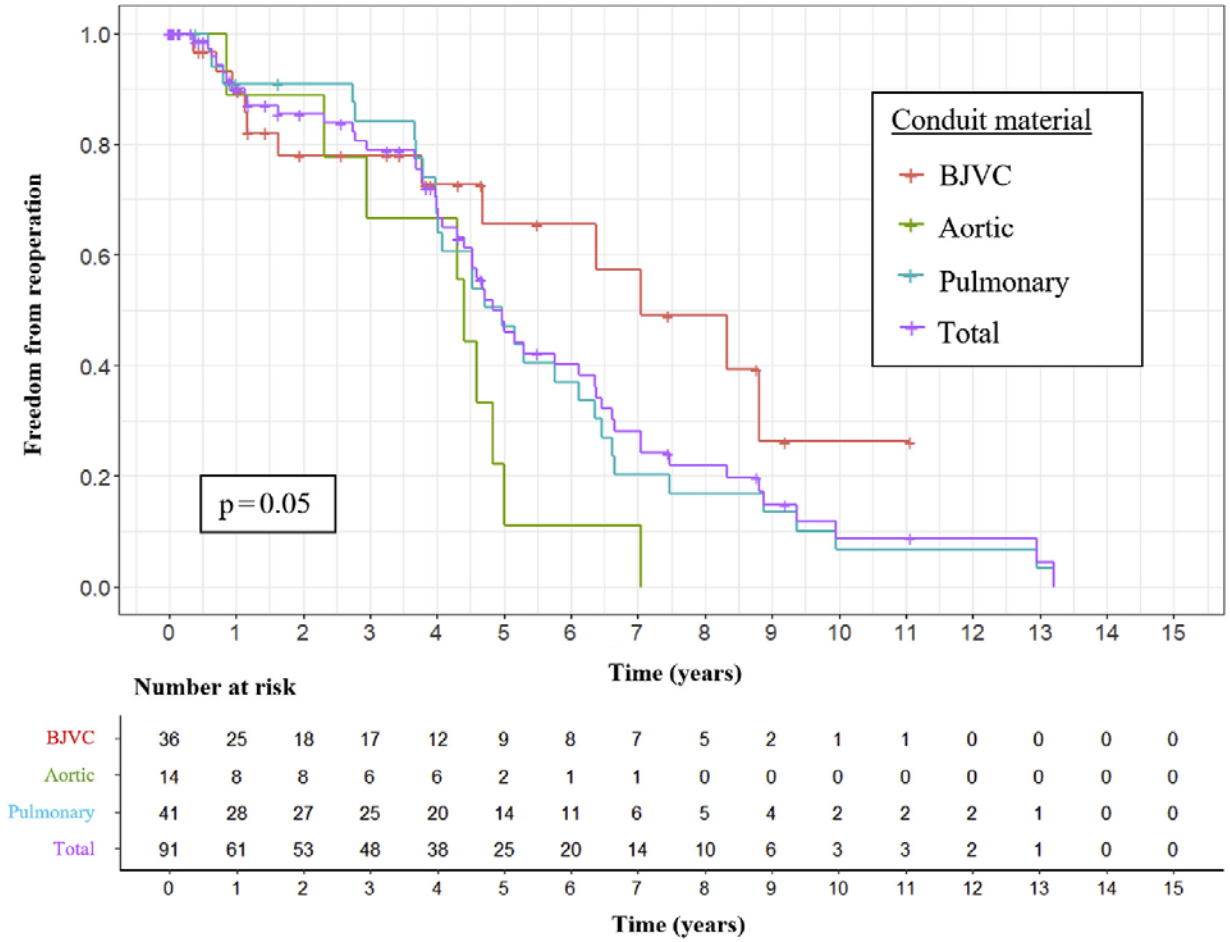


**Figure 7: Kaplan-Meier analysis of freedom from reoperation (Herrmann et al.[2]). (Aortic, aortic homograft; BJVC, bovine jugular vein conduit; Pulmonary, pulmonary homograft.)**

Ismail et al.[5] compared the incidence of thrombosis among cohorts of patients who received various conduit types for extracardiac TCPC. The reported incidence of thrombosis was 7 (11.29%) for the 66 patients in the Contegra BJVC cohort. Using the log-rank test for Kaplan-Meier curve comparisons, this was higher in comparison to the PTFE cohort (p=0.0003), where no thrombosis events were reported in the 103 patients, but not statistically significantly different compared to the PET cohort, where the incidence of thrombosis was 6 (16.2%). The authors reported that there was also a statistically significant association between BJVC and thrombosis when they conducted multivariate analysis of preoperative and operative variables (HR: 3.06, 95% CI: 1.02 -1.72 [*sic*], p=0.047). The authors provided no further discussion of how they selected and built their multivariate models for Cox proportional-hazard modelling. In addition, the authors investigated the association between required intervention for thrombosis and conduit type and found no statistically significant difference between the two groups who had reported thrombosis events (BJVC vs. PET; p=0.283). The authors reported that one Contegra patient required a reintervention for a non-thrombotic cause. This patient experienced a TCPC fenestration. No additional information was provided regarding this patient. The authors stated that there was no statistically significant association between need for reintervention (for

thrombotic or other causes) and conduit type (HR: 0.66; 95% CI:0.27-1.64; p=0.37). As noted previously, the report did not provide a summary of follow-up time after conduit implant for any of the cohorts.

Patel et al.[3] reported that one (7%) of the 15 pediatric patients who received a Contegra BJVC to replace the RVOT as part of the Ross operation at their facility between 1998 and 2016 required a removal and replacement of their Contegra BJVC. The patient had the initial Ross operation at 8 months of age and required pulmonary artery balloon angioplasty 9 months post-initial procedure due to distal conduit anastomosis stenosis. Additionally, 10.5 years after the initial operation, the patient had the device removed and replaced with a new Contegra BJVC due to valve stenosis and regurgitation. The authors reported that 5-year survival with freedom from pulmonary valve replacement was not statistically significantly different between the Contegra BJVC cohort and the Pulmonary Homograft cohort (100% vs. 80%, respectively; p=0.2).

Detzner et al.[6] reported the case of a pregnant 20-year-old patient with a history of congenital heart disease and a repaired double outlet right ventricle who presented with New York Heart Association functional class II symptoms. She previously (at age 4) had a Rastelli procedure where she received an aortic valve homograft for the right ventricle-pulmonary artery conduit (RVPAC). At 12 years of age, she had the RVPAC replaced with a Contegra BJVC (22 mm). Significant RVPAC dysfunction was confirmed with echocardiogram along with moderate stenosis and regurgitation. Eight years after the Contegra BJVC implant, the treating physicians decided to replace the dysfunctional BJVC using TPV implantation. The TPV placement was successfully completed when she was at 13-week gestation of her dichorionic twins. The patient experienced fetal demise of one of her twins at 23-week gestation but delivered the second twin without complication at 30-week gestation. The patient had been followed for 3 years after delivery.

***Other Safety Events***

*Two of the retrospective cohort studies provided summaries of other adverse events [3, 5] in patients who received Contegra BJVC implants. Patel et al.[3] provided a statistical analysis of observed "late term" adverse events by conduit type.*

Ismail et al.[5] reported on several other safety events for their cohort of patients who received various conduit types as part of an extracardiac TCPC operation. Serious arrhythmias were reported postoperatively in two (3%) of the 66 patients who received a Contegra BJVC. One patient who was 3.5 years old at implant (18 mm Contegra BJVC) developed an atrioventricular block which necessitated a permanent pacemaker implant as treatment. The other patient was reportedly 34 years old at implant (22 mm Contegra BJVC) and developed supraventricular tachycardia which was medically managed. The authors reported no occurrence of arrhythmia in patients who received other conduit types (PET or PTFE). No statistical comparison among the groups was performed for this specific adverse event. The study also noted that two (3%) of the 66 Contegra patients developed protein losing entropy 27 months after the initial extracardiac TCPC operation. One patient was 4.5 years old at implant (18 mm Contegra BJVC) and the other was 4.9 years old at implant (16 mm Contegra BJVC). No cases of protein losing enteropathy were mentioned for the PET and PTFE groups, and no statistical comparison among

the groups was reported for this adverse event. In addition, the study reported hepatic stiffness and fibrosis in the Contegra patients. Eight (12%) of the 66 Contegra patients had hepatic stiffness assessed using transient elastography (FibroScan). The median time from extracardiac TCPC procedure to elastography measurement for this subcohort was 9.5 years (IQR:6.5-11 years). All eight patients had advanced fibrosis according to the METAVIR histological index based on the results from the elastography measurements. However, liver function tests were reportedly all within the normal range for these 8 patients.

Patel et al.[3] provided a comparison of "late complications" for their age matched cohort of patients who received either a Contegra BJVC or a pulmonary homograft as part of the Ross procedure. Late complications analyzed (in addition to endocarditis which is summarized in a preceding section) were gastrointestinal bleed, pneumonia, and subdural bleed. Categorical outcomes for these events were compared by conduit type using the chi square test. No statistically significant difference was observed between the Contegra BJVC cohort and the pulmonary homograft cohort for any of these late complications. Again, the authors did not define the timeframe for late complications, and the median follow-up time for the BJVC cohort (1.7 years, IQR: 0.5-4.9 years) was much shorter than that for the pulmonary homograft cohort (6.8 years, IQR 1.9-13.4 years).

**Evidence Assessment**

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

The evidence derived from this systematic literature review has limitations that are important to consider when interpreting the findings. The literature search identified 5 retrospective cohort studies and 4 case reports. Retrospective cohort studies and case reports 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 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 (as was done in 2 of the 5 retrospective cohort studies), or multivariate modelling is completed with the adjustment for known or potential confounders (as was done in 3 of the 5 retrospective cohort studies), unmeasured confounding, or lack of/insufficient balance for differences in covariates can cause confounded or biased assessments of safety 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 device over time periods (7-28 years) long enough for probable significant changes in therapy or patient demographics, and only two of these studies considered the impact of treatment period in their analyses. Additionally, results from single site studies (3 of the 5 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 might have resulted in different search results, 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, which are sent to FDA as MDRs.

**Conclusions Based on the Literature Review**

Review of the literature published between June 1, 2019 and May 31, 2020 revealed the following observations:

- Based on these publications, short-term or operative mortality and long-term mortality rates appeared comparable between conduit types regardless of the reason for treatment (e.g., truncus arteriosus, extracardiac TCPC).

- There were two statistically significant differences in short-term or operative outcomes/adverse events for patients who received a Contegra BJVC versus other conduit types. One study[1] found that for patients treated for truncus arteriosus there was a statistically significant association (bivariate) between BJVC and a higher occurrence of MACE (18/55, 33%) compared to pulmonary allografts (11/83, 13%) and aortic allografts (11/53, 21%) (p=0.04). However, when multivariate logistic regression was conducted this difference appeared attributable to the size of the conduit selected. Additionally, one study[5] found a statistically significant increase in ventilation time for patients who received a Contegra BJVC for extracardiac TCPC compared to patients who received a PTFE conduit (24 hours vs. 14 hours, respectively; p=0.019).

- There did not appear to be a consistent association between Contegra BJV conduits and need for reoperation or reintervention (or earlier reoperation or reintervention) compared to other conduit types. One study [2] found that Contegra BJVC had a protective effect compared to homografts in terms of freedom from reoperation after initial truncus arteriosis repair. Patients implanted with Contegra BJVC experienced longer freedom from reoperation when compared to patients who received aortic homografts (p=0.05). Another study [4] noted that the rate of explantation (over the full study period) was higher for the Contegra BJVC (mean follow-up time 4 years) compared to decellularized pulmonary homografts (mean follow-up time 2 and 6 years depending on subcohort). Freedom from explantation at 10 years was 82.7% (SE: 3.2) for the Contegra BJVCs, and 96.7% (SE: 2.1) for decellularized pulmonary homografts.

- One study [5] found an association between Contegra BJVC and thrombosis incidence (7/66, 11%) compared to PTFE conduit and thrombosis incidence (0/103, 0%) in patients who underwent extracardiac TCPC (p = 0.0003).

- In last year's literature review, endocarditis was a main focus of many of the publications. The association between Contegra and endocarditis was not the main focus of any of the retrospective cohort studies reviewed this year. While four studies

discussed endocarditis or infection in Contegra patients, endocarditis rates were not consistently stratified, or statistically compared, by conduit type in these studies. Two of the studies provided statistical comparisons of endocarditis rates. One study [4] found that the rate of freedom for endocarditis at 10 years was statistically significantly lower for patients who received a Contegra BJVC (90.4%, SE: 2.25) compared to decellularized pulmonary homografts (96.2%, SE: 2.1) and cryopreserved homografts (97.4%, SE: 1.2). The other study found no association between conduit type and endocarditis more than 30 days after implant [3]. The other retrospective cohort studies discussed "infection" or endocarditis and reported no reinterventions due to infection [5], or a low rate of infective endocarditis (2.8%) [2] compared to previous studies.

## 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 2021:

- Annual distribution number
- MDR review
- Literature review

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