Executive Summary

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

H020003

Prepared by the Center for Devices and Radiological Health
for the September 19, 2023 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 2022 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 between May 1, 2022 and April 30, 2023.

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 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 461 devices were sold in the U.S., and 220 devices were implanted. At least 207 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 for suspected device-associated deaths, serious injuries, and device 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 77 MDRs regarding Contegra identified in the FDA's MDR database between May 1, 2022 and April 30, 2023. Of the 77 MDRs, 1 MDR was unrelated to patient outcomes and 15 MDRs were sourced from journal articles. The 15 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 61 unique MDRs, all submitted by the manufacturer.

Patient Demographic Data

Of the 61 MDRs, 57 (93%) were received from the United States. Patient gender information was included in 58 MDRs; 31 involved males and 27 involved females. Patient age was included in 59 MDRs; 50 were pediatric patients and 9 were adults. Table 1 summarizes this information.

Table 1: Patient Demographic Data (Total 61 MDRs; involve 50 pediatric patients)

Demographic Data		Percentage	Number of MDRs containing the demographic
Reporting Country	US : OUS	93% : 7%	57 : 4 (61 Total)
Patient Gender	Male : Female	53% : 47%	31 : 27 (58 Total)
Patient Age	Pediatric : Adult	85% : 15%	50 : 9 (59 Total)
Pediatric Only: Age Range: 1 year – 20 years; Average Age: 12.6 ± 9 years			

Primary Reported Events

The 61 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 2023 PAC Review

Primary Reported Event	Total MDR Count	Patient Age (year)*		TTEO (month)**	
		Pediatric (<22)	Adult (≥22)	Range	Mean
Stenosis	**15**	12	3	9 - 192	109
Device replaced (reason not provided)	**34**	29	3	4 - 200	76
Valve regurgitation / Insufficiency / Pulmonary insufficiency	**1**	0	1	141	-
Aneurysm	**1**	1	0	79	-
Conduit dilation	**1**	1	0	13	-
Endocarditis	**5**	3	2	20 - 216	105
Inadequate size for patient	**3**	3	0	21 - 83	47
Thrombus	**1**	1	0	1	-
Grand Total	**61**	50	9		

*Two MDRs reported unknown age of patient.

**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 2020, 2021, and 2022 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 MDRs in 2020, 2021, 2022 & 2023

Primary Reported Event	2020 PAC	2021 PAC	2022 PAC	2023 PAC
	MDR Count (%)	MDR Count (%)	MDR Count (%)	MDR Count (%)
Stenosis	36 (39%)	20 (33.3%)	13 (31%)	15 (25%)
Device replaced (reason not provided)	32 (35%)	35 (58.3%)	21 (50%)	34 (55.8%)
Valve regurgitation/ Insufficiency / Pulmonary insufficiency	7 (8%)	0	3 (7%)	1 (1.6%)
Inadequate size for patient	3 (3.3%)	0	1 (2.3%)	3 (5%)
Arrhythmia	4 (4.4%)	3 (5%)	1 (2.3%)	0
Increased pressure gradient	2 (2%)	0	0	0
Infection/endocarditis/sepsis	3 (3.3%)	2 (3.3%)	1 (2.3%)	5 (8%)
Conduit dilation/aneurysm	2 (2%)	0	2 (5%)	2 (3%)
Pulmonary edema/ hemorrhage	0	0	0	0
Thrombus	1 (1%)	0	0	1 (1.6%)
Adhesions	1 (1%)	0	0	0
Unknown	1 (1%)*	0	0	0
Total	**92**	**60**	**42**	**61**

*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 61 MDRs involving 61 injuries are summarized below.

Stenosis (n=15 MDRs, including 12 pediatric patients)

Stenosis of conduit or pulmonary artery is reported in 15 MDRs. In these 15 reports, stenosis (in conjunction with calcification, obstruction, pulmonary regurgitation or insufficiency, patient outgrowth and/or elevated pressure gradients) was identified in patients between 9 and 192 months post implant.

Of the stenosis reports, one reflected a mid-term event (within one-year post Contegra implant) in a pediatric patient. An echocardiogram showed significant bilateral branch pulmonary stenosis with associated right ventricular hypertension. The patient underwent a catheterization with a serial balloon dilation of both the proximal right and left pulmonary arteries. No additional adverse patient effects were reported.

Fourteen reports (involving 11 pediatric patients) reflected late events of stenosis (greater than one-year post implant) and the patients required interventions between 2 to 15 years post implant without additional adverse effects reported. Overall, the interventions required for the 11 pediatric patients with

late events of stenosis included transcatheter pulmonary valve (TPV) implantations conducted as valve-in-valve (6) and surgical replacement of pulmonary valve (5).

Device replacement[1] – reason for replacement not reported (n=34 MDRs; 29 pediatric patients)

Thirty-four (34) MDRs indicate that Contegra was replaced, 29 involving pediatric patients. Although the reasons for the device replacement were not reported in the MDRs, 14 of the 34 reports described that the valved conduit was replaced with a larger size device between 4 and 200 months post Contegra implant. Four (4) of the reports described that the conduit was replaced with a conduit of the same size and model. In the remaining 16 MDRs, no information was available regarding the reason for device replacement and the device was not returned to the manufacturer for analysis. Fourteen (14) of these 16 MDRs included transcatheter pulmonary valve (TPV) implantations conducted as valve-in-valve procedures.

Pulmonary insufficiency (n=1 MDRs; 0 pediatric patients)

One (1) MDR reported moderate pulmonary insufficiency at 11 years and 9 months post Contegra implant. A transcatheter pulmonary valve (TPV) was implanted valve-in-valve. No additional adverse patient effects were reported.

Aneurysm (n=1 MDR; 1 pediatric patient)

In an 8-year-old patient, the Contegra device was explanted and replaced with a larger pulmonary valved conduit of the same model after 6 years and 7 months duration post implant. The reason for the replacement was conduit insufficiency. It was reported that aneurysmal dilation and the appearance of a pseudoaneurysm were noted at the distal end of the conduit, which was found to be likely secondary to outflow obstruction due to the patient's history of hypoplastic pulmonary arteries.

Thrombus (n=1 MDR; 1 pediatric patient)

Approximately 4 weeks post implant of the Contegra device in a 2-year-old patient, it was explanted and replaced with a conduit of the same size and model. The reason for replacement was the valve not properly opening due to adhesion of the valve leaflet to the wall of the blood vessel due to thrombus. No additional adverse patient effects were reported.

Conduit dilation (n=1 MDR; 1 pediatric patient)

In a 14-month-old patient, the Contegra device was explanted and replaced with a conduit of the same size and model after 1 year and 1 month post-implant. The reason for replacement was dilation of the conduit due to a distal obstruction. Dense fibrous reaction at the pulmonary artery confluence was reported.

Endocarditis (n=5 MDR; 3 pediatric patient)

Five (5) MDRs reported the Contegra device was explanted and replaced due to endocarditis. One (1) MDR indicated that 1 year and 8 months after implant in a 2-year-old patient analysis of the conduit showed conduit degeneration, old thrombotic formation observed at the proximal anastomosis of 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.

conduit and chronic inflammation indicating chronic endocarditis according to the physician. One (1) MDR reported 2 years and 6 months post implant of the Contegra device in a 6-year-old patient the conduit was explanted and replaced with a homograft due to endocarditis and vegetation was present on the valve. One (1) MDR indicated Contegra was explanted and replaced with a homograft 3 years and 10 months post implant of the conduit in a 4-year-old patient due to MRSA endocarditis. Two (2) MDRs reported Contegra was explanted and replaced after 18 years post implant due to endocarditis. One of the two MDRs did not state the organism cultured and the other MDR indicated the organism cultured was *streptococcus sanguinis*.

Inadequate size for patient (n=3 MDR; 3 pediatric patient)

Three (3) MDRs indicated the Contegra device required re-intervention due to the conduit being an inadequate size for the patient. One (1) MDR reported approximately 3 years post-implant, a stent was implanted inside the conduit to expand it. One (1) MDR indicated that 6 years and 11 months post-implant of the Contegra device in an 8-year old patient, a TBV was implanted valve-in-valve due to somatic outgrowth of the original conduit resulting in stenosis. One (1) MDR reported 1 year and 9 months post-implant of the Contegra device in a 1-year-old patient, a balloon valvuloplasty procedure was performed to expand the device.

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 (BJV) 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 2022 literature review. The search was limited to articles published in English from 05/01/2022 through 04/30/2023.

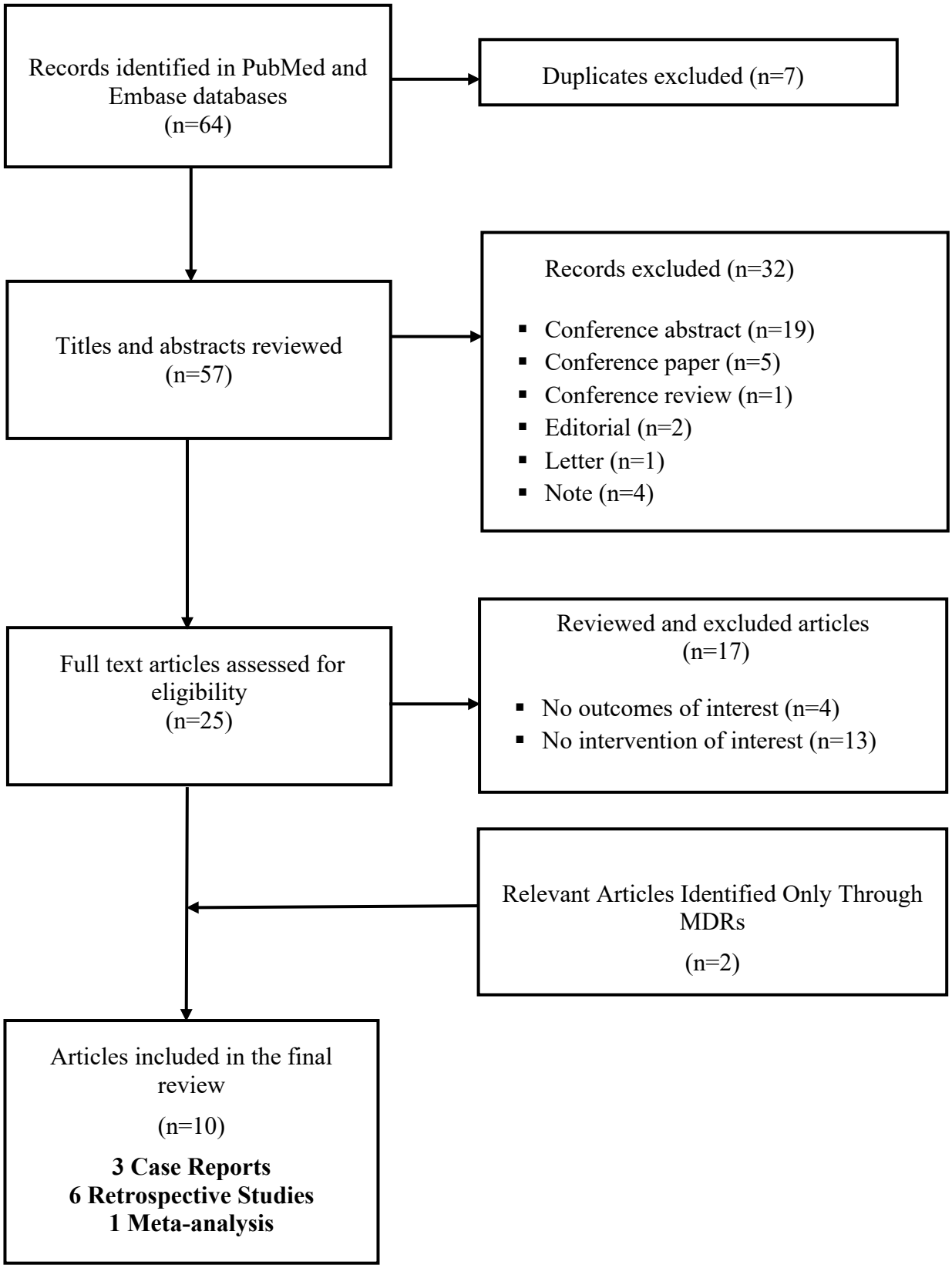
Figure 2 depicts the article retrieval and selection process including the criteria for exclusion. A total of 64 (9 PubMed; 55 EMBASE) articles were retrieved. Seven articles were duplicates. The remaining 57 articles were subjected to review of titles and abstracts. Thirty-two (32) articles were excluded from full-text review for reasons listed: Nineteen (19) were conference abstracts, five (5) were conference papers, one (1) was a conference review, two (2) were editorials, one (1) was a letter, and four (4) were notes. Twenty-five (25)

full-text articles were retrieved and screened. Of these 25 articles, 17 were excluded from further review for reasons listed: Four (4) had no outcomes of interest and thirteen (13) had no intervention of interest. A total of 8 articles were retained for inclusion in the final review.

Of note, in addition to the articles retrieved from PubMed and EMBASE databases, there were 13 unique publications identified through the review of the device manufacturer's adverse event reports submitted through the MedWatch system (MDR reports). Six articles were out of this review's search date range. Three 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. Two of the four did not fit the inclusion criteria as they did not provide any outcomes related specifically to Contegra. Two of the articles were included in the final review.

A total of 10 articles were included in this systematic literature review.

Figure 2. Article retrieval and selection process



Characteristics of Publications Included in Evidence Assessment (n=10)

There were six retrospective studies, three case reports, and 1 meta-analysis identified in this literature review.

Of the retrospective studies, one was conducted in the U.S. (n=1) [1] and five focused on countries outside of the U.S. These studies were conducted in Europe (registry; n=1) [2], Korea (n=1) [3], China (n=1) [4], Switzerland (n=1) [5], and Sweden (n=1) [6]. All three case reports were located outside the U.S. Two of these case reports were from Spain [7], [8] and one case report was from Poland [9]. The meta-analysis was conducted at Erasmus University Medical Center in the Netherlands [10].

A total of 890 patients were involved in four of six retrospective studies and three case reports, with a total of 453 treated with the Contegra device. In the remaining retrospective studies, Schuler et al. reported 69 patients in their study with infective endocarditis [5]. However, the total number of patients implanted with Contegra was not reported. Lewis et al. specified 455 patients were involved with 625 total conduits implanted [6]. Of those 625 conduits, 192 were implanted Contegra devices. In the meta-analysis conducted by Wang et al., 37,078 patients were included with the Contegra device accounting for 41.9% of the xenografts implanted [10].

Four retrospective studies and the meta-analysis study described the use of Contegra for pulmonary valve replacement (PVR). Schuler et al. 2023 retrospectively reviewed all episodes of infective endocarditis [5]. Kim et al. described the potential risk factors for early failure of the Contegra device in the right ventricular outflow tract due to graft-patient size mismatch [3].

Follow up durations were provided in five of the six retrospective studies. One retrospective study did not report follow up time. Mean follow up durations were provided in two retrospective studies and median follow-up durations were provided in three retrospective studies. Bobylev et al. and Dong et al. reported mean follow up durations ranging from 1.4 years to 6.4 years [2]-[4]. Bonilla-Ramirez et al., Kim et al., and Lewis et al., reported median follow-up durations ranging from 25.1 months to 8.7 years [1],[3],[6]. Wang et al. reported in their meta-analysis a median follow-up duration of 6.49 years [10]. Of the three case reports, duration of follow up did not exceed 23 months and was specified in two out of three papers. The ages of patients in the included studies ranged from 17 days to 23 years. Five of the retrospective studies and all three of the case studies included patients (at time of implant) with ages indicated for the Contegra device (<18 years old) [1], [3]-[6], [7]-[9]. One of the retrospective studies and the meta-analysis included patients older than 18 years. Bobylev et al. reported a mean age of 19.1 years (SD: 12.4) for the decellularized pulmonary homograft cohort and 15.3 years (SD: 9.5) for the BJV cohort [2]. Wang et al. reported in the meta-analysis an overall mean age of 23 years with Contegra patients with a mean age of 7.41 years [10]. The percent of males included in the studies ranged from 47% [3] to 68.4% [10]. Appendix A contains more details on study and patient population characteristics.

Safety Results Discussions

All-cause mortality

All-cause mortality was broken down by cohorts of patients who received the Contegra device in 3 of the 6 retrospective studies and in the meta-analyses study. In the Dong et al. study there were no early

mortalities reported in their cohort [4]. The remaining 2 retrospective studies reported all-cause mortality in all cohorts combined. No case reports described long term mortality, as the maximum duration of follow-up among all patients was 23 months.

In Bonilla-Ramirez et al., survival in the 3 conduit groups was as follows: aortic homografts - 84% at 5 years, pulmonary homografts – 89% at 5 years, and bovine jugular vein - 90% at 5 years [1]. In Bobylev et al., freedom from death at 10 years was 97% in bovine jugular vein conduits and 98.1% in decellularized pulmonary homografts [2]. Kim et al. reported 7 deaths (6.1%) in all patients who underwent right ventricular outflow tract reconstruction using Contegra, including 3 in-hospital deaths (2.6%) during the median follow-up duration of 25.1 months [3]. The overall survival rate at 3 years in this study was 94.8%.

The meta-analyses (Wang et al.) reported in a supplementary table an early all-cause mortality rate of 3.0% (CI 2.34%, 3.85%) in xenografts and 4.19% (CI 2.86%, 6.13%) in Contegra conduits [10]. Cardiac early mortality rates were 2.45% (CI 1.84, 3.26) in xenografts and 3.07% (CI 1.74%, 5.39%) in Contegra conduits. Please note these early all-cause mortality rates are overall and not per year. Late all-cause mortality rates were 0.68%/year (CI 0.51%, 0.90%) in xenografts and 1.10%/year (CI 0.78%, 1.54%) in Contegra conduits. Cardiac late mortality rates were 0.54%/year (CI 0.39%, 0.74%) in xenografts and 0.56%/year (CI 0.37%, 0.86%) in Contegra conduits [10].

Schuler et al. reported 5 deaths (7%) and Lewis et al. reported a 91.4% survival rate [5], [6]. However, both studies did not report specific survival rates for those implanted with just the Contegra conduit. For example, Schuler et al. reported 5 deaths out of 69 pediatric infective endocarditis patients identified in nationwide retrospective data in Switzerland [5]. Those patients may or may not have had the Contegra conduit implanted at time of death. In Lewis et. al., there was a 91.4% survival rate for all patients in the study including those with pulmonary homograft, aortic homograft, and Contegra implanted [6]. Although the specific Contegra survival rates are not reported in these two studies, the overall death and survival rates are consistent with rates seen for Contegra in the literature.

Adverse events

Short-term adverse events were only reported in one retrospective study and no case reports. Dong et al. implanted both handmade expanded polytetrafluroethylene (ePTFE) valved conduits (HVCs) and BJV conduits for RVOT reconstruction [4]. Six in-hospital complications were reported in the study but were not differentiated between the HVC and BJV conduits except as noted for mediastinal infection. The complications were as follows: 2 patients had major bleeding, 1 with HVC had mediastinal infection, 1 patient with preoperative left ventricular dysfunction had delayed sternal closure, 1 patient had pericardial effusion requiring pericardial drainage, and 1 patient had postoperative moderate tricuspid regurgitation with moderate conduit insufficiency.

Infective Endocarditis

Infective endocarditis (IE) was reported in five of the retrospective studies and in one case study. In 3 of the retrospective studies and the meta-analysis study the rates of IE were higher in the bovine jugular vein conduits (BJV) when compared to homograft conduits. In the fourth study Kim et al. noted 10 out of 115 (8.7%) patients developed definite or possible endocarditis and that careful surveillance for infection is required after Contegra implantation [3]. In Bonilla-Ramirez et al., endocarditis occurred in one patient with a BJV graft and one patient with a pulmonary homograft who had undergone conduit stent placement

[1]. One case report discussed the incidence of Q-Fever (QF) endocarditis which is described below [7].

Bobylev et al. performed a matched comparison of patients who received decellularized pulmonary homografts (DPH) with patients who received BJV conduits considering patient age, type of heart defect, and previous procedures [2]. In their study freedom from endocarditis at 5 years was 93.7% in BJV and 98.5% in DPH. At 10 years, freedom from endocarditis was 87.1% in BJV and 96.5% in DPH [2].

Lewis et al. reported for all patients, 18 of 625 conduits (2.9%) were replaced due to conduit endocarditis [6]. Of these 4 of 288 (1.4%) were pulmonary homografts, 5 of 145 (3.4%) were aortic homografts, and 9 of 192 (4.7%) were BJV grafts. The authors noted that there was significant difference between rates of endocarditis in pulmonary homografts and BJV (P-value=0.04). However, the higher incidence of endocarditis in BJV grafts did not lead to a greater frequency of conduit failure when compared to the pulmonary graft. The authors also noted pulmonary homografts were less susceptible to conduit exchange due to endocarditis when compared to BJV grafts. This study only accounted for cases of conduit endocarditis which required surgical intervention and not those that were treated medically, which is a noted limitation [6].

Schuler et al. reported definite IE in 58% (40/69) and possible IE in 42% (29/69) in all the subjects regardless of cause (i.e., conduits, prosthetic valves, any type of congenital heart disease repaired with a prosthetic material) [5]. Out of all the cases 48 subjects (70%) developed IE postoperatively. Forty one percent (24/48) of the postoperative IE cases were related to prosthetic valves affecting only the right ventricular to pulmonary artery (RV-PA) conduit. Out of the 24 cases 18 (75%) were associated with the Contegra valve conduit, 4 (17%) were associated with the Melody valve, 1 (4%) was associated with homograft, and 1 (4%) was associated with the Shelhigh-conduit. Limitations noted in this study included a low statistical power due to the sample size and the study's focus was on all causes of IE, not solely on the Contegra device [5]. Additionally, the total number of conduits implanted during this timeframe is not reported. Therefore, rates of infective endocarditis for each conduit cannot be determined from this data.

In the meta-analysis study, Wang et al. aimed to provide an overview of outcomes after right ventricular outflow tract reconstruction using different valve substitutes in different age groups for different indications [10]. The literature was systematically searched for articles published between January 2000 and June 2021. Subgroup analyses were performed including one specific to Contegra. In that subgroup analysis Wang et al. reported an endocarditis rate of 1.17%/year (CI: 0.86, 1.59) for Contegra (n=36) and 0.80%/year (CI: 0.60, 1.09) for the overall xenograft group (n=69) [10].

Kim et al. reported ten patients (8.7%) developed IE within the Contegra conduit of which 8 patients were definite endocarditis and 2 patients with possible endocarditis. In the 8 patients the median duration from Contegra implantation to the development of IE was 385 days (IQR 171-746 days) [3]. Of the 8 patients 4 were successfully treated with antibiotics while the remaining 4 required explanation due to severe stenosis in the conduit. The 2 patients with possible endocarditis were successfully treated with antibiotics [3].

One case report from Huguet et al. described a case of QF endocarditis in an 8-year-old patient that was implanted with Contegra 20 months prior [7]. According to the article, QF is a worldwide zoonotic disease caused by *Coxiella burnetii* and is usually transmitted from farm animals, mainly cattle, sheep, and goats, via inhalation of contaminated aerosols. The Contegra valve was replaced with an aortic homograft 3 weeks after treatment began for the QF endocarditis [7].

Replacement, reintervention, regurgitation, stenosis and thrombosis

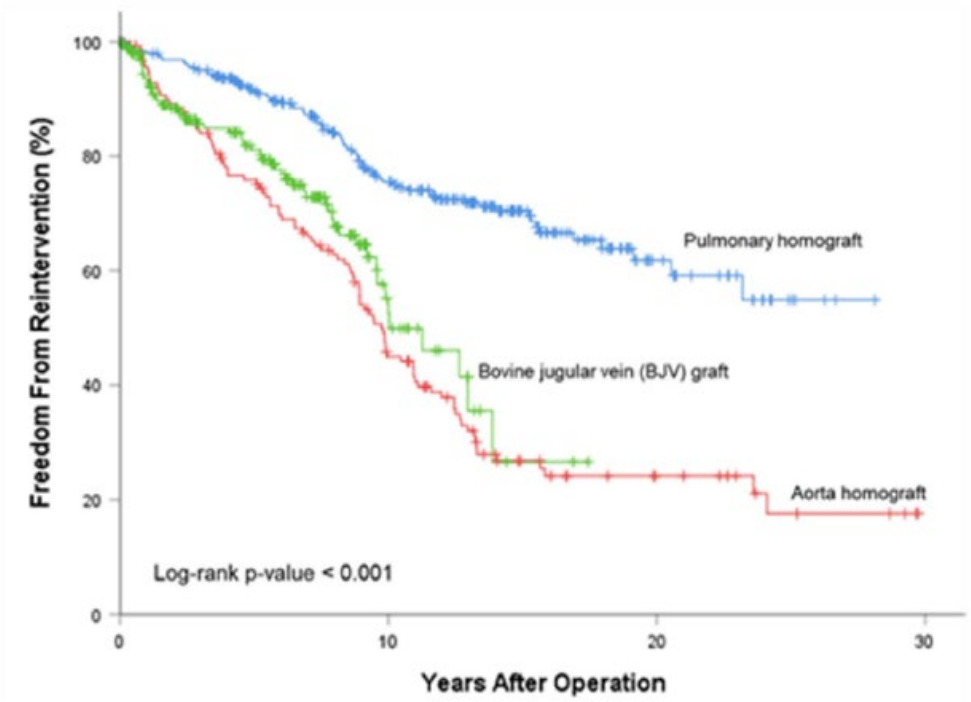
Four of the retrospective studies and the meta-analysis provide Contegra-specific data [1]-[3],[6],[10]. Two of the retrospective cohort studies, Bonilla-Ramirez et al. and Lewis et al., provided an analysis of the association between freedom from reintervention and replacement with conduit type [1], [6]. Kim et al. focused on Contegra explantation due to conduit endocarditis, stenosis, valve regurgitation and valve regurgitation combined with distal stenosis [3]. Bobylev et al. analyzed the association between freedom from conduit deterioration and freedom from explantation between bovine jugular vein (BJV) and decellularized pulmonary homografts (DPH) [2]. Dong et al. reported number of reinterventions and degree of conduit insufficiency in their retrospective study [4]. Wang et al. reported the rates per year of reintervention in their study [10]. Three of the case studies discussed explantation of the Contegra device, summarized below.

Bonilla-Ramirez et al. studied conduit-related risk factors in patients who underwent truncus repair at their institution between 1995 and 2019. In their study they reported the following freedom from reintervention rates at 5 years: 13% for aortic homografts, 23% for pulmonary homografts, and 44% for bovine jugular vein [1]. Bonilla-Ramirez et al. reported the following freedom from replacement rates at 5 years: 23% for aortic homografts, 42% for pulmonary homografts, and 78% for bovine jugular vein [1].

Lewis et al. noted that the rate of freedom from reintervention (FFR) for all patients in the study was 37.8% at 30 years [6]. As shown in Figure 3a, 54.9% at 28 years were for pulmonary homografts, 17.6% at 30 years for aortic homografts, and 26.6% at 17 years for BJV grafts. The authors noted that there was no difference in FFR between the pulmonary homografts and BJV grafts (P-value=0.80, Figure 3b) for the propensity score-matched subgroup [6].

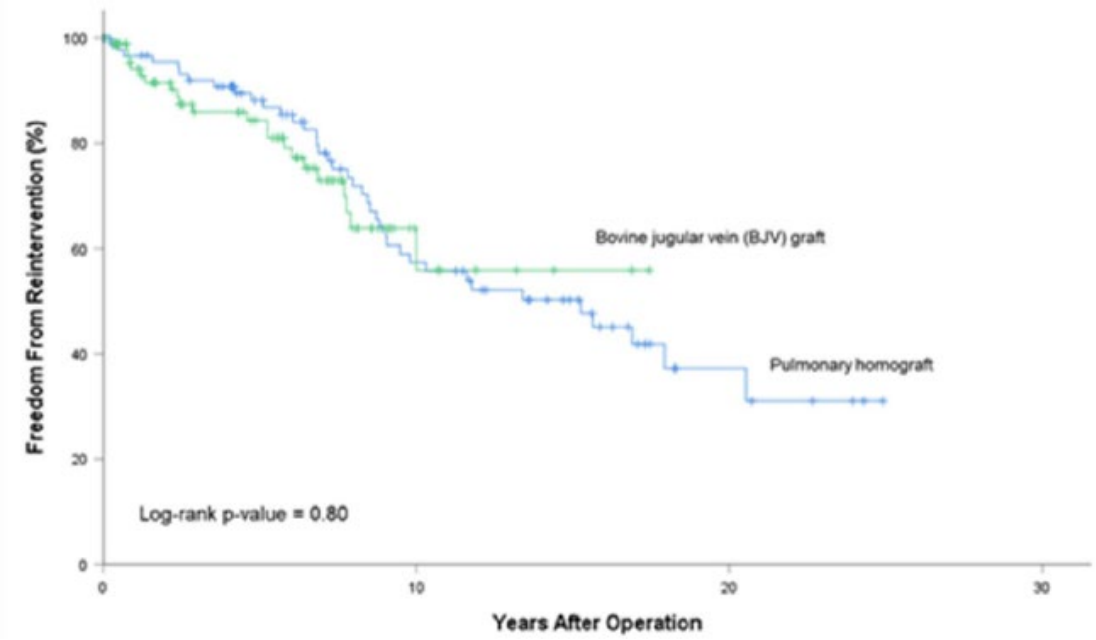
Figure 3. Freedom from reintervention, by conduit type: (a) all patients, (b) propensity score-matched subgroup

(a)



Conduit Type	Number at Risk			
Pulmonary homograft	288	159	24	0
BJV graft	192	21	0	0
Aorta homograft	145	54	12	0

(b)



Conduit Type	Number at Risk		
Pulmonary homograft	92	35	6
BJV graft	92	8	0

Over the course of 30 years Lewis et al. reported freedom from conduit replacement (FCR) for all conduits to be 47.4% [6]. Pulmonary homografts had a rate of 79.6% at 10 years, 68.6% at 20 years, and 66.0% at 30 years. For aortic homografts, 10-, 20-, and 30-year was 49.8%, 31.5%, and 23.0% respectively. For BJV grafts, 10- and 19 year was 68.1% and 46.0% respectively. Propensity score matching was conducted for pulmonary homografts and BJV. This subgroup of patients was reported to have an overall 25-year FCR rate of 36.6%. Lewis et al. noted that FCR was similar between pulmonary homografts and BJV grafts (*P*-value=0.26) [6].

In Kim et al. 2022, Contegra explantation was performed for 15 patients due to conduit endocarditis in 4 patients, stenosis in 5 patients, Contegra valve regurgitation in 2 patients, valve regurgitation combined with distal stenosis in 2 patients and preemptive conduit replacement in 2 patients [3]. The reported explantation free survival rate at 3-years was 78.4%. Right ventricle outflow tract (RVOT) lesions were reported in 34 out of 115 patients due to stenosis (20 patients), regurgitation (8 patients), and significant valve regurgitation with distal anastomotic site stenosis (6 patients). At 3 years post initial implantation freedom from the development of significant RVOT lesions was reported to be 62.6% [3].

Bobylev et al. reported freedom from explantation at 5 years was 91.3% for bovine jugular vein conduits and 98% for decellularized homografts [2]. At 10 years the freedom from explantation was 81.7% for BJV and 95.5% for DPH. Bobylev et al. reported the following freedom from conduit deterioration (stenosis and regurgitation) at 5 years: 59.6% for BJV and 78% for DPH. At 10 years the freedom from conduit deterioration was 39.6% for BJV and 65.6% for DPH [2].

Dong et al. shared initial experience of short-term surgical outcomes of implanting handmade expanded polytetrafluroethylene valved conduits (HVCs) and BJV conduits for RVOT reconstruction [4]. The study is a retrospective study which includes twenty-seven pediatric patients who underwent the Ross procedure in a single center from January 2018 to January 2022. Twenty-one (21) patients received the HVC and 6 patients received BJV conduits. Dong et al. reported three patients with BJV conduits had 5 reinterventions during the follow-up period. They also reported the mean degree of conduit insufficiency at 1 year after surgery was 0.9 ± 0.5 in BJV conduits and 1.1 ± 0.5 in HVCs (p=0.497) [4].

Wang et al. reported in their meta-analysis a reintervention rate of 5.74%/year for Contegra and 3.47%/year for the overall xenograft group [10].

Huguet et al. was a case report describing a case of Q Fever (QF) endocarditis in an 8-year-old patient that was implanted with Contegra 20 months prior [7]. The patient had a history of congenital heart disease consisting of double outlet right ventricle (DORV) with ventricular septal defect (VSD) and pulmonary artery stenosis. He underwent a Rastelli procedure when he was 2 years old. Twenty months prior to the endocarditis, they closed the VSD with a bovine pericardial patch and placed a Contegra conduit. The Contegra valve was replaced after 3 weeks of treatment for the endocarditis [7].

Two case reports, Rudzinski et al. and Martin et al., briefly discuss the explant of the Contegra conduit for the SAPIEN 3 device [9], [8]. Rudziniski et al. reported an 18-year-old female, diagnosed with Tetralogy of Fallot, underwent Contegra transcatheter pulmonary valve replacement due to severe pulmonary insufficiency [9]. In the case report described by Martin et al. a 16-year-old male patient with the diagnosis of pulmonary atresia had undergone Contegra conduit replacement at 8-years of age, for a larger size [8]. He underwent a second replacement due to worsening functional class, dysfunctional conduit with moderate stenosis and insufficiency in addition to dilation of the right ventricle with mildly decreased

systolic function [8].

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. However, it should be noted that several of the studies offer limited data to assess the safety event rates of Contegra in pediatric patients.

This systematic literature review summarizes the reported safety data of the Contegra device for use in pediatric patients published between May 1, 2022 and April 30, 2023. Compared to the results reported in the previous review, infective endocarditis continues to be prevalent in this review. However, last year's retrospective studies provided limited information regarding other adverse events. The retrospective studies in this year's report do report rates of all-cause mortality, reintervention and replacement of the Contegra device.

These studies also face similar limitations to those discussed in the previous review. The lack of randomization, retrospective study designs, differential follow up, and combined pediatric and adult patient populations are potential sources of bias unchanged from the prior assessment. Validity and generalizability are also limited for similar reasons described in the prior review. With a wide range of median follow up times, these retrospective studies are subject to bias due to confounding resulting from the length of follow up and potential changes in therapy or demographics over time. Additionally, generalizability is still limited due to four of the six retrospective studies being conducted at a single site.

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 Report.

Conclusions Based on the Literature Review

Review of the literature published between 05/01/22 and 04/30/23 revealed the following observations:

- Survival rates were specifically reported for Contegra in three (3) retrospective studies and the meta-analysis. The rates ranged from 90% to 97% with different follow-up timepoints. For those studies with comparator devices, the rates of survival were no worse than the comparators. In Bonilla-Ramirez et al., survival in Contegra was 90% at 5 years (higher than rates reported for pulmonary homografts and aortic homografts in the same study) [1]. In Bobylev et al. freedom from death at 10 years was 97% in Contegra [2], and in Kim et al. overall survival rate at 3 years was 94.8% [3]. In the meta-analysis, Wang et al. reports late mortality rates of 1.10%/year (all-cause) and 0.56%/year (cardiac) [10].

- Infective endocarditis was reported in five of the retrospective studies with varying rates. Bobylev et al. reported freedom of endocarditis rate of 93.7% for BJV at 5 years and 87.1% at 10 years [2].

Wang et al. reported an endocarditis rate of 1.17%/year for Contegra [10]. In 3 of the retrospective studies and the meta-analysis study the rates of IE were higher in the bovine jugular vein conduits (BJV) when compared to homograft conduits. However, in Lewis et al. it was noted that the higher incidence of endocarditis in BJV grafts did not lead to a greater frequency of conduit failure when compared to the pulmonary graft [6]. Kim et al. noted 10 out of 115 (8.7%) patients developed definite or possible endocarditis and that careful surveillance for infection is required after Contegra implantation [3]. Overall, these rates are consistent with previously reported rates of IE in Contegra in the literature.

- Rates of reintervention and replacement of the Contegra valve were reported in four (4) of the retrospective studies and the meta-analysis. Rates of freedom from replacement (or explantation) were most frequently reported with varied rates and follow-up timepoints. Freedom from explantation at 3 years of 78.4% is the lowest reported rate and freedom from explantation at 5 years of 91.3% is the highest reported rate. Bonilla-Ramirez et al. reported higher freedom of reintervention at 5 years for Contegra (44%) as compared to aortic homografts (13%) and pulmonary homografts (23%). They also reported higher freedom of replacement rates at 5 years for Contegra (78%) as compared to aortic homografts (25%) and pulmonary homografts (42%) [1]. Lewis et al. reported lower rates of freedom from reintervention and replacement for Contegra as compared to pulmonary homografts in the overall group [6]. However, the rates of reintervention and replacement in Contegra were similar to pulmonary homografts in the propensity score-matched subgroup. Kim et al. reported explantation free survival rate at 3-years of 78.4% [3]. Bobylev et al. reported freedom from explantation at 5 years was 91.3% and 81.7% at 10 years for Contegra [2]. Wang et al. reported in the meta-analysis a reintervention rate of 5.74%/year for Contegra [10].

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 2024:

- Annual distribution number
- MDR review and
- Literature review

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Appendix A. Evidence Tables

Study Characteristics and Outcomes of Retrospective Studies (n=6)			
Study Details	**Patients**	**Intervention(s)**	**Safety Outcomes Assessed for Contegra**
US			
Reference: Bonilla-Ramirez et. al. **Study Design:** Single-center retrospective study **Purpose:** To study conduit-related risk factors for mortality, conduit reintervention, conduit replacement, and pulmonary artery (PA) reinterventions after truncus repair. **Funding:**	**Number of Patients:** 107 **Median Age:** 17 days **Male N (%):** **Diagnosis N (%):** **Note:**	**Intervention:** Truncas repair: aortic homografts (53%), pulmonary homograft (37%), bovine jugular conduit (9%) **Comparator:** n/a **Median Follow-up Period:** 7 years **Inclusion criteria:** All patients who underwent truncus arteriosus repair at Texas Children's Hospital between May 1995 and January 2019. We only studied RV-PA conduits implanted at initial repair of truncus arteriosus. **Exclusion criteria:** n/a	**Mortality (all-cause):** 5 years: 84% survival (aortic homografts), 89% (pulmonary homografts), 90% (bovine jugular vein) **Perioperative Mortality: (<90 days post-procedure):** **Mortality (>90 days post-procedure):** **Adverse events (<90 days post procedure):** **Infective endocarditis N (%):** **Conduit deterioration:** **Reintervention:** 5 years - freedom from conduit reintervention: 13% (aortic homografts), 23% (pulmonary homografts), 44% (bovine jugular vein) **Replacement:** 5 years - freedom from conduit replacement: 23% (aortic homografts), 42% (pulmonary homografts), 78% (bovine jugular vein)
OUS			
Reference: Kim et al. 2022 **Study Design:** Single-center retrospective study **Purpose:** To investigate potential risk factors for early failure of bovine jugular vein conduit (Contegra) implantation for right ventricular outflow tract (RVOT) in the context of graft-patient size mismatch. **Funding:** NR	**Number of Patients:** Total: 115 **Median Age Years:** 10.3 months (IQR: 5.7 - 26.9) Neonate: 11 (9.6%) **Male N (%):** 54 (47%) **Diagnosis N (%):** Tetralogy of Fallot or its variants: 92 (80%) Truncus arteriosus: 11 (9.6%) Aortic Stenosis (with Ross procedure): 7 (6.1%) Other: 5 (4.3%) **Note:** Variants included were pulmonary atresia with ventricular	**Intervention:** Contegra **Comparator:** n/a **Median Follow-up Period:** 25.1 months (IQR 14.8 - 37.7 months) **Inclusion criteria:** Patients receiving their first Contegra implantation, including new RVOT reconstructions or replacements of other types of conduits between 2016-2019. **Exclusion criteria:** NR	**Mortality (all-cause):** 7 (6.1%) **Perioperative Mortality: (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis N (%):** 10 (8.7%) **Conduit deterioration:** NR **Reintervention:** Explantation occurred in 15 patients **Replacement:** NR

	septal defect and Fallot type double outlet right ventricle.		
Reference: Bobylev et al. 2023 **Study Design:** Retrospective review of the ESPOIR Registry and RVOT Conduit Registry **Purpose:** Matched comparison of bovine jugular vein conduits (BJV) and decellularized pulmonary homografts (DPH) considering patient age, type of congenital heart defect, and the number of previous heart operations. **Funding:** Open Access funding enabled and organized by Projekt DEAL. This study was supported by a grant from the European Union's Seventh Framework Programme for Research, Technological Development and Demonstration under Grant Agreement No. 278453.	**Number of Patients:** 319 DPH patients were matched to 319 BJV patients **Mean Age, Years (at implant):** 19.1 (DPH) & 15.3 (BJV) **Male N (%):** 63% (DPH) & 53% (BJV) **Diagnosis N (%) (DPH vs BJV):** TOF: 45 vs. 60 Ross: 13 vs. 8 PI/PS: 14 vs. 8 PA: 10 vs. 8 DORV: 5 vs. 6 TAC: 4 vs. 6 TGA: 3 vs. 4 Other 6 vs. 0 **Note:**	**Intervention:** Contegra (BJV) **Comparator:** DPH **Mean Follow-up Period, Years:** 4.4 (DPH) vs. 6.4 (BJV) **Inclusion criteria:** Patients who had received a DPH in the ESPOIR registry; BJV patients for matching were chosen from the updated RVOT Conduit Registry. Matching was performed on the basis of patient's age category at implantation, the type of congenital heart defect, the number of previous operations, and the number of pervious PVR. **Exclusion criteria:** In 42 out of the 361 DPH patients, no match was found within the RVOT Conduit Registry.	**Mortality (all-cause):** Freedom from death at 5 years (%): 97.0 (BJV), 98.1 (DPH); 10 years: 97.0 (BJV), 98.1 (DPH) **Perioperative Mortality: (<90 days post-procedure):** **Mortality (>90 days post-procedure):** **Adverse events (<90 days post procedure):** **Infective endocarditis:** Freedom from endocarditis at 5 years (%): 93.7 (BJV), 98.5 (DPH); 10 years: 87.1 (BJV), 96.5 (DPH) **Conduit deterioration:** Freedom from degeneration (stenosis and regurgitation) at 5 years (%): 59.6 (BJV), 78 (DPH); 10 years: 39.6 (BJV), 65.5 (DPH) **Reintervention:** **Replacement:** Freedom from explantation at 5 years (%): 91.3 (BJV), 98 (DPH); 10 years: 81.7 (BJV), 95.5 (DPH)
Reference: Dong et al. 2022 **Study Design:** Retrospective review of 27 children who underwent Ross procedure in a single center from January 2018 to January 2022 **Purpose:** To share initial experience and evaluation of short-term surgical outcomes of implanting handmade expanded polytetrafluroethylene (ePTFE) valved conduits (HVCs) for RVOT reconstruction **Funding:** This study was supported by the Natural Science Foundation of China (82070322), Shanghai Municipal Science and Technology Commission Research Project	**Number of Patients:** 27 total; 6 patients with BJV, 21 patients with HVCs **Mean Age, Years (at implant):** 8.0 $\pm$ 3.8 years **Male N (%): N**=16; 59% **Diagnosis N (%) Note:**	**Intervention:** HVC **Comparator:** BJV **Mean Follow-up Period, Years:** 1.4 (range, 0.1-3.7 years) **Inclusion criteria:** Patients who underwent Ross procedure at Shanghai Children's Medical Center between January 2018 and January 2022 **Exclusion criteria:** n/a	**Mortality (all-cause):** n/a **Perioperative Mortality: (<90 days post-procedure):** There was no hospital mortality. **Mortality (>90 days post-procedure):** n/a **Adverse events (<90 days post procedure):** In-hospital complications occurred in 6 patients (22%): 2 patients had major bleedings, 1 patient with HVC had mediastinal infection, 1 patient with preoperative left ventricular dysfunction had delayed sternal closure, 1 patient had pericardial effusion requiring pericardial

(19411950200), and Shenkang Cutting-Edge Research Project (SHDC12018128).			drainage, and 1 patient had postoperative moderate tricuspid regurgitation with moderate conduit insufficiency. **Infective endocarditis:** n/a **Conduit deterioration:** The mean degree of conduit insufficiency at 1 year after surgery was 0.9 ± 0.5 in BJV conduits, and 1.1 ± 0.5 in HVCs (p = 0.497); Three patients (11%) with HVCs developed moderate conduit insufficiency; no patients had more than moderate conduit insufficiency. **Reintervention:** Three patients with BJV conduits had 5 reinterventions on the conduit during the follow-up period. No patients with HVCs required reintervention. **Replacement:** n/a ***Note:*** *No risk factor for conduit dysfunction was identified by the Cox proportional hazard analysis.*
Reference: Lewis et al. 2022 **Study Design:** Single center retrospective study **Purpose:** To evaluate the long-term performance of the pulmonary homograft, aorta homograft, and bovine jugular vein graft conduits used and assess risk factors for conduit failure. **Funding:** Open access funding provided by Lund University.	**Number of Patients:** Total: 455 **Mean Age at Operation, Years:** 6.4 ± 5.8 **Male (%):** 54.9% **Diagnosis N (%):** PA/VSD: 106 (23.3%) Tetrology of Fallot: 121 (26.6%) Truncus arteriosus: 77 (16.9%) TGA/VSD/PS: 33 (7.3%) PS, PI, PA/IVS: 33 (7.3%) AS, AI: 32 (7.0%) All others: 53 (11.6%) **Note:** There were 475 patients who received 647 RV-PA conduits. 20 patients failed to meet the inclusion criteria and were excluded from the study.	**Intervention:** Contegra (BJV) and cryopreserved homografts **Comparator:** n/a **Median Follow-up Period:** 8.7 years (IQR 4.3-13.3 years) **Inclusion criteria:** Patients who received an RV-to-PA conduit from January 1, 1990 to December 31, 2019. Patients with two-ventricle circulation. **Exclusion criteria:** Patients with single-ventricle circulation. Any patient in a study where it was not possible to accurately ascertain any of the study endpoints. **Note:** Follow-up was longer for homografts than for BVJ grafts, as their use was initiated in 2003	**Mortality (all-cause):** Overall survival rate: 91.4% **Perioperative Mortality: (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis N (%):** All patients, 18 of 625 conduits (2.9%) were replaced due to conduit endocarditis: 4 of 288 (1.4%) pulmonary homografts, 5 of 145 aortic homografts (3.4%), and 9 of 192 (4.7%) BJV grafts There was a significant difference between rates of endocarditis in pulmonary homografts and BJV

			grafts (P-value=0.04) **Conduit deterioration:** NR **Reintervention:** FFR for all patients: 37.8% at 30 years: 54.9% at 28 years for pulmonary homografts, 17.6% at 30 years for aortic homografts, and 26.6% at 17 years for BJV grafts. There was no difference in FFR between pulmonary homografts and BJV grafts (P-Value=0.80) **Replacement:** FCR for pulmonary homografts at 10 years 79.6%, at 20 years 68.6%, and at 28 years 66% FCR for aortic homografts at 10 years 49.8%, at 20 years 31.5%, and at 30 years 23% FCR for BJV grafts at 10 years 68.1% and at 19 years 46% FCR was similar between pulmonary homografts and BJV grafts (P-value=0.26)
Reference: Schuler et al. 2023 **Study Design:** Retrospective nationwide multicenter study **Purpose:** To build a prospective data collection of the microbiological spectrum, diagnosis, predisposing risk factors, clinical course, complications, therapy, and outcome of pediatric IE in Switzerland. **Funding:**	**Number of Patients:** Total 69 **Median Age Years:** 6.39 (0.81-12.60 IQR) **Male N (%):** 42 (61%) **Diagnosis N:** TOF: 9 PA: 7 DORV: 5 Truncus arteriosus communis: 4 TGA: 3 HLHS: 2 DORV + TA: 1 Unbalanced AVSD: 1 Ventricular septal defect: 8 Bicuspid aortic valve: 6 AVSD: 4	**Intervention:** n/a **Comparator:** n/a **Median Follow-up Period:** NR **Inclusion criteria:** Less than 18 years of age, treated between 2011-2020. Patients fulfilling the modified Duke criteria for definite or possible IE. **Exclusion criteria:** NR **Note:** This study included patients with prosthetic valve, patient with previous IE, patients with unrepaired cyanotic CHD including palliative shunts and conduits or patients with any type of CHD repaired with a prosthetic material within 6 months	**Mortality (all-cause):** 5 (7%) **Perioperative Mortality: (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis N (%):** Definite IE 40 (58%) Possible IE 29 (42%) Postoperative IE 48 (70%) Prosthetic valve associated with IE affected only the RV-PA conduit in 24 of 48 (41%) postoperative IE. Of these 18 (75%) were the Contegra valve conduit. 4 of 24 (17%) were

	Aortic valve stenosis: 3 Atrial septal defect: 2 Absent pulmonary valve:1 Shone-complex: 1 Complete AV block: 1 Other: 11 **Note:**	after procedure or lifelong if residual shunt remains.	associated with the Melody valve. 1 (4%) homograft and 1 (4%) Shelhigh-Conduit. **Conduit deterioration:** n/a **Reintervention:** n/a **Replacement:** n/a

Abbreviations: RVOT: right ventricular outflow tract; RV-PA: right ventricle to pulmonary artery; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect; PS: pulmonary stenosis; PI: pulmonary insufficiency; PA: pulmonary atresia; IVS intact ventricular septum, AS: aortic stenosis; AI: aortic insufficiency; FCR: freedom from conduit replacement; BJV: bovine jugular vein; FFR: freedom from reintervention; IE: infective endocarditis; CHD: congenital heart disease; IQR: interquartile ranges; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; TA: tricuspid atresia; AVSD: atrioventricular septal defect; AV: atrioventricular

Study Characteristics and Outcomes of Case Studies (n=3)			
Study Details	**Patients**	**Intervention(s)**	**Safety Outcomes Assessed**
OUS			
Reference: Huguet et al. 2022 **Country:** Spain **Study Design:** Case Report **Purpose:** To report a rare case of Q Fever (QF) endocarditis in an 8-year-old patient that was implanted with Contegra 20 months prior. **Funding:** n/a	**Patient(s) (N):** 1 **Age, years:** 8 **Sex:** male **Diagnosis:** History of congenital heart disease consisting of double outlet right ventricle (DORV) with ventricular septal defect (VSD) and pulmonary artery stenosis; Underwent a Rastelli procedure when he was 2 years old. Twenty months prior to endocarditis, closed the VSD with a bovine pericardial patch and placed a Contegra prosthetic pulmonary valve **Note:**	**Intervention:** Replaced Contegra after 3 weeks of treatment. During the surgery, multiple vegetations were observed on the conduit mainly adhering to the leaflets, and an aortic homograft was placed. **Comparator:** n/a **Follow-up Period:** 23 months from treatment discontinuation **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** n/a **Perioperative Mortality: (<90 days post-procedure):** n/a **Mortality (>90 days post-procedure):** n/a **Adverse events (<90 days post procedure):** n/a **Infective endocarditis:** n/a **Conduit deterioration:** n/a **Reintervention:** n/a **Replacement:** n/a *Note: A TTE revealed a 7x10 mm vegetation at the prosthetic valve without significant valvular dysfunction, mild pulmonary regurgitation, and mild pulmonary stenosis. He was diagnosed with Q Fever (QF) endocarditis. QF is usually transmitted from farm animals, mainly cattle, sheep, and goats, via inhalation of contaminated aerosols. Acute QF is usually asymptomatic in children.*

			Endocarditis is the predominant form of chronic infection and has been observed in 1-16% of reported cases of QF, but few pediatric cases have been reported and even fewer have been associated with prosthetic material.
Reference: Rudzinski et al. 2022 **Country:** Poland **Study Design:** Case Study **Purpose:** To provide large field of view intravascular ultrasound offering tomographic perspective online for accurate sizing during transcatheter pulmonary valve replacement **Funding:** NR	**Patient(s) (N):** 1 **Age, years:** 18 **Sex:** F **Diagnosis:** Tetralogy of Fallot Underwent surgical correction in childhood **Note:**	**Intervention:** Contegra **t**ranscatheter pulmonary valve replacement with SAPIEN 3 **Comparator:** n/a **Follow-up Period:** **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** n/a **Perioperative Mortality: (<90 days post-procedure):** n/a **Mortality (>90 days post-procedure):** n/a **Adverse events (<90 days post procedure):** n/a **Infective endocarditis:** n/a **Conduit deterioration:** n/a **Reintervention:** n/a **Replacement:** Contegra valve explant due to severe pulmonary insufficiency **Note:** RVOT dimensions were assessed in angiography using the sizing balloon. These dimensions corresponded with CMR measurements. A Vision PV035 10MHz intravascular ultrasound was used as a research periprocedural imaging. IVUS showed RVOT with significantly bigger dimensions. Following pre-stenting, a larger SAPIEN was successfully deployed. IVUS was used to verify valve expansion.
Reference: Martin et al 2022 **Country:** Spain **Study Design:** Case Study **Purpose:** To report the pitfalls responsible for coronary compression following percutaneous pulmonary valve implantation with respect to the size of the balloon used for the sizing test.	**Patient(s) (N): 1** **Age, years: 16 years** **Sex: M** **Diagnosis:** Situs inversus totalis and pulmonary atresia with interventricular communication Surgica history: neonatal period palliative systemic to pulmonary shunt procedure, 8 months of age a	**Intervention:** Percutaneous pulmonary valve (SAPIEN 3) implantation after RVOT stenting **Comparator:** n/a **Follow-up Period:** 6 months post procedure **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** n/a **Perioperative Mortality: (<90 days post-procedure):** n/a **Mortality (>90 days post-procedure):** n/a **Adverse events (<90 days post procedure):** During the patient's recovery, he developed chest pain. It was confirmed that the patient

Funding: Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, through the CIBER en enfermedades cardovasculares	16 mm Contegra conduit was placed, 8 years later conduit was replaced for a 20 mm conduit. **Note:**		developed coronary compression secondary to PPVI. **Infective endocarditis:** n/a **Conduit deterioration:** n/a **Reintervention:** n/a **Replacement:** PPVI was required due to patient presenting with worsening functional class, dysfunctional conduit with moderate stenosis and insufficiency in addition to dilation of the right ventricle with mildly decreased systolic function.

Abbreviations: RVOT: right ventricular outflow tract; CMR: cardiac magnetic resonance; IVUS: intravascular ultrasound; PPVI: percutaneous pulmonary valve implantation

Study Characteristics and Outcomes of Meta-Analyses Study (n=1)			
Study Details	**Patients**	**Intervention(s)**	**Safety Outcomes Assessed for Contegra**
Reference: Wang et al. **Study Design:** Meta-analyses **Purpose:** To provide an overview of outcomes after RVOT reconstruction using different valve substitutes in different age groups for different indications. **Funding:** NR	**Number of Patients:** 37,078 (217 articles) **Mean Age:** 22.86 years overall (7.41 years for Contegra) **Male N (%):** 68.4% **Diagnosis N (%):** Aortic valve disease (Ross procedure, 46.6%), Tetralogy of Fallot (TOF, 27%) **Note:**	**Intervention:** homografts (83.7%), xenograft (32.6%), (41.9% Contegra of all xenografts) Comparator: n/a **Median Follow-up Period:** 240,581 patient-years **Inclusion criteria:** Articles published between January 2000 and June 2021 reporting on clinical and/or echocardiographic outcomes after RVOT reconstruction with valve substitutes. **Exclusion criteria:** N/A	**Mortality (all-cause):** Early mortality: 3% (all cause) & 2.45% (cardiac) overall xenograft group; Early mortality: 4.19% (all cause) & 3.07% (cardiac) Contegra **Perioperative Mortality: (<90 days post-procedure):** **Mortality (>90 days post-procedure):** Late mortality: 0.68%/y (all cause) & 0.54%/y (cardiac) overall xenograft group; Late mortality: 1.10%/y (all cause) & 0.56%/y (cardiac) Contegra; **Adverse events (<90 days post procedure):** **Infective endocarditis N (%):** 1.17%/year Contegra; 0.80%/y overall xenograft group Conduit deterioration: **Reintervention:** 5.74%/y Contegra; 3.47%/y overall xenograft group **Replacement:**