FDA Executive Summary

Prepared for the

Fall 2022 review by the

FDA's Pediatric Advisory Committee

H020003

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

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 2021 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 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 Act) 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 394 devices were sold in the U.S., and 227 devices were implanted. At least 220 of the devices were implanted in pediatric (<22 years) patients.

MEDICAL DEVICE REPORT REVIEW

Overview of MDR Database

The medical device reports 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 57 MDRs regarding Contegra identified in the FDA's MDR database between June 1, 2021 and April 30, 2022[1]. Of the 57 MDRs, 15 MDRs were related to journal articles. The 15 MDRs related to journal

[1] Please note that the reporting period for this year's analysis is 11 months due to the need to perform the MDR analysis prior to the 12-month reporting period date. Next year's analysis will be from 05/01/22 – 04/30/23 to account for this adjustment.

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 42 unique MDRs, all submitted by the manufacturer.

Patient Demographic Data

Of the 42 MDRs, 42 (100%) were received from the United States. Patient gender information was included in 42 MDRs; 25 involved males and 17 involved females. Patient age was included in 41 MDRs; 39 were pediatric patients and 2 were adults. Table 1 summarizes this information.

Table 1: Patient Demographic Data (Total 42 MDRs; involve 39 pediatric patients)

Demographic Data		Percentage	Number of MDRs containing the demographic
Reporting Country	US : OUS	100% : 0%	42 : 0 (42 Total)
Patient Gender	Male : Female	60% : 40%	25 : 17 (42 Total)
Patient Age	Pediatric : Adult	95% : 5%	39 : 2 (41 Total)
Pediatric Only: Age Range: 10 months – 21 years; Average Age: 11.9 ± 7.6 years			

Primary Reported Events

The 42 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 2022 PAC Review

Primary Reported Event	Total MDR Count	Patient Age (year)		TTEO (month)*	
		Pediatric (<22)	Adult (≥22)	Range	Mean
Stenosis	**13**	12	1	26 - 181	95
Device replaced (reason not provided)	**21**	21	0	0 - 276	66
Valve regurgitation	**3**	3	0	13 - 158	88
Aneurysm (RVOT)	**1**	1	0	unknown	-
Arrhythmia	**1**	1	0	0	-
Conduit dilation	**1**	0	1	168	-
Endocarditis	**1**	1	0	162	-
Inadequate size for patient	**1**	1	0	85	-
Grand Total	**42**	40	2		

*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 2019, 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 2019, 2020, 2021 & 2022

Primary Reported Event	2019 PAC MDR Count (%)	2020 PAC MDR Count (%)	2021 PAC MDR Count (%)	2022 PAC MDR Count (%)
Stenosis	51 (48%)	36 (39%)	20 (33.3%)	13 (31%)
Device replaced (reason not provided)	38 (36%)	32 (35%)	35 (58.3%)	21 (50%)
Valve regurgitation/ insufficiency	6 (6%)	7 (8%)	0	3 (7%)
Inadequate size for patient	4 (4%)	3 (3.3%)	0	1 (2.3%)
Arrhythmia	2 (2%)	4 (4.4%)	3 (5%)	1 (2.3%)
Increased pressure gradient	2 (2%)	2 (2%)	0	0
Infection/endocarditis/sepsis	2 (2%)	3 (3.3%)	2 (3.3%)	1 (2.3%)
Conduit dilation/aneurysm	1 (1%)	2 (2%)	0	2 (5%)
Pulmonary edema/ hemorrhage	0	0	0	0
Thrombus	0	1 (1%)	0	0
Adhesions	0	1 (1%)	0	0
Unknown	0	1 (1%)*	0	0
Total	**106**	**92**	**60**	**42**

*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 42 MDRs involving 42 injuries are summarized below.

Stenosis (n=13 MDRs, including 12 pediatric patients)

Stenosis of conduit or pulmonary artery continued to be the most frequently reported event. In these 13 reports, stenosis (in conjunction with calcification, obstruction, pulmonary regurgitation or insufficiency, patient outgrowth and/or elevated pressure gradients) was identified in patients between 26 and 181 months post implant.

Of the stenosis reports, none reflected early and mid-term events (within one-year post Contegra implant) in pediatric patients. Thirteen reports (involving 12 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 13 patients with stenosis included transcatheter pulmonary valve (TPV) implantations conducted as valve-in-valve (7) and surgical replacement of pulmonary valve (6).

Device replacement[2] – reason for replacement not reported (n=21 MDRs; 21 pediatric patients)

Twenty-one MDRs indicate that Contegra was replaced, all involving pediatric patients. Although the reasons for the device replacement were not reported in the MDRs, 14 of the 21 reports described that the valved conduit was replaced with a larger size device between 1 and 142 months post Contegra implant. One of the reports described that the conduit was replaced with a smaller size device. Two of the reports described that the conduit was replaced with a conduit of the same size and model. In the remaining 4 MDRs, no information was available regarding the reason for or size of device replacement and the device was not returned to the manufacturer for analysis.

Valve regurgitation (n=3 MDRs; 3 pediatric patients)

Three (3) MDRs reported valve regurgitation between 13 and 159 months post Contegra implant. One patient had a Contegra valve explanted and replaced with a larger conduit of the same model. One patient had a Contegra valve explanted and replaced with a larger conduit of a different model. One patient required a TPV valve-in-valve implantation. No additional adverse patient effects were reported.

Aneurysm (RVOT) (n=1 MDR; 1 pediatric patient)

In a 10-month-old patient, the Contegra device was explanted and replaced with a larger pulmonary valved conduit of the same model after an unknown duration post implant. The reason for the replacement was right ventricular outflow tract (RVOT) aneurysm. The physician noted that there was RVOT stenosis present and "the aneurysm was a true aneurysm with no suture line rupture."

Arrhythmia (n=1 MDR; 1 pediatric patient)

On the same day as implant of the Contegra device, a 7-year-old female had a biventricular defibrillator implanted due to complete heart block and a history of spontaneous sustained ventricular tachycardia. 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 defibrillator.

Conduit dilation (n=1 MDR; 0 pediatric patient)

As reported by a family member, a 36-year-old female patient was implanted with a 22mm Contegra device for approximately 14 years. The report states that "the conduit has expanded through the ribs and is about to break through the skin." The conduit remains implanted and no additional adverse patient effects were reported.

Endocarditis (n=1 MDR; 1 pediatric patient)

In a 17-year-old patient, the Contegra device was explanted and replaced with an unknown device after 13 years and 6 months post implant. The reason for replacement was bacterial endocarditis. Prior to explanting the valved conduit, the patient was treated with 6 weeks of antibiotics. The physician also reported there was stenosis and mild insufficiency.

Inadequate size for patient (n=1 MDR; 1 pediatric patient)

2 "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.

In a 7-year-old male patient, the Contegra device was explanted and replaced with a larger pulmonary valved conduit of the same model after 7 years and 1 month post implant. The reason for replacement was due to patient outgrowth of the original conduit. No additional adverse patient effects were reported.

Conclusions Based on the MDR Review

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

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

CONTEGRA LITERATURE REVIEW

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

Methods
A search of the PubMed and EMBASE databases were conducted for published literature using the search terms: "Contegra" OR "Bovine Jugular Vein" OR "Pulmonary Valved Conduit," which were the same terms used in the 2021 literature review. The search was limited to articles published in English from 06/01/2021 through 04/30/2022[3].

Figure 2 depicts the article retrieval and selection process including the criteria for exclusion. A total of 66 (9 PubMed; 57 EMBASE) articles were retrieved. Six articles were duplicates. The remaining 60 articles were subjected to review of titles and abstracts. Twenty-six (26) articles were excluded from full-text review due to the abstracts not being relevant based on the inclusion and exclusion criteria. A total of 34 articles were retained for full text review. Thirty-three (33) full-text articles were retrieved and screened (one full-text could not be retrieved). Of these 33 articles, 22 were excluded from further review for reasons listed: Five (5) had no outcomes of interest, nine (9) had no intervention of interest, one (1) was outside publication date range, two (2) were not peer reviewed, two (2) were not populations of interest, and three (3) were reviewed for prior PAC meetings.

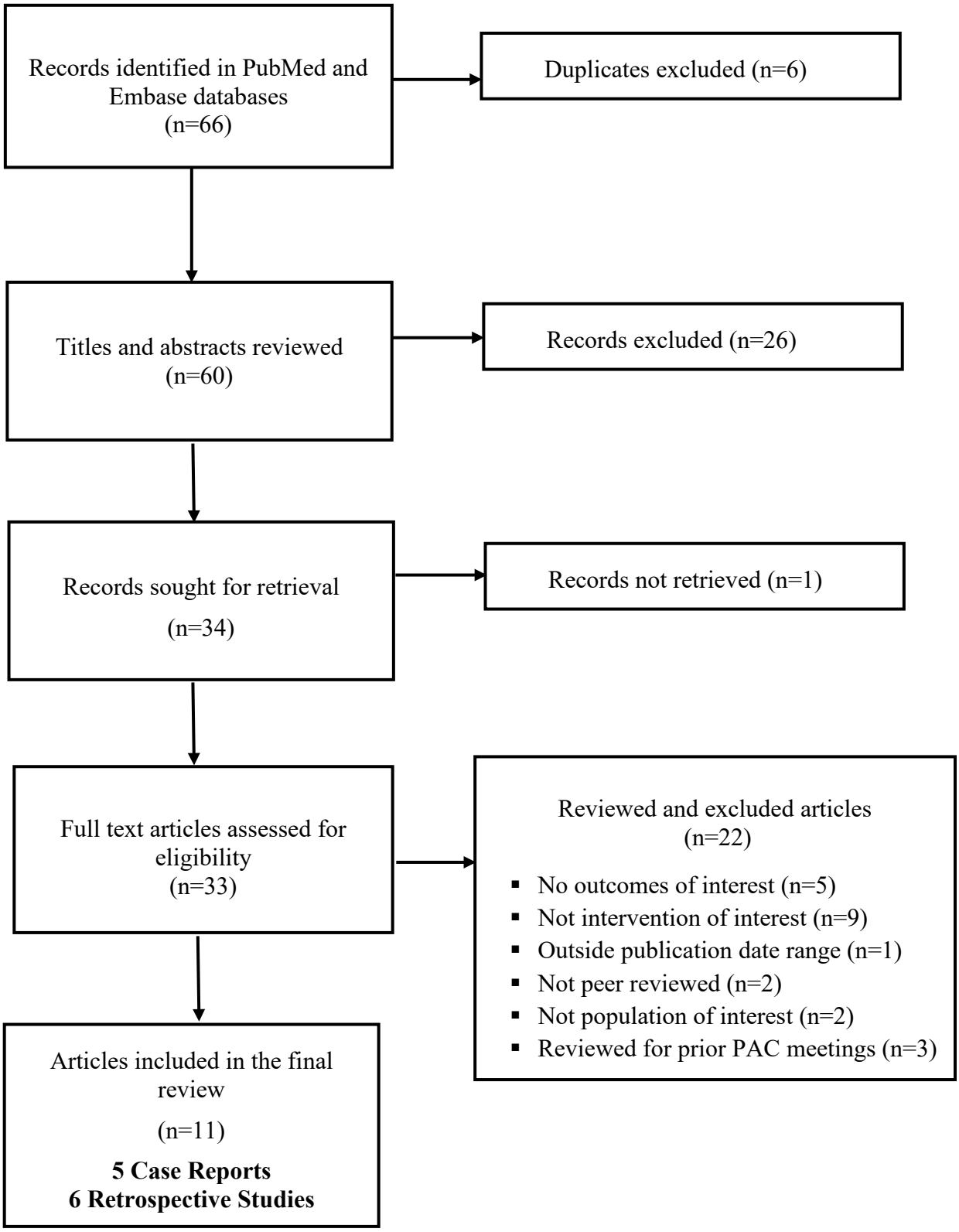
Of note, in addition to the articles retrieved from PubMed and EMBASE databases, there were 15 publications identified through the review of the device manufacturer's adverse event reports submitted through the MedWatch system (MDR reports). Ten articles were out of this review's search date range. Two of the articles mentioned in the MDRs were also identified during this literature search. The abstracts of the remaining three articles were reviewed to determine if they should be included in the final literature review. None of the three fit the inclusion criteria as they did not provide any outcomes related specifically to

[3] Please note that the reporting period for this year's analysis is 11 months due to the need to perform the literature review prior to the 12-month reporting period date. Next year's review will be from 05/01/22 – 04/30/23 to account for this adjustment.

Contegra.

A total of 11 articles were included in this systematic literature review.

Figure 2. Article retrieval and selection process



Characteristics of Publications Included in Evidence Assessment (n=11)

There were six retrospective studies and five case reports identified in this literature review. One of the retrospective studies included a systematic literature review in addition to the cohort study, however the systematic literature review data was not included as the literature was published prior to June 1, 2021 [1].

Of the retrospective studies, one was conducted in the U.S. (n=1) [2] and five focused on countries outside of the U.S. These studies were conducted in Australia (n=2) [1], [4], Canada (n=1) [3], Germany (n=1) [6], and Turkey (n=1) [5]. One case report was from the U.S. [7], while four others were located outside the U.S. These case reports were from Oman [8], India [9], Germany [11], and Poland [10], respectively.

A total of 1,490 patients were involved in five of six retrospective studies and five case reports, with a total of 533 treated with the Contegra device. Marathe et al. did not specify the number of patients but reported the number of Contegra conduits (303) implanted in patients [1].

Three retrospective studies described the use of Contegra for pulmonary valve replacement (PVR) [1],[2],[6]. Yakut et al. 2021 retrospectively reviewed all episodes of infective endocarditis [5]. Luxford et al. described the use of Contegra for aortic stenosis [4]. Al Mosa et al. 2021 described Contegra in repaired tetralogy of Fallot, double outlet right ventricle (DORV), and tetralogy of Fallot or DORV and pulmonary atresia [3].

Follow up durations were provided in five of the six retrospective studies, with medians ranging from 29 months to 10 years [1]-[6]. Ahmed et al. 2022 reported a median follow up duration of 29 months (IQR: 6-62 months) [2]. One retrospective study did not report follow up time [5]. Of the five case reports, duration of follow up did not exceed 18 months and was specified in three out of five papers. Three cases were followed up long term (>90 days; range: 3-18 months),[7],[8],[10] and two cases did not specify the follow up time [9],[11].

The ages of patients in the included studies ranged from 10 days to 21 years [3],[10]. Pajak et al. 2021 included two patients who were 10 and 14 days old [10]. The average ages of patients included in Al Mosa et al. 2021 was 21 years (±12). The percent of males included in the studies ranged from 56.3% [6] to 76% [5]. Appendix A contains more details on study and patient population characteristics.

Safety Results Discussions

All-cause mortality

Al Mosa et al. reported there were no early or late mortalities in their cohort [3]. In Marathe et al., survival in the 3 conduit groups was as follows: pulmonary homografts - 96% (CI 93%, 98%) at 5 years, 95% (CI 92%, 97%) at 10 years, Contegra conduits - 94% (CI 91%, 97%) at 5 years, 91% (CI 81%, 96%) at 10 years and aortic homografts - 89% (CI 78%, 95%) at 5 years, 89% (CI 78%, 95%) at 10 years [1]. Perioperative and longer-term mortality rates were not reported in any of the remaining retrospective studies. There were no deaths reported among the five case reports. No case reports described long term mortality, as the maximum duration of follow-up among all patients was 18 months.

Adverse events

Short-term adverse events (occurring less than 90 days post-procedure) were not reported in any retrospective studies. One retrospective study reported late adverse events (n=1) [3]. Al Mosa et al. reported late adverse events in 16 (40%) Contegra patients (HR: 1.9; 95% CI: 0.7-4.8; P=.18) [3]. These late adverse events included reintervention, infective endocarditis, and arrhythmia events postoperatively.

Postoperative complications were reported in one case report [10]. Pajak et al. described two cases undergoing staged and primary Yasui operations following Kanter's operative techniques with no complications, although a 10-day old female newborn required reoperation due to a LV-right atrial shunt and was later discharged [10].

Infective Endocarditis

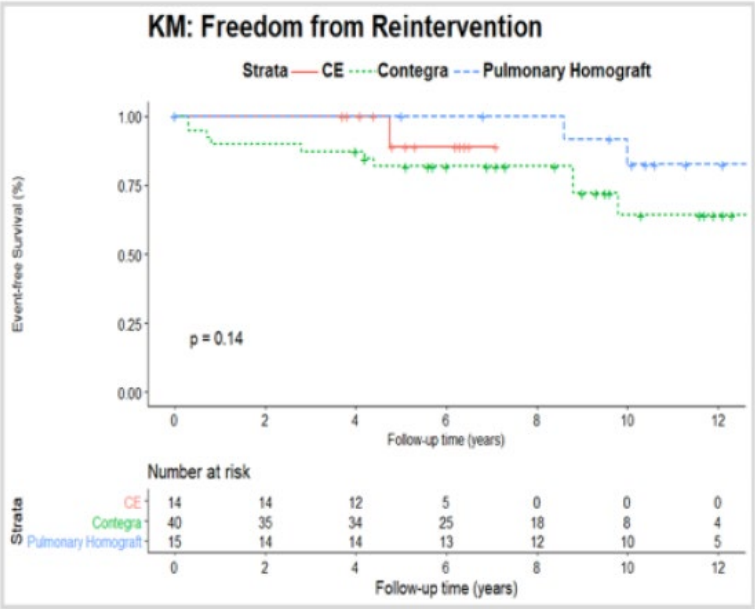
Infective endocarditis (IE) was the most commonly reported outcome in retrospective studies (n=5 studies) [1]-[3],[5],[6]. In Ahmed et al., IE was reported in two (3.2%) Contegra patients [2]. In Al Mosa et al., IE was reported in eight (20%) (HR: 1.7; 95% CI: 0.44-6.3; P=.45) Contegra patients [3]. In Stammnitz et al. 2022, IE occurred in 24 (6%) Contegra patients and Marathe et al. reported IE in 10% of Contegra patients. In two articles, the risk of IE was higher for Contegra compared with homografts (Stammnitz: HR: 5.62; 95% CI: 2.42–13.07; P<0.001 [6]) & (Marathe: OR: 11.06, 95% CI: 3.34, 36.66; p<0.001 [1]). However, according to the study limitations in Stammnitz et al. no exact data on the hemodynamics of the RV-to-PA conduit before IE were available, and differences such as potentially higher flow velocities across the Contegra conduit compared with homografts may be a contributor to different IE rates [6]. Of note in Marathe et al., the procedures were performed by different surgeons in 3 different institutes over 2 decades. The choice of conduit was at the discretion of the surgeon. The original patients of interest (implanted with pulmonary homograft or BJV conduits) exhibited considerable differences on covariates, evidenced by only approximately half the patients being matched on propensity scores [1]. Yakut et al. retrospectively reviewed 47 IE events in 45 patients. Of them, there were 14 episodes of IE reported in Contegra patients (the number of patients with Contegra implants was not reported) [5]. No case reports described infective endocarditis.

Replacement, reintervention, regurgitation, stenosis and thrombosis

Three retrospective studies [1], [3], [4] and three case reports [7], [9], [10] described replacement, reintervention, regurgitation, and stenosis.

One retrospective study reported conduit replacement outcomes (n=1) [4]. Luxford et al. reported one replacement (14.3%) out of seven Contegra patients.

Two retrospective studies reported conduit reintervention (n=2) [1], [3]. In Al Mosa et al., 11 (28%) Contegra patients required reintervention (HR: 3.4; 95% CI: 0.92-13; P=.066). Figure 3B below shows Kaplan-Meier curves for freedom from reintervention for Carpentier-Edwards (CE), Contegra, and pulmonary homograft.



In Marathe et al. 2021, 89 (29%) Contegra patients required reintervention. Freedom from reintervention for Contegra was 74% at 5 years (CI 67-79%) and 37% (25-49%) at 10 years; Contegra conduits were at a greater risk for reintervention ($p<0.001$) compared to pulmonary homografts [1]. A comparison between aortic homografts and BJV conduits demonstrated no difference between the 2 groups with regards to reintervention. Of note, in both the Al Mosa et al. and Marathe et al. articles, Contegra patients were younger at implant and received smaller valves as compared to the comparator valves.

Nair et al. was a case report in which mild stenosis at the origin of the left pulmonary artery was found in one patient which was assessed via repeated computerized tomography (CT) angiography (the timing of follow-up was not specified) [9]. In another case report, LaPar et al., [7] a patient with pulmonary atresia with intact ventricular septum (PA/IVS) was followed for three months after undergoing right ventricle to pulmonary artery (RV-PA) conduit exchange to the 14-mm Contegra conduit device. At the follow up, echocardiography revealed a moderate to severe decrease in right ventricle (RV) systolic function and moderate tricuspid regurgitation (TR). At longer term follow up of 18 months, Pajak et al. described two cases undergoing staged and primary Yasui operations following Kanter's operative techniques who were in good condition, NYHA Class I, but waiting for heart catheterization due to RV-PA distal Contegra stenosis [10].

No retrospective studies reported conduit deterioration or thrombosis outcomes. No case reports described conduit deterioration, reintervention, replacement, or thrombosis outcomes. See Appendix A for more details on outcomes.

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.

This systematic literature review summarizes the reported safety data of the Contegra device for use in pediatric patients published between June 1, 2021 and April 30, 2022. Compared to the results reported in the previous review, infective endocarditis is more prevalent in this review. In the previous report, the association between Contegra and endocarditis was not the main focus of any of the retrospective cohort studies reviewed. Infective endocarditis was the most common outcome in retrospective studies reviewed this year, reported in over half of retrospective studies. Compared to prior year's review, the retrospective studies this year focused on the association between Contegra and IE and provided limited information regarding other adverse events.

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 06/01/21 and 04/30/22 revealed the following observations:

- Infective endocarditis was reported in five studies, although rates varied across studies. Ahmed et al. reported infective endocarditis in only 3.2% of Contegra patients, while Stammintz et al. found that risk of infective endocarditis was higher for Contegra patients (HR: 5.62; 95% CI: 2.42–13.07; P<0.001) compared with homografts [2], [6]. Yakut et al. was focused entirely on infective endocarditis, retrospectively reviewing patients with events. There were 47 events in 45 patients, with over one-third (14 events) occurring in 45 Contegra patients [5].

- Short-term adverse events were not reported in any studies, compared to three the previous year. Only one study, Al Mosa et al., included late adverse events which occurred in 40% of Contegra patients (HR: 1.9; 95% CI: 0.7-4.8; P=.18) [3].

- Statistically significant differences in reintervention rates between Contegra and other conduits was found in one study. Marathe et al. found statistically significant difference in reintervention rates between Contegra and pulmonary homografts. Of the 303 Contegra conduits that were implanted, 89 (29%) Contegra conduits required reintervention. Contegra conduits were at a greater risk for reintervention (p<0.001) compared to PHG [1]. In the same study, a comparison between aortic homografts and BJV conduits demonstrated no difference between the 2 groups with regards to reintervention. This study also has limitations as a retrospective observational study in that the procedures were performed by different surgeons in 3 different institutes over 2 decades, the choice

of conduit was at the discretion of the surgeon, descriptions of 'failed' conduits were subjective and non-standardized, the mode of conduit failure was not evaluated, and there was no uniformity in the anti-coagulation strategies.

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 2023:

- 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: Ahmed et al. 2022[2] **Study Design:** Retrospective cohort study at a single institution **Purpose:** To report the incidence, outcomes, and possible risk factors of endocarditis following TPVR and SPVR where there is a consistent strategy or conduit placement / replacement as well as antibiotic use / prophylaxis for both modes of implantation. **Funding:**	**Number of Patients:** Total: 165 Contegra: 63 (37%) **Median Age Years (SD):** 13 (IQR: 12-21) **Male N (%):** 97 (58.8) **Diagnosis N (%):** Tetralogy of Fallot: 85 (51.5) Truncus arteriosus: 27 (16.3) DORV: 11 (6.7) Pulmonary atresia: 9 (5.5) Other: 33 (20) **Note:** Study included 165 patients with 170 separate PVR procedures; specifically, 107 TPVR and 63 SPVR valves. Contegra valves implanted in 63 patients. Outcomes reported are for Contegra patients only. Patients were retrospectively grouped as IE-positive and IE-negative.	**Intervention:** Contegra **Comparator:** Melody **Median Follow-up Period (IQR):** 29 months (6-62 months) IE-positive: 47 months (10-92 months) IE-negative: 27 months (4-62 months) (p=.22) **Inclusion criteria:** Patients who underwent BJV graft implantation (trans-catheter and surgical) in the pulmonary position from March 1, 2010 to December 31, 2019 at Cincinnati Children's Hospital Medical Center. **Exclusion criteria:** NR	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis N (%):** 2 (3.2) **Conduit deterioration:** NR **Reintervention:** NR **Replacement:** NR
OUS			
Reference: Stammnitz et al. 2022[6] **Country:** Germany **Study Design:** Retrospective review of German NR-CHD database **Purpose:** To identify specific long-term risk factors for IE after percutaneous pulmonary valve implantation or surgical pulmonary valve replacement. **Funding:** Competence Network for Congenital Heart Defects (Federal Ministry of Education and Research /grant number 01GI0601) and the National	**Number of Patients:** Total: 1,170 Contegra: 403 **Median Age Years (IQR):** Total: 12 (5–20) Contegra: 4 (0–9) **Male N (%):** Total: 659 (56.3) Contegra: 242 (60.0) **<18 years N (%):** Total: 792 (67.7) Contegra: 372 (92.3) **Diagnosis N (%):** Tetralogy of Fallot: 376 (32.1) Common arterial trunk: 156 (13.3) Congenital aortic valvar stenosis: 95 (8.1) **Note:** Study included 1,170 patients. There were 403 Contegra patients. Patient characteristics and outcomes reported are for Contegra patients only. There were 445	**Intervention:** Pulmonary valve implantation or replacement **Median Follow-up Period Years (IQR):** Total: 10 (6-10) Contegra: 5 (2-8) **Inclusion criteria:** Included in NR-CHD database; patients and parents/guardians of patients aged <18 years gave written informed consent; CHD with at least 1 SPVR or PPVI before January 1, 2018. **Exclusion criteria:** NR	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis:** 24/403 (6.0) Risk of IE was higher for Contegra (HR: 5.62; 95% CI: 2.42–13.07; P<0.001) compared with homografts. **Conduit deterioration:** NR **Reintervention:** NR **Replacement:** NR

Register for Congenital Heart Defects (Federal Ministry of Education and Research/grant number 01KX2140).	Contegra devices implanted in 403 patients.		
Reference: Al Mosa et al. 2021[3] **Country:** Canada **Study Design:** Retrospective cohort study **Purpose:** To assess the long-term outcome and incidence of adverse events following PVR in repaired Tetralogy of Fallot (rTOF). Specifically, the development of endocarditis and prosthesis failure requiring reintervention. Secondarily, to observe symptomatic improvement and echocardiographic progression postoperatively and how prosthesis choice may impact these parameters. **Funding:** None	**Number of Patients:** Total: 69 in 3 groups 1) Contegra: 40 -18 mm: 4 (10%) -20 mm: 9 (23%) -22 mm: 27 (68%) 2) Pulmonary homograft: 15 3) Carpentier-Edwards: 14 **Mean Age Years (SD):** Overall: 21 Contegra: 16.7 (8.5) **Male N (%):** Total: 43 (62) Contegra: 27 (68) **Diagnosis in Contegra Patients N (%):** TOF: 33 (83) DORV—TOF type: 7 (18) TOF/DORV with pulmonary atresia: 12 (30)	**Intervention:** Contegra **Comparator:** Pulmonary homograft, Carpentier-Edwards **Follow-up Period Years Mean (SD):** Overall 8.5 (4.7) 8.2 (3.3) for Contegra **Inclusion criteria:** Consecutive patients with previously rTOF with maintained RV to pulmonary artery native anatomy who underwent PVR operations from 1990 to 2015; patients with DORV (tetralogy type) and patients with TOF or DORV and pulmonary atresia who were repaired with a TAP and preserved their native RVOT; operated on by the same surgeon. **Exclusion criteria:** Patients with rTOF who had RV to pulmonary artery valved conduit implanted at their primary corrective operation.	**Mortality (all-cause):** 0 **Perioperative Mortality (<90 days post-procedure):** 0 **Mortality (>90 days post-procedure):** 0 **Adverse events (<90 days post procedure):** NR **Late adverse events Overall N (%):** 16 (40) (HR: 1.9; 95% CI: 0.7-4.8; P=.18) **Infective endocarditis N (%):** 8 (20) (HR: 1.7; 95% CI: 0.44-6.3; P=.45) **Conduit deterioration:** NR **Reintervention N (%):** 11 (28) (HR: 3.4; 95% CI: 0.92-13; P=.066) **Surgical redo-PVR only:** 6 (15) **Transcatheter valve implantation:** 7 (18) **Replacement:** NR **Arrythmic events post-PVR:** 7 (18)
Reference: Luxford et al. 2021[4] **Country:** Australia **Study Design:** Retrospective observational study **Purpose:** To review the midterm outcomes of the infant Ross/Ross-Konno procedure with respect to mortality and early morbidity, the need for reintervention, and functional and echocardiographic outcomes including the rate of autograft dilation. **Funding:** NR	**Number of Patients:** Total: 35 Contegra: 7 (20%) **Median Age Days (IQR):** 49 (17-135) **Male N (%):** 28 (80) **Diagnosis N (%):** Congenital heart disease: 12 (34.3) Associated genetic diagnoses: 5 (14.3) **Notes:** The only outcome reported for Contegra specifically was reintervention.	**Intervention:** Ross/Ross-Konno procedure **Median Follow-up Period Years (IQR):** 4.1 (2.6-9.5) **Inclusion criteria:** Underwent a Ross/Ross-Konno procedure at the Children's Hospital at Westmead, Sydney, Australia between January 1995 and December 2018; younger than 12 months of age. **Exclusion criteria:** NR	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis:** NR **Conduit deterioration:** NR **Reintervention:** NR **Replacement:** 1
Reference: Marathe et al. 2021[1] **Country:** Australia **Study Design:** Retrospective multi-center cohort study **Purpose:** To compare the long-term performance of pulmonary	**Patients N (%):** Total: 674 conduits implanted in 586 patients Pulmonary homografts: 305 (45) BJV conduits: 303 (45) Median conduit size mm (IQR): 18.0 (14.0-20.0)	**Intervention:** BJV conduits **Comparator:** Pulmonary homografts, aortic homografts **Follow-up Period Years:** Total: 6.4 (IQR 3.1 to 10.7) Pulmonary homograft: 9.4 (IQR 4.1 to	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR

homografts, BJV conduits, and aortic homografts. **Funding:** None	≤15 mm: 106 (35) >15 mm: 197 (65) Aortic homografts: 66 (10) **Median Age Years (IQR):** Pulmonary homograft: 13.4 (7.3, 16.3) BJV conduit: 3.5 (0.9, 10.4) Aortic homograft: 3.4 (0.5, 10.8) (P <0.001) **Male N (%):** Pulmonary homograft: 188 (62) BJV conduit: 182 (60) Aortic homograft: 36 (55) **Diagnosis N (%) (Pulmonary homograft vs. BJV conduit vs. Aortic homograft):** TOF/PS: 96 (31) vs. 63 (21) vs. 7 (11) PA: 60 (20) vs. 109 (36) vs. 21 (32) AS: 74 (24) vs. 58 (19) vs. 12 (18) Truncus/TGA/DORV/others: 75 (25) vs. 73 (24) vs. 26 (39)	13.6) BJV conduit: 4.7 (IQR 2.4 to 6.9) Aortic homograft: 10.1 (IQR 4.3 to 12.4) **Inclusion criteria:** Patient age at time of surgery: 1 day to 20 years; Date of surgery between January 1, 2000 to December 31, 2018; prosthesis implanted: Homograft (aortic or pulmonary) or bovine jugular vein conduit (Contegra) implanted between the right ventricle and pulmonary arteries; congenital heart disease requiring primary valve implantation or reoperation for pulmonary valve replacement **Exclusion criteria:** Age at surgery outside the inclusion criteria; any other valve type (mechanical valves, xenografts, stented or stentless bioprosthetic valves); location of implantation outside stipulated study locations.	**Infective endocarditis:** 10% BJV conduits more likely to be affected by infective endocarditis (OR: 11.06, 95% CI: 3.34, 36.66; p<0.001) compared to pulmonary homografts. **Conduit deterioration:** NR **Reintervention N (%):** 89 (29) BJV conduits were at a greater risk for reintervention (p<0.001) compared to pulmonary homografts. **Replacement:** NR
Reference: Yakut et al. 2021[5] **Country:** Turkey **Study Design:** Retrospective chart review at a single center **Purpose:** To present the risk factors, clinical and laboratory findings, treatment management, and risk factors for morbidity and mortality of pediatric patients with IE at a single center. **Funding:** None	**Number of Patients:** Total: 45 47 IE events in 45 patients **Mean Age Years (SD):** 7.6 (4.7) (range: 2.4 months to 16 years) **Male N (%):** 34 (76) **Diagnosis N (%):** CHD: 41 (87.2) of 47 IE events **Note:** IE was the only outcome reported specific to Contegra patients. Number of Contegra patients was not reported.	**Intervention:** NR **Follow-up Period:** NR **Inclusion criteria:** Patients aged ≤ 18 years diagnosed with definite/possible IE episodes according to the modified Duke criteria; followed up at study clinic between May 2000 and March 2018. **Exclusion criteria:** NR	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis:** 47 events in 45 patients; 14 episodes occurred in Contegra patients. Mean time from previous surgery and/or therapeutic intervention and IE attack was 4.5±3.7 years (range: 3.6 months to 13 years). **Conduit deterioration:** NR **Reintervention:** NR **Replacement:** NR

Abbreviations: AHG: aortic homograft; APV: absent pulmonary valve; AVSD: atrioventricular septal defect; BJV: bovine jugular vein; CPV: composite porcine valve; DORV: double outlet right ventricle; IE: infective endocarditis; IQR: interquartile range; MAPCA: major aortopulmonary collateral artery; NR: not reported; NR-CHD: National Register for Congenital Heart Defects; PA: pulmonary atresia; PDA: patent ductus arteriosus; PHG: pulmonary homograft; PS: pulmonary stenosis; PV: pulmonary valve; PVR: pulmonary valve replacement; RVOTR: right ventricular outflow tract reconstruction; RV-PA: right ventricle to pulmonary artery; RVPAC: right ventricle to pulmonary artery conduit; RCT: randomized control trial; SD: standard deviation; SVD: structural valve degeneration; SPVR: surgical pulmonary valve replacement; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; TPVR: trans-catheter pulmonary valve replacement; TVD: tricuspid valve dysplasia.

Study Characteristics and Outcomes of Case Studies (n=5)			
Study Details	**Patients**	**Intervention(s)**	**Safety Outcomes Assessed**
US Case Reports			
Reference: LaPar et al. 2021[7] **Country:** USA **Study Design:** Case report **Purpose:** To describe the cone tricuspid valvuloplasty technique to achieve a biventricular circulation in a neonate with PA/IVS and an Ebsteinoid TV **Funding:** NR	**Patient(s) (N):** 1 **Age, months:** 9 **Sex:** Male **Diagnosis:** Trisomy 21, Pulmonary atresia with intact ventricular septum (PA/IVS)	**Intervention:** RV-PA conduit exchange to a 14-mm Contegra (Medtronic, Minneapolis, MN) **Comparator:** n/a **Follow-up Period:** 3 months (at 12 months of age) **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** moderately to severely decreased RV systolic function, moderate tricuspid regurgitation (TR) **Infective endocarditis:** NR **Conduit deterioration:** "patent RV-PA conduit" demonstrated by echocardiography **Reintervention:** NR **Replacement:** NR
OUS Case Reports			
Reference: Maddali et al. 2021[8] **Country:** Oman **Study Design:** Case report **Purpose:** To highlight the role of intraoperative bronchoscopy in providing guidance for obtaining optimal bronchial decompression that was achieved by an initial pulmonary arteriopexy followed by an aortopexy. **Funding:** None	**Patient(s) (N):** 1 **Age, months:** 4 **Sex:** Male **Diagnosis:** Tetralogy of Fallot, absent pulmonary valve (APV) and 1q21.1 chromosomal microdeletion	**Intervention:** intracardiac repair on hypothermic cardiopulmonary bypass involving implantation of 14 mm glutaraldehyde-preserved valve-containing bovine jugular vein graft [Contegra, Medtronic Inc., Minneapolis MN, USA] **Comparator:** n/a **Follow-up Period:** 6 weeks and 6 months **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis:** NR **Conduit deterioration:** NR **Reintervention:** <u>At 1 month:</u> the right bronchus showed adequate patency thereby avoiding any surgical or cardiological re-intervention (confirmed by computerized tomography (CT)) **Replacement:** NR <u>At 6 weeks:</u> confirmed by CT "complete relief of the previously noted narrowing of the distal trachea as well as narrowing of the proximal right and left mainstem bronchi" [See Figure 1b in original paper]. <u>At 6 months:</u> no airway compromise
Reference: Nair et al. 2021[9] **Country:** India **Study Design:** Case report **Purpose:** To report the successful surgical repair of an unusual case of a pulmonary dominant trunk in the absence of coarctation or interruption, despite some degree of hypoplasia of the ascending aorta.	**Patient(s) (N):** 1 **Age, days:** 23 **Sex:** NR **Diagnosis:** common arterial trunk, pulmonary dominant trunk with mild aortic hypoplasia	**Intervention:** 12 mm Contegra pulmonary valved conduit (Medtronic, MN, USA) **Comparator:** n/a **Follow-up Period:** NR **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis:** NR **Conduit deterioration:** NR **Reintervention:** NR **Replacement:** NR <u>Note:</u> Postoperative echocardiogram (time not indicated) showed an intact ventricular septal patch

Funding: None			and smooth flow into the conduit and pulmonary arteries. Repeated CT angiography revealed mild stenosis at the origin of the left pulmonary artery.
Reference: Pajak et al. 2021[10] **Country:** Poland **Study Design:** Case report **Purpose:** To report on two cases of newborns with staged and primary Yasui operation following Kanter's operative Techniques. **Funding:** NR	**Patient(s) (N):** 2 **Age, days:** Case 1: 10 days Case 2: 14 days **Female N (%):** 2 (100) **Diagnosis:** Case 1: D-malposition of the great arteries, double outlet right ventricle (DORV, Taussig-Bing type), subaortic stenosis, sub pulmonary VSD, IAA (type A) and patent arterial duct Case 2: LVOTO (conal septum posterior malalignment), large VSD, atrial septal defect (ASD), IAA (type B) with a retroesophageal right subclavian artery and patent arterial duct	**Intervention:** Case 1: 12 mm valved conduit Contegra with a bovine jugular vein (Medtronic Inc, MN, USA) *Note: primary Yasui correction in cross-clamp circulation with deep hypothermia* *Case 2: 14 mm pulmonary valved conduit* Contegra *Note: staged repair beginning with aortic arch reconstruction and then Yasui correction with the Rastelli-type procedure was performed with VSD closure at 8 months with 14 mm pulmonary valved conduit (Contegra)* **Comparator:** n/a **Follow-up Period:** 18 months **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis:** NR **Conduit deterioration:** NR **Reintervention:** NR **Replacement:** NR Case 1: post-operatively required reoperation due to LV-right atrial shunt, patient was discharged in good condition At 18 months: Both cases were in good condition (NYHA, Class I)
Reference: Sobh et al. 2021[11] **Country:** Germany **Study Design:** Case report **Purpose:** To report a rare association of common arterial trunk with left pulmonary artery sling and highlight the importance of cross-sectional imaging in complex congenital cardiac lesions. **Funding:** None	**Patient(s) (N):** 1 **Age, months:** 20 **Sex:** female **Diagnosis:** Surgical correction of the pulmonary sling and change of the right ventricular to pulmonary artery conduit to a bigger size was performed *Note: Cardiac catheterization and bronchoscopy were performed at 18 months of age. The patient had an enlarged and hypertrophied right ventricle with normal function; moderate conduit stenosis and moderate*	**Intervention:** explantation of the RV-PA conduit and replaced with a 14-mm Contegra graft **Comparator:** n/a **Follow-up Period:** NR **Inclusion criteria:** n/a **Exclusion criteria:** n/a	**Mortality (all-cause):** NR **Perioperative Mortality (<90 days post-procedure):** NR **Mortality (>90 days post-procedure):** NR **Adverse events (<90 days post procedure):** NR **Infective endocarditis:** NR **Conduit deterioration:** NR **Reintervention:** NR **Replacement:** NR *No adverse events reported after implantation of Contegra conduit.*

	conduit insufficiency (via echocardiography). Tracheal stenosis and severe left main bronchial stenosis was found via bronchoscopy. Ectasia of the pulmonary artery bifurcation was also found and thought to be the reason for the bronchial stenosis.		

Abbreviations: APV: absent pulmonary valve; BJV: bovine jugular vein; CT: computerized tomography; IAA: interrupted aortic arch; IE: infective endocarditis; NR: not reported; SD: standard deviation; PA/IVS: Pulmonary atresia with intact ventricular septum; SVD: structural valve degeneration; TR: tricuspid regurgitation.