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Coronary anomalies in tetralogy of Fallot – A meta-analysis

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ABSTRACT

Background: An anomalous coronary artery is reported in 2% to 23% of patients with tetralogy of Fallot (TOF). Knowledge of coronary anatomy prior to corrective surgery is vital to avoid damage to vessels crossing the right ventricular outflow tract (RVOT). A meta-analysis on the prevalence of anomalous coronary arteries in TOF is lacking to date. Here, an overview of coronary anomalies in TOF is provided and implications for patient management are discussed.

Methods: PubMed, Embase and Web of Science were searched. Analysis was done using Revman 5.3 (Cochrane Community, London). The primary analysis focused on the origin and proximal course of the right and left coronary arteries. In addition, the prevalence of large conus arteries and coronary arteriovenous fistulas (CAVF) was calculated.

Results: Twenty-eight studies, encompassing 6956 patients, were included; 6% of TOF patients have an anomalous coronary artery. Hereof, 72% cross the RVOT; the majority of the remaining 28% courses behind the aorta. Six percent of patients have a large conus artery and 4% a CAVF. Other coronary anomalies include a left or right coronary artery from the pulmonary trunk or left or right pulmonary artery, coronary tree hypoplasia and anastomoses between coronary and bronchial arteries.

Conclusions: The prevalence of coronary anomalies in TOF is 4–6%. In patients with an anomalous coronary artery, 72% cross the RVOT. The combined risk of encountering an anomalous coronary artery or a large conus artery crossing the RVOT is 10.3%. Coronary anatomy should be defined before surgery and the surgical approach adapted accordingly.

1. Introduction

Congenital heart disease is the most common congenital defect with an estimated prevalence of 9/1000 live births. However, significant geographical differences exist in prevalence, ranging from 1.9/1000 livebirths in Africa to 9.3/1000 live births in Asia [1]. Of patients with congenital heart disease, around 5% presents with tetralogy of Fallot (TOF) [1]. In TOF, morphological anomalies consist of a ventricular septal defect, overriding aorta, pulmonary stenosis and right ventricular hypertrophy as secondary feature [2]. Anomalous coronary arteries (ACA) as part of the spectrum of congenital heart disease have been described since the 1960's [3]. Since then, many reports have described the embryologic development and the clinical relevance of different anomalies, including the prevalence of ACA in congenital heart disease. An anomalous origin of a coronary artery is more common in patients with TOF than in the general population with a prevalence reported between 2% and 23% [4,5] as opposed to ≤1% in the general population [6,7]. As in the general population, not all variations of ACA are of equal clinical importance. In TOF, vessels crossing the right ventricular outflow tract (RVOT) are the most relevant (Supplemental Fig. 1). Cases are described where knowledge of an ACA crossing the RVOT prior to surgery was lacking and did not become clear during surgery, causing it to be damaged, followed by myocardial infarction or patient demise [3,8–11]. A potentially complicating factor for the delineation of the coronary anatomy is that TOF is associated with a counterclockwise rotation (when viewed from above) of the aortic root (from below, as on CT-scan, the rotation is clockwise). This results in a more anterior position of the right coronary sinus (Supplemental Fig. 1) [9].

Abbreviations: TOF, tetralogy of Fallot; ACA, anomalous coronary artery; RVOT, right ventricular outflow tract; CAVF, coronary arteriovenous fistula; CI, confidence interval.

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Many reports on coronary anatomy in TOF exist, however a meta-analysis comparing current knowledge on the prevalence of ACA is lacking to date. We aim to provide a meta-analysis of the true prevalence of coronary anomalies in TOF, presenting a structured overview of anatomical variants encountered and implications for patient management.

2. Methods

The study was executed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [12] (details in 'Supplementary Data A'). PubMed, Embase and Web of Science were searched (see 'Supplementary Data B' for search strategy). No time period restrictions were applied. Papers in English and French were included. After removal of duplicates, all titles and abstracts were screened for usefulness for review and meta-analysis. Studies found eligible for meta-analysis were retrospective and prospective cohort and case series studies describing the coronary anatomy in the entire anatomical spectrum of TOF. Case reports and case studies were excluded due to selection bias if used for analysis. No studies were excluded based on methods used for defining coronary anatomy (e.g. post-mortem examination, coronary angiography, computed tomography (CT)-scan etc.). After screening all full texts of the eligible studies for the presence of clear descriptions of the coronary origins and preferably also a proximal course of the ACA, the final selection for analysis was made (Fig. 1).

The analysis focused primarily on the origin and proximal course of the main coronary arteries: the right coronary artery (RCA) and left coronary artery (LCA), which branches into the left anterior descending artery (LAD) and left circumflex artery (LCx). Included were coronary arteries originating from the contralateral coronary artery or sinus of Valsalva (including accessory LAD's) and solitary coronary arteries (see 'Supplemental Fig. 2' for examples). These are the anomalies with the potentially largest clinical impact if not adequately identified and were grouped for analyses as 'ACA'. During review of the ACA, it was noticed that larger than normal conus arteries and coronary arteriovenous fistulas (CAVF) were also systematically described in several studies [5,10,13–25]. The conus artery (also called infundibular artery) is the first anteriorly departing branch of the RCA; it may also originate from a separate ostium in the right sinus of Valsalva (Supplemental Fig. 3). A large conus artery is considered a normal variation rather than a coronary anomaly. Large conus arteries and CAVF were added to the analyses (Fig. 1). A large conus artery was defined as being of the same diameter as or larger than the RCA and supplying the RVOT. CAVF was defined as an anomalous connection between a coronary artery and another cardiac compartment (e.g. right atrium) or great artery.

Using Microsoft Excel, the coronary anomalies described in each included study were divided per ACA into 1) origin and 2) proximal course, if described. Also, diagnostic methods (coronary angiography, echocardiography, CT-scan, per operative observations or post mortem autopsy) were described and any additional anatomic abnormalities other than the ACA were noted. For every artery not described in the included papers, it was assumed to follow its normal course. Large conus arteries and CAVF were scored separately. For analysis Revman 5.3 (Cochrane Community, London) was used. First, meta-analyses for the overall prevalence of ACA and, as subgroup analysis, the proportion hereof that crosses the RVOT were conducted. Standard errors were calculated per study using the prevalence of ACA described in decimals. The statistical method used to combine inferences across studies was the generic inverse variance approach (see Revman 5.3). Random effects analysis was applied because of presence of heterogeneity (I^2 = 71–97%). When the prevalence was 1 or 0, prevalence with its confidence intervals could not be estimated so 0.99 and 0.01 were used respectively. For analysis, weight was assigned to each study by the statistical program based on the standard error and size of the study population. The same methods were used for analyses of large conus arteries and CAVF.

3. Results

3.1. Eligible studies for meta-analysis (Fig. 1)

3.1.1. ACA

Twenty-eight studies were included for analysis of the prevalence of ACA. Hereof, 20 studies were included for the analysis of ACA crossing the RVOT. Six studies [14,18,23,26–28] were excluded because they did not report the number of arteries crossing the RVOT. The other two studies [29,30] were excluded because of very small numbers (n = 2 and n = 1 resp.) of ACA.

3.1.2. Large conus arteries and CAVF

Thirteen studies of the initial 28 were included for the analysis on large conus arteries. Thirteen studies did not report on large conus arteries, two studies that did find large conus arteries were excluded because the number of conus arteries was not further defined [9,15].

For CAVF, 5 studies of the initial 28 were found eligible for analysis. The excluded 23 studies did not report on the presence of CAVF.

3.2. Prevalence

3.2.1. ACA

The overall prevalence of ACA in TOF is 6% (confidence interval (CI): 5–7%, Fig. 2) based on 6956 patients from the combined studies. Seventy-two percent (CI: 59–86%, Fig. 3) of ACA cross the RVOT, in a total of 262 patients. In most cases an LAD originating from the RCA or right sinus of Valsalva was the artery crossing the RVOT. Solitary coronary arteries from either the right or left sinus of Valsalva and anomalous LCx' have also been described crossing the RVOT [4,13–16,18,24,31,32]. Branches of a solitary coronary artery can take multiple courses after take-off as shown by Dabizzi et al. [16]. In this study a solitary coronary artery originating from the right coronary sinus was found with the RCA following its normal course, the LAD coursing over the RVOT and de LCx taking an interarterial course. Rarely encountered, but also described are solitary coronary arteries originating from the non-facing sinus by Kervancioglu et al. [13] (2 cases in 607 patients (0.3%), both crossing the RVOT).

An accessory LAD was described separately in 8 studies, constituting 31% (CI: 24–38%) of encountered ACA in 233 patients [5,13,14,17,19,20,25,33]. In 6 of these 8 studies a wide range is described for these vessels crossing the RVOT (0–100%) and accessory LAD's accounted for 0–50% of all vessels crossing the RVOT [5,13,17,20,25,33]. If the accessory LAD did not cross the RVOT, in 2 cases it was described to course below it [5,33], in other cases this was not further specified.

The majority of the remaining 28% of ACA follow a retro-aortic course. This course was described in several studies for an anomalous RCA and LCx, but not for an anomalous LAD [9,13,15–17,19,22,34]. Origins of these variations are described from the contralateral sinus and contralateral coronary artery, but not further specified in most studies.

Overall, there is a 4.3% chance that a patient has an ACA crossing the RVOT.

3.2.2. Large conus arteries and CAVF

Six percent (CI: 4–9%, Fig. 4) of patients can be expected to have a large conus artery based on meta-analysis of 2781 patients.

The estimated overall prevalence of CAVF based on 2516 patients is 4% (CI: 2–6%). The majority of the CAVF form a connection between a coronary artery and the pulmonary artery. It was not further specified whether the term "pulmonary artery" referred to the pulmonary trunk (main pulmonary artery) or to the right or left pulmonary artery. Also, connections between a coronary artery and the right atrium [15,16], ventricles [13] or right atrial appendage [5] have been described.

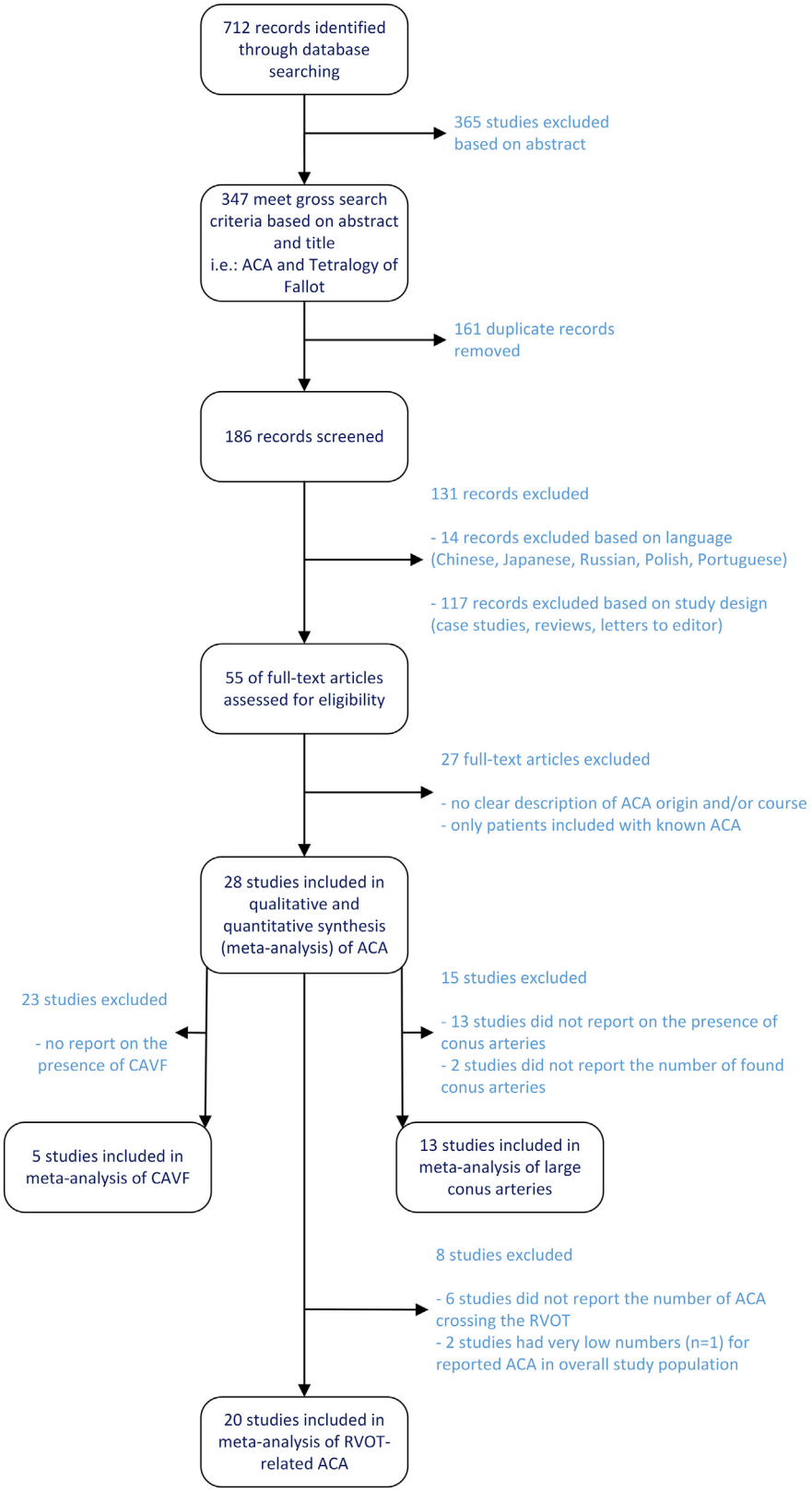

Fig. 1. Flow diagram of study inclusion. ACA = anomalous coronary artery, CAVF = coronary arteriovenous fistula, RVOT = right ventricular outflow tract.

3.2.3. Other coronary anomalies in TOF

Other coronary anomalies described in TOF are an anomalous LCA, RCA or both from the pulmonary sinus, trunk or arteries [4,25,35–45]. In the present study, 8 cases of an RCA from the pulmonary trunk were observed [4,25,35,37,42–45]. In 1 case the anomalous RCA arose from the anterior pulmonary sinus [45]. In two cases the patient had a total anomalous origin of the coronary arteries from the pulmonary trunk [35,37]. In the first, both arteries originated from the pulmonary

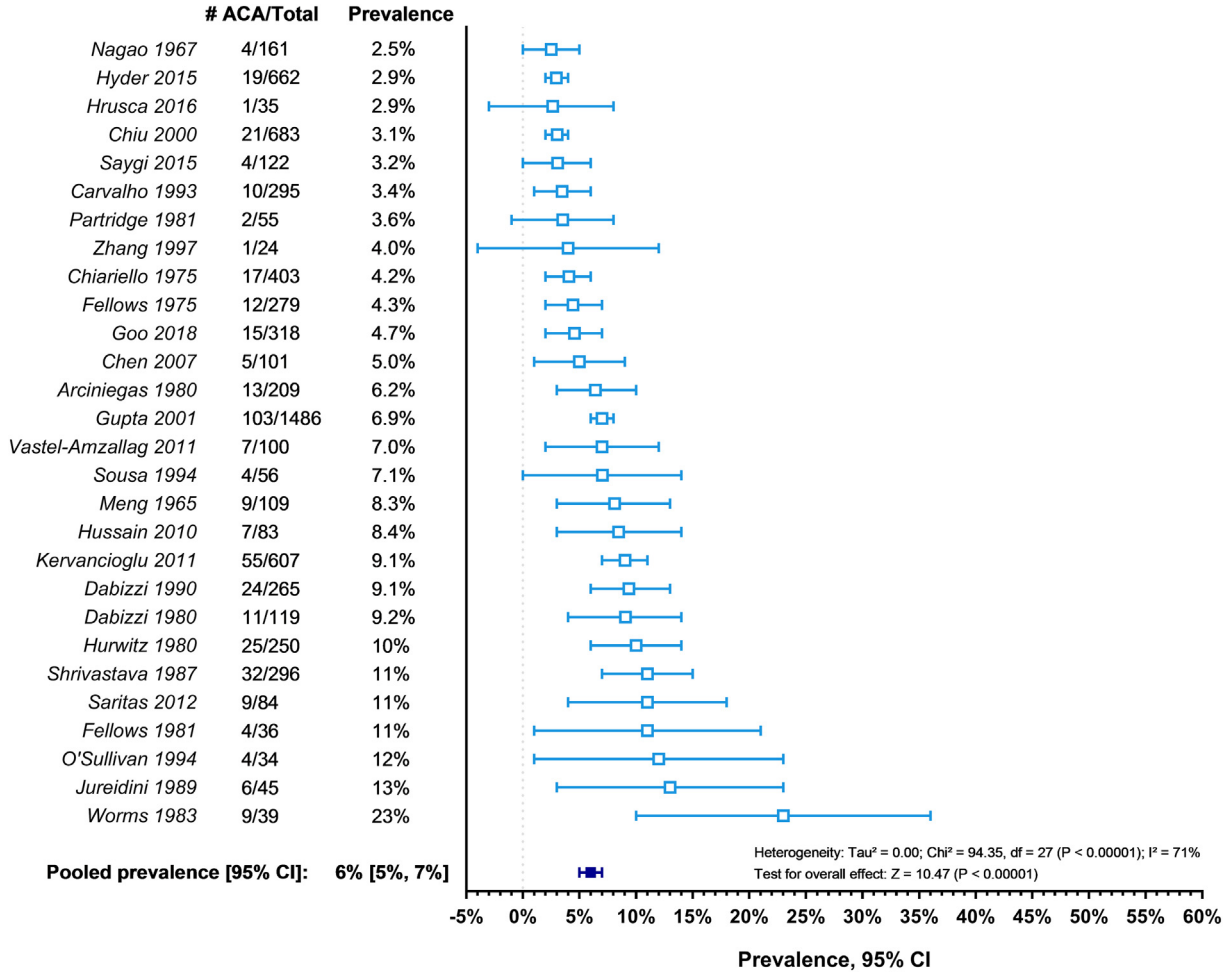

Fig. 2. Overall prevalence of ACA in tetralogy of Fallot [4,5,9,10,13–31,33,34,50,51,55]. ACA = anomalous coronary artery.

valve sinuses [35], in the second, both coronary arteries arose above the pulmonary sinus from the pulmonary trunk [37]. Also, cases with hypoplasia of the entire coronary tree and anastomoses between coronary and bronchial arteries have been described [15,16].

4. Discussion and clinical implications

Key findings in this meta-analysis of coronary artery anomalies in TOF are: 1) The overall prevalence of coronary anomalies in TOF is 4–6%. 2) In patients with an ACA, 72% of the anomalous arteries cross the RVOT and 3) The risk of encountering an ACA or large conus artery crossing the RVOT is 10.3%.

Different methods of visualization of the coronary anatomy were used in the included studies, with coronary angiography as the main tool. Quite remarkable results are from Worms et al. [5], reporting a prevalence of 23% of ACA in TOF. Since no other study in the analysis approaches this number, possibly some selection bias was involved. Due to the low number of included patients, its weight in the analysis was low and did not change the results significantly. The use of CT-scan provided a smaller range of reported ACA than coronary angiography (2.8–7% versus 1.2–10% resp.). The same applies to conus arteries (1.6–24% versus 0–40%). CT-scan thus appears the more accurate imaging modality. However, it must be noted that fewer studies were based on CT-scan than on coronary angiography (4 versus 19). Fistulas were only reported in articles using coronary angiography, so no comparison on accuracy could be made. Transthoracic echocardiography was used in one study [20] and found the same prevalence of ACA and conus arteries as coronary angiography. However, transthoracic echocardiography is known to be dependent on the patients' physique. Jureidini et al. [20] accordingly report for two adolescents that the transthoracic echocardiography images were inadequate to visualize the coronary artery anatomy. Concordance rate between coronary angiography and surgery was 50–100% [9,22,31,33] and between CT-scan and surgery 92.1–100% [17,23,24]. Six studies found additional anomalies during surgery or defined the anatomy differently than described before based on coronary angiography or CT-scan [4,5,17,26,31,33]. In two cases this resulted in damage of the coronary anomaly [4,5]. No studies have been found comparing coronary angiography and CT-scan directly.

As a result of their size, large conus arteries supply a larger area than usual, making them an important factor to consider when scheduling surgery. Variants have been described that reach the apex of the heart [15,16,19]. Especially these variants might complicate differentiating between an extraordinary large conus artery and an accessory LAD. Due to this, our estimation of 6% might be lower than the actual prevalence, because conus arteries might have been diagnosed as accessory LAD's in several studies. Dabizzi et al. [16] described that a large conus artery can resemble an accessory LAD on coronary angiography, especially in the anteroposterior projection. In the study group of 1486 consecutive patients from Gupta et al. [14], none had a large conus artery, but an accessory LAD was present in 27 patients (1.8%). It seems unlikely that with an expected prevalence of 6% according to our calculation no large conus arteries were observed in such a large cohort. Possibly some of the accessory LAD's described by Gupta et al. [14] are actually large conus arteries. The main difference between the two

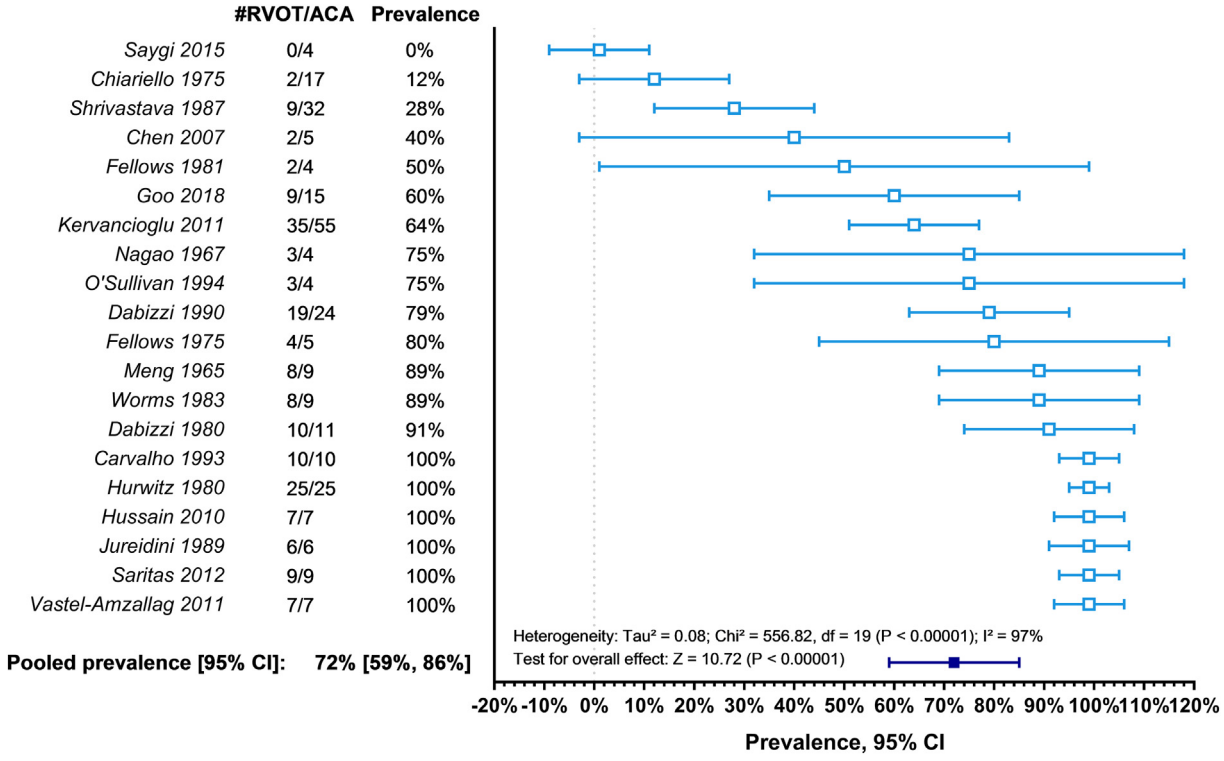

Fig. 3. Prevalence of ACA crossing the RVOT [4,5,9,10,13,15–17,19–22,24,25,31,33,34,50,51,55]. RVOT = right ventricular outflow tract, ACA = anomalous coronary artery.

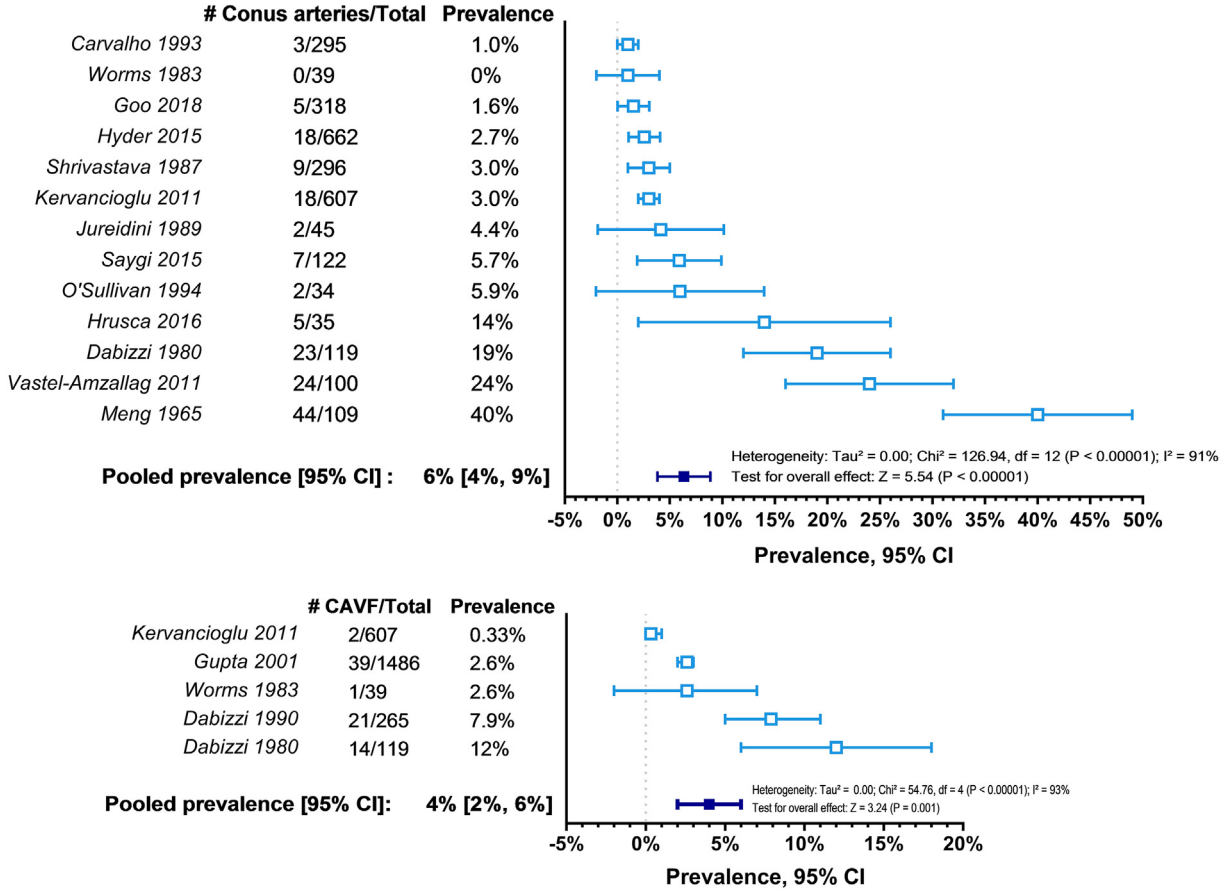

Fig. 4. Prevalence of large conus arteries and CAVF [5,10,13–25]. CAVF = coronary arteriovenous fistula.

vessels is that the conus artery does not follow the interventricular groove in contrast to the LAD [46]. When using coronary angiography to differentiate, the best option according to Li et al. [46] is using the straight lateral view and not only a laid-back view on which the courses of these two arteries might look very similar. The presence of septal branches should also help to identify an ACA crossing the RVOT as an LAD rather than a large conus artery. However, it is described by Dabizzi et al. [16] that the first septal branch in most patients with an LAD arising from the RCA is absent, thus possibly complicating the correct interpretation of coronary angiography images when using the presence of septal branches as a criterium.

4.1. Study limitations

One limitation of this study is that only PubMed, Embase and Web of Science were searched. It is possible that articles in other databases are omitted that would have been included had they been present in one of these databases. Not all studies contain consecutively included patients, leaving potential for selection bias.

4.2. Clinical implications

In many cases the coronary anatomy can be easily delineated at inspection of the cardiac surface during surgery. However, inspection is complicated if the course of the vessels is intramyocardial, deeply embedded in epicardial fat or at reoperation due to scar tissue. Knowledge of coronary anatomy prior to (re)operation of TOF is relevant for the surgical strategy to avoid damage of an artery crossing the RVOT. CT-angiography is considered a suitable tool to visualize an ACA [6,7,24]. After comparison of the literature it appears more accurate than coronary angiography, with a concordance rate compared to surgery of >92% [17,23,24]. Given also that a CT-scan is non-invasive, CT-angiography should be considered before coronary angiography. However, physicians might be apprehensive using CT-scan as primary assessment tool because of radiation exposure, especially in children. Yet, with improving techniques the radiation doses are declining. Alternatively, transthoracic echocardiography and Magnetic Resonance Imaging (MRI) can both be used [7]. In adults, echocardiography is not routinely used for imaging of the coronary anatomy, because of the lower spatial resolution of transthoracic echocardiography compared to CT or MRI [6]. Also, the acoustic windows are often suboptimal in adult patients and very dependent on the patients' physique [6,20]. For (small) children however, transthoracic echocardiography can be the first choice to detect abnormal coronary arteries in TOF. Zeppilli et al. [47] showed that for coronary artery screening in athletes (mean age 30 ± 12 years) satisfactory transthoracic echocardiograms could be obtained in 90% of cases, suggesting that transthoracic echocardiography can be adequately performed in adults. It must be noted however that athletes usually have good acoustic windows. When there is suspicion of any coronary anomaly and transthoracic echocardiography images provide insufficient information, an additional CT or MRI-scan should be considered [48]. The coronary artery visibility can be influenced by several factors such as heart rate, body size and the size of the coronary arteries [17,34]. An MRI has a lower accuracy than CT-angiography both in adults and in children. Also, it is not advised for young children due to the necessity of sedation for the majority of young children (<7 years) [6,7] and for patients with a pacemaker.

Large differences in prevalence of CAVF were observed between the included studies, indicating that the diagnosis of fistulas is difficult. However, CAVF are not clinically important per se. Large (audible) fistulas are advised to close regardless of symptoms, because of the risk of myocardial ischemia by shunting and the consequences of ischemia, e.g. ventricular dysfunction and arrhythmias [49]. Closure can be done surgically or by transcatheter intervention [49]. Small to moderate fistulas only need closing when a patient presents with symptoms indicative of myocardial ischemia or when cardiac morphologic adjustments (such as dilation of cardiac compartments) due to shunting develop. CAVF can increase in diameter over time and will need follow up every 3–5 years [49].

An ACA can pose difficulties for surgery of the pulmonary stenosis in TOF. The artery might be damaged when incising the RVOT and it is important to know beforehand if the surgical approach has to be adapted to the coronary anatomy. An ACA crossing the RVOT prohibits transannular patch augmentation. Thus, if the pulmonary valve annulus is too small and must opened, other techniques should be used. The first option uses separate approaches through incision of the main pulmonary artery and right ventriculotomy, then the valve annulus can be opened, and a patch can be inserted under the ACA. The second option is to use a right ventricle to pulmonary trunk conduit reconstruction, an option that makes it possible to spare the pulmonary valve [21,24,27,50]. A third option is the double outflow or main pulmonary artery reverse flap technique. With this technique, a flap is created from the pulmonary trunk and folded backwards, so it traverses the coronary artery. The proximal part of the flap is then sutured to the basal side of the ventriculotomy. Autologous or xenograft pericardium can be used to complete the tract. With this technique it is also possible to spare the pulmonary valve. To be able to use this technique adequately, the patient must have a non-hypoplastic main pulmonary artery [51,52]. Another option is a transatrial and transpulmonary approach. Through the atrial incision muscular resection of the proximal part of the RVOT obstruction can be done. Transpulmonary, the pulmonary trunk can be enlarged with a patch. Using this approach Pontailler et al. [53] succeeded in 53% of cases to spare the pulmonary valve annulus. It is advised to wait with total repair of TOF until the child is at least 8 kg to make surgery technically easier. A Blalock shunt can help to temporize complete repair [21,24,27,28,51].

Despite proper preparation, inadvertent damage of an (anomalous) coronary artery might occur. In these cases, emergency bypass grafting or re-anastomosis to the aorta of the distal end of the severed artery are effective techniques to restore the blood circulation [8,11,54].

The coronary artery following a retro-aortic or septal course is usually benign and correction is in most cases not required [6,7]. Coronary arteries following an interarterial course are potentially malignant and pose a risk of sudden cardiac death during exercise. This variation should be examined for additional characteristics that increase the risk of sudden cardiac death, such as an intramural course and slit-like ostium. If the coronary course is deemed malignant, correction should take place. This is often done by unroofing of the intramural part of the coronary artery or ostioplasty [6,7].

Surgical correction of an anomalous origin of a coronary artery from the pulmonary sinus, trunk or left or right pulmonary artery is advised. This can be done by reimplantation of the coronary arteries into their respective sinus of Valsalva or through a baffle reconstruction (Takeuchi repair) [37,39,41].

5. Conclusions (see also the graphical abstract)

In conclusion, 6% (CI: 5–7%) of TOF patients have an ACA. Of these, 72% (CI: 59–86%) cross the RVOT. In most cases this is an anomalous LAD originating from the RCA or right sinus of Valsalva. Overall, the possibility of the presence of an ACA that crosses the RVOT is 4.3%. Large conus arteries are seen in 6% (CI: 4–9%) of cases, making the total prevalence of surgically relevant arteries crossing the RVOT 10.3%. CAVF are seen in 4% (CI: 2–6%) of Fallot patients and usually do not require intervention. To adequately visualize the coronary arteries different imaging modalities can be used. A CT-angiography is in most cases preferred and has the highest accuracy, but in order to avoid radiation exposure transthoracic echocardiography can be an adequate primary survey method in children as well.

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CRediT authorship contribution statement

Claire J. Koppel: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization. **Monique R.M. Jongbloed:**Conceptualization, Writing - review & editing, Supervision.**Philippine Kiès:**Writing - review & editing.**Mark G. Hazekamp:**Writing - review & editing.**Bart J.A. Mertens:**Methodology, Formal analysis, Writing - review & editing.**Martin J. Schalij:**Writing - review & editing.**Hubert W. Vliegen:**Conceptualization, Writing - review & editing, Supervision.

Declaration of competing interest

None.

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