GREAT ORMOND STREET HOSPITAL

Kawasaki disease as we don't know it

Dr Filip Kucera

INTRODUCTION

- Leading cause of acquired heart disease (developed world)
- Unknown cause
- Seasonal variations and clustering
- Genetic component of the disease
- Coronary artery aneurysms in 19%

  (39% patients < 12 months)

1. Can Kawasaki disease be only diagnosed clinically ?

CLINICAL FEATURES

Classic (typical) KD

- Minimum of 3-5 days of fever together with ≥ 4 of the 5 major clinical criteria including
  - Rash
  - Non-purulent conjunctivitis
  - Oral changes (red, cracked lips, strawberry tongue)
  - Changes in the extremities (swelling and erythema of the hands and feet)
  - Cervical lymphadenopathy

Incomplete (atypical) KD

- Minimum of 3-5 days of fever together with < 4 of the above 5 major clinical criteria

- Major clinical criteria may not develop at the same time.
- BCG scar reactivation is often present.
- Echocardiographic diagnosis of coronary aneurysms confirms the diagnosis of KD.

Circulation
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https://doi.org/10.1161/CIR.0000000000000484

AHA SCIENTIFIC STATEMENT

Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association

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BACKGROUND: Kawasaki disease is an acute vasculitis of childhood that leads to coronary artery aneurysms in ≈25% of untreated cases. It has been reported worldwide and is the leading cause of acquired heart disease in children in developed countries.

METHODS AND RESULTS: To revise the previous American Heart Association guidelines, a multidisciplinary writing group of experts was convened to review and appraise available evidence and practice-based opinion, as well as to provide updated recommendations for diagnosis, treatment of the acute illness, and long-term management. Although the cause remains unknown, discussion sections highlight new insights into the epidemiology, genetics, pathogenesis, pathology, natural history, and long-term outcomes. Prompt diagnosis is essential, and an updated algorithm defines supplemental information to be used to assist the diagnosis when classic clinical criteria are incomplete. Although intravenous immune globulin is the mainstay of initial treatment, the role for additional primary therapy in selected patients is discussed. Approximately 10% to 20% of patients do not respond to initial intravenous immune globulin, and recommendations for additional therapies are provided. Careful initial management of evolving coronary artery abnormalities is essential, necessitating an increased frequency of assessments and escalation of thromboprophylaxis. Risk stratification for long-term management is based primarily on maximal coronary artery luminal dimensions, normalized as *Z* scores, and is calibrated to both past and current involvement. Patients with aneurysms require life-long and uninterrupted cardiology follow-up.

CONCLUSIONS: These recommendations provide updated and best evidence-based guidance to healthcare providers who diagnose and manage Kawasaki disease, but clinical decision making should be individualized to specific patient circumstances.

Early treatment is critical, don’t delay treatment awaiting an echo!

LABORATORY TEST FOR KAWASAKI DISEASE

JAMA Pediatrics | Original Investigation

Diagnosis of Kawasaki Disease Using a Minimal Whole-Blood Gene Expression Signature

Victoria J. Wright, PhD; Jethro A. Herberg, PhD; Myrsini Kaforou, PhD; Chisato Shimizu, MD; Hariklia Eleftherohorinou, PhD; Hannah Shailes, PhD; Anouk M. Barendregt, BSc; Stephanie Menikou, PhD; Stuart Gormley, MRes; Maurice Berk, PhD; Long Truong Hoang, PhD; Adriana H. Tremoulet, MD; John T. Kanegaye, MD; Lachlan J. M. Coin, PhD; Mary P. Glodé, MD; Martin Hibberd, PhD; Taco W. Kuijpers, PhD; Clive J. Hoggart, PhD; Jane C. Burns, MD; Michael Levin, FRCPCH; for the Immunopathology of Respiratory, Inflammatory and Infectious Disease Study (IRIS) Consortium and the Pediatric Emergency Medicine Kawasaki Disease Research Group (PEMKDRG)

IMPORTANCE To date, there is no diagnostic test for Kawasaki disease (KD). Diagnosis is based on clinical features shared with other febrile conditions, frequently resulting in delayed or missed treatment and an increased risk of coronary artery aneurysms.

OBJECTIVE To identify a whole-blood gene expression signature that distinguishes children with KD in the first week of illness from other febrile conditions.

DESIGN, SETTING, AND PARTICIPANTS The case-control study comprised a discovery group that included a training and test set and a validation group of children with KD or comparator febrile illness. The setting was pediatric centers in the United Kingdom, Spain, the Netherlands, and the United States. The training and test discovery group comprised 404 children with infectious and inflammatory conditions (78 KD, 84 other inflammatory diseases, and 242 bacterial or viral infections) and 55 healthy controls. The independent validation group comprised 102 patients with KD, including 72 in the first 7 days of illness, and 130 febrile controls. The study dates were March 1, 2009, to November 14, 2013, and data analysis took place from January 1, 2015, to December 31, 2017.

MAIN OUTCOMES AND MEASURES Whole-blood gene expression was evaluated using microarrays, and minimal transcript sets distinguishing KD were identified using a novel variable selection method (parallel regularized regression model search). The ability of transcript signatures (implemented as disease risk scores) to discriminate KD cases from controls was assessed by area under the curve (AUC), sensitivity, and specificity at the optimal cut point according to the Youden index.

RESULTS Among 404 patients in the discovery set, there were 78 with KD (median age, 27 months; 55.1% male) and 326 febrile controls (median age, 37 months; 56.4% male). Among 202 patients in the validation set, there were 72 with KD (median age, 34 months; 62.5% male) and 130 febrile controls (median age, 17 months; 56.9% male). A 13-transcript signature identified in the discovery training set distinguished KD from other infectious and inflammatory conditions in the discovery test set, with AUC of 96.2% (95% CI, 92.5%-99.9%), sensitivity of 81.7% (95% CI, 60.0%-94.8%), and specificity of 92.1% (95% CI, 84.0%-97.0%). In the validation set, the signature distinguished KD from febrile controls, with AUC of 94.6% (95% CI, 91.3%-98.0%), sensitivity of 85.9% (95% CI, 76.8%-92.6%), and specificity of 89.1% (95% CI, 83.0%-93.7%). The signature was applied to clinically defined categories of definite, highly probable, and possible KD, resulting in AUCs of 98.1% (95% CI, 94.5%-100%), 96.3% (95% CI, 93.3%-99.4%), and 70.0% (95% CI, 53.4%-86.6%), respectively, mirroring certainty of clinical diagnosis.

CONCLUSIONS AND RELEVANCE In this study, a 13-transcript blood gene expression signature distinguished KD from other febrile conditions. Diagnostic accuracy increased with certainty of clinical diagnosis. A test incorporating the 13-transcript disease risk score may enable earlier diagnosis and treatment of KD and reduce inappropriate treatment in those with other diagnoses.

Table 2. Genes Included in the Diagnostic Signature

Gene Symbol	Gene Name	HGNC Identification No.	Probe Identification No.	Location	Logistic Regression Coefficient[a]
CACNA1E	Calcium voltage-gated channel subunit alpha1 E	1392	7510647	1q25.3	0.955
DDIAS	DNA damage-induced apoptosis suppressor	26351	2570019	11q14.1	0.844
KLHL2	Kelch-like family member 2	6353	1070593	4q32.3	0.789
PYROXD2	Pyridine nucleotide-disulphide oxidoreductase domain 2	23517	1684497	10q24.2	0.727
SMOX	Spermine oxidase	15862	270068	20p13	0.675
ZNF185	Zinc finger protein 185 with domain	12976	6840674	Xq28	0.646
LINC02035	Long intergenic non-protein coding RNA 2035	52875	3236239	3q21.1	0.561
CLIC3	Chloride intracellular channel 3	2064	5870136	9q34.3	0.464
S100P	S100 calcium-binding protein P	10504	1510424	4p16.1	−0.405
IFI27	Interferon alpha-inducible protein 27	5397	3990170	14q32.12	−0.426
HS.553068	BX103476 NCI_CGAP_Lu5 *Homo sapiens* cDNA clone	NA	1470450	NA	−0.599
CD163	CD163 molecule	1631	2680092	12p13.31	−0.638
RTN1	Reticulon 1	10467	6860193	14q23.1	−0.690

"**the signature** distinguished KD from febrile controls, with […] **sensitivity of 85.9%** […], and **specificity of 89.1%** […]."

2. Should patients with Kawasaki disease be treated with Aspirin and immunoglobulins (IVIG) ?

ASPIRIN & IV IMMUNOGLOBULINS (IVIG)

Several publications have shown that high dose ASPIRIN does not affect aneurysm formation

Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. Terai M, et al. Pediatr. 1997;131(6):888.

The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Durongpisitkul K et al. Pediatrics. 1995;96(6):1057.

Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited.AUHsieh KS, Weng KP, Lin CC, Huang TC, Lee CL, Huang SM SOPediatrics. 2004;114(6):e689. 2004 Nov 15.

IVIG effect is dose dependant

	Aspirin 30-50mg/kg/day
	prevalence of coronary abnormalities (30 days)
Aspirin alone	17.5%
IVIG <1 g/kg and aspirin	13.5%
IVIG 1 to 1.6 g/kg and aspirin	9.8%
IVIG 2 g/kg and aspirin	3.5%

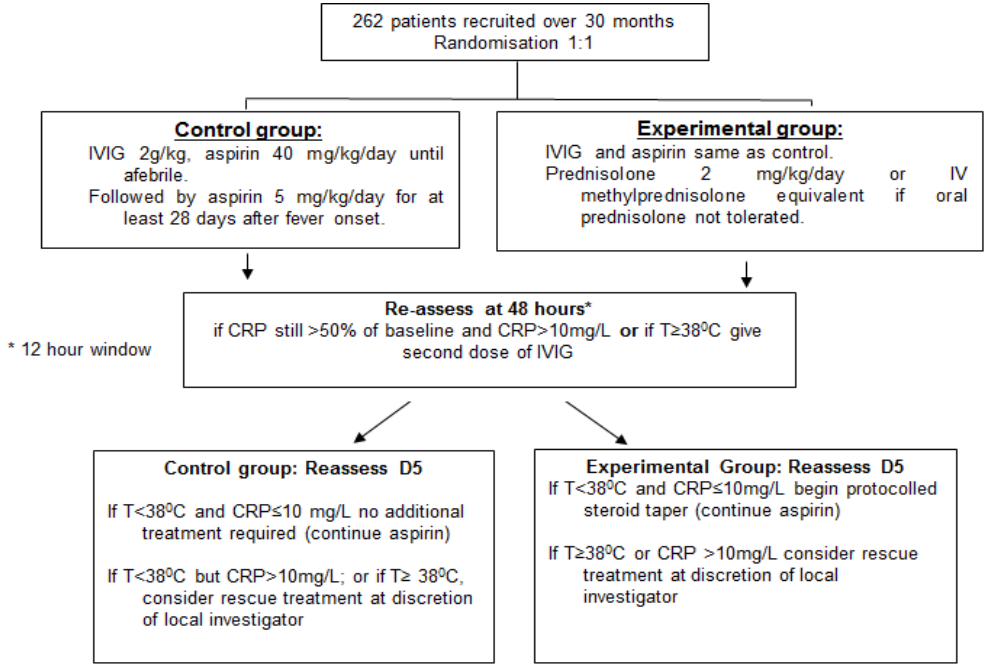
Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose.Terai M et al. SOJ Pediatr. 1997

STEROIDS

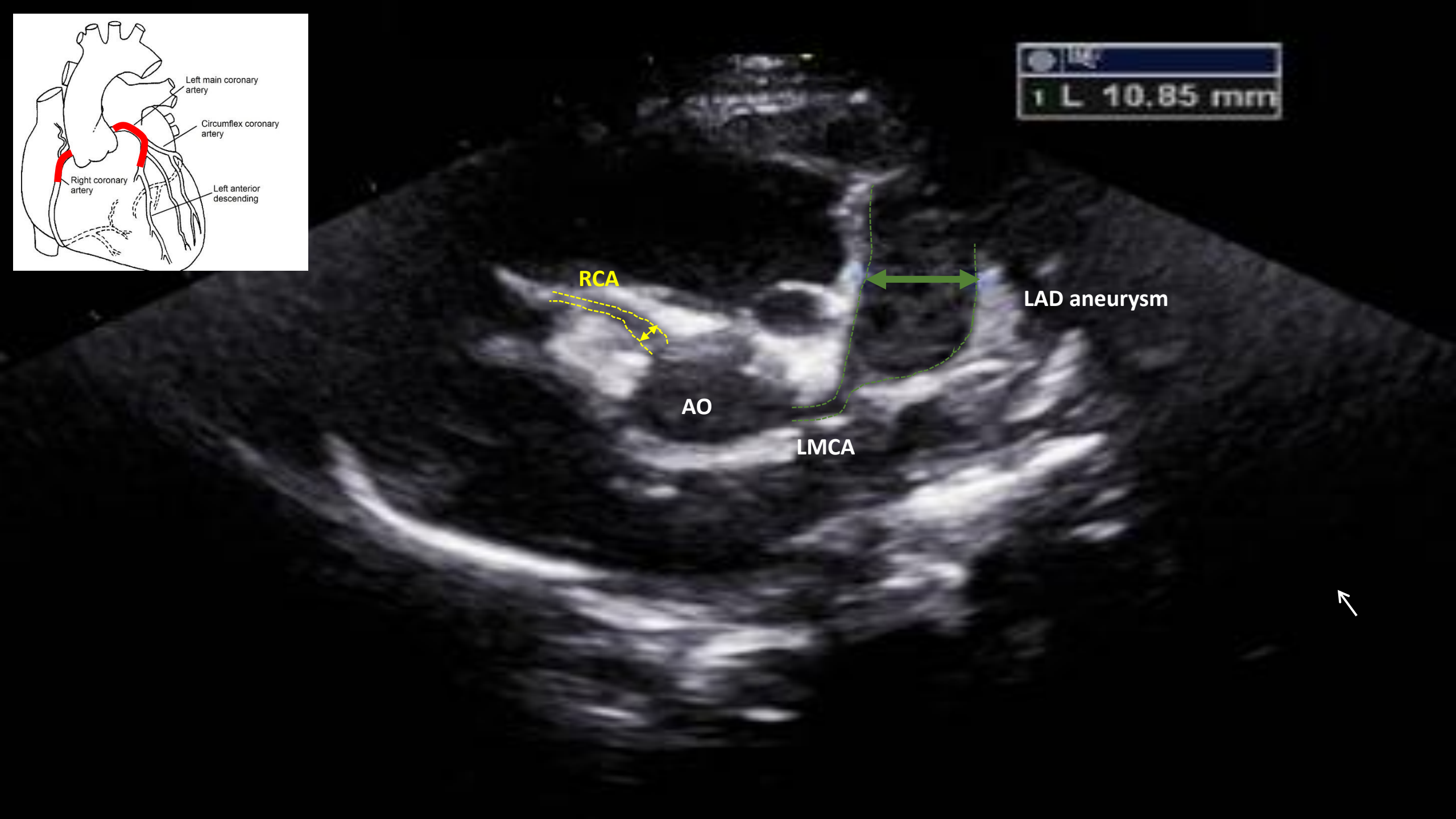
- **IVIG resistance** (fever >48hr, age <12 months, aneurysms, shock)
- lower rate of CA abnormalities with steroids plus IVIG compared with IVIG alone
- effect more pronounced if given as part of initial rather than rescue therapy

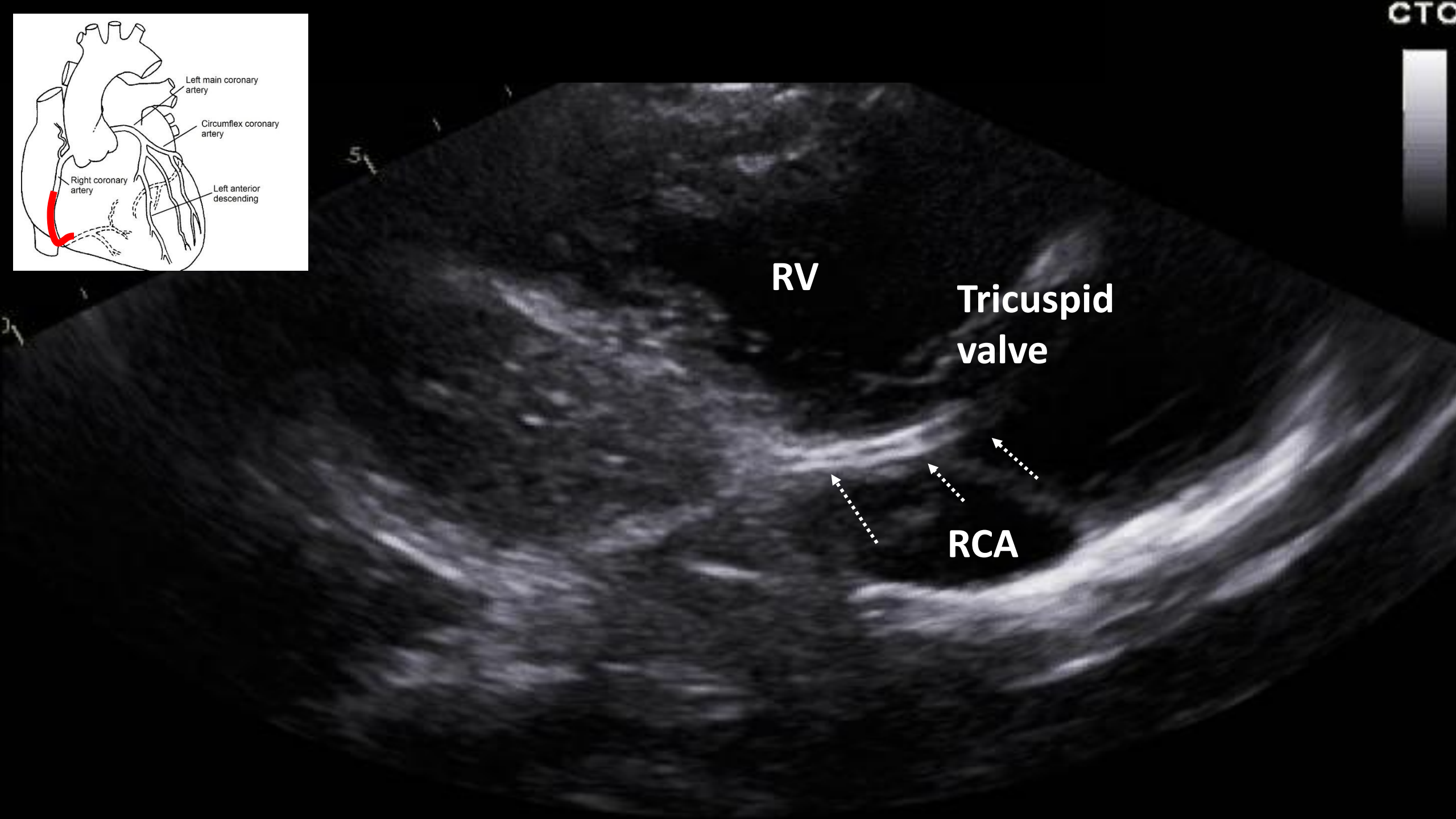
Coronary Artery Complication in Kawasaki Disease and the Importance of Early Intervention : A Systematic Review and Meta-analysis. Chen S et al. JAMA Pediatr. 2016;170(12):1156.

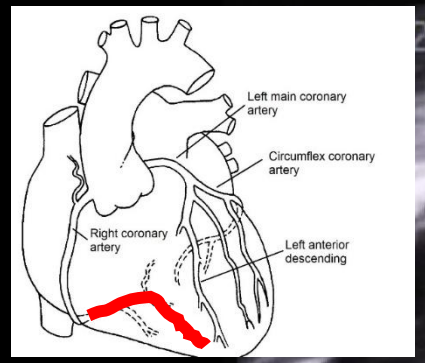
KD-CAAP trial: Multi-centre, randomised, open-label, blinded endpoint assessed, trial of corticosteroids plus intravenous immunoglobulin (IVIG) and aspirin, versus IVIG and aspirin for prevention of coronary artery aneurysms in Kawasaki disease.



3. What are the limitations of echocardiography ?


Left main coronary artery
Circumflex coronary artery
Right coronary artery
Left anterior descending
1 L 10.85 mm
RCA
AO
LMCA
LAD aneurysm


Left main coronary artery
Circumflex coronary artery
Right coronary artery
Left anterior descending
RV
Tricuspid valve
RCA


Left main coronary artery
Circumflex coronary artery
Right coronary artery
Left anterior descending

Soft
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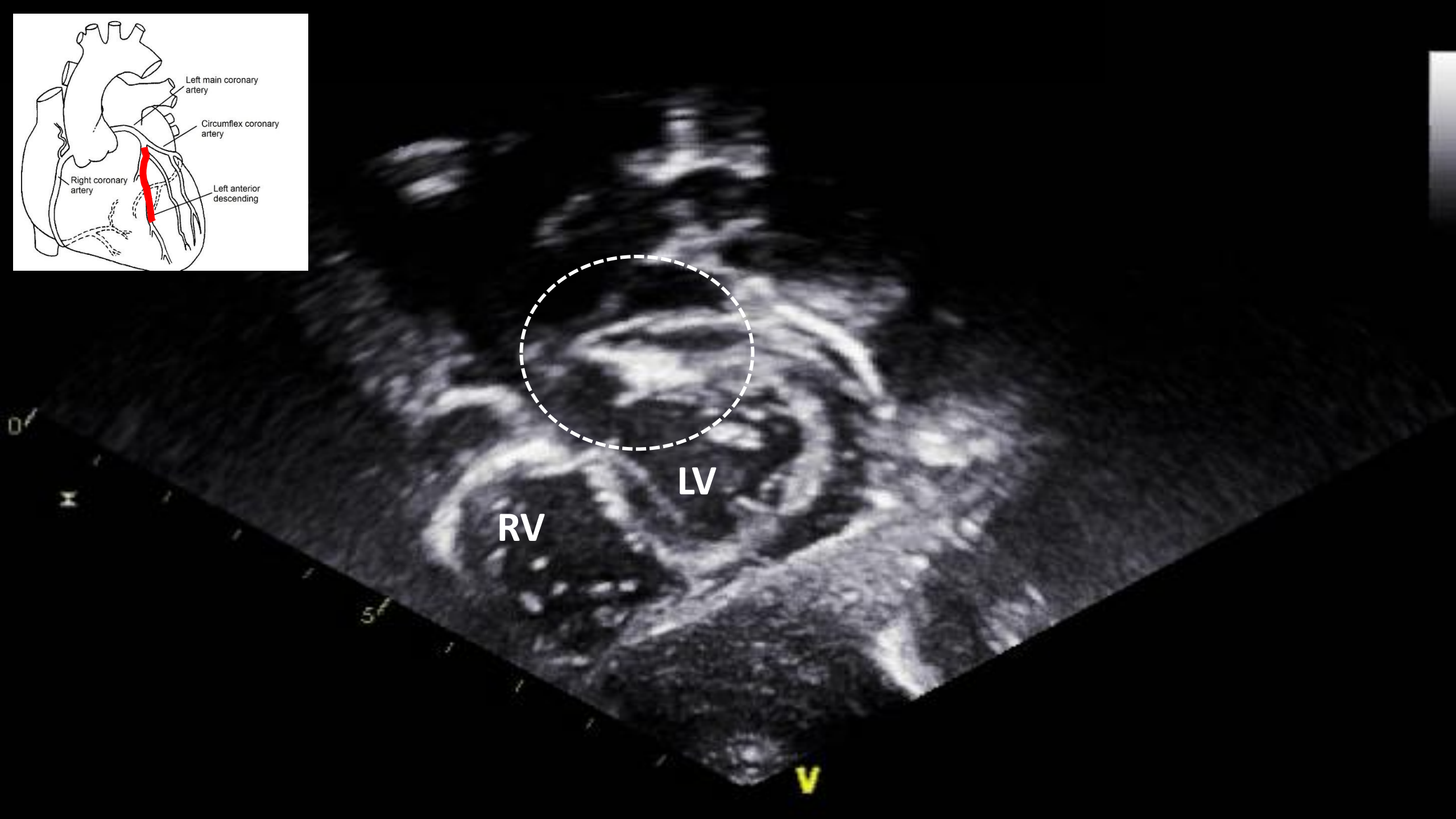
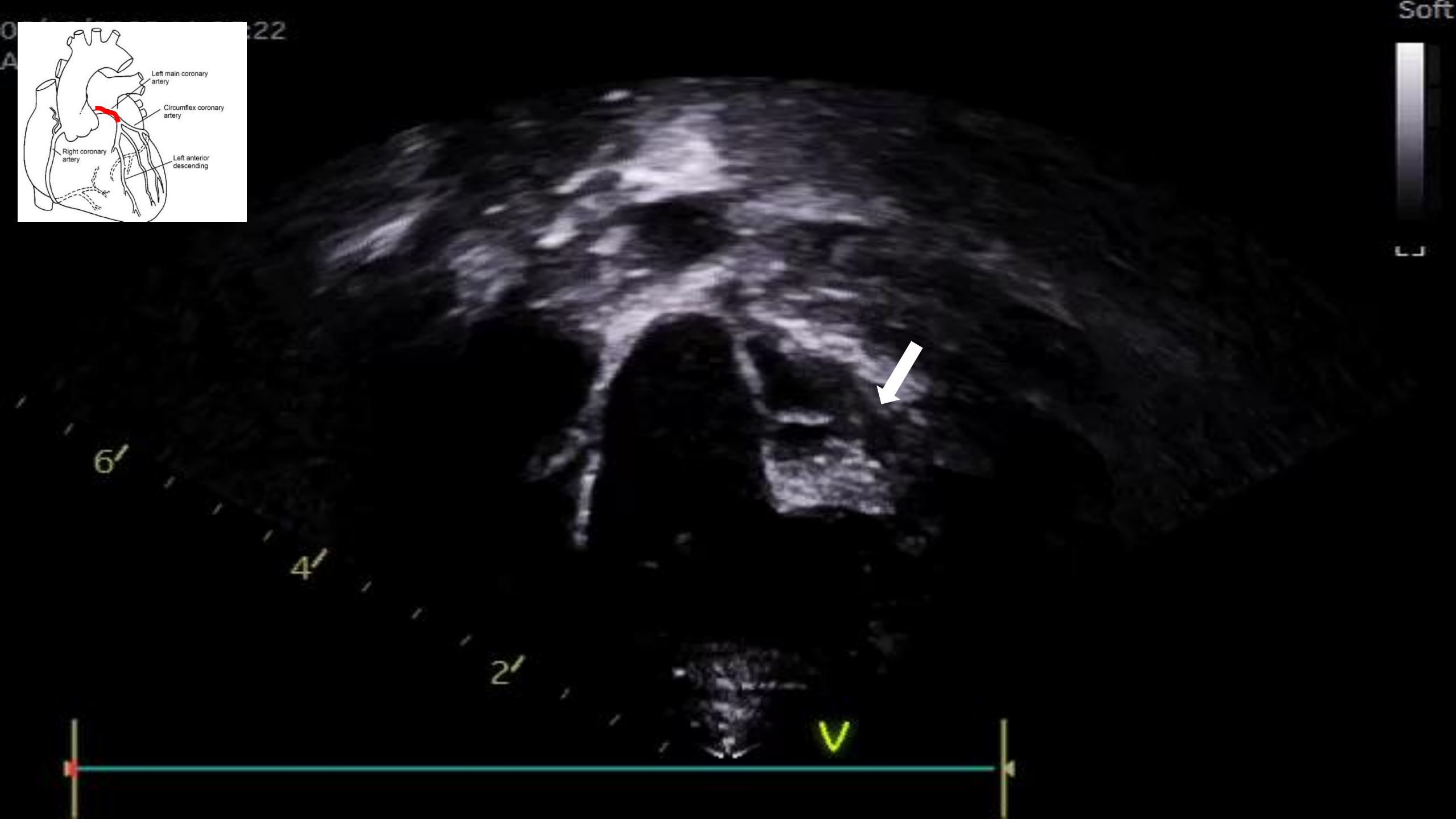
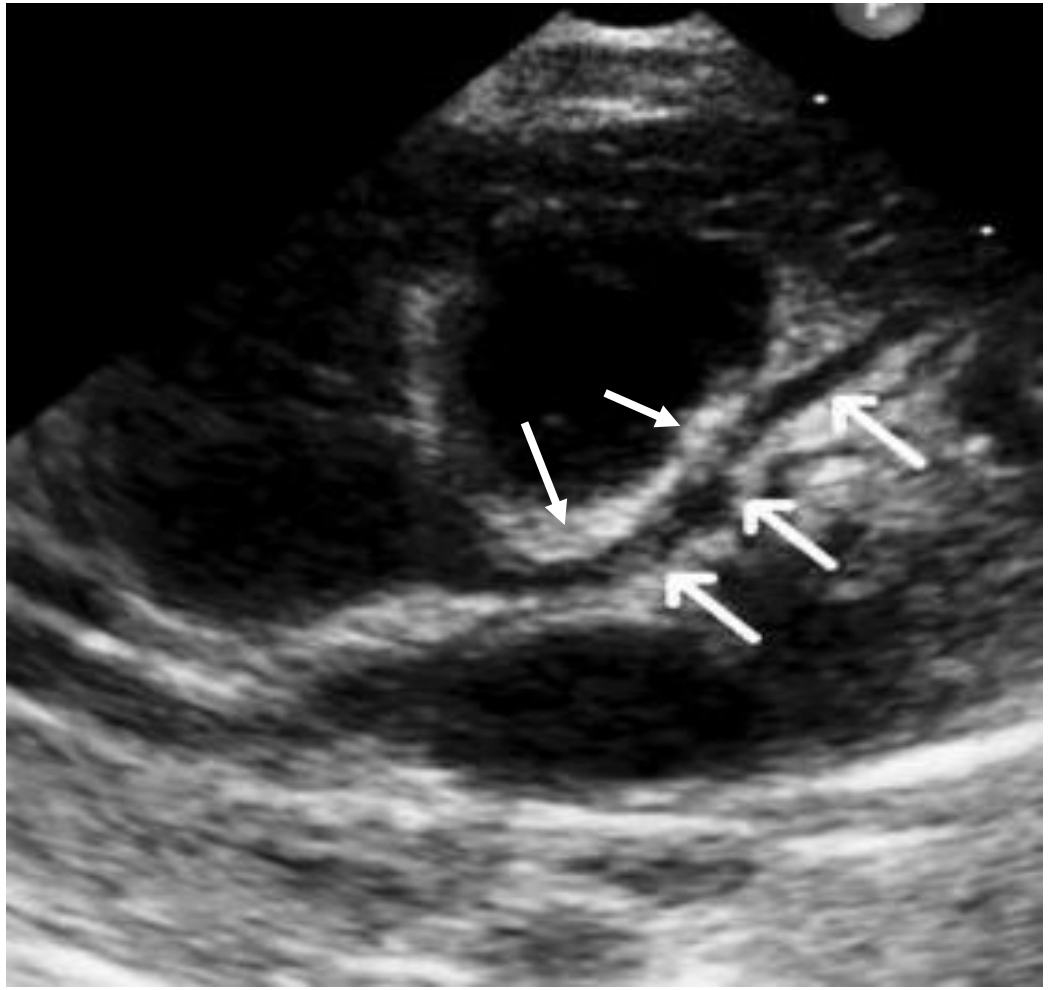

Left main coronary artery
Circumflex coronary artery
Right coronary artery
Left anterior descending
LV
RV


Left main coronary artery
Circumflex coronary artery
Right coronary artery
Left anterior descending
Soft
6
4
2
V

PERIVASCULAR ECHOBRIGHTNESS



Perivascular brightness of coronary arteries in Kawasaki disease.

Yu JJ[1], Jang WS, Ko HK, Han MK, Kim YH, Ko JK, Park IS.

Author information

Abstract

OBJECTIVE: Because perivascular echo brightness (PEB) of coronary arteries has been proposed as a criterion for diagnosis of incomplete Kawasaki disease, we assessed the clinical importance of PEB during the acute phase of disease.

STUDY DESIGN: We enrolled 58 patients with Kawasaki disease who underwent two-dimensional strain analysis of images of pericoronary tissue taken during the acute and the convalescent phases. Echogenicity of pericoronary tissue and of the blood pool was determined by speckle tracking in the respective areas of imaging as the averages of integrated backscatter over a single cardiac cycle. PEB was defined as echogenicity of pericoronary tissue minus blood pool.

RESULTS: PEB did not differ in the acute phase in patients and control subjects (P = .10) and between phases of disease (P = .25). In comparison between patient groups, the presence of pericardial effusion was higher in patients with higher PEB during the acute phase (n = 30) than in the remaining patients (33% versus 4%, P < .01).

CONCLUSIONS: PEB did not differ between patients and control subjects and is only associated with the presence of pericardial effusion during the acute phase of Kawasaki disease. Our data do not confirm the reliability of PEB as a useful diagnostic sign of incomplete Kawasaki disease.

Pediatr Cardiol. 2019 Jan;40(1):147-153. doi: 10.1007/s00246-018-1971-z. Epub 2018 Sep 8.

Examining the Utility of Coronary Artery Lack of Tapering and Perivascular Brightness in Incomplete Kawasaki Disease.

Rabinowitz EJ[1], Rubin LG[2], Desai K[3], Hayes DA[4], Tugertimur A[4], Kwon EN[4], Dhanantwari P[4], Misra N[4], Stoffels G[5], Blaufox AD[4], Mitchell E[4].

Author information

Abstract

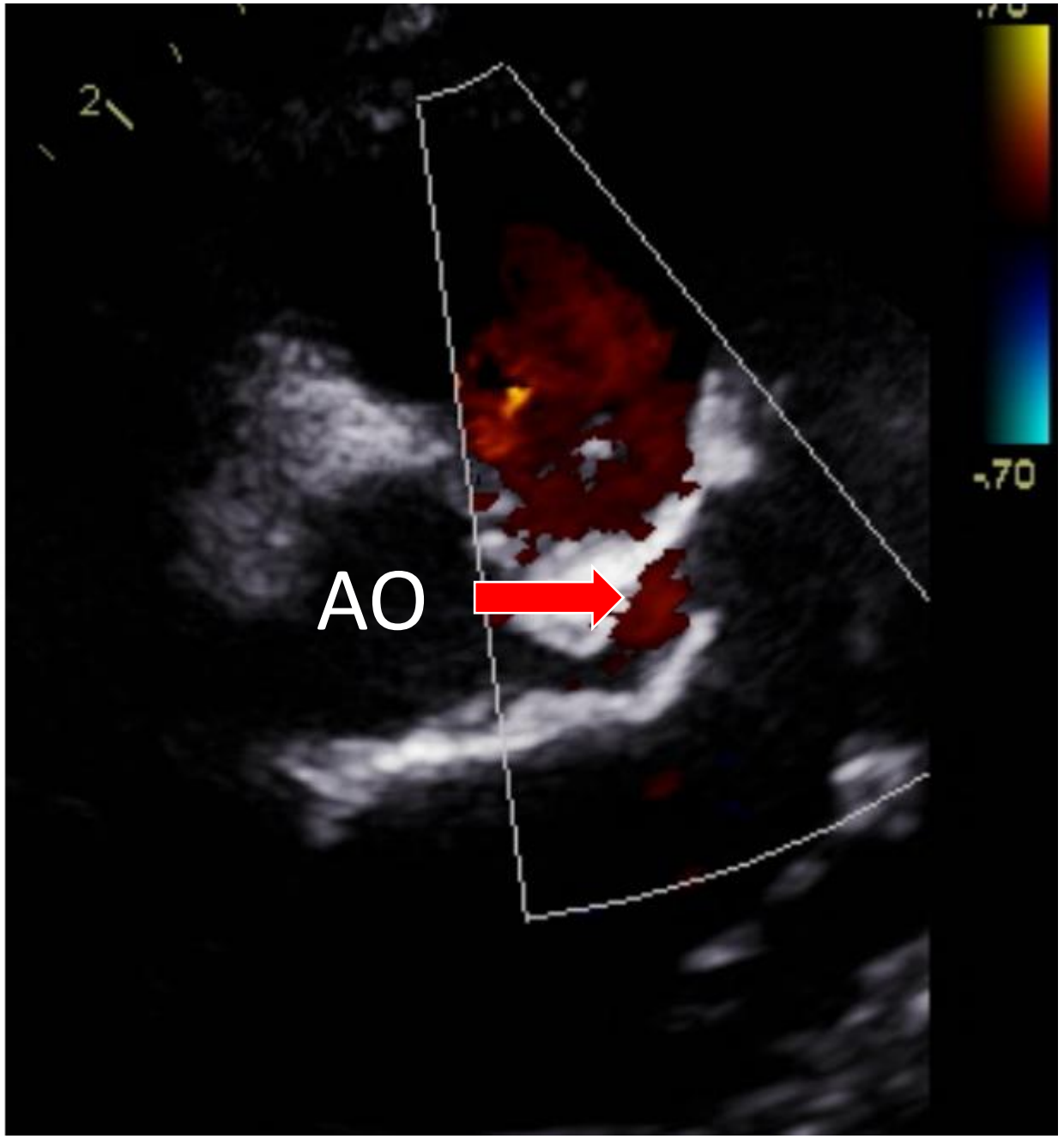
BACKGROUND: In 2017, the AHA published revised guidelines for the diagnosis of Kawasaki disease (KD). In the absence of compelling data supporting or refuting the utility of lack of tapering (LT) and perivascular brightness (PB), expert panel consensus removed LT and PB from consideration. We hypothesize that LT and PB are unreliable, subjective findings, non-specific to KD, which can be seen in systemic febrile illnesses without KD and in normal controls.

METHODS: We performed a single-center retrospective study from 1/2008 to 12/2016. De-identified coronary artery (CA) echocardiographic clips from patients 0-10 years old were interpreted blindly by six pediatric cardiologists. Subjects were grouped as follows: (1) healthy: afebrile with benign murmur, (2) KD: IVIG treatment, 4-5 clinical criteria at presentation, (3) incomplete KD (iKD): IVIG, 1-3 clinical criteria, (4) Febrile: ≥3 days of fever, no IVIG, KD not suspected. The presence or absence of LT and PB was recorded. Inter-rater and intra-rater reliabilities were analyzed using intra-class correlation coefficient, Fleiss' Kappa and Cohen's Kappa coefficients.

RESULTS: We interpreted 117 echocardiograms from healthy (27), KD (30), iKD (32), and febrile (28) subjects. Analysis showed moderate agreement in CA z score measurements. LT and PB were observed by most readers in control groups. LT exhibited fair inter-reader agreement (reliability coefficient 0.36) and PB slight inter-reader agreement (reliability coefficient 0.13). Intra-rater reliability was inconsistent for both parameters.

CONCLUSIONS: LT and PB are subjective, poorly reproducible features that can be seen in febrile patients without KD and in healthy children.

KEYWORDS: Acquired heart disease; Coronary vessel disease; Incomplete Kawasaki disease; Kawasaki disease; Lack of tapering; Perivascular brightness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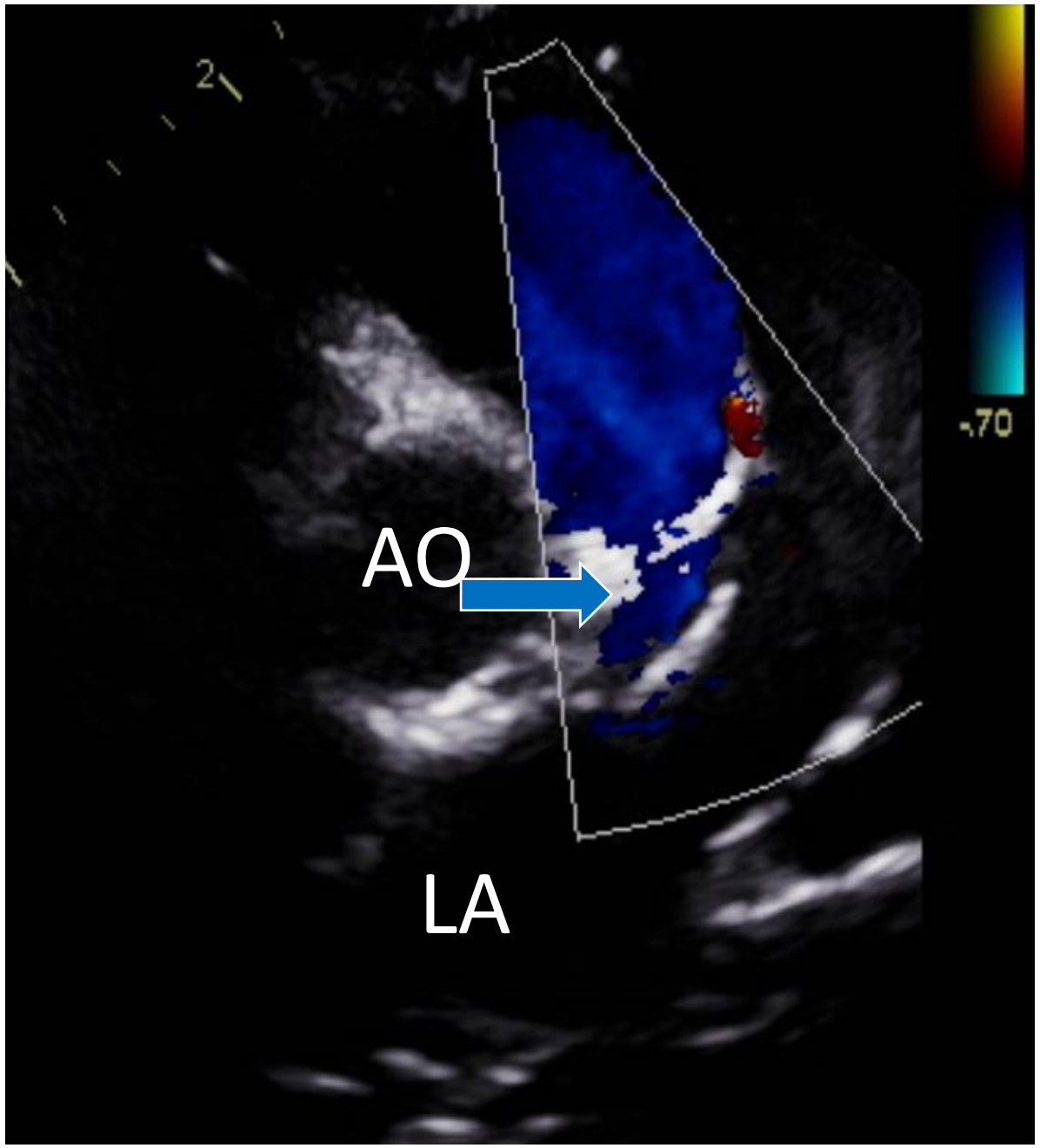
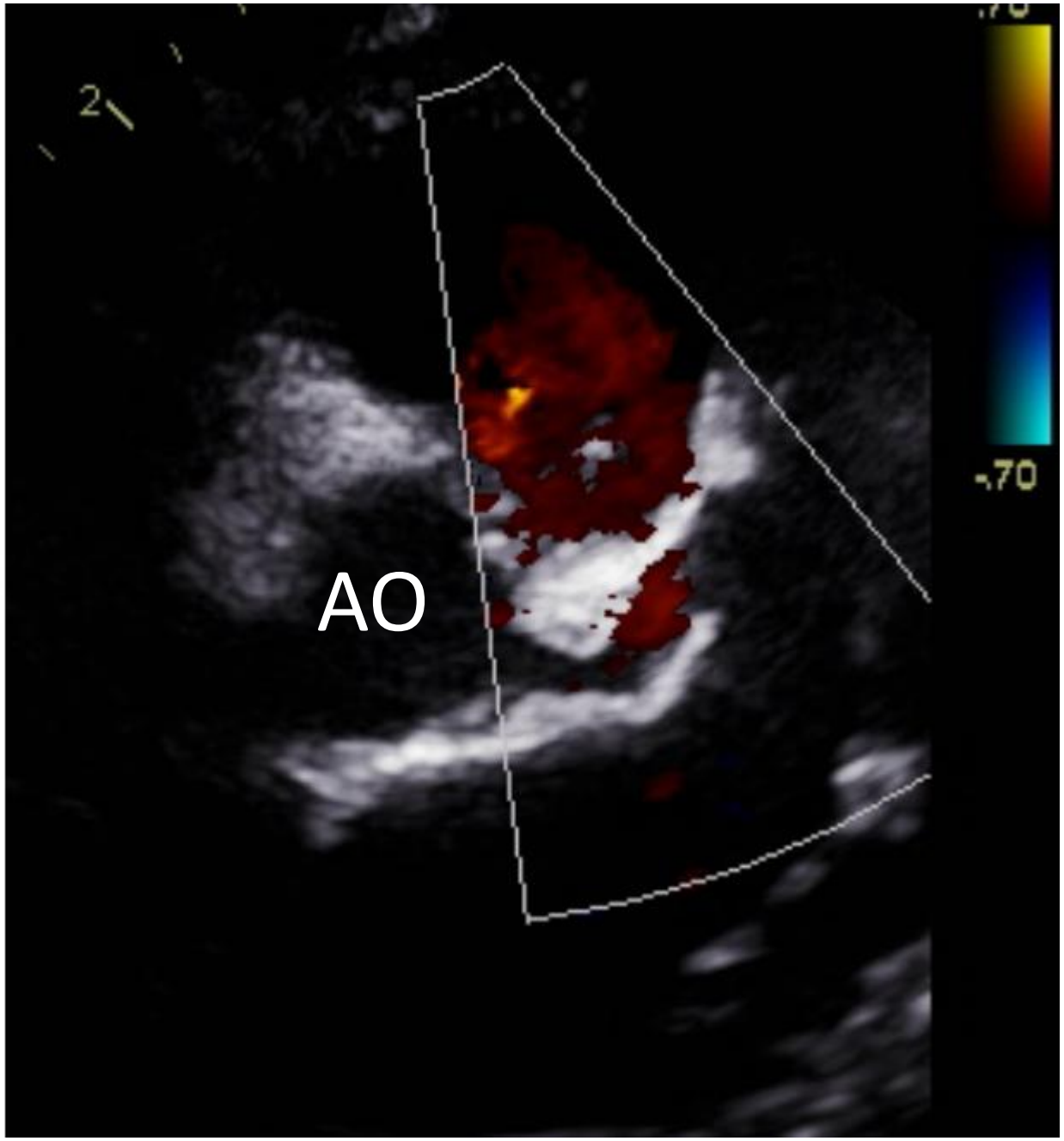

AO
LA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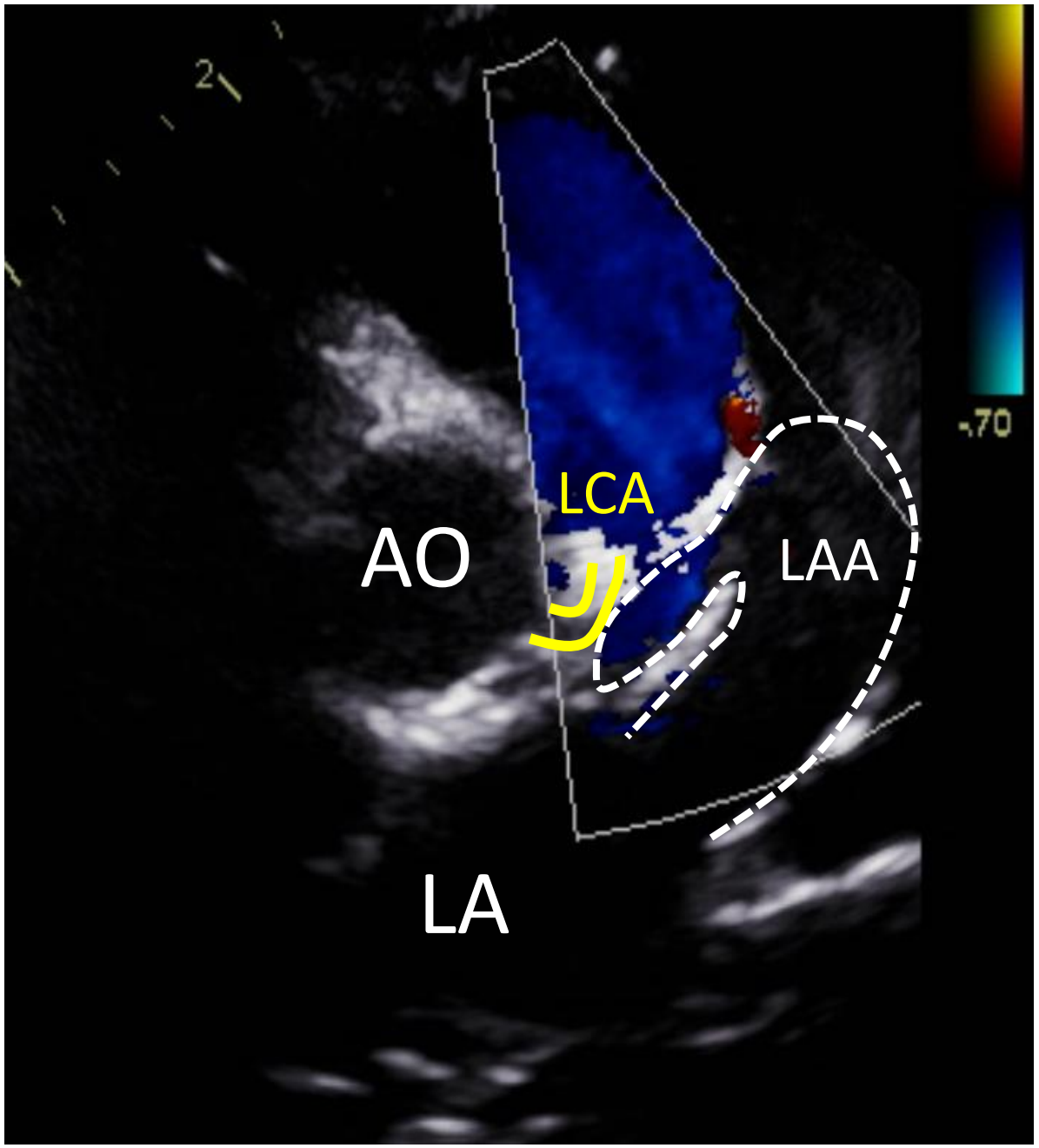
LCA
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LAA
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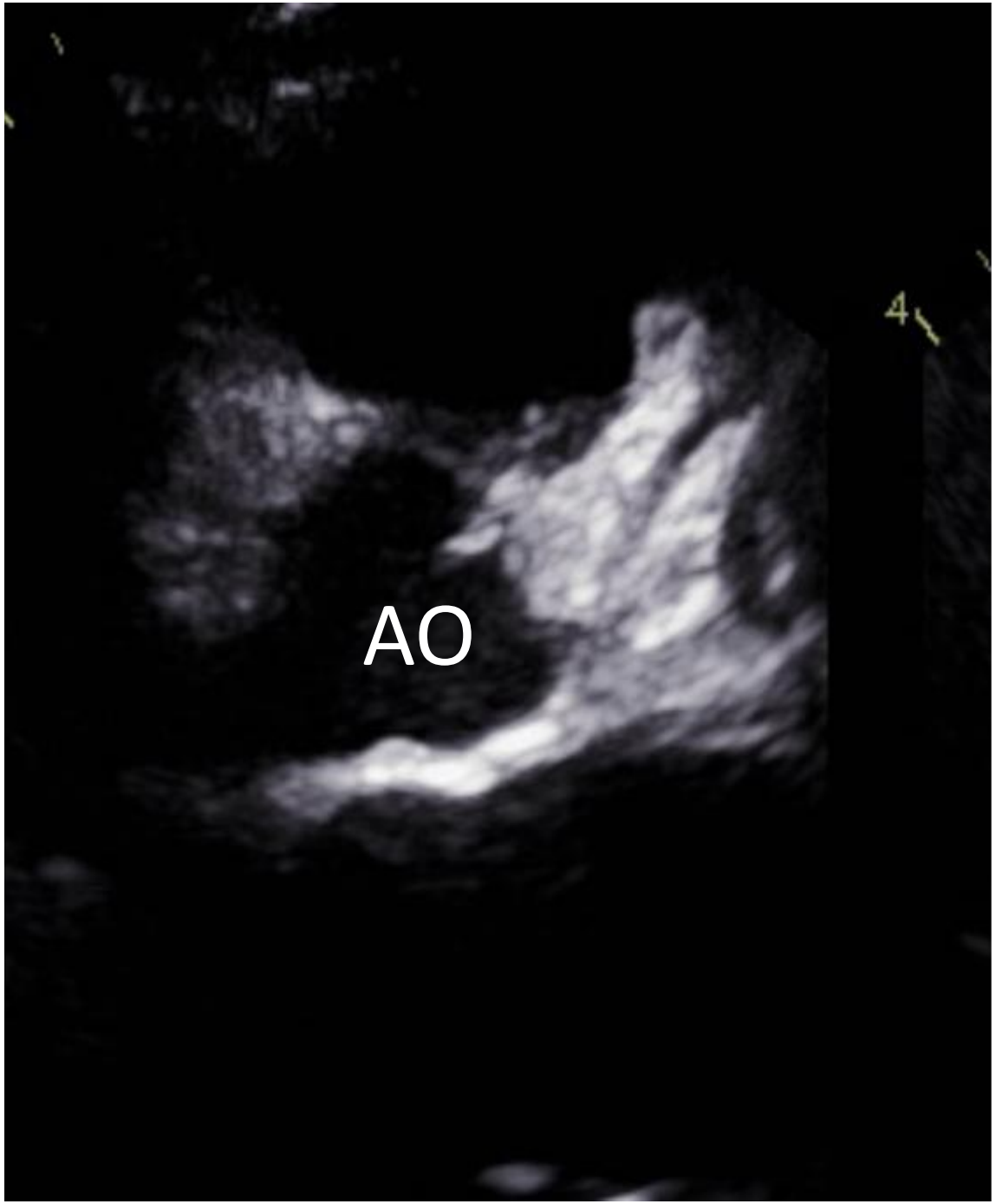
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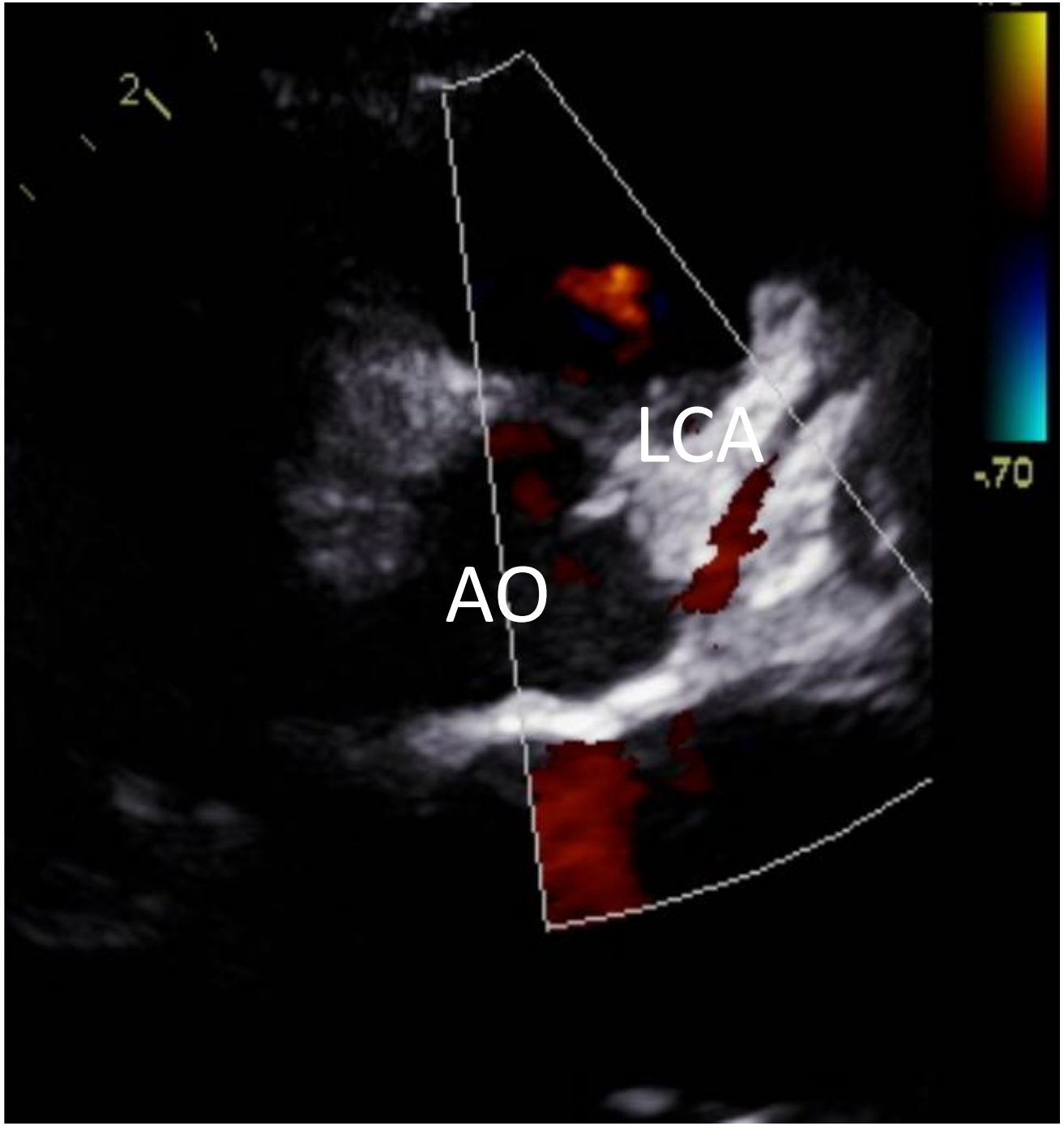
LCA
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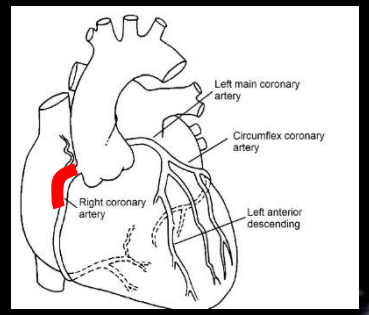
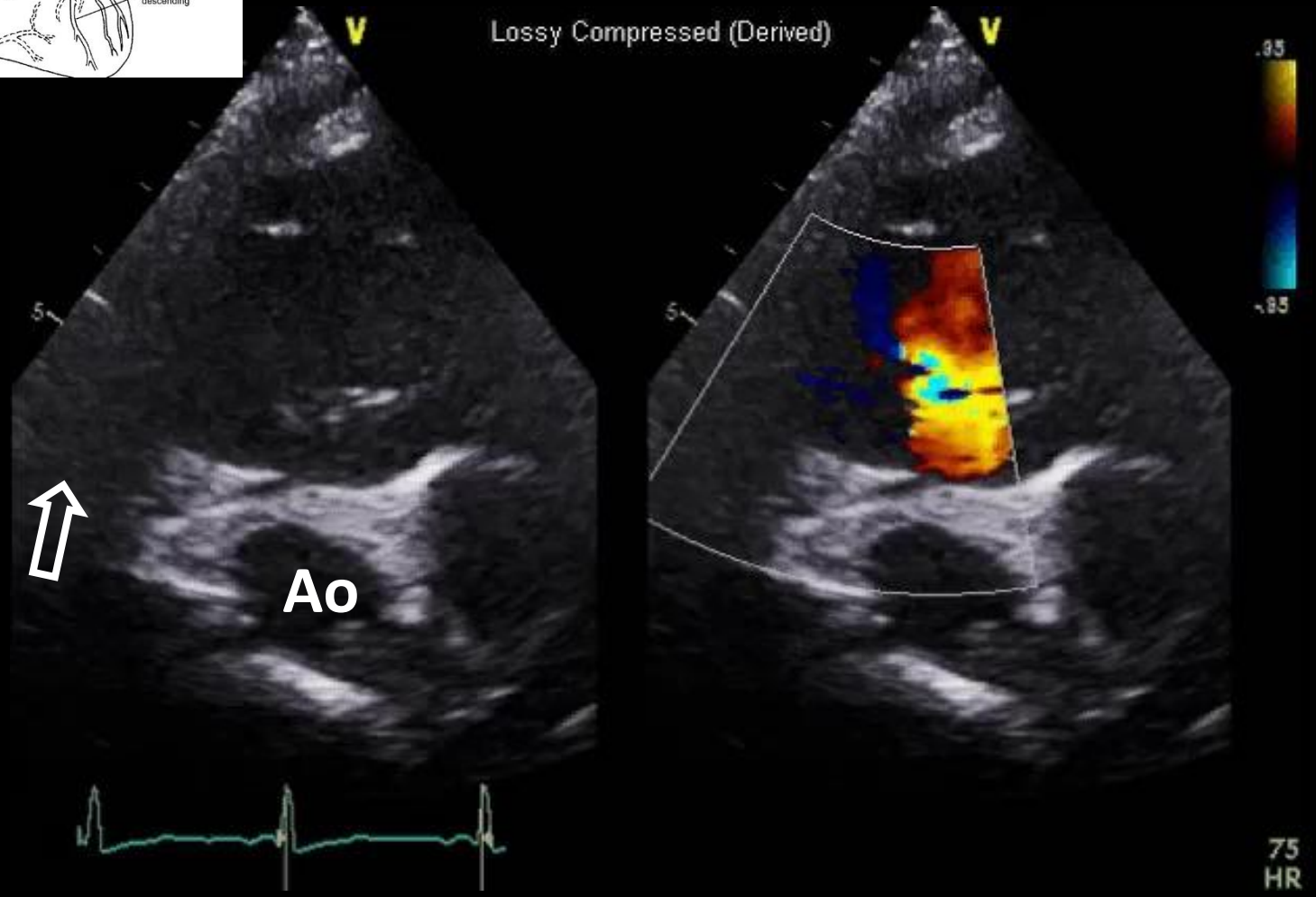

Left main coronary artery
Circumflex coronary artery
Right coronary artery
Left anterior descending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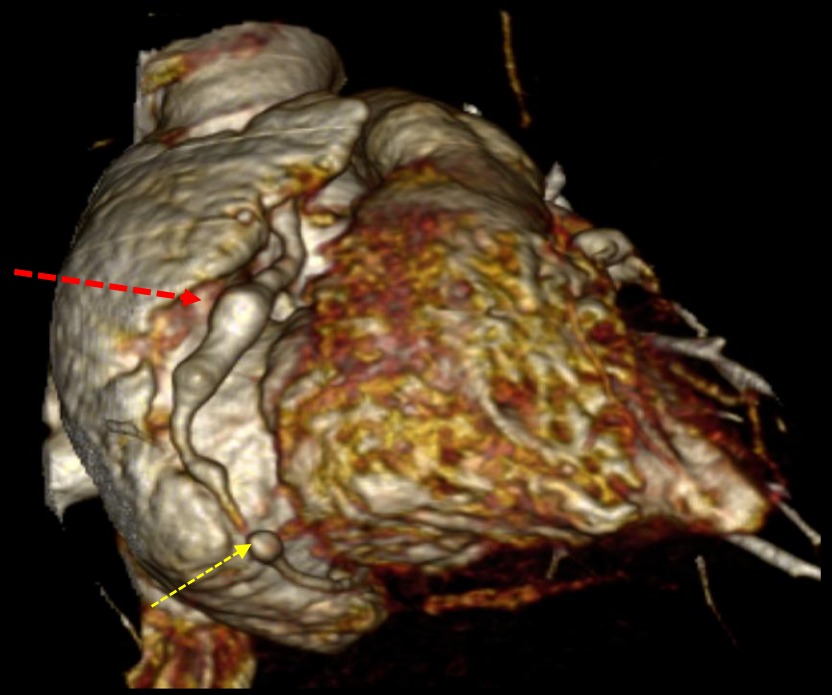
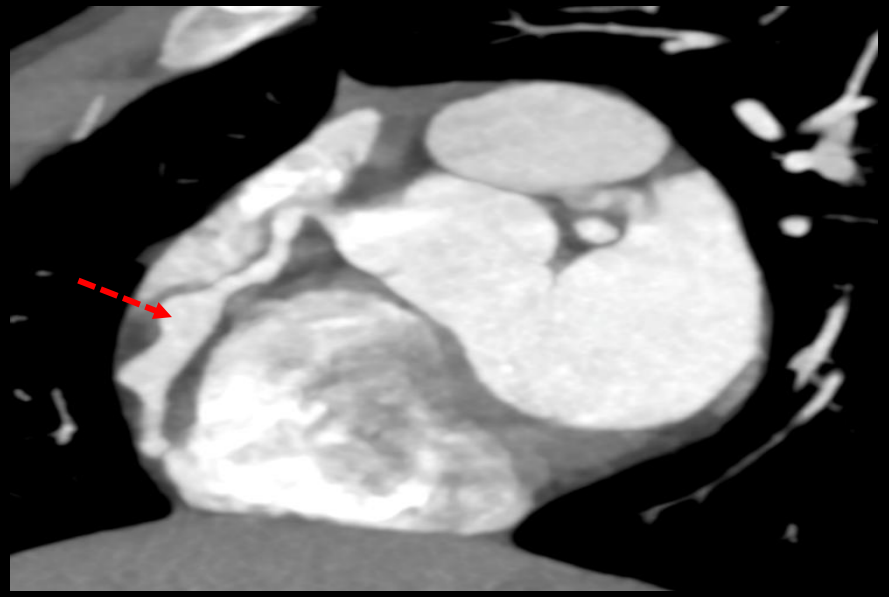




CTA vs ECHO

Yu et al. (**24 patients**) – echo **failed to detect 8 small aneurysms** located in mid and distal segments. CTCA also detected a stenosis of LAD.

Xing et al. (**48 patients**) - **4 aneurysms were missed** in the LCA (*n* = 3) and LAD (*n* = 1) on echo. In addition, stenosis and calcification were missed in the LCA (*n* = 3).

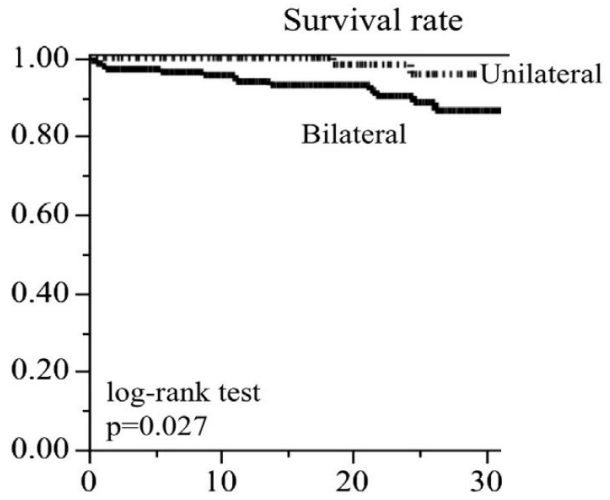
Peng et al. (**12 patients**) - echo **missed 8 of the 30 aneurysms** detected by CTCA. These lesions were location in the LAD (*n* = 2), LCX (*n* = 1), and RCA (*n* = 5). In addition, echocardiography missed calcification and stenotic lesions.

Duan et al. (**19 patients**) echo **failed to detect 7 aneurysms**. Good correlation between echocardiography and CTCA for the size of the detected aneurysms.

4. What determines the prognosis in Kawasaki disease?

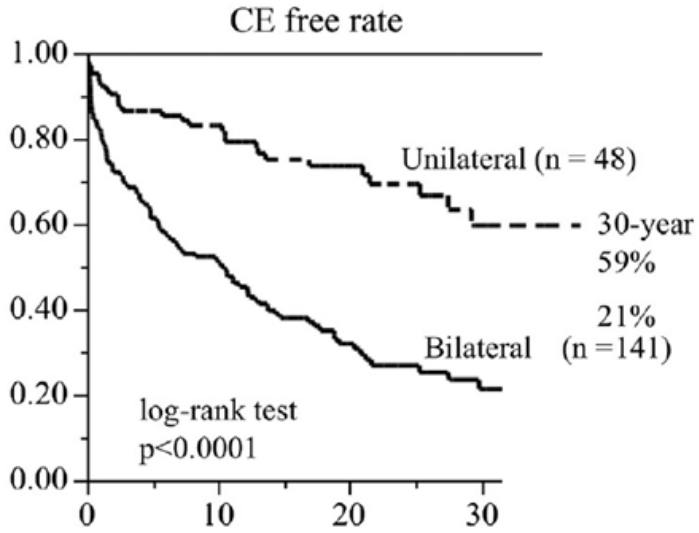
Survival rate

Survival rate	Unilateral CAA	Bilateral CAA	Total
10-year	100% (n=83)	97% (n=120)	97% (n=203)
20-year	96% (n=54)	93% (n=74)	95% (n=128)
30-year	96% (n=17)	87% (n=26)	90% (n=43)



Cardiac event (CE) free rate

CE free rate	Unilateral CAA	Bilateral CAA	Total
10-year	83% (n=68)	51% (n=68)	64% (n=136)
20-year	73% (n=42)	31% (n=28)	48% (n=70)
30-year	59% (n=13)	21% (n=11)	36% (n=24)



Etsuko Tsuda et al. A survey of the 3-decade outcome for patients with giant aneurysms caused by Kawasaki disease Am Heart J. 2014 Feb;167(2):249-58

Figure 1. Kaplan-Meier Survival Curves for Coronary Events in the Classification by the Internal Diameter *z* Score of Coronary Artery Aneurysms in Male and Female Patients

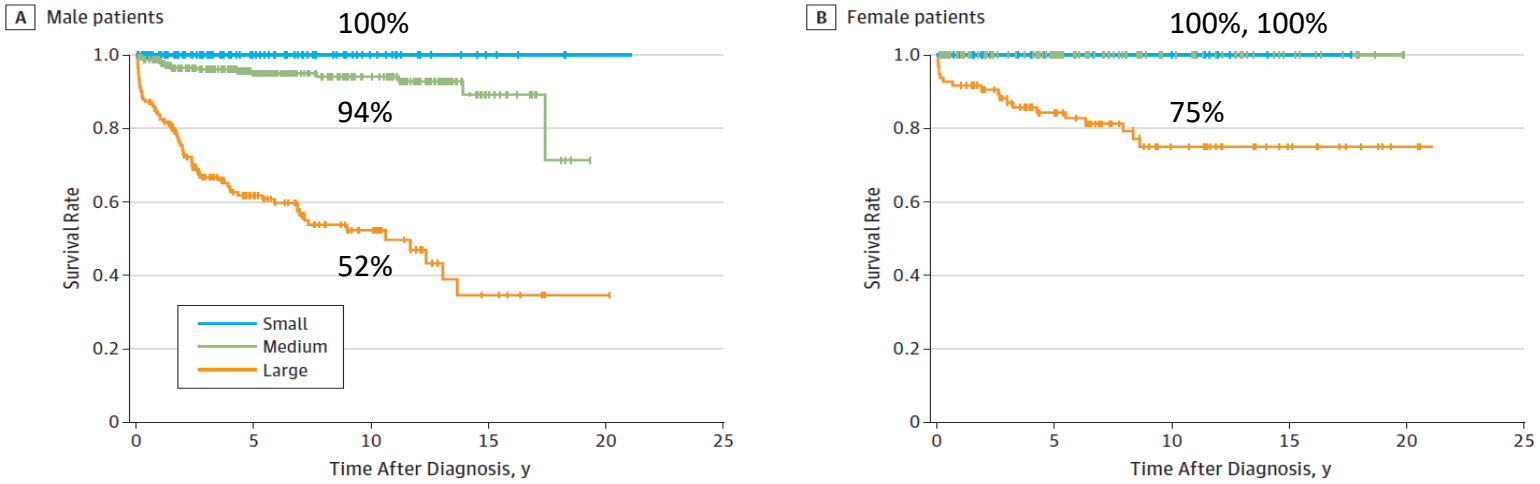
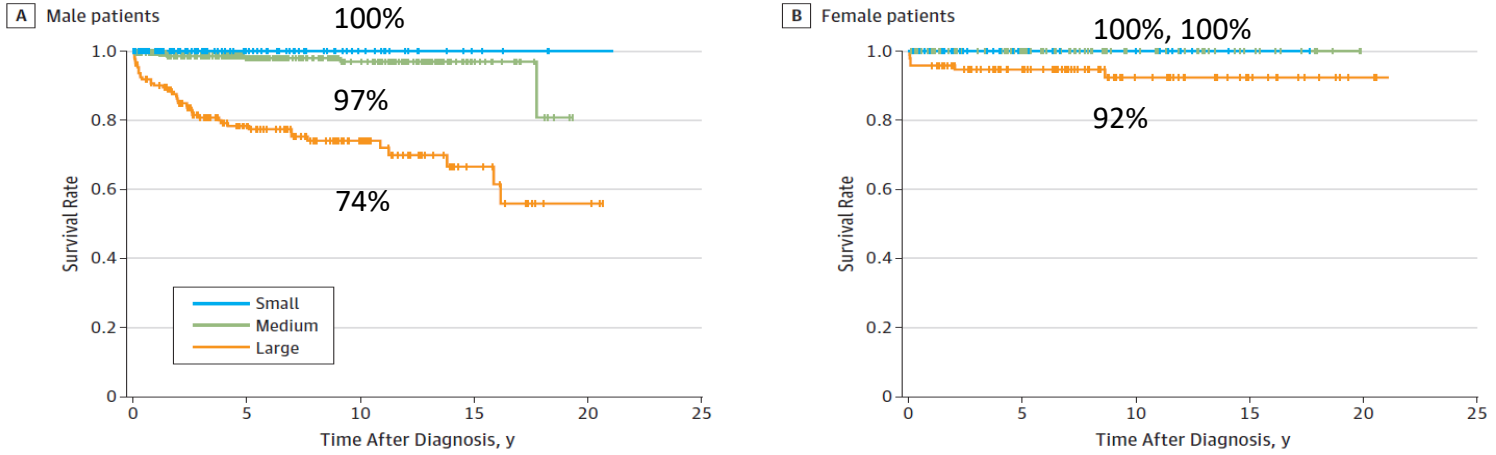
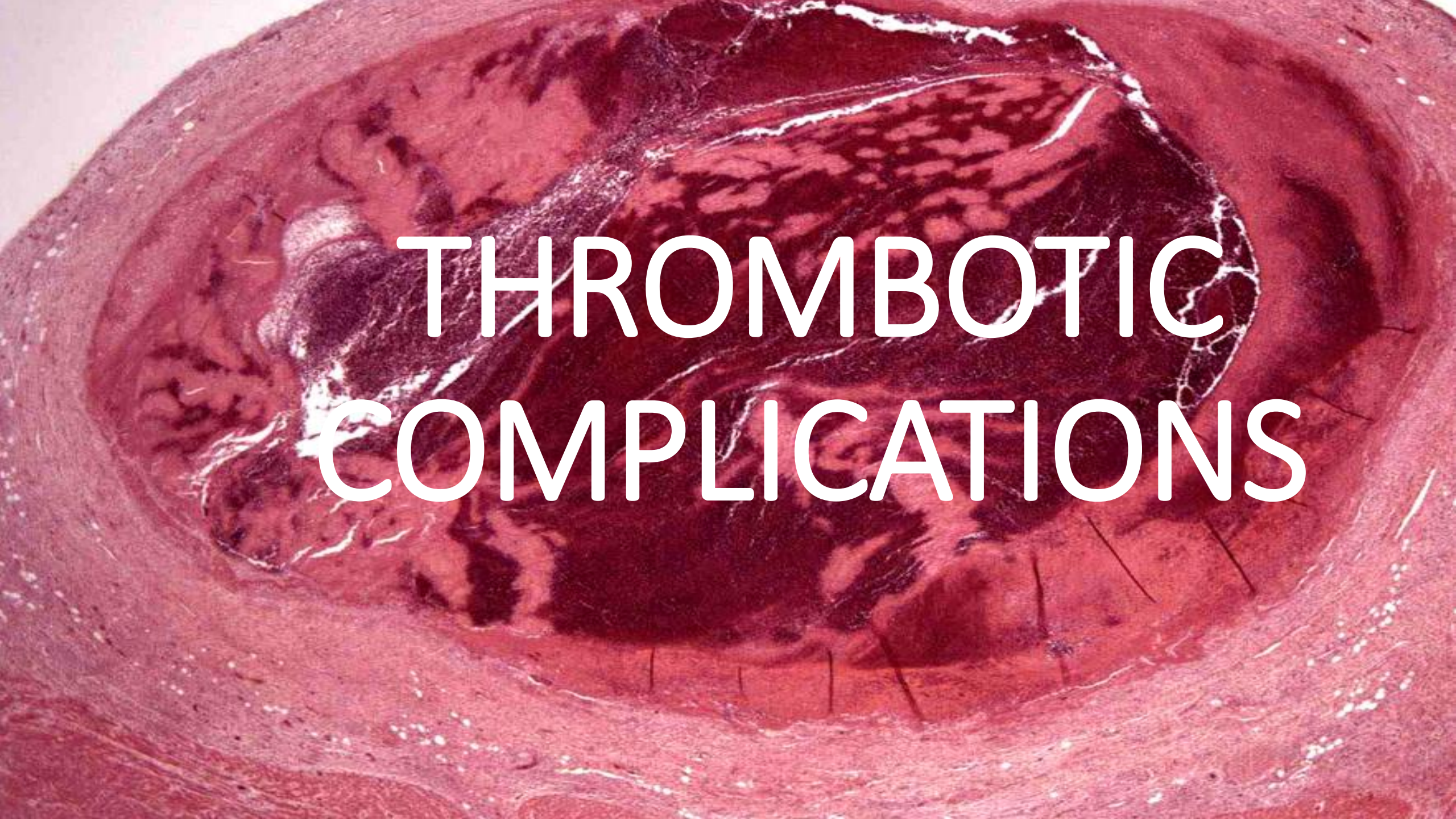
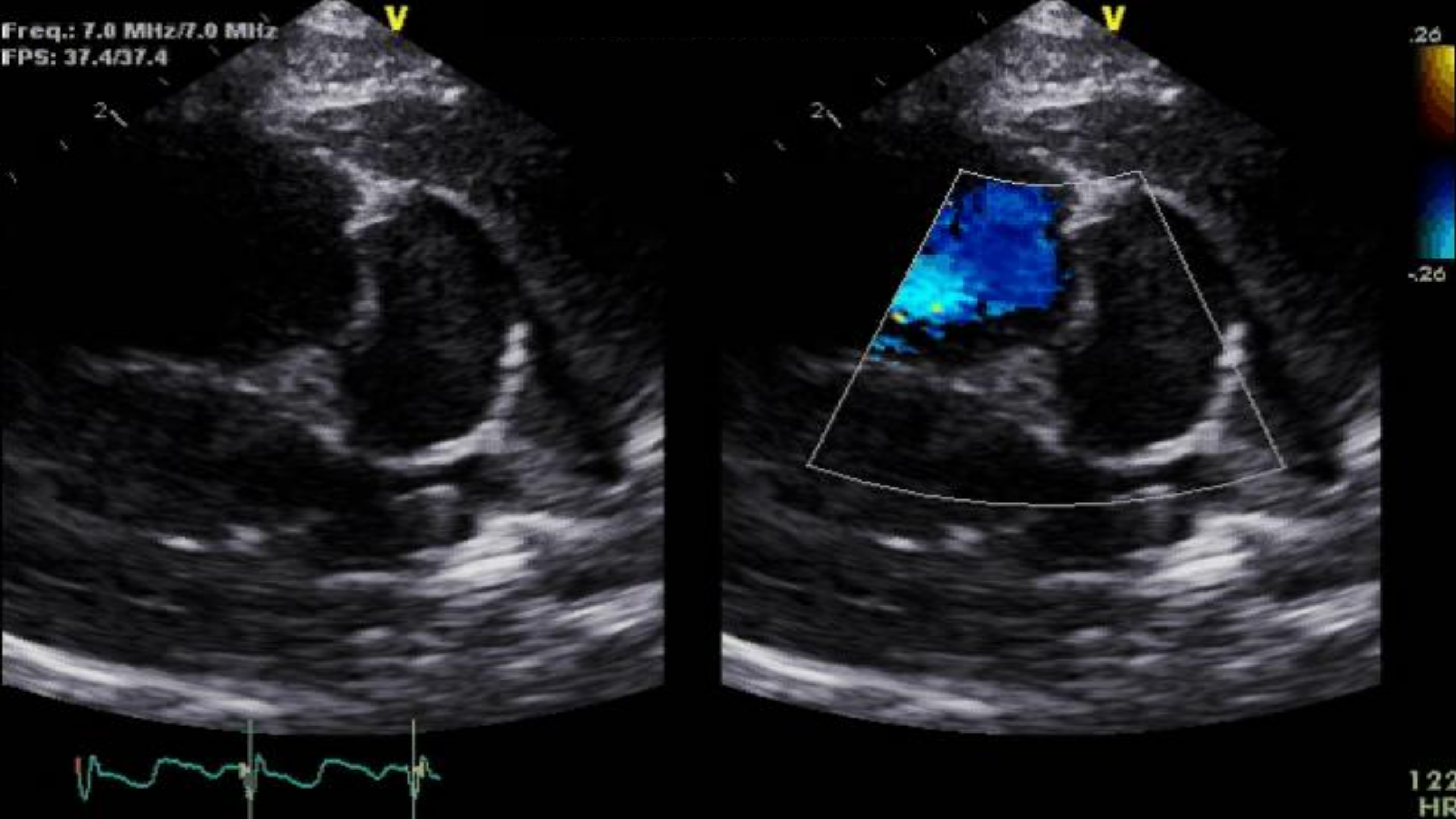


Figure 2. Kaplan-Meier Survival Curves for Major Adverse Cardiac Events in the Classification by the Internal Diameter *z* Score of Coronary Artery Aneurysms in Male and Female Patients



Association of Severity of Coronary Artery Aneurysms in Patients With Kawasaki Disease and Risk of Later Coronary Events Masaru Miura, et al. JAMA Pediatr. 2018;172(5)


THROMBOTIC
COMPLICATIONS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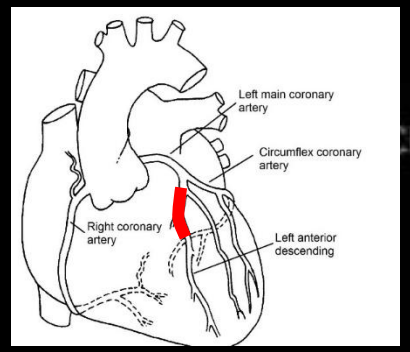
122
HR

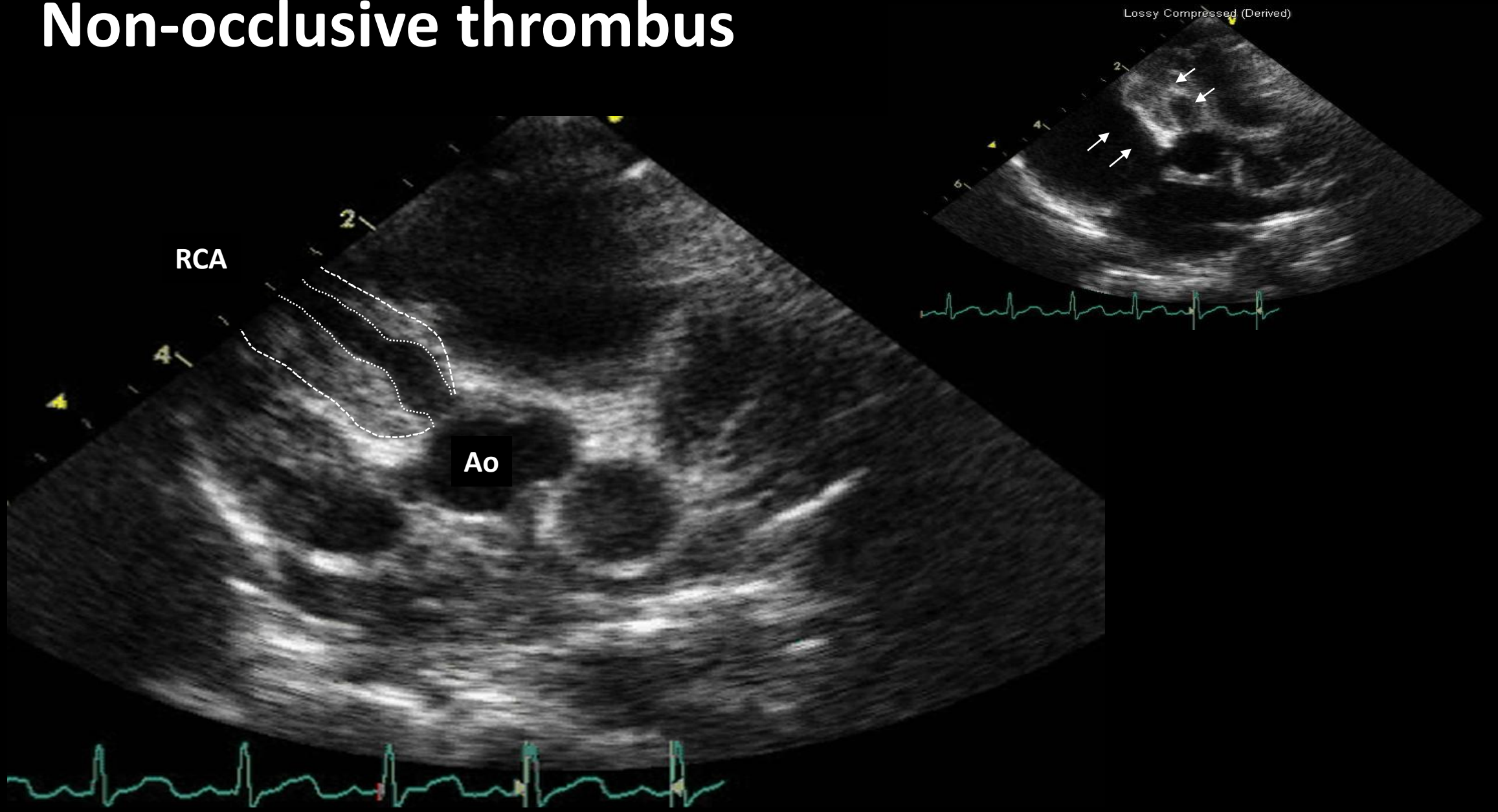
Non-occlusive thrombus



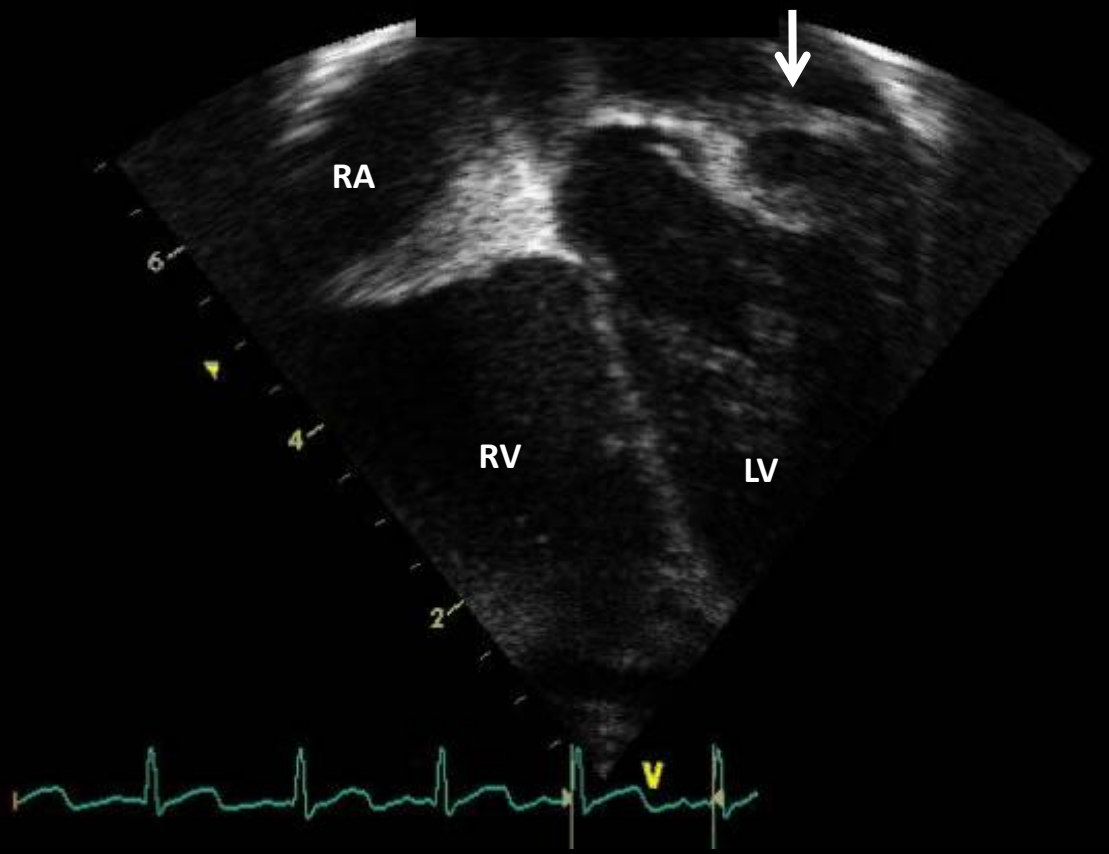
Soft

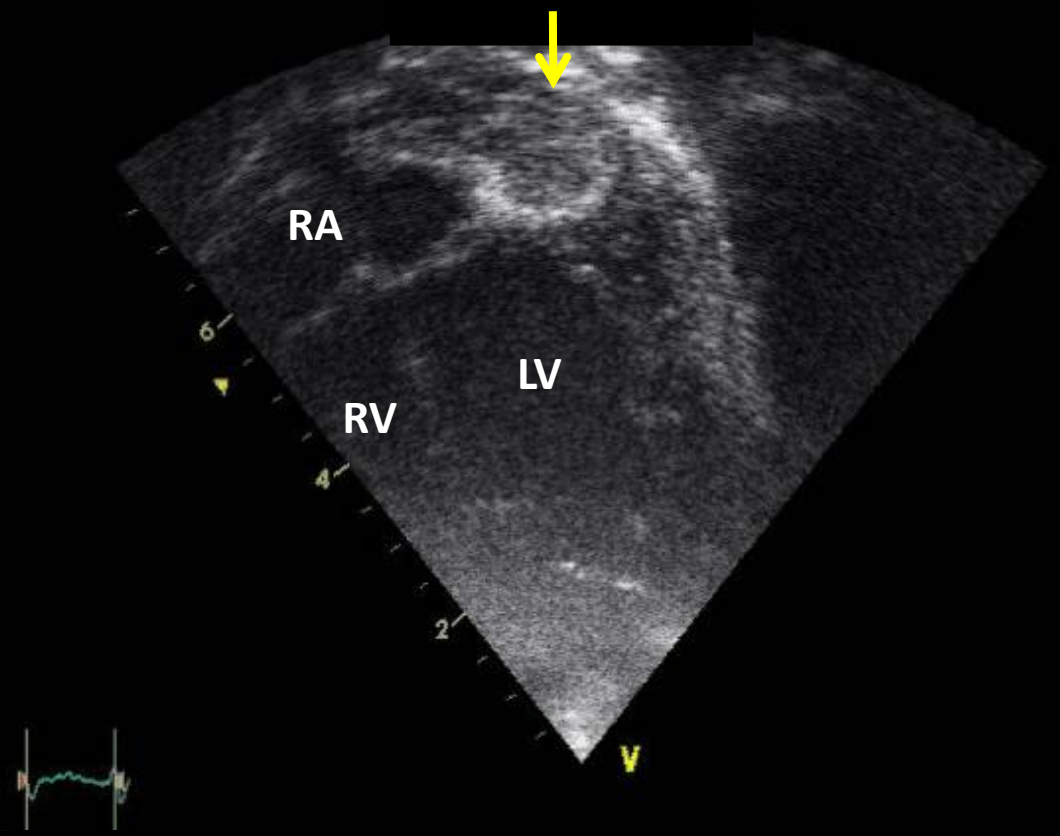
142
HR

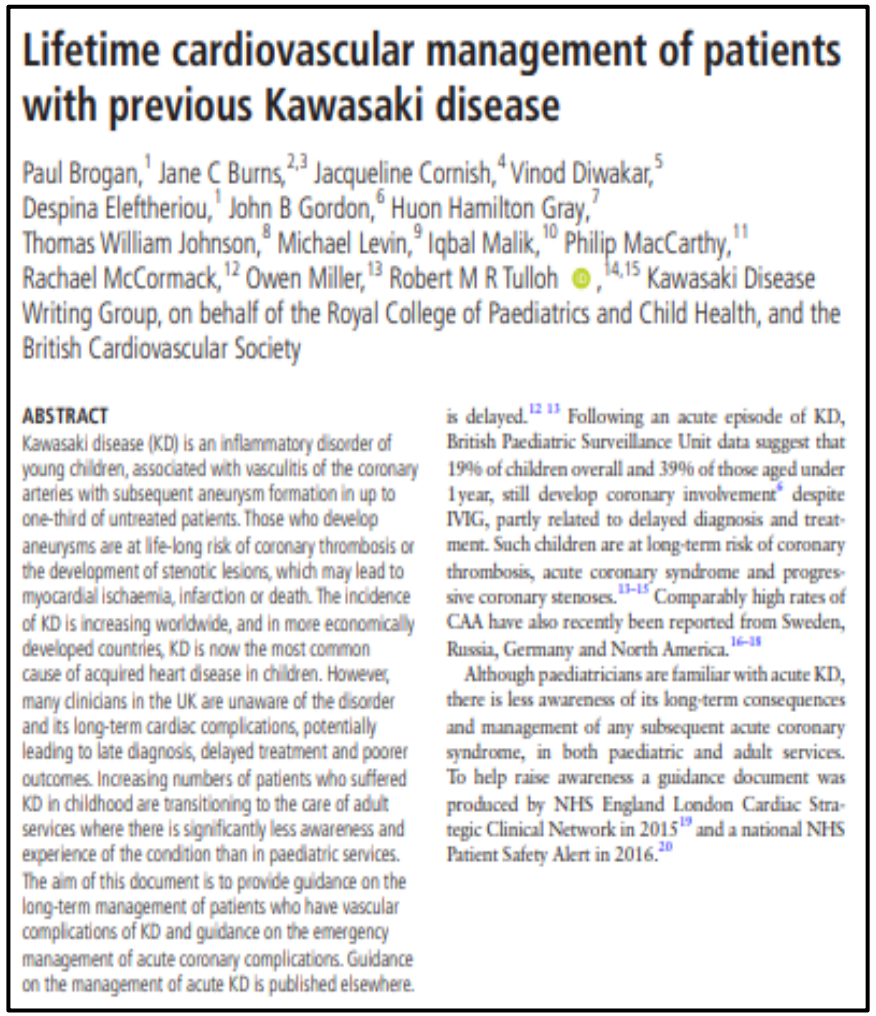
Non-occlusive thrombus



ACUTE CORONARY THROMBOSIS







Lifetime cardiovascular management of patients with previous Kawasaki disease

Paul Brogan,[1] Jane C Burns,[2,3] Jacqueline Cornish,[4] Vinod Diwakar,[5] Despina Eleftheriou,[1] John B Gordon,[6] Huon Hamilton Gray,[7] Thomas William Johnson,[8] Michael Levin,[9] Iqbal Malik,[10] Philip MacCarthy,[11] Rachael McCormack,[12] Owen Miller,[13] Robert M R Tulloh ,[14,15] Kawasaki Disease Writing Group, on behalf of the Royal College of Paediatrics and Child Health, and the British Cardiovascular Society

ABSTRACT

Kawasaki disease (KD) is an inflammatory disorder of young children, associated with vasculitis of the coronary arteries with subsequent aneurysm formation in up to one-third of untreated patients. Those who develop aneurysms are at life-long risk of coronary thrombosis or the development of stenotic lesions, which may lead to myocardial ischaemia, infarction or death. The incidence of KD is increasing worldwide, and in more economically developed countries, KD is now the most common cause of acquired heart disease in children. However, many clinicians in the UK are unaware of the disorder and its long-term cardiac complications, potentially leading to late diagnosis, delayed treatment and poorer outcomes. Increasing numbers of patients who suffered KD in childhood are transitioning to the care of adult services where there is significantly less awareness and experience of the condition than in paediatric services. The aim of this document is to provide guidance on the long-term management of patients who have vascular complications of KD and guidance on the emergency management of acute coronary complications. Guidance on the management of acute KD is published elsewhere.

is delayed.[12 13] Following an acute episode of KD, British Paediatric Surveillance Unit data suggest that 19% of children overall and 39% of those aged under 1 year, still develop coronary involvement[6] despite IVIG, partly related to delayed diagnosis and treatment. Such children are at long-term risk of coronary thrombosis, acute coronary syndrome and progressive coronary stenoses.[13–15] Comparably high rates of CAA have also recently been reported from Sweden, Russia, Germany and North America.[16–18]

Although paediatricians are familiar with acute KD, there is less awareness of its long-term consequences and management of any subsequent acute coronary syndrome, in both paediatric and adult services. To help raise awareness a guidance document was produced by NHS England London Cardiac Strategic Clinical Network in 2015[19] and a national NHS Patient Safety Alert in 2016.[20]

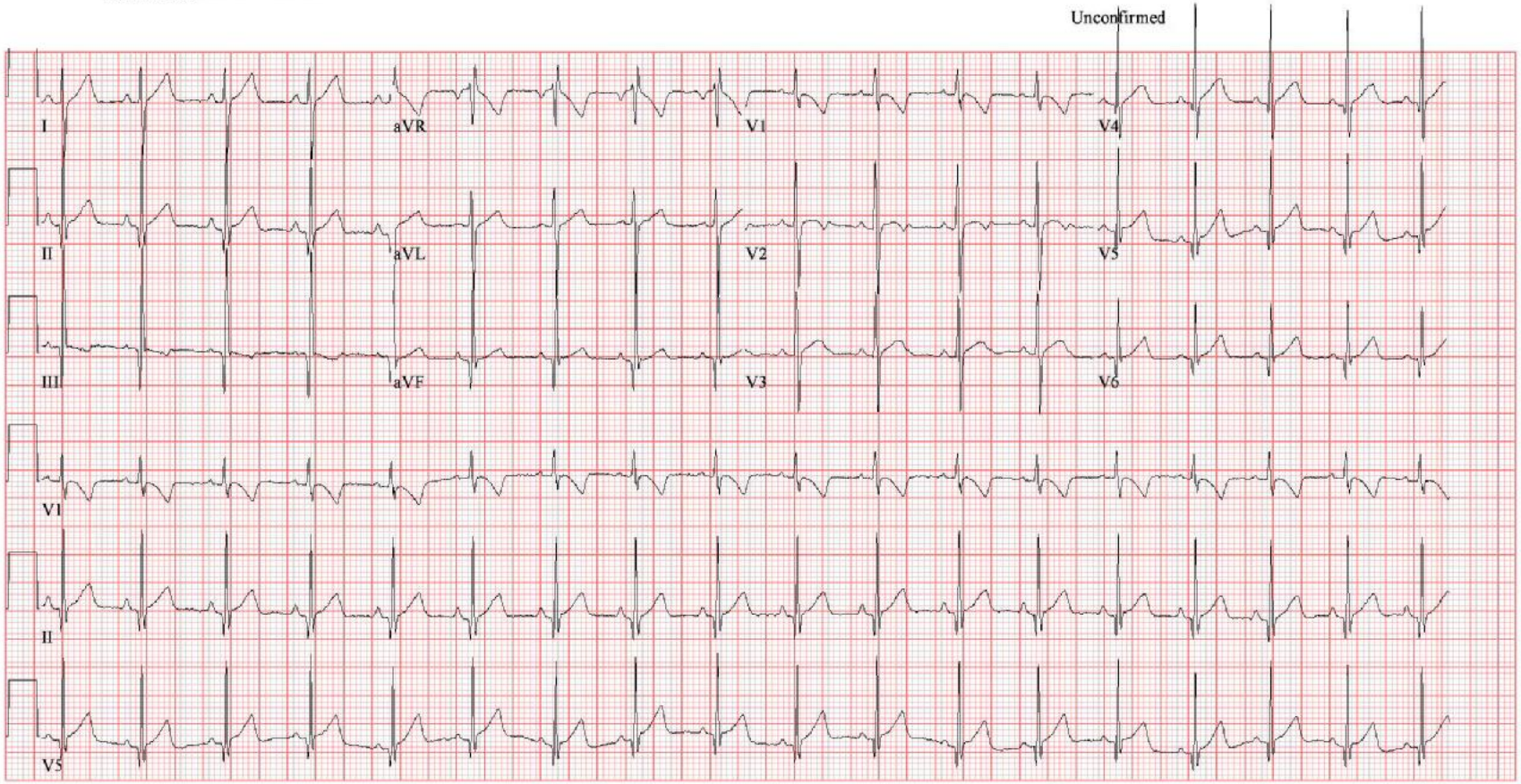
"initial ECG and troponin may be unremarkable"

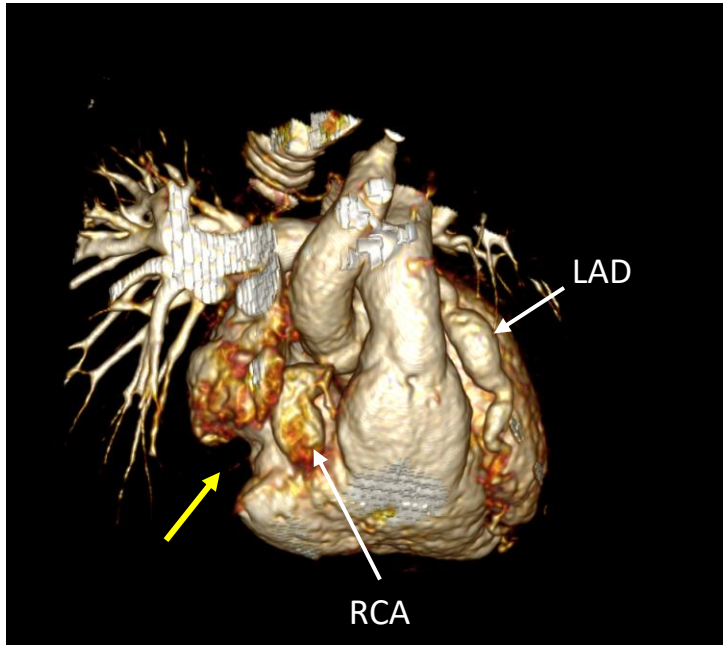
"An unusual feature of children with persistent significant coronary involvement as a consequence of KD is that they can develop significant coronary collaterals over time, such that even complete thrombotic occlusion of a coronary artery may not result in myocardial ischaemia. Coronary thrombosis per se is therefore not necessarily a call to action if there is no myocardial territory at risk but always requires rapid review of antithrombotic strategy and of the overall management plan. The presence of myocardial ischaemia is the most important factor that should prompt consideration of coronary intervention."

"In all patients with a previous history of KD CAA, an initial ECG and troponin may be unremarkable"

*** Pediatric ECG analysis * **
Normal sinus rhythm
Normal ECG

Unconfirmed





EMERGENCY PATHWAY

NHS
Guy's and St Thomas'
NHS Foundation Trust

Kawasaki Disease Pathway Children < 16 years

Person Specific Protocol

London Ambulance Service NHS Trust
Patient Specific Protocol

This document MUST be shown to the ambulance crew immediately upon their arrival

This protocol has been specifically prepared for the patient named below and details the treatment to be given in specified circumstances.

Reason for protocol:

Elia has Kawasaki disease. He is known to Dr Filip Kucera, Paediatric Cardiologist at Great Ormond Street Hospital. Elia is at high risk of having a coronary artery thrombosis, leading to acute myocardial ischaemia or myocardial infarction. As Elia is an infant, his symptoms may be non-specific and could include inconsolable crying or persistent lethargy, pallor, excessive sweating or breathlessness. There is also a risk that Elia could present with a sudden cardiac arrest.

Specific Treatment / Instructions:

In the event of a sudden illness, Elia's parents and the medical teams involved in his care have agreed to the following plan. Elia's parents have been advised to contact the London Ambulance Service immediately. His acute management will include the following:

- If there is any concern that Elia could be having an acute coronary event, he should be **transported without delay to Evelina London Children's Hospital**.
- If his illness is obviously non-cardiac in nature (obvious respiratory infection, acute gastroenteritis, rash etc.), he should be taken to his nearest hospital, Homerton Hospital, where he should be prioritised to see the on call paediatric team as soon as possible.
- If there is any doubt with regards to whether his presentation is of cardiac vs non-cardiac aetiology, he should be **considered to be having a possible coronary artery event, and transported to Evelina London Children's Hospital.**
- Emergency services should be aware that, due to his age, **Elia may not present with typical signs and symptoms of myocardial ischaemia, and that his ECG may be normal, and the Troponin may remain negative even in the face of a coronary artery thrombosis.**
- In the event of Elia presenting with a **cardiac arrest or peri-arrest picture**, Basic and Advanced Life Support should be initiated and he should be transported to **Evelina London Children's Hospital.**

In the event of a clinical emergency, please initiate emergency treatment as per the above letter, and contact the Cardiology Registrar / Fellow at Great Ormond Street Hospital (via switchboard on local phone 1632 OR bleep 0548).

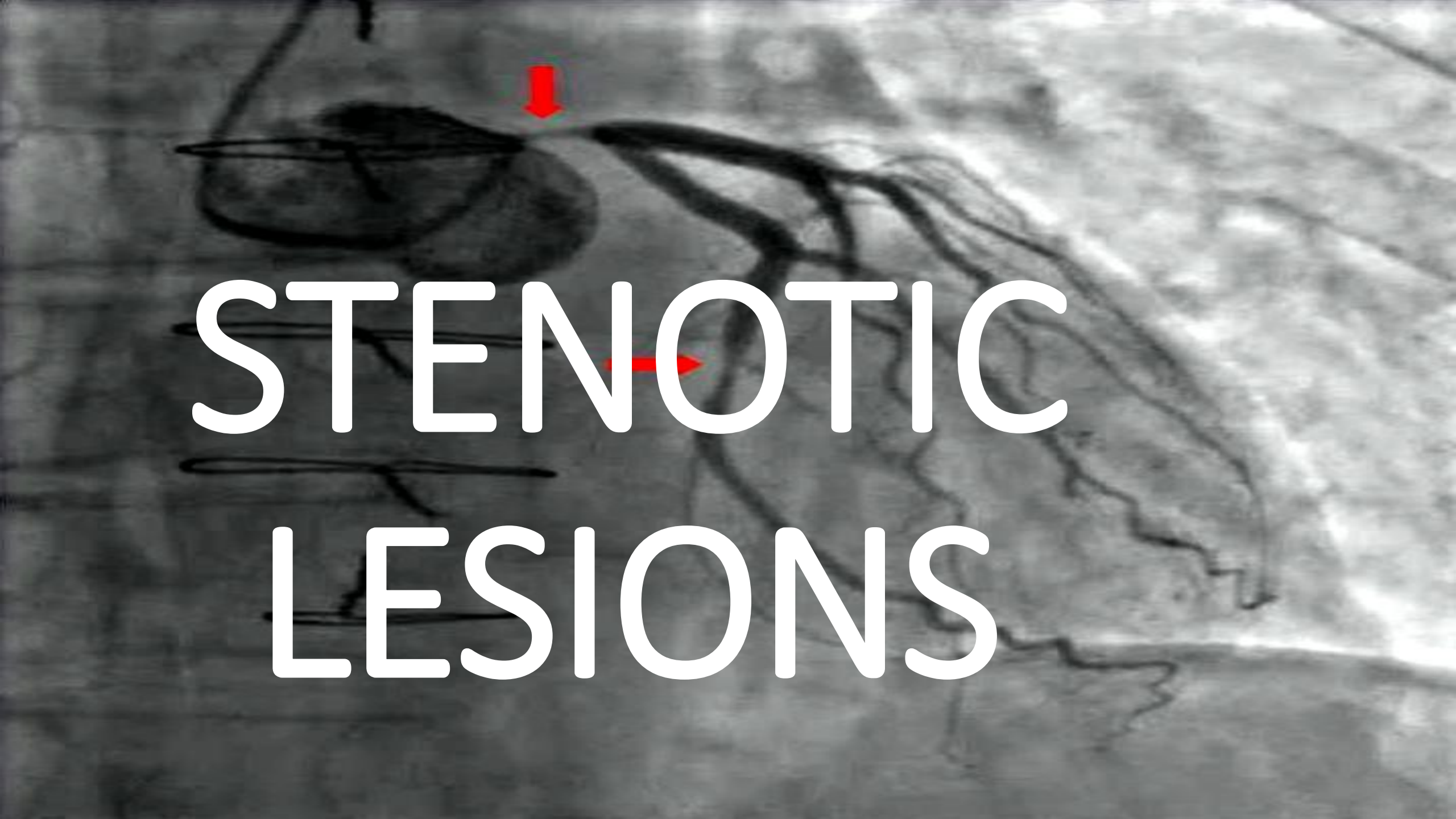
Name of Responsible Clinician:

Dr Filip Kucera, Paediatric Cardiologist

Facility:

Great Ormond Street Hospital for Children NHS Foundation Trust

Tel: 020 7405 9200


STENOTIC
LESIONS

Luminal Myofibroblastic Proliferation

Fatal obliterative coronary vasculitis in Kawasaki disease

Michael Ellis McConnell, MD, David Ward Hannon, MD, Robert Dennis Steed, MD, and Mary G. F. Gilliland, MD

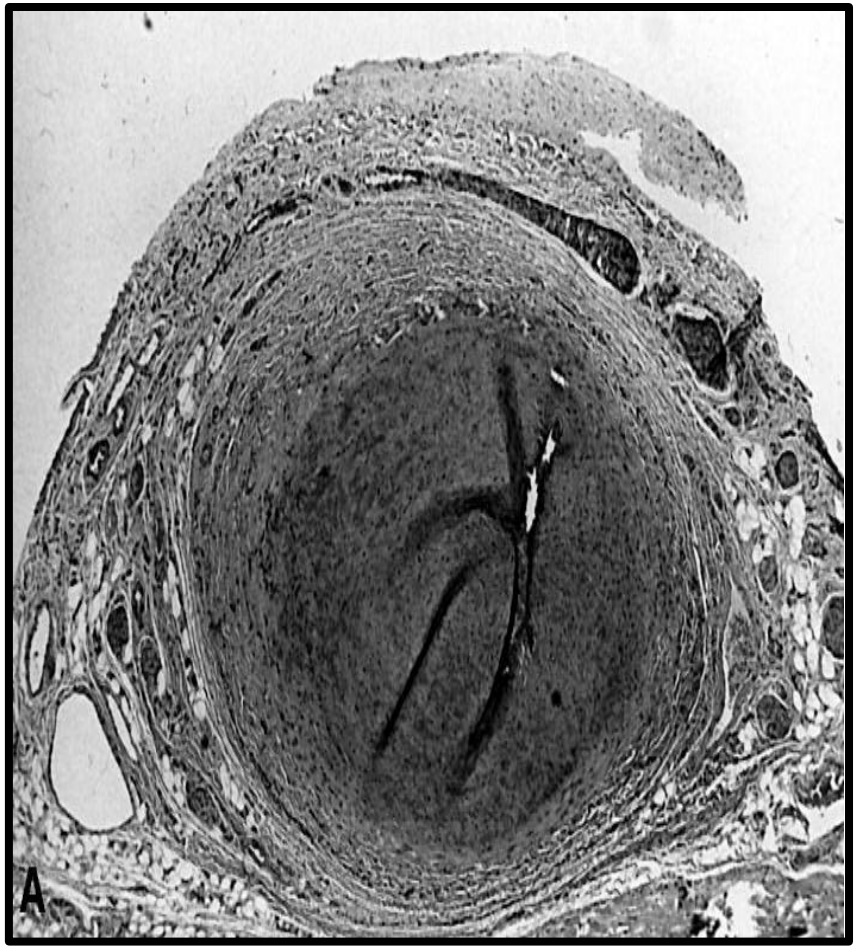
We report a unique case of Kawasaki disease with late sudden death from obliteration of the lumen of the full length of the left anterior descending coronary artery. Sequential echocardiograms showed early uniform coronary dilatation that resolved before sudden death. The implications of obliterative "healing" of coronary ectasia are unknown. (J Pediatr 1998;133:259-61)

Late mortality after Kawasaki disease is rare. Several large series report that late myocardial infarction or sudden death is limited to patients with thrombosis in giant coronary artery aneurysms (>8 mm of the entire left anterior descending coronary artery and left main coronary without focal coronary stenosis or coronary aneurysms.

Case Report

A 3½-year-old black child with a history of asthma had signs of lower respiratory infection and reactive airway disease. He received antibiotics, inhaled and systemic steroids, and ibuprofen. Ten days later his respiratory symptoms improved, and during the next 3 days he had fever to

IVIG Intravenous gamma globulin

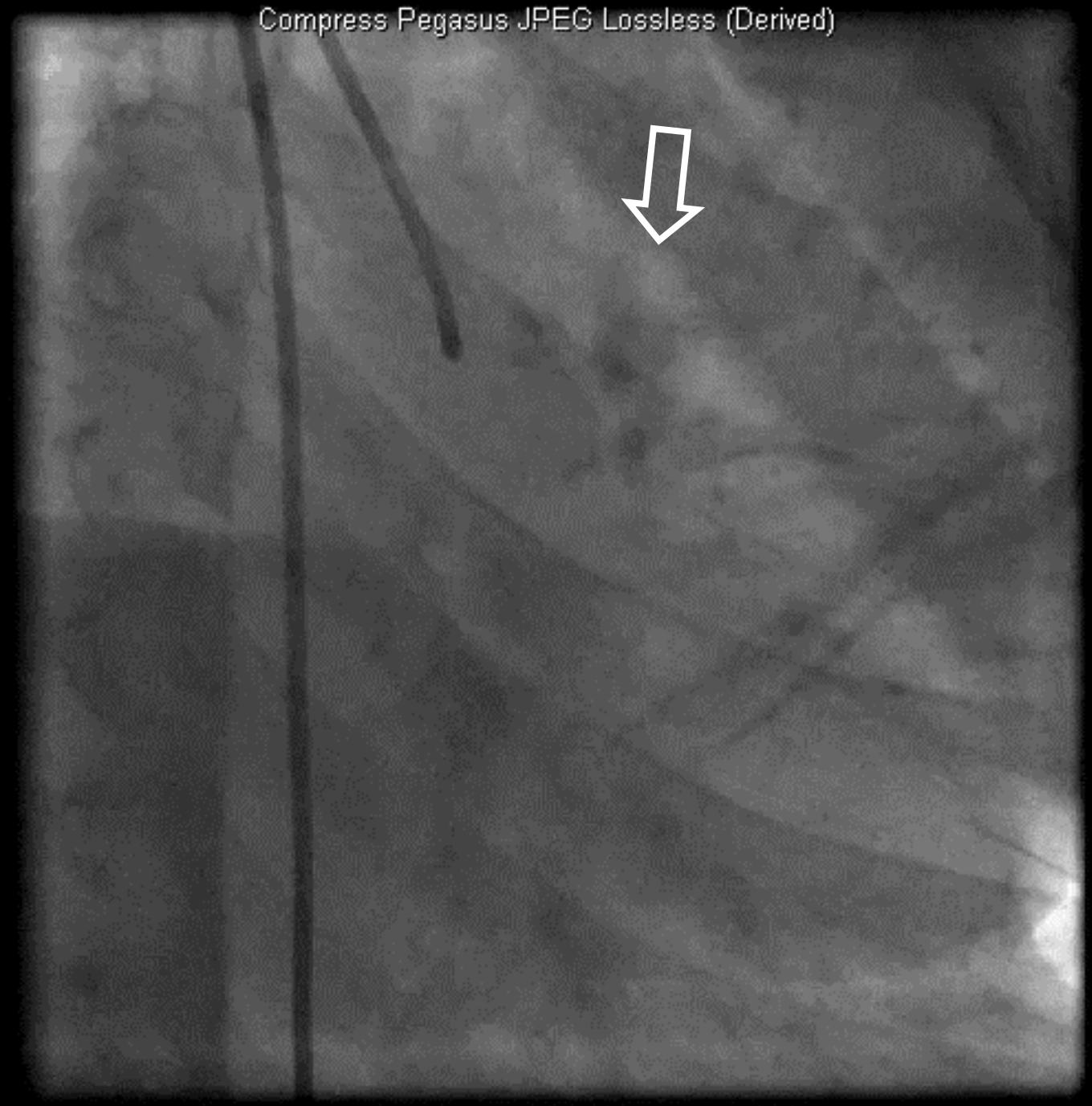


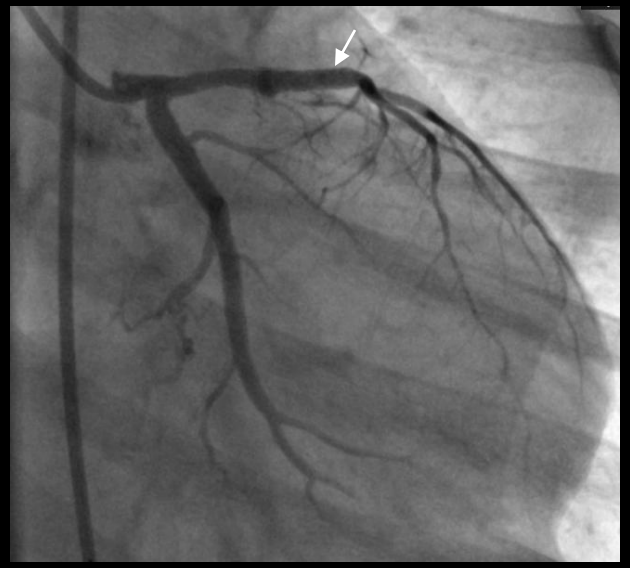
- † after 7 months
- 17 week: LMCA 3.1mm, LAD 2.3mm, RCA 2.1mm

Case	Time since onset	Cause of death/TX	CA pathology
1	10 days	Myocarditis	SA/C-LMP
2	13 days	Ruptured LAD CAA	Waning necrotizing arteritis, thrombosed. SA/C-LMP LAD
3	2 wks	Ruptured LCAA, TX	CABG & over-sewn [illegible], no SA/C- LMP visible
4	2.5 wk	Ruptured giant LAD CAA	Giant CAA LAD, x2 RCA. SA/C-LMP
5	2.5 wk	Ruptured left main CAA	RCAA thrombosed. SA/C-LMP
6	2.5 wk	MI	CAA RCA, LAD, thrombosed. SA/ C-LMP LAD occluded
7	3 wk	MI	Thrombosed CAA. SA/C-LMP
8	3 wk	Ruptured CAA	CAA, fresh & organizing thrombi, calcified. SA/C-LMP
9	3 wk	Ruptured giant LAD CAA	Fresh thrombi, LAD, LCx, RCAA
10	3.5 wk	MI	RCAA fresh thrombus. LCA SA/C-LMP
11	3–4 wk	Thrombosed mesenteric aneurysm, organizing, recanalized, SI infarct	Aneurysms, CA/ Fresh thrombus RCA. Severe SA/C-LMP
12	3–4 wk	MI	CAAs fresh & organizing calcified thrombi. Long dilated thrombosed CAs with SA/C-LMP to 95%
13	4 wk	Ruptured RCIAA	Multiple CAA, SA/C-LMP CAs
14	4 wks	MI	CAAs, LAD, LCx thrombosed. SA/C-LMP, severe
15	4 wk	Massive MI	CAA, LAD, thrombosed. SA/C- no LMP
16	4 wk	MI	CAAs, [illegible] LCA, LAD, LCx, thrombosed
17	4–5 wk	MI	CAAs, LAD, LCX, RCA, large fresh thrombi, SA/C-LMP
18	5 wk	MI	Acute thrombosis LCxCAA, RCAA, SA/C-LMP
19	5 wk	MIs	Giant LAD CAA, fresh & organizing thrombi, calcified, recanalized, RCAA, SA/C-LMP, severe
20	6 wk	MI	CAA, fresh, organizing & organized thrombi
21	6 wk	MI	RCAA fresh thrombus. SA/C-LMP LAD & LtCx, organized thrombi
22	6.5 wk	MI	CAA, fresh, organizing, organized thrombi, calcified
23	2 mo	MI	CAA, RCA, LAD, fresh, calcified, organizing thrombi, calcified
24	3 mo	MI; TX	CAAs, organizing, organized calcified thrombi. RCAA, long fresh thrombus. Focal SA/C-LMP
25	4.5 mo	MI	CAA & SA/C-LMP
26	5 mo	MI;TX	RCAA no thrombi. Marked SA/C-LMP
27	7.5 mo	MI	Multiple CAA, no thrombi. Marked SA/C-LMP RCA, LCx, LAD, 90–10 stenosed
28	10 mo	MI	SA/C-LMP to 95% stenotic, or fresh thrombus
29	1 yr	MI	Giant CAA, organizing thrombus. SA/C-LMP LAD, 4 cm dilation
30A	15 mo	MI; TX1	RCAA fresh & organized thrombus. LCAA organizing thrombus, calcified SA/C-LMP
30B	11.5 yr	MI; TX2	CAs to 90% luminal stenosis
30C	14 yr	CA insufficiency; TX3	Luminal occlusion LAD, RCA, LCx. Intimal foamy Mac SMC. Mast cells
31	16 mo	MI	Lt main CAA thrombosed. SA/C-LMP, LCx, LAD, RCA
32	18 mo	Chronic ischemia; TX	RCAA. SA/C-LMP, no thrombi
33	2 yr	MI; TX	Lt main CAA, fresh & organizing thrombi, calcified
34	16 yr	Incidental finding during cardiac catheterization for WPW; aneurysm resected	RCAA. SA/C-LMP
35	19 yr	MI	SA/C-LMP to 80% stenotic
36	U	MI	Thrombosed CAA
37	U	MI; TX	LADCAA, fresh thrombus. SA/C-LMP thrombi, organized, recanalized, calcified
38	U	MI	Giant CAA LAD, fresh & organizing, thrombi, re-canalized, calcified. RCAA. SA/C-LMP to 90% stenosis
39	U	MI	RCAA, long fresh thrombus, CAA thrombus, organized, calcified
40	U	MI	CAAs, fresh thrombi
41	U	MI	Giant CAAs, fresh & organizing thrombi, calcified. SA/C-LMP

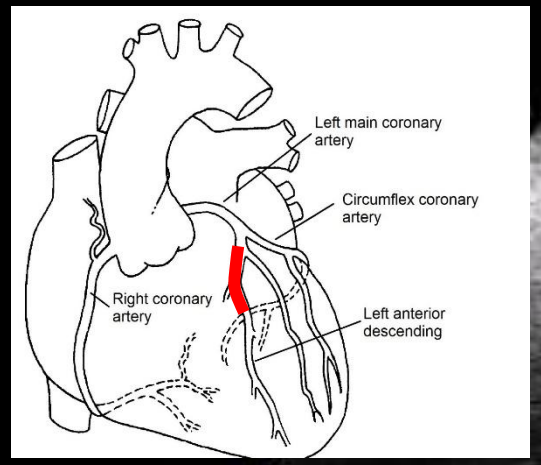
(n = 41) **Specimens from 32 autopsies, 8 cardiac transplants, and an excised coronary aneurysm**

Orenstein JM,et al. (2012) Three Linked Vasculopathic Processes Characterize Kawasaki Disease: A Light and Transmission Electron Microscopic Study





LAD after rotational ablation and stenting



Lossy Compressed (Derived)

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68
HR

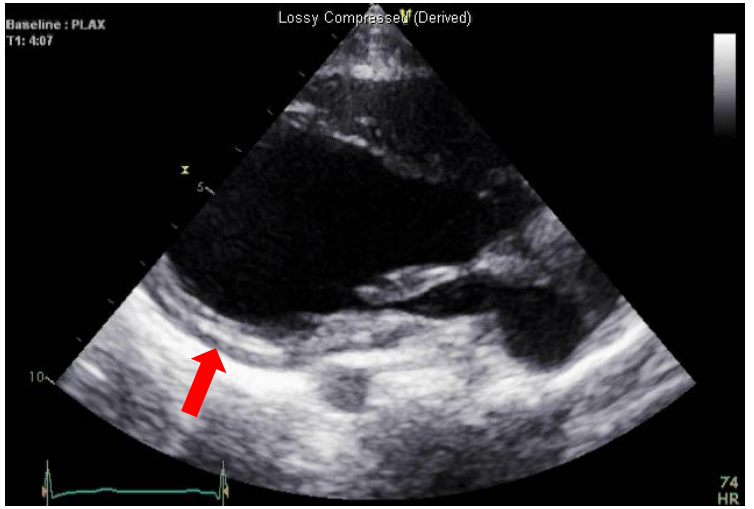
STRESS ECHOCARDIOGRAPHY

- exercise, dobutamine, and dipyridamole stress

  sensitivity 85%, 80%, and 78%

  specificity of 77%, 86%, and 91%

Stress echocardiography for the diagnosis and risk stratification of patients with suspected or known coronary artery disease: a critical appraisal. R Senior, et al. Heart. 2005 Apr



- N = 47 Tx.

  sensitivity 88.9% (95% CI 51.8%, 99.7%)

  specificity 91.9% (95% CI, 71.8%, 98.3%)

Utility of exercise stress echocardiography in pediatric cardiac transplant recipients: a single-center experience. Chen MH1,et al. J Heart Lung Transplant. 2012 May;31(5):517-23.

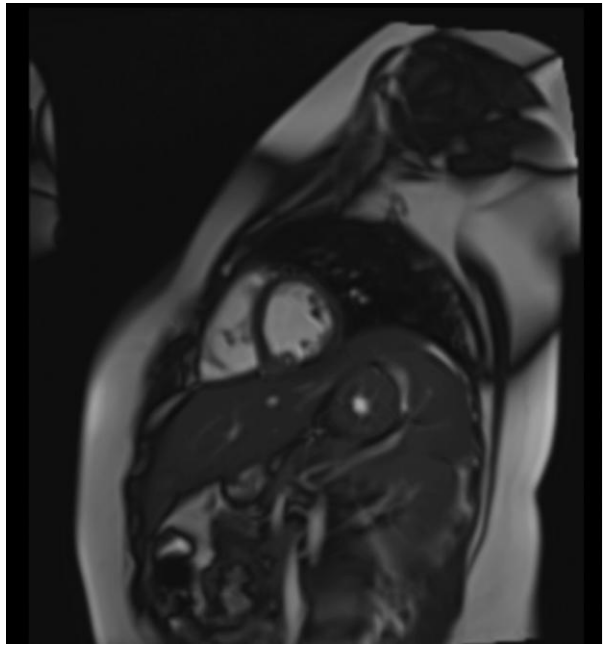
STRESS MRI

- N=761

  sensitivity 89.1% (95% CI, 84-93%)

  specificity 84.9% (95% CI, 76.6-91.1%)

Diagnostic performance of cardiac stress perfusion MRI in the detection of coronary artery disease using fractional flow reserve as the reference standard: a meta-analysis. Desai RR1, Jha S. AJR Am J Roentgenol. 2013 Aug;201(2):W245-52

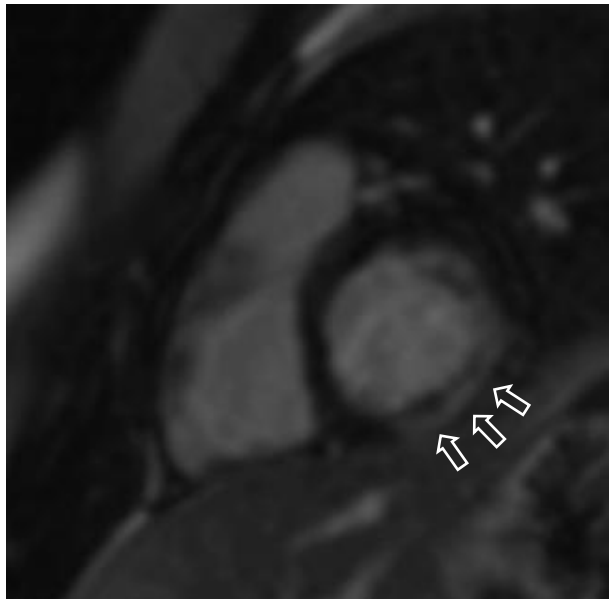


- N=58, median age 14.1 y (IQR 10.9–16.2)

  sensitivity 100% (95% CI: 71.6–100%),

  specificity 98% (95% CI: 86.7–99.9%)

Utility of adenosine stress perfusion CMR to assess paediatric coronary artery disease, Hopewell N. Ntsinjana, Oliver Tann, et al. Eur Heart J Cardiovasc Imaging. 2017 Aug; 18(8): 898–905.



5. How should we anticoagulated patients with Kawasaki disease?

Aneurysm	Z score
Dilatation	+2.0 to +2.5
Small	+2.5 to +5.0
Medium	+5.0 to +10.0
Giant	> +10.0 or > 8mm

McCrindle at al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease, A Scientific Statement for Health Professionals From the American Heart Association

Risk Level	Low-Dose ASA	Anticoagulation (Warfarin or LMWH)	Dual Antiplatelet Therapy (ASA+Clopidogrel)	β-Blocker	Statin
1: No involvement	6–8 wk then discontinue	Not indicated	Not indicated	Not indicated	Not indicated
2: Dilation only	Continuation after 6–8 wk is reasonable	Not indicated	Not indicated	Not indicated	Not indicated
3.1: Small aneurysm, current or persistent	Continue	May be considered	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered
3.2: Small aneurysm, regressed to normal or dilation only	Continue, but discontinuation may also be considered	Not indicated	Not indicated	Not indicated	Empirical therapy may be considered
4.1: Medium aneurysm, current or persistent	Continue	May be considered	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered
4.2: Medium aneurysm, regressed to small aneurysm	Continue	Not indicated	May be considered	Not indicated	Empirical therapy may be considered
4.3: Medium aneurysm, regressed to normal or dilation only	Continue	Not indicated	May be considered	Not indicated	Empirical therapy may be considered
5.1: Large and giant aneurysm, current or persistent	Continue	Reasonably indicated	May be considered in addition to anticoagulation	May be considered	Empirical therapy may be considered
5.2: Large or giant aneurysm, regressed to medium aneurysm	Continue	Reasonably indicated	May be considered as an alternative to anticoagulation	May be considered	Empirical therapy may be considered
5.3: Large or giant aneurysm, regressed to small aneurysm	Continue	May be considered	May be considered as an alternative to anticoagulation	May be considered	Empirical therapy may be considered
5.4: Large or giant aneurysm, regressed to normal or dilation only	Continue	Not indicated	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered

IN PATIENTS WITH GIANT ANEURYSMS:

- (meta-analysis 6 studies) **WARFARIN** + **ASPIRIN** lower rates of MI (odds ratio 0.27; 95% CI 0.11-0.63) and death (OR 0.18; 95% CI 0.02-0.29) compared with **ASPIRIN ALONE**

  Cardiology. 2014;129(1) Su D1 et al. Safety and efficacy of warfarin plus aspirin combination therapy for giant coronary artery aneurysm secondary to Kawasaki disease: a meta-analysis)

- no difference in thrombotic CA occlusions between **LMWH** and **WARFARIN**

  Long-term anticoagulation in Kawasaki disease: Initial use of low molecular weight heparin is a viable option for patients with severe coronary artery abnormalities.AUManlhiot C, Brandão LR, Somji Z, Chesney AL, MacDonald C, at al. Pediatr Cardiol. 2010;31(6):834.

Clinical Trial > J Pediatr Hematol Oncol. 2015 Jan;37(1):1-9.
doi: 10.1097/MPH.0000000000000291.

Prasugrel in children with sickle cell disease: pharmacokinetic and pharmacodynamic data from an open-label, adaptive-design, dose-ranging study

Lori Styles [1], Darell Heiselman, Lori E Heath, Brian A Moser, David S Small, Joseph A Jakubowski, Chunmei Zhou, Rupa Redding-Lallinger, Matthew M Heeney, Charles T Quinn, Sohail R Rana, Julie Kanter, Kenneth J Winters

Affiliations + expand

PMID: 25493452 DOI: 10.1097/MPH.0000000000000291

Abstract

Introduction: This phase 2 study was designed to characterize the relationship among prasugrel dose, prasugrel's active metabolite (Pras-AM), and platelet inhibition while evaluating safety in children with sickle cell disease. It was open-label, multicenter, adaptive design, dose ranging, and conducted in 2 parts. Part A: Patients received escalating single doses leading to corresponding increases in Pras-AM exposure and VerifyNow® P2Y12 (VN) platelet inhibition and decreases in VNP2Y12 reaction units and vasodilator-stimulated phosphoprotein platelet reactivity index. Part B: Patients were assigned daily doses (0.06, 0.08, and 0.12 mg/kg) based on VN pharmacodynamic measurements at the start of 2 dosing periods, each 14±4 days. Platelet inhibition was significantly higher at 0.12 mg/kg (56.3%±7.4%; least squares mean±SE) compared with 0.06 mg/kg (33.8%±7.4%) or 0.08 mg/kg (37.9%±5.6%). Patients receiving 0.12 mg/kg achieved ≥30% platelet inhibition; only 1 patient receiving 0.06 mg/kg exceeded 60% platelet inhibition. High interpatient variability in response to prasugrel and the small range of exposures precluded rigorous characterization of the relationship among dose, Pras-AM, and platelet inhibition.

Safety: No hemorrhagic events occurred in Part A; 3 occurred in Part B, all mild and self-limited.

Conclusions: Most children with sickle cell disease may achieve clinically relevant platelet inhibition with titration of daily-dose prasugrel.

Am J Hematol. 2018 Dec; 93(12): 1493–1500.
Published online 2018 Oct 2. doi: 10.1002/ajh.25273
PMCID: PMC6282821
PMID: 30187935

A dose-ranging study of ticagrelor in children aged 3-17 years with sickle cell disease: A 2-part phase 2 study

Lewis L. Hsu,[✉1] Sharada Sarnaik,[2] Suzan Williams,[3] Carl Amilon,[4] Jenny Wissmar,[5] Anders Berggren,[5] and on behalf of the HESTIA1 Investigators

Associated Data

▸ **Supplementary Materials**

Abstract

Go to: ▸

Antiplatelet treatment is a potential therapeutic approach for sickle cell disease (SCD). Ticagrelor inhibits platelet aggregation and is approved for adults with acute coronary syndrome and following myocardial infarction. HESTIA1 (NCT02214121) was a 2-part, phase 2 dose-finding study generating ticagrelor exposure, platelet inhibition, and safety data in children with SCD (3-17 years). In part A (n = 45), patients received 2 ticagrelor single doses, 0.125-2.25 mg/kg (washout ≥7 days), then 7 days of twice-daily (bid) dosing with 0.125, 0.563, or 0.75 mg/kg. In the 4-week blinded Part B extension (optional), patients received ticagrelor (0.125, 0.563, or 0.75 mg/kg bid; n = 16) or placebo (n = 7). Platelet reactivity decreased from baseline to 2 hours postdosing, and returned to near baseline after 6 hours postdosing. Dose-dependent platelet inhibition was seen with ticagrelor; mean relative $P2Y_{12}$ reaction unit inhibition 2 hours after a single dose ranged from 6% (0.125 mg/kg) to 73% (2.25 mg/kg). Ticagrelor plasma exposure increased approximately dose proportionally. No patients experienced a hemorrhagic event during treatment. No differences were seen between groups in pain ratings and analgesic use during Part B. Ticagrelor was well tolerated with no safety concerns, no discontinuations due to adverse events (AEs), and reported AEs were mainly due to SCD. In conclusion, a dose-exposure-response relationship for ticagrelor was demonstrated in children with SCD for the first time. These data are important for future pediatric studies of the efficacy and safety of ticagrelor in SCD.

Direct Oral Anticoagulants

Table 1 Use of direct oral anticoagulant in ischaemic heart disease

Study	Study target	Drugs	Results	Notes
ESTEEM trial ($n = 1883$)	Patients with ACS (STEMI or NSTEMI), on aspirin therapy • Phase 2	Ximelagatran, direct factor II inhibitor	• At 6 months 26% reduction of ischaemic outcome • 97% increase of major bleeding	Drug removed from the market for hepatic toxicity
RUBY-1 trial ($n = 1279$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Darexaban, direct factor Xa inhibitor	• At 6 months no reduction of ischaemic outcome • 128% increase of major bleeding	No further studies planned
RE-DEEM trial ($n = 1861$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Dabigatran, direct factor II inhibitor	• At 6 months 77-327% increase of major bleeding according to the dose tested	No further studies planned
ATLAS-ACS-TIMI ($n = 3491$)	Patients with ACS, on aspirin or aspirin and thienopyridine • Phase 2	Rivaroxaban, direct factor Xa inhibitor	• 31% reduction of ischaemic outcome • Dose-dependent increase in bleeding episodes	
APPRAISE trial ($n = 1715$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Apixaban, direct factor Xa inhibitor	• At 6 months and at 5 mg bid 27% reduction of the ischaemic outcome • Dose-dependent increase in major bleeding episodes	Riduzione dell' outcome ischaemico more significant for aspirin only
APPRAISE 2 Trial ($n = 7392$)	High-risk patients after ACS, on aspirin and clopidogrel therapy • Phase 3	Apixaban 5 mg bid, direct factor Xa inhibitor	• Study suspended early for excessive major bleeding episodes without benefits in ischaemic outcome	
ATLAS-ACS2-TIMI ($n = 15\,526$)	Patients with ACS, on aspirin and thienopyridine • Phase 3	Rivaroxaban 2.5 mg or 5 mg bid, direct factor Xa inhibitor	• At 2.5 mg bid reduction of primary ischaemic outcome, reduction cardiovascular mortality, and total mortality, reduction intrastent thrombosis • Increase major and intracranial bleeding events, but not fatal bleeding events	
GEMINI ACS ($n = 3.037$)	Patients with ACS, on clopidogrel or ticagrelor, without aspirin • Phase 2	Rivaroxaban 2.5 mg bid, direct factor Xa inhibitor	• Compared with aspirin similar bleeding events. Ischaemic outcome similar	Study underpowered for evaluation of ischaemic events
COMPASS trial ($n = 27\,395$)	Patients with stable cardiovascular disease divided in three groups: aspirin alone, aspirin + Rivaroxaban 2.5 mg bid, Rivaroxaban only 5 mg bid • Phase 3	Rivaroxaban 2.5 mg bid +aspirin vs. rivaroxaban 5 mg bid vs. aspirin	• Reduction of the composite outcome of cardiovascular death, infarction, stoke. Reduction total mortality • Increase of major bleeding episodes but not fatal or critical bleeding episodes	
COMPASS trial (coronaropatia) ($n = 24\,824$)	Patients enrolled in the COMPASS with stable coronary artery disease • Phase 3	Rivaroxaban 2.5 mg bid + aspirin vs. rivaroxaban 5 mg bid vs. aspirin	• Reduction of the composite outcome of cardiovascular death, infarction, stoke. Reduction total mortality	

Use of direct oral anticoagulant in ischaemic heart disease: the COMPASS study Luca A.European Heart Journal Supplements (2019) 21 (Supplement B), B84–B87

Direct Oral Anticoagulants

Table 1 Use of direct oral anticoagulant in ischaemic heart disease

Study	Study target	Drugs	Results	Notes
ESTEEM trial ($n = 1883$)	Patients with ACS (STEMI or NSTEMI), on aspirin therapy • Phase 2	Ximelagatran, direct factor II inhibitor	• At 6 months 26% reduction of ischaemic outcome • 97% increase of major bleeding	Drug removed from the market for hepatic toxicity
RUBY-1 trial ($n = 1279$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Darexaban, direct factor Xa inhibitor	• At 6 months no reduction of ischaemic outcome • 128% increase of major bleeding	No further studies planned
RE-DEEM trial ($n = 1861$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Dabigatran, direct factor II inhibitor	• At 6 months 77-327% increase of major bleeding according to the dose tested	No further studies planned
ATLAS-ACS-TIMI ($n = 3491$)	Patients with ACS, on aspirin or aspirin and thienopyridine • Phase 2	Rivaroxaban, direct factor Xa inhibitor	• 31% reduction of ischaemic outcome • Dose-dependent increase in bleeding episodes	
APPRAISE trial ($n = 1715$)	Patients with ACS (STEMI or NSTEMI), on aspirin and clopidogrel therapy • Phase 2	Apixaban, direct factor Xa inhibitor	• At 6 months and at 5 mg bid 27% reduction of the ischaemic outcome • Dose-dependent increase in major bleeding episodes	Riduzione dell' outcome ischaemico more significant for aspirin only
APPRAISE 2 Trial ($n = 7392$)	High-risk patients after ACS, on aspirin and clopidogrel therapy • Phase 3	Apixaban 5 mg bid, direct factor Xa inhibitor	• Study suspended early for excessive major bleeding episodes without benefits in ischaemic outcome	
ATLAS-ACS2-TIMI ($n = 15\,526$)	Patients with ACS, on aspirin and thienopyridine • Phase 3	Rivaroxaban 2.5 mg or 5 mg bid, direct factor Xa inhibitor	• At 2.5 mg bid reduction of primary ischaemic outcome, reduction cardiovascular mortality, and total mortality, reduction intrastent thrombosis • Increase major and intracranial bleeding events, but not fatal bleeding events	
GEMINI ACS ($n = 3.037$)	Patients with ACS, on clopidogrel or ticagrelor, without aspirin • Phase 2	Rivaroxaban 2.5 mg bid, direct factor Xa inhibitor	• Compared with aspirin similar bleeding events. Ischaemic outcome similar	Study underpowered for evaluation of ischaemic events
COMPASS trial ($n = 27\,395$)	Patients with stable cardiovascular disease divided in three groups: aspirin alone, aspirin + Rivaroxaban 2.5 mg bid, Rivaroxaban only 5 mg bid • Phase 3	Rivaroxaban 2.5 mg bid +aspirin vs. rivaroxaban 5 mg bid vs. aspirin	• Reduction of the composite outcome of cardiovascular death, infarction, stoke. Reduction total mortality • Increase of major bleeding episodes but not fatal or critical bleeding episodes	
COMPASS trial (coronaropatia) ($n = 24\,824$)	Patients enrolled in the COMPASS with stable coronary artery disease • Phase 3	Rivaroxaban 2.5 mg bid + aspirin vs. rivaroxaban 5 mg bid vs. aspirin	• Reduction of the composite outcome of cardiovascular death, infarction, stoke. Reduction total mortality	

Use of direct oral anticoagulant in ischaemic heart disease: the COMPASS study Luca A.European Heart Journal Supplements (2019) 21 (Supplement B), B84–B87

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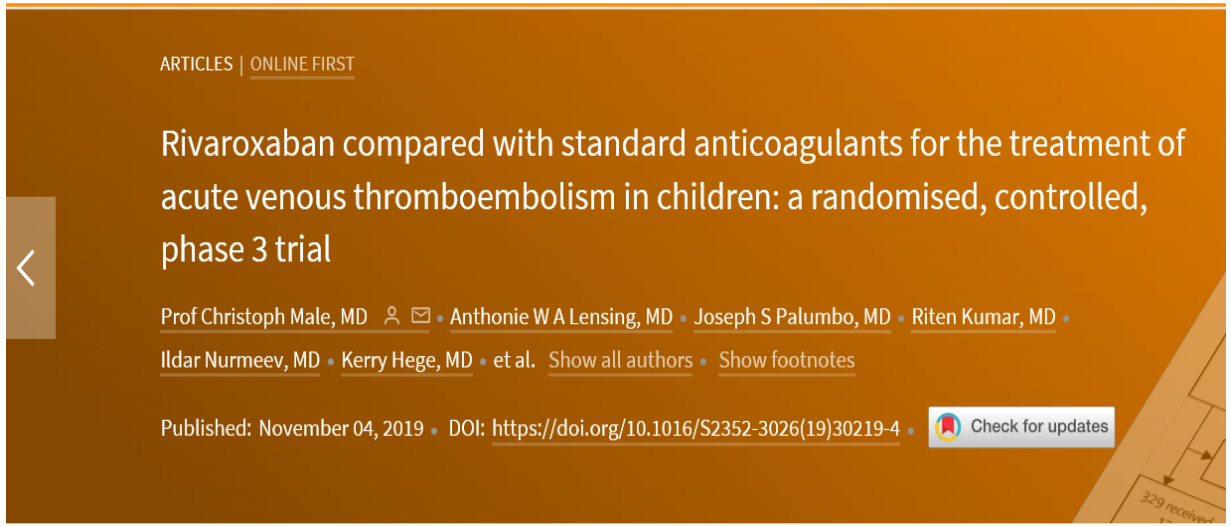

ARTICLES | ONLINE FIRST

Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial

Prof Christoph Male, MD • Anthonie W A Lensing, MD • Joseph S Palumbo, MD • Riten Kumar, MD • Ildar Nurmeev, MD • Kerry Hege, MD • et al. Show all authors • Show footnotes

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"In children with acute venous thromboembolism, treatment with **rivaroxaban** resulted in a similarly low recurrence risk and **reduced thrombotic burden without increased bleeding**, as compared with **standard anticoagulants**."

Kawasaki disease: case report of a diagnostic dilemma and often a missed diagnosis

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Background Management of cardiovascular sequelae to Kawasaki disease (KD) is challenging to adult cardiologists. Vasculitis of medium-sized arteries especially coronary arteries often leads to focal intimal thickening and aneurysmal dilatation of one or more coronary arteries. It needs special attention to recognize coronary artery involvement because of potential long-term morbidity and mortality. We present a case of diagnostic dilemma in young adult Chinese male with KD.

Case summary This asymptomatic patient was found to have deep Q waves in anterior leads on screening electrocardiography and was thought to have myocarditis after depiction of wall motion abnormality on echocardiography, later to be confirmed to have left anterior descending artery (LAD) territory infarct on cardiac magnetic resonance imaging. Coronary computed tomography angiogram depicted proximal LAD aneurysm with calcified plaque/thrombus. Additionally, there was an 18 mm giant right coronary artery (RCA) aneurysm with braid-like appearance and soft plaque (mural thrombus). His previous medical history included fever and cervical lymphadenopathy. Because of the high risk he was commenced on long-term low-dose aspirin and β-adrenergic-blocking agent to reduce myocardial oxygen consumption; however, 3 years later, he presented to the emergency department with acute inferior myocardial infarction. He was noted to have total occlusion of the proximal RCA and was treated aggressively with thrombectomy and percutaneous balloon angioplasty followed by medical management with β-blockers, sacubitril/valsartan, clopidogrel, and rivaroxaban without subsequent adverse cardiovascular events.

Discussion Kawasaki disease is one of the main causes of coronary artery disease in young adults and can be easily overlooked.

Keywords Case report • Kawasaki disease • Adult • Coronary artery aneurysm • Coronary artery disease • Plaque • Thrombus

6. Is there any long term risk in patients with normal coronary arteries ?

- KD mouse model - link between coronary arteritis and **accelerated atherosclerosis**

Chen S, et al. Marked acceleration of atherosclerosis after Lactobacillus casei-induced coronary arteritis in a mouse model of Kawasaki disease. Arterioscler Thromb Vasc Biol 2012;32:e60-71.

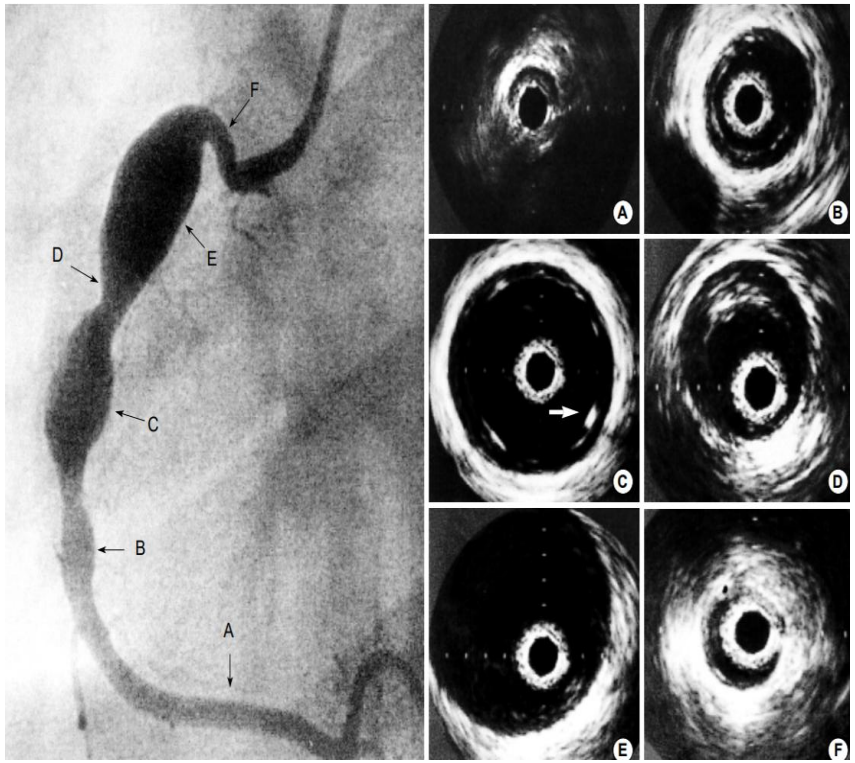
- **↘ myocardial flow reserve** in patient with “normal” CA

Muzik O, et al. Quantification of myocardial blood flow and flow reserve in children with a history of Kawasaki disease and normal coronary arteries using positron emission tomography. J Am Coll Cardiol 1996;28:757-62.

- **Persistance of markers of endothelial injury** (even in patients without CAA)

Cardiovascular status after Kawasaki disease in the UK V Shah, G. Christof, et al. Heart BMJ 2015

- **Thickened intima-media complex** in persistent / regressed CAA and in angiographically normal CA



Suzuki A, et al. Functional behavior and morphology of the coronary artery wall in patients with Kawasaki disease assessed by intravascular ultrasound. J Am Coll Cardiol 1996;27:291-6.

STATINS

- **Pravastatin improves** endothelial function and reduces low-grade **chronic inflammation** in patients with coronary aneurysms

Duan C et al. World J Pediatr. 2014 Aug;10(3):232-7. Effect of pravastatin on endothelial dysfunction in children with medium to giant coronary aneurysms due to Kawasaki disease.

- ***Statins Study in Kawasaki Disease Children With Coronary Artery Abnormalities***

(12/2022, 25 centres, Shanghai, China)

-> effects on CAs and cardiac events

CONCLUSION

- Don’t delay treatment awaiting an echo
- Always aim for zero CRP and zero fever
- Use of steroids
- Luminal myofibroblastic proliferation

THANK YOU FOR YOUR ATTENTION