14th International Kawasaki Disease Symposium (IKDS)

Montreal, Canada
Hotel Bonaventure

14th IKDS Co-Presidents

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ikds.org

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14th International Kawasaki Disease Symposium (IKDS)

ikds.org

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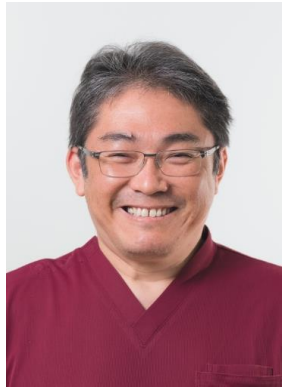
HOSPITAL INFANTIL
DE ESPECIALIDADES DE CHIHUAHUA



Fujito Numano
Niigata, Japan

save the children
NIIGATA UNIV

Federica Anselmi
Paris, France

université PARIS-SACLAY

CeRéMAIA

Rakesh Kumar Pilania
Chandigarh, India

POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH CHANDIGARH

Alan Wang
Chicago, IL, USA

Take Home Messages – Day 1

14th International Kawasaki Disease Symposium

August 27, 2024

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Pediatric Immunology
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Hospital Infantil de Especialidades de Chihuahua

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Cardiology Kawasaki Disease Program
The Children's Hospital of Philadelphia

Conflict-of-Interest Disclosures

Presenters:	Luisa Berenise Gámez González Matthew D. Elias
Any direct financial payments including receipt of honoraria	None
Membership on advisory boards or speakers' bureaus	None
Funded grants or clinical trials	None
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	None

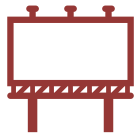
Day 1 Summary

Around the Globe

Etiology and Basic Science

Tomisaku Kawasaki Memorial Lecture

Genetics and Environmental Science



Poster Sessions

Acute KD Imaging

Around the Globe: IKDS Survey Responses

Groups – Country / Region	Year	Countries	Institutions	Members
Nationwide Survey of Epidemiology of KD in South Korea (guidance of the Korean Society of KD) | **South Korea**	1991	1	90	10-20
Registro Regionale della Malattia di Kawasaki Emilia Romagna | **Italy**	2002	1	10	10-20
Japan Kawasaki Disease Genome Consortium (JKDGC) | **Japan**	2009	1	40	20-50
Kawasaki Study Group | **Netherland**	2012	1	18	10-20
REKAMLATINA (Red de Enfermedad de Kawasaki en América Latina) | **Latin-America**	2013	20	86	100 +
International Kawasaki Disease Registry (IKDR) | **N-Am / International**	2013	8	51	20-50
SOCIETI | **UK**	2015	1	10	20-50
KAWARACE | **Spain**	2015	1	95	100 +
Kawasaki Disease Comparative Effectiveness (KIDCARE) trial | **USA**	2016	1	30	20-50
Asia Pacific Kawasaki Disease Association | **Eastern Asia / South-Pacific**	2016	14	30	50-100
Genetic Prediction of KD Treatment Resistance (GENESYS) | **USA / North-Am**	2018	2	6	10-20
Indian Society of Kawasaki Disease | **India**	2018	1	10	50-100
Cardiac Catheterization in Kawasaki Disease registry (CCinKD registry) |**Germany / Europe**	2019	6	16	20-50
JIR COHORT KD (KAWANET) and MIS-C | **Europe**	2019	11	87	20-50
AMED Study Group | **Japan**	2020	1	150	50-100
Cape Town Kawasaki Group | **South Africa**	2020	1	2	10-20
COVASAKI network | **Italy**	2020	1	18	20-50
KAWARABI (Kawasaki Disease Arab Initiative) | **MENA**	2021	14	24	20-50
Kawasaki disease Sweden (SwedKD) | **Sweden**	2021	1	1	10-20
Collaborated Surveillance by 4 Associations Working for Pediatric Critical Medicine (JMKsurvey) | **Japan**	2022	1	50	10-20

Adapted from presentation by Dr. Nagib Dahdah

Around the Globe: IKDS Survey Responses

Groups – Country / Region	Year	Countries	Institutions	Members
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REKAMLATINA (Red de Enfermedad de Kawasaki en América Latina) | **Latin-America**				00 +
International Kawasaki Disease Registry (IKDR) | **N-Am / International**				0-50
SOCIETI | **UK**				0-50
KAWARACE | **Spain**				00 +
Kawasaki Disease Comparative Effectiveness (KIDCARE) trial | **USA**				0-50
Asia Pacific Kawasaki Disease Association | **Eastern Asia / South-Pacific**				-100
Genetic Prediction of KD Treatment Resistance (GENESYS) | **USA / North-Am**				0-20
Indian Society of Kawasaki Disease | **India**				-100
Cardiac Catheterization in Kawasaki Disease registry (CCinKD registry) |**Germany / Europe**				0-50
JIR COHORT KD (KAWANET) and MIS-C | **Europe**	2019	11	87	20-50
AMED Study Group | **Japan**	2020	1	150	50-100
Cape Town Kawasaki Group | **South Africa**	2020	1	2	10-20
COVASAKI network | **Italy**	2020	1	18	20-50
KAWARABI (Kawasaki Disease Arab Initiative) | **MENA**	2021	14	24	20-50
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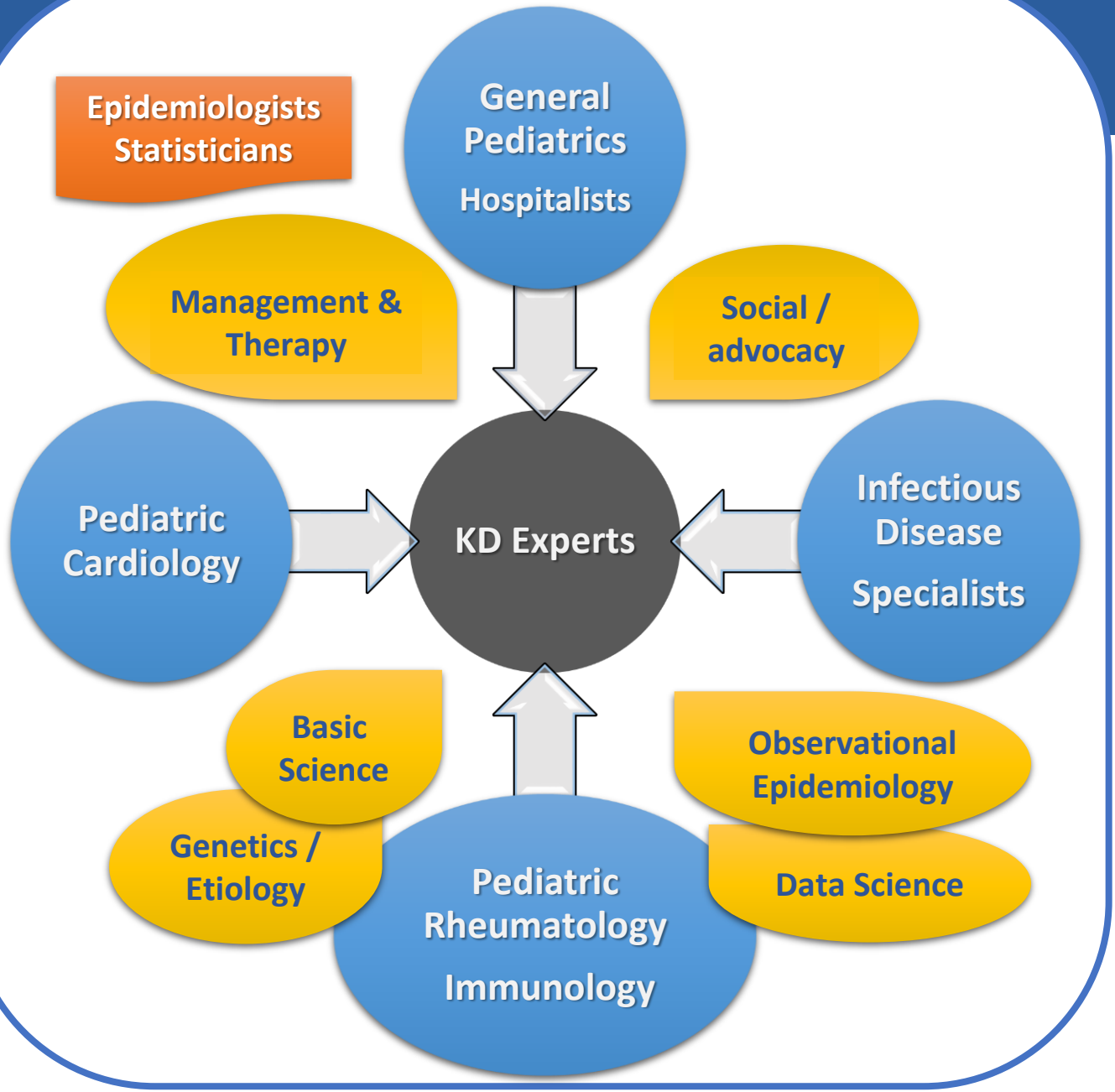
Collaborated Surveillance by 4 Associations Working for Pediatric Critical Medicine (JMKsurvey) | **Japan**	2022	1	50	10-20

Majority of KD organizations:

- Organized governance
- Steering committee
- No formal funding
- Peer-reviewed publications

Adapted from presentation by Dr. Nagib Dahdah



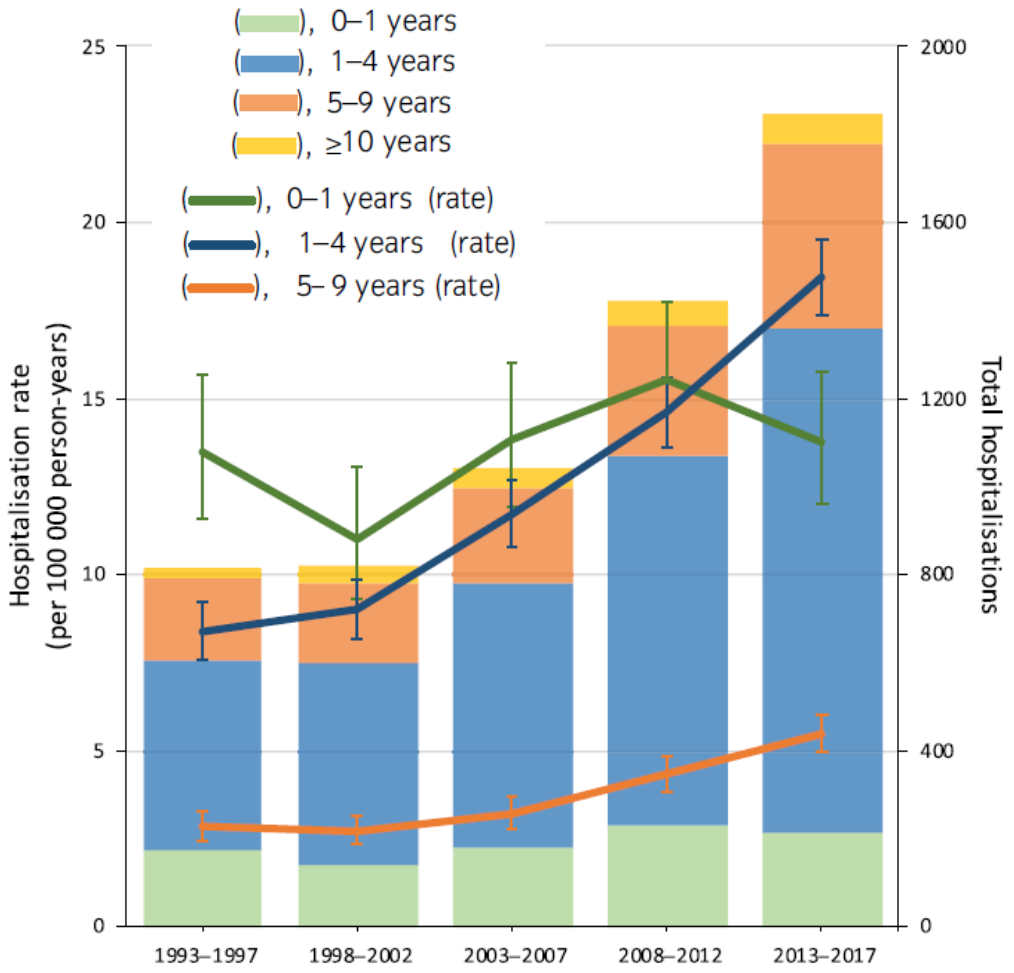
Collaboration

Shared vision

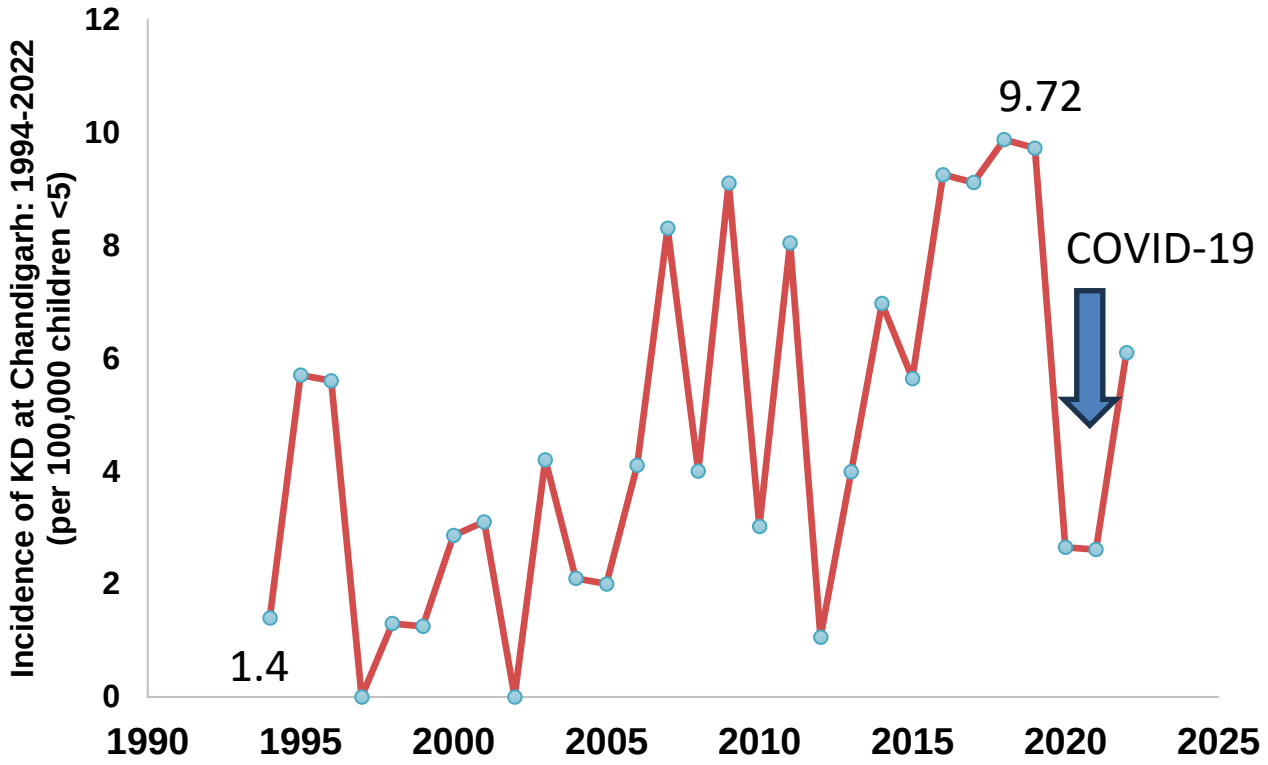
Expand the expertise circle

Adapted from presentation by Dr. Nagib Dahdah

Around the Globe:
Increasing Prevalence of Kawasaki Disease



3.5% annual increase in KD hospitalization rate over 25 years in Australia

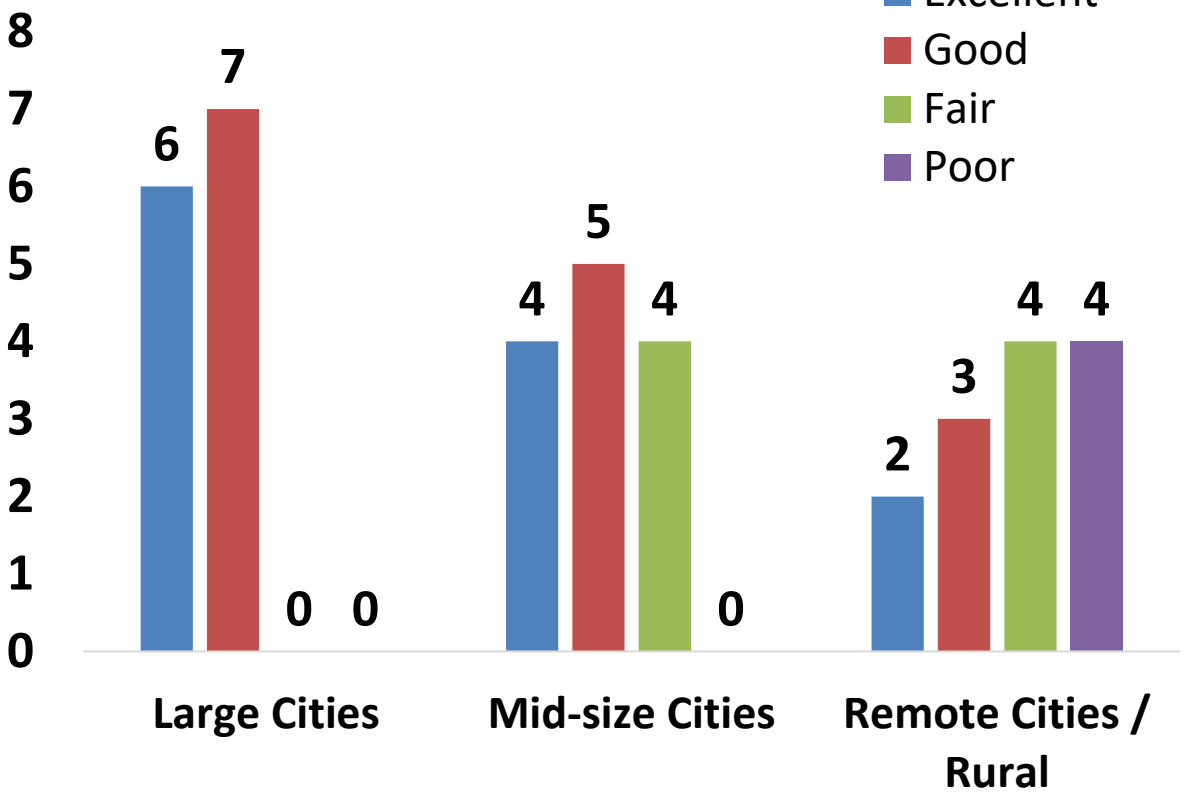


Increasing number of cases of KD in India

Lucas R, et al. *Journal of Paediatrics and Child Health*. 2022.
Presentation by Dr. Davinder Singh-Grewal

Adapted from presentation by Dr. Surjit Singh

Around the Globe: Access to Appropriate KD Care



REKAMLATINA
RED DE ENFERMEDAD DE KAWASAKI EN AMÉRICA LATINA

Survey Among Latin America Network

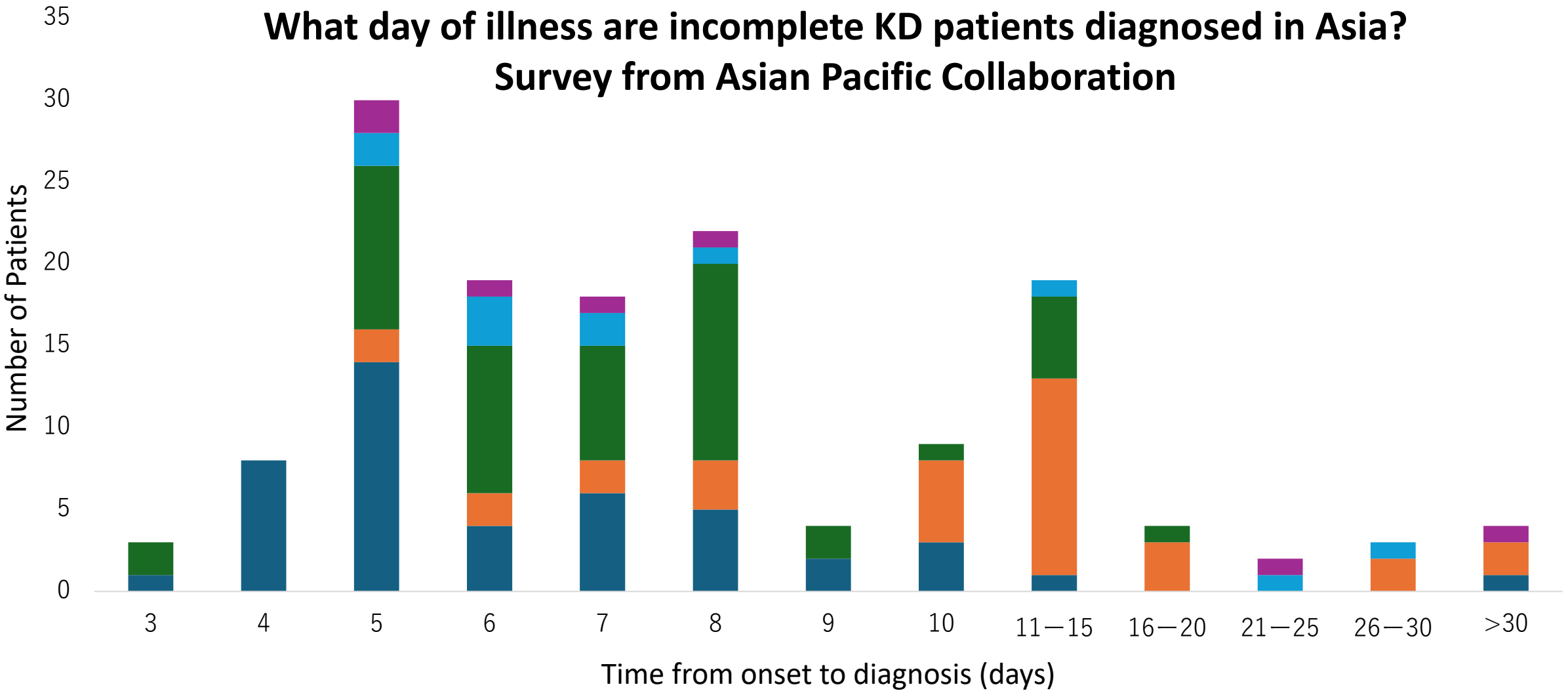
61 responses among 15 countries:

Adequate knowledge of KD in your country?	61%
Timely diagnosis/treatment of KD?	43%
Cardiology consultation available?	98%
Available echo?	95%
Available IVIG?	89%
Available biologic therapies?	43%

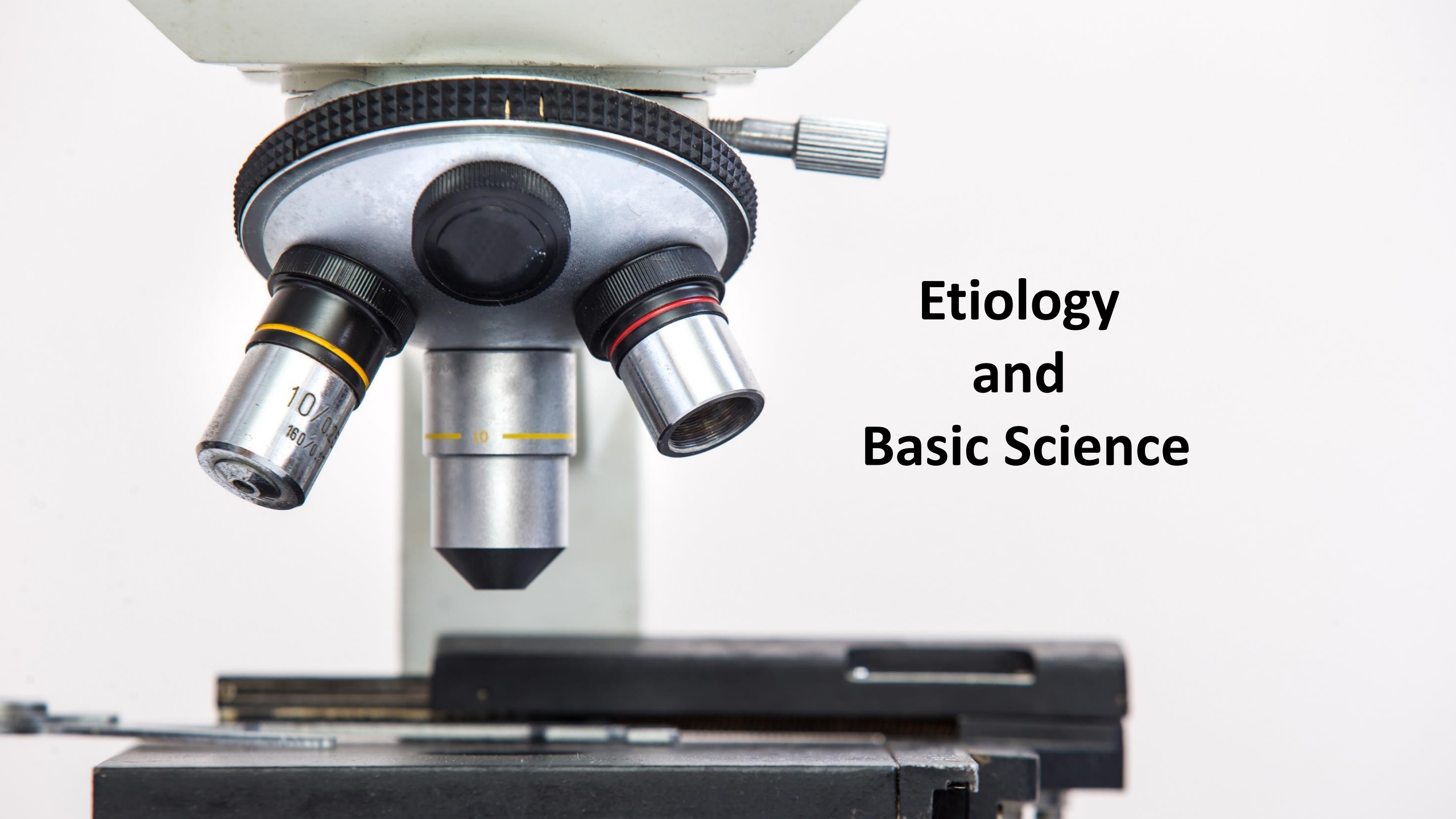
Adapted from Alzyoud R, et al. *Pediatric Cardiology*. 2023.

Adapted from presentation by Dr. Marco Antonio Yamazaki-Nakashimada

Around the Globe: Importance of Increasing Awareness



Adapted from presentation by Drs. Kazuyuki Ikeda and Hiromichi Hamada



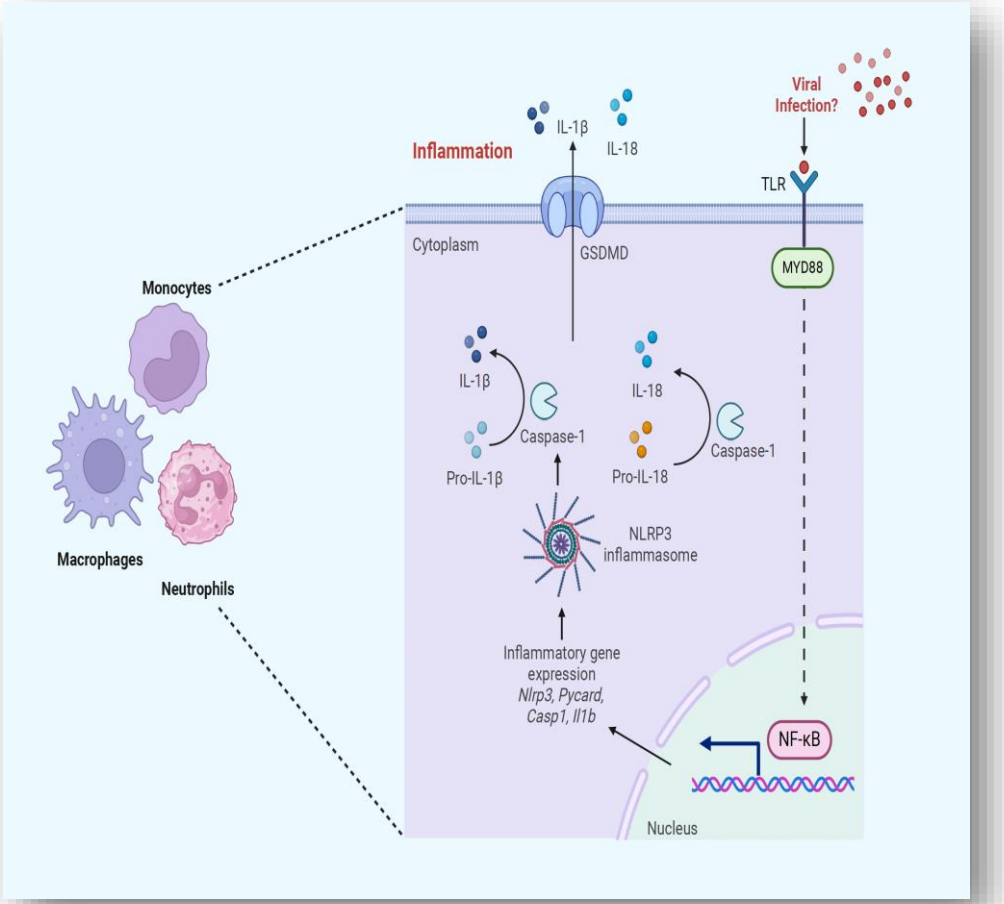
Etiology and Basic Science

Etiology and Basic Science (Animal Studies): Role of IL-1 in Pathogenesis and Treatment

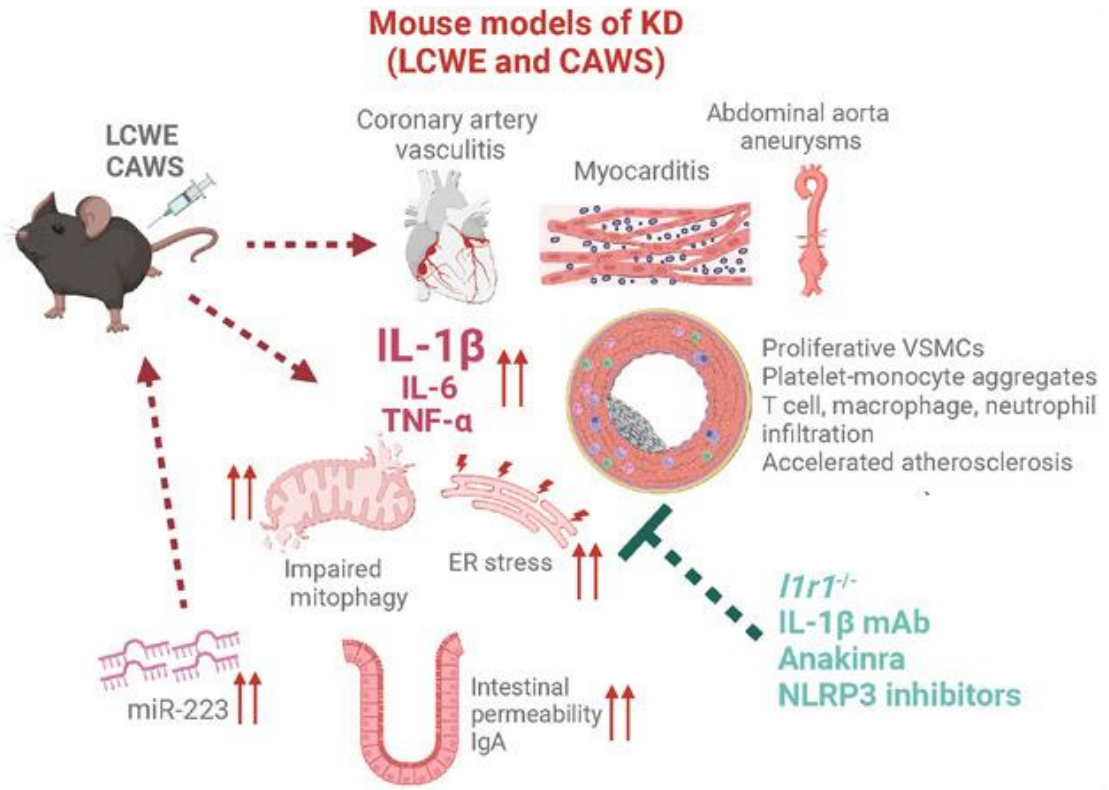
IL-1β is crucial for host defense against infections.

Uncontrolled and dysregulated production of IL-1β is linked to the development of a broad variety of inflammatory diseases, including KD.

Increased expression of genes related to either IL-1β production or IL-1 signaling components during human KD



Etiology and Basic Science (Animal Studies): Role of IL-1 in Pathogenesis and Treatment



- Evidence suggests that mouse models of KD (LCWE, CAWS) are IL-1β mediated.
- Blocking IL-1β pathway (ex: IVIG, anakinra) reduces development of coronary arteritis.

Atici AE, et al. *Canadian Journal of Cardiology.* 2024.

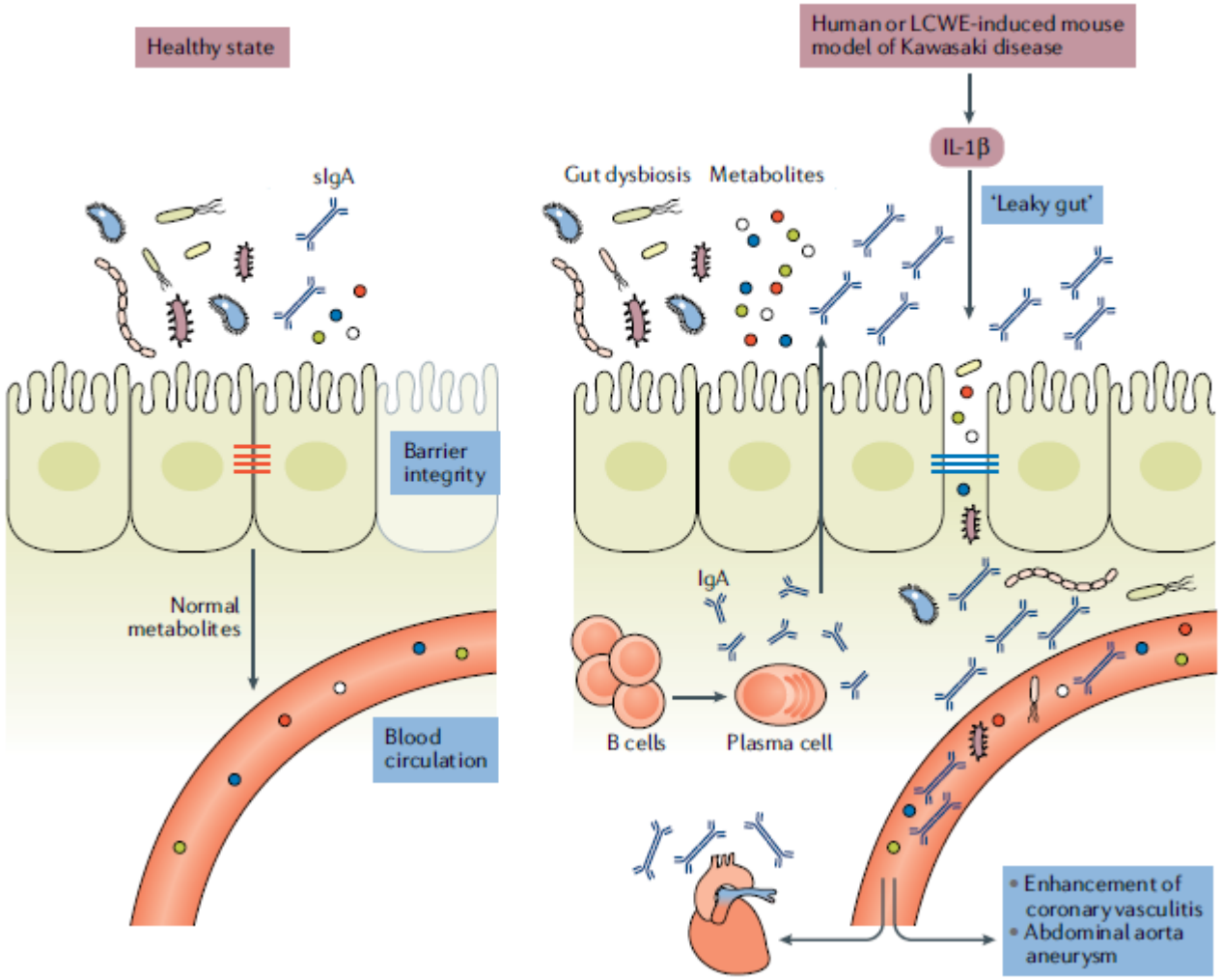
Adapted from presentation by Drs. Moshe Arditi and Asli Ekin Atici

Etiology and Basic Science (Animal Studies): Role of IL-1 in Pathogenesis and Treatment

Human trials targeting IL-1R		
Clinical trials exploring the inhibition of the IL-1 pathway using the IL-1Ra (Anakinra)	ANAKID; phase I/II[180]	ClinicalTrials.gov identifier NCT02179853; North America
	Kawakinra; phase II[49]	ClinicalTrials.gov identifier NCT02390596; Europe
	ANACOMP; phase III	ClinicalTrials.gov identifier NCT04656184; Europe

IL-1Ra, interleukin-1 receptor antagonist.

Etiology and Basic Science (Animal Studies): Role of the Gut Microbiome



Gut vascular axis in KD??

Evidence of increased intestinal permeability and dysregulated intestinal immune response in LCWE mouse model

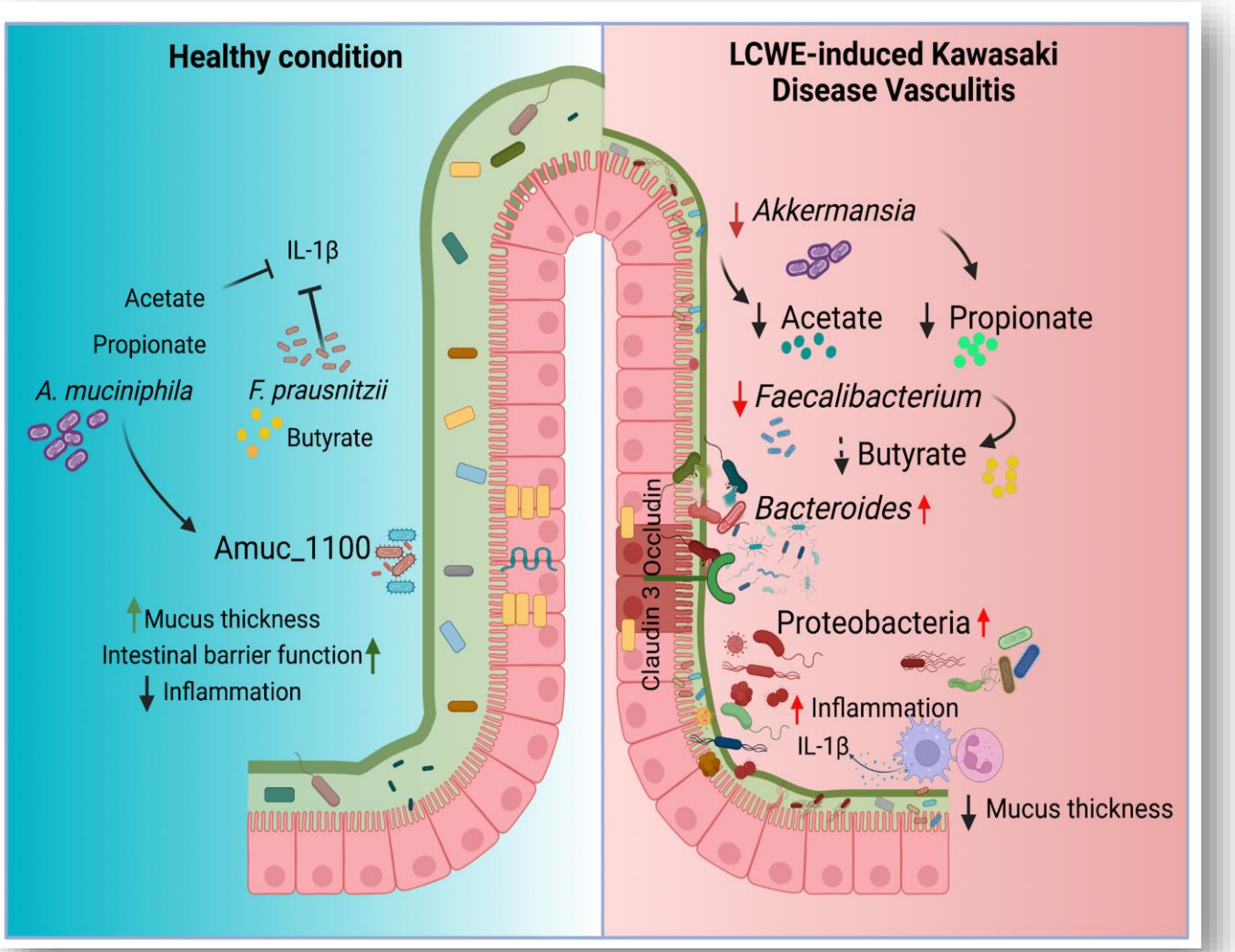
Excessive IL-1β release increases intestinal permeability while IVIG decreases permeability

Differences exist in intestinal microbiota composition between KD patients and healthy controls

Rivas MN, et al. *Nature Reviews.* 2020
Jena PK, et al. *bioRxiv* 2024.05.28.596258

Adapted from presentation by Dr. Magali Noval Rivas

Etiology and Basic Science (Animal Studies): Role of the Gut Microbiome



Gut vascular axis in KD??

The development of CV was associated with alterations in the intestinal microbiota composition.

A decreased abundance of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*.

Oral supplementation with either of these live or pasteurized individual bacteria, or with short-chain fatty acids 43 (SCFAs) produced by them, attenuated CV inflammation

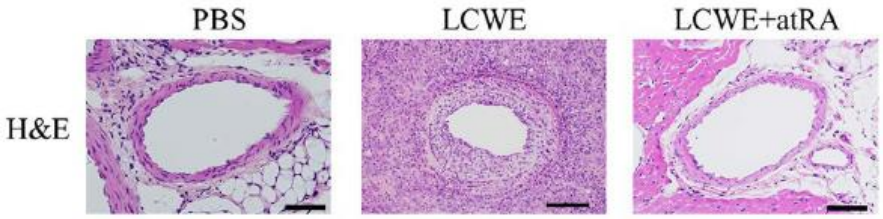
Rivas MN, et al. *Nature Reviews.* 2020
Jena PK, et al. *bioRxiv* 2024.05.28.596258

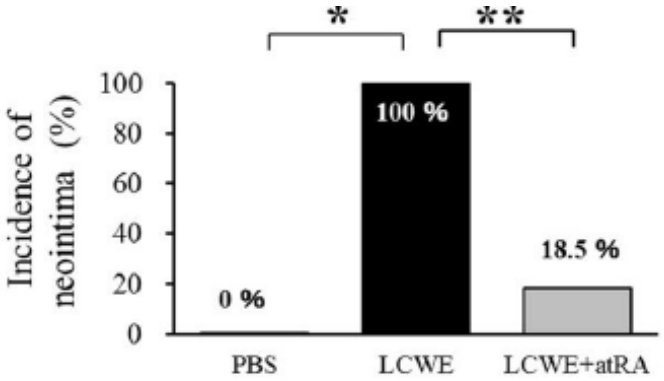
Adapted from presentation by Dr. Magali Noval Rivas

Etiology and Basic Science (Animal Studies): Therapeutic Strategies from Mouse Models

All-trans-retinoic acid (atRA)

- Suppressed CA inflammation
- Reduced incidence of CA stenosis
- Suppressed migration of smooth muscle cells

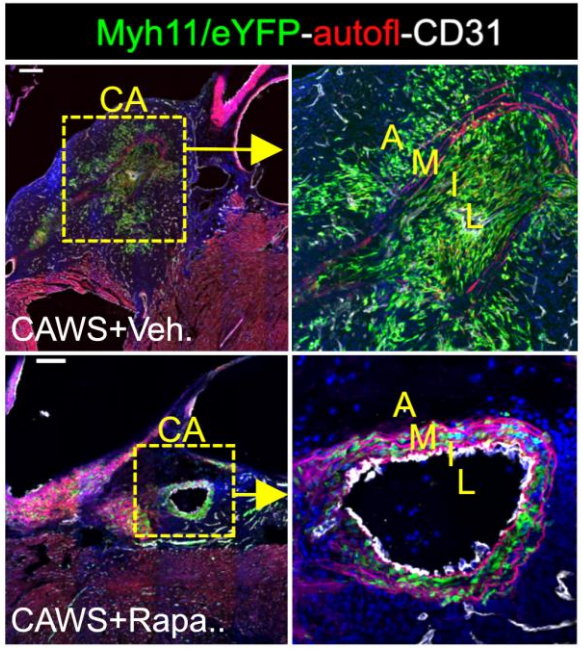


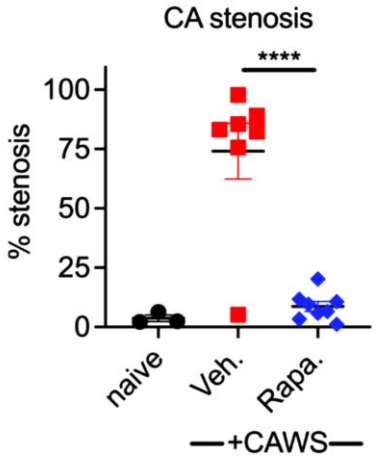


Suganuma E, et al. *Scientific Reports.* 2021.

mTOR inhibitor

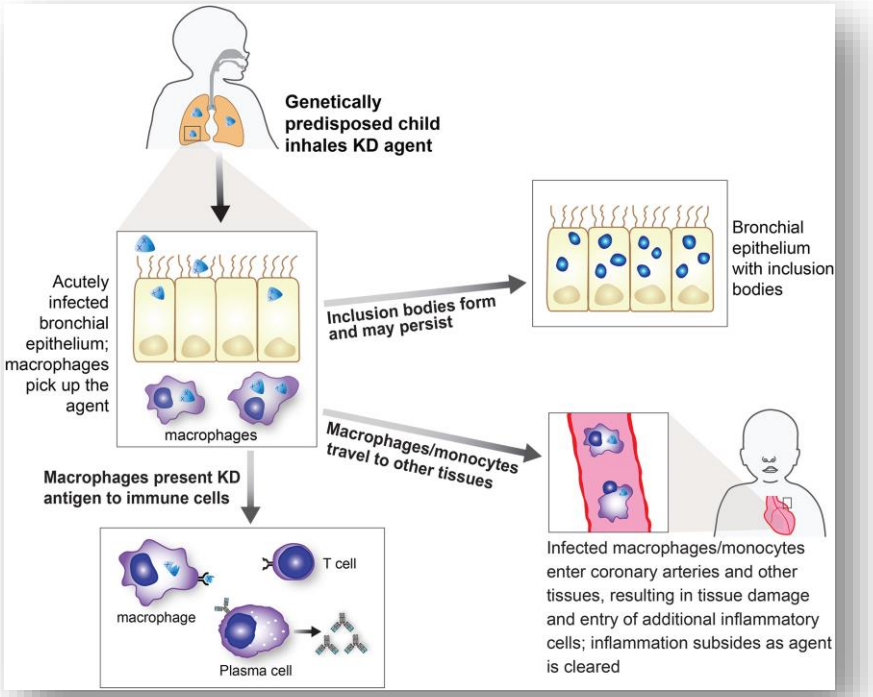
- Pharmacologic mTOR inhibition stops luminal myofibroblast formation and CA stenosis
- mTOR inhibitor (sirolimus) could prevent stenosis in high-risk KD patients with giant CAA





Adapted from presentation by Drs. Eisuke Suganuma and Angus Stock

Etiology and Basic Science: Potential Viral Etiology of KD



Sequencing of VH genes from plasmablasts isolated from KD patients revealed <u>Convergent VH3-74 antibody responses</u> in 12/12 patients

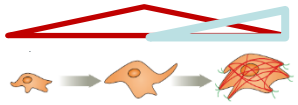
- Antibodies recognize specific peptide sequence likely derived from KD infectious agent
- The results support one predominant "new" infectious agent as the cause of KD

Yellow=VH3-74 heavy chain
Green=paralogs of VH3-74 with similarity scores <u>≥</u>80%

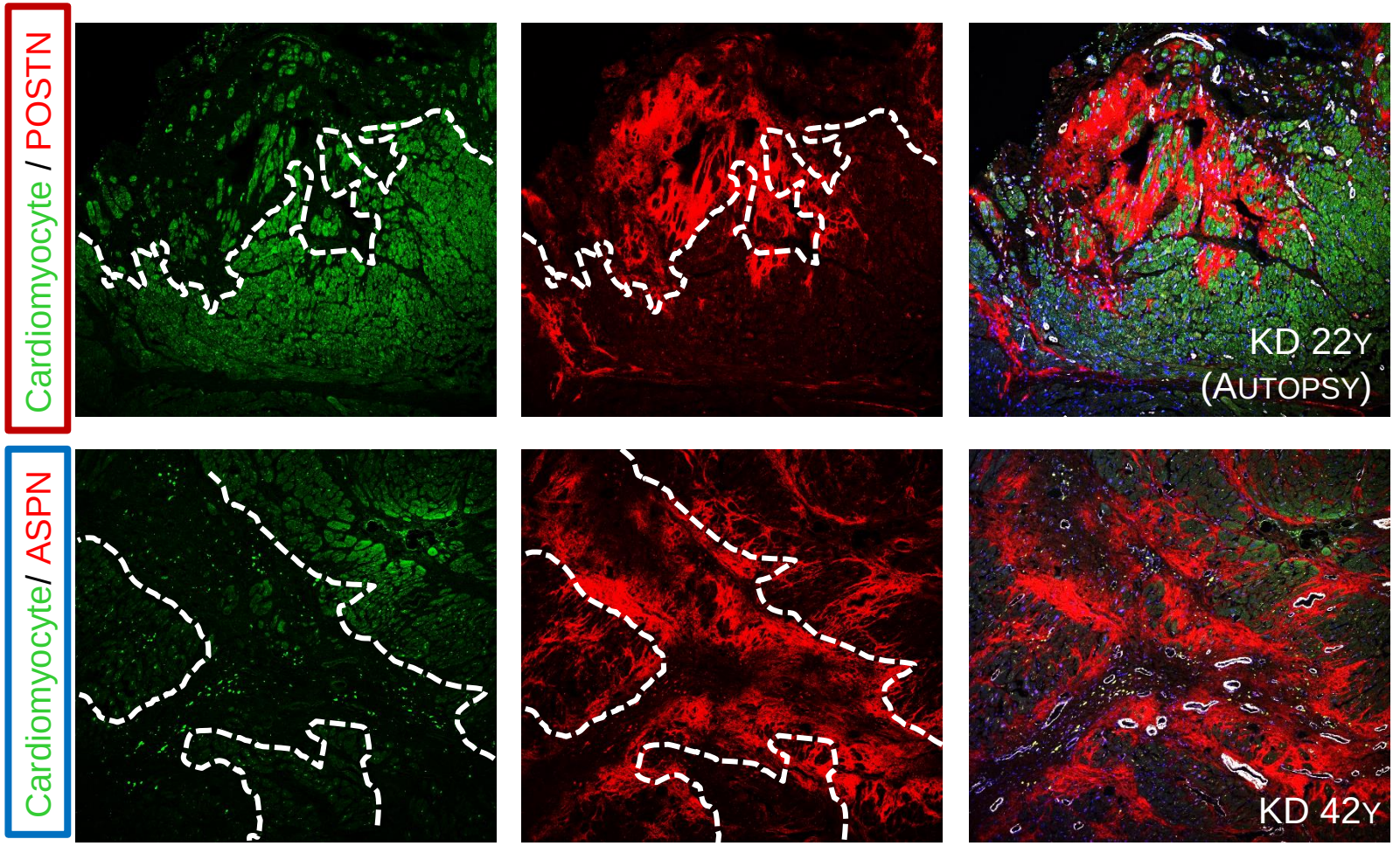
Patient	MAb	IGHV	PB isotype
KD1	KD1-2B1	3-74*01	IgA
	KD1-1H8	3-74*01	IgA
	KD1-2F3	1-18*01	IgM
KD2	KD2-1D10	3-74*01	IgG
KD3	KD3-1C10	3-74*01	IgA
KD4	KD4-2H4^{CE}	3-74*01	IgG
KD5	KD5-2D7	3-74*01	IgG
	KD5-2D10	3-74*01	IgG
KD6	KD6-2B2^{CE}	3-33*01	IgA
	KD6-2H3^{CE}	3-15*01	IgG
	KD6-2H8	3-74*01	IgA
	KD6-1A10^{CE}	3-33*03	IgA
KD7	KD7-2H5	3-74*01	IgA
	KD7-1B5	3-33*01	IgA
	KD7-1E6	3-23*01	IgA
	KD7-1D3	3-23*01	IgA
	KD7-2A9	5-10-1*03	IgA
KD8	KD8-1D4^{CE}	3-72*01	IgA
	KD8-2E9	3-74*01	IgG
	KD8-2C10	3-74*01	IgA
	KD8-2A9	3-21*01	IgM
	KD8-2A5	3-72*01	IgM
KD9	KD9-2F6	3-73*01	IgA
	KD9-2B1	3-21*01	IgG
	KD9-1E9	1-69*01	IgG
KD10	KD10-1G3	3-73*01	IgA
	KD10-1A8	3-74*01	IgG
	KD10-1F7^{CE}	1-2*02	IgA
	KD10-2F6	3-74*01	IgG
KD11	KD11-2E4	3-74*01	IgA
	KD11-2A12^{CE}	3-21*01	IgA
KD12	KD12-2A1^{CE}	3-74*01	IgA
	KD12-1F10^{CE}	3-21*01	IgA
	KD12-2A10^{CE}	3-15*07	IgG
	KD12-1G7^{CE}	3-66*01	IgA
	KD12-1H2^{CE}	3-21*01	IgA

Adapted from presentation by Drs. Anne Rowley and Susan Baker

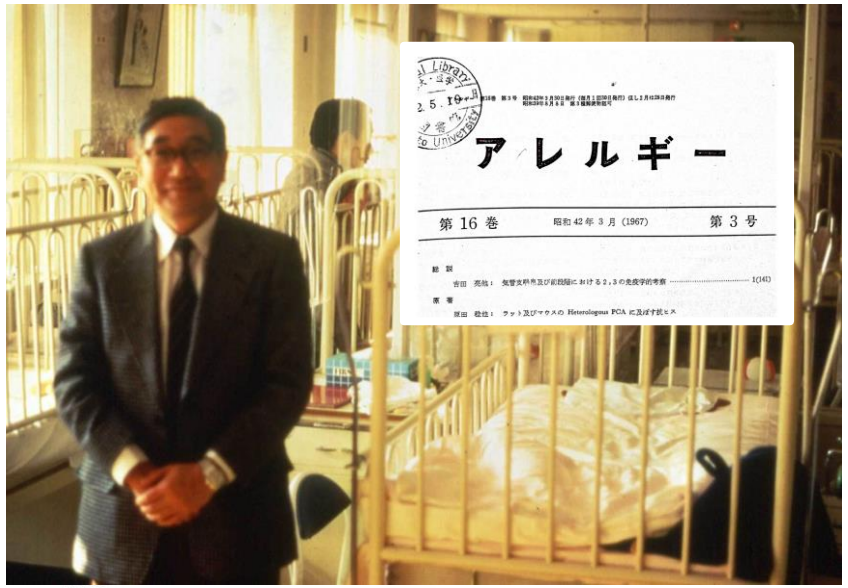
Etiology and Basic Science: Dynamic Changes in Ventricular Remodeling

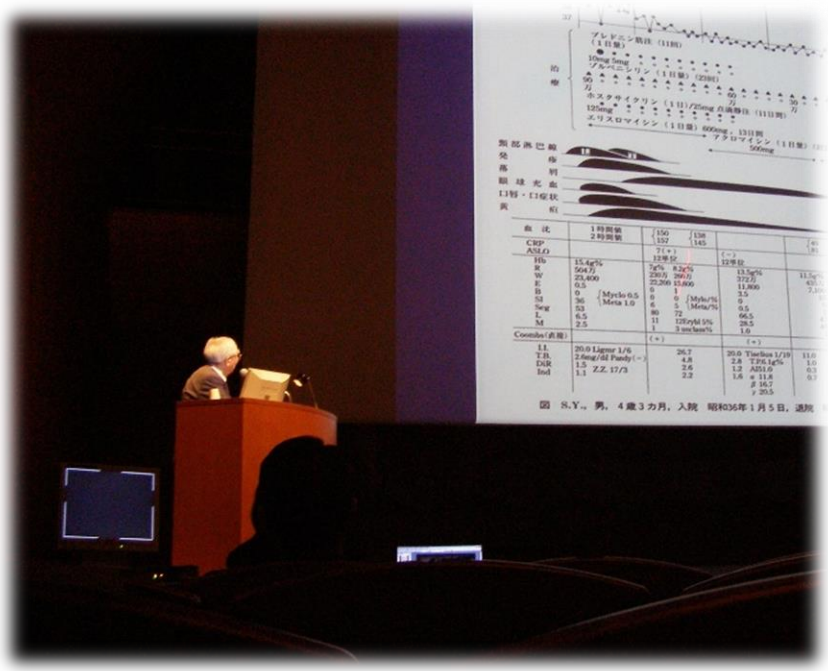


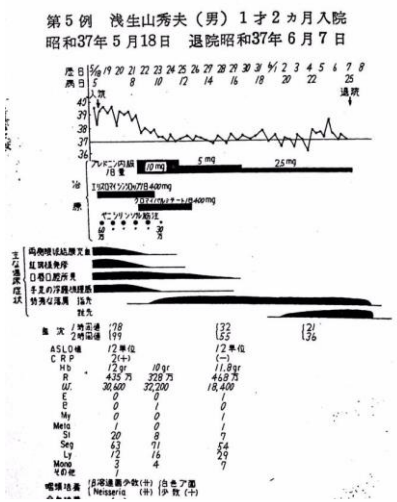
Cardiac fibrosis is progressive and dynamic in each KD patient

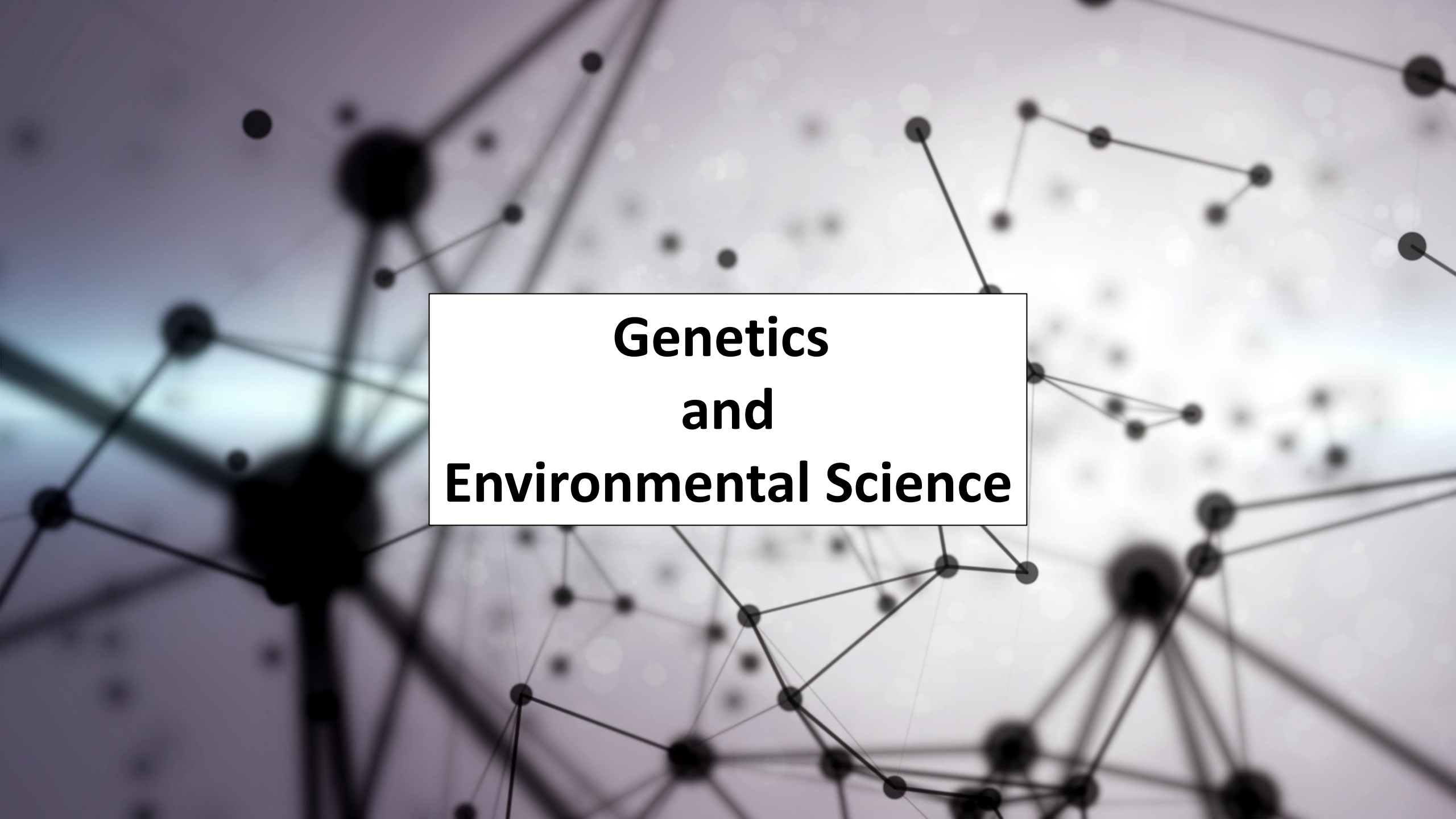


Dr. Kawasaki Memorial Lecture








Genetics
and
Environmental Science

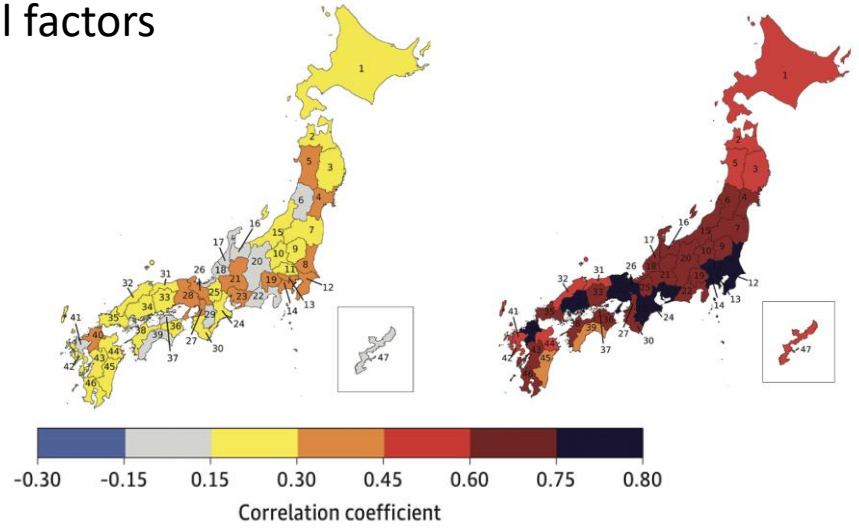
Genetics and Environmental Science: Temporal Clustering and Climatology

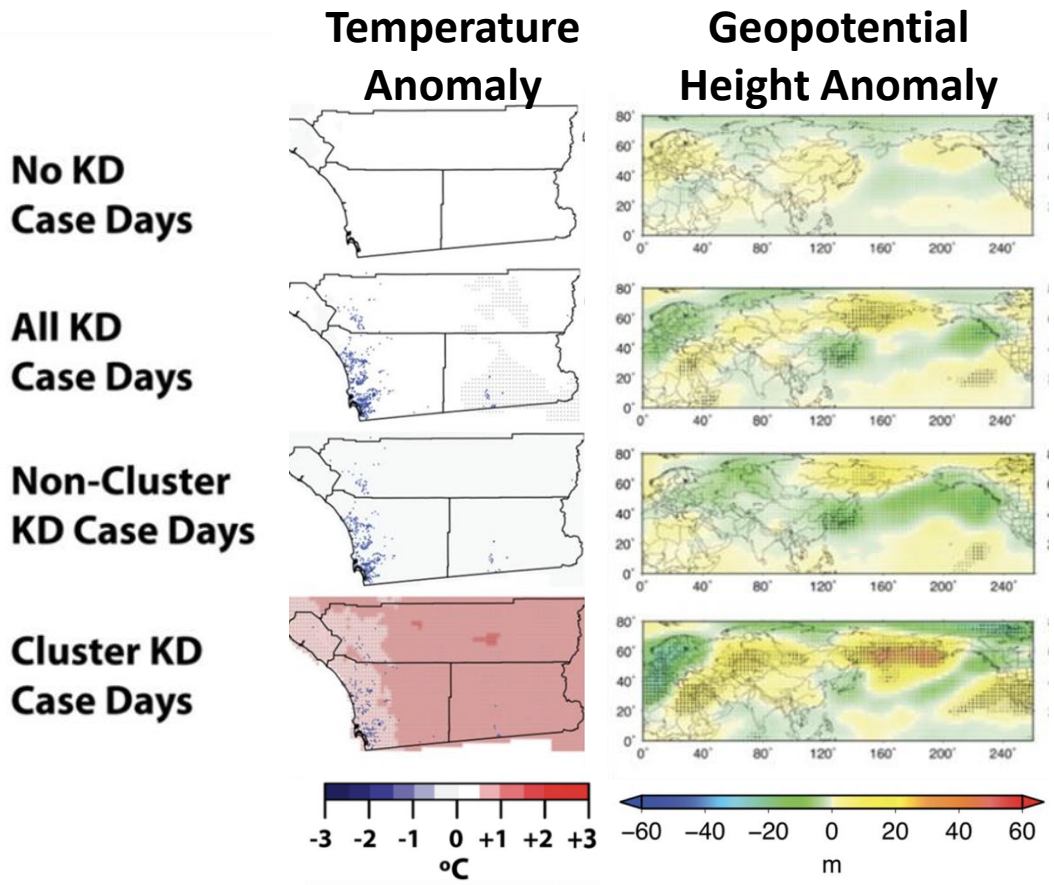
>1000 KD cases in San Diego over 15 years

- Temporal clusters of KD cases noted
- Associated with regional air temperature anomalies and large-scale atmospheric circulation patterns

Seasonal pattern across Japan, 1988-2019

- Higher correlations of incidence across regions in older patients compared to infants
- Suggest combination of environmental and social factors





DeHaan LL, et al. *JAMA Network Open*. 2024.

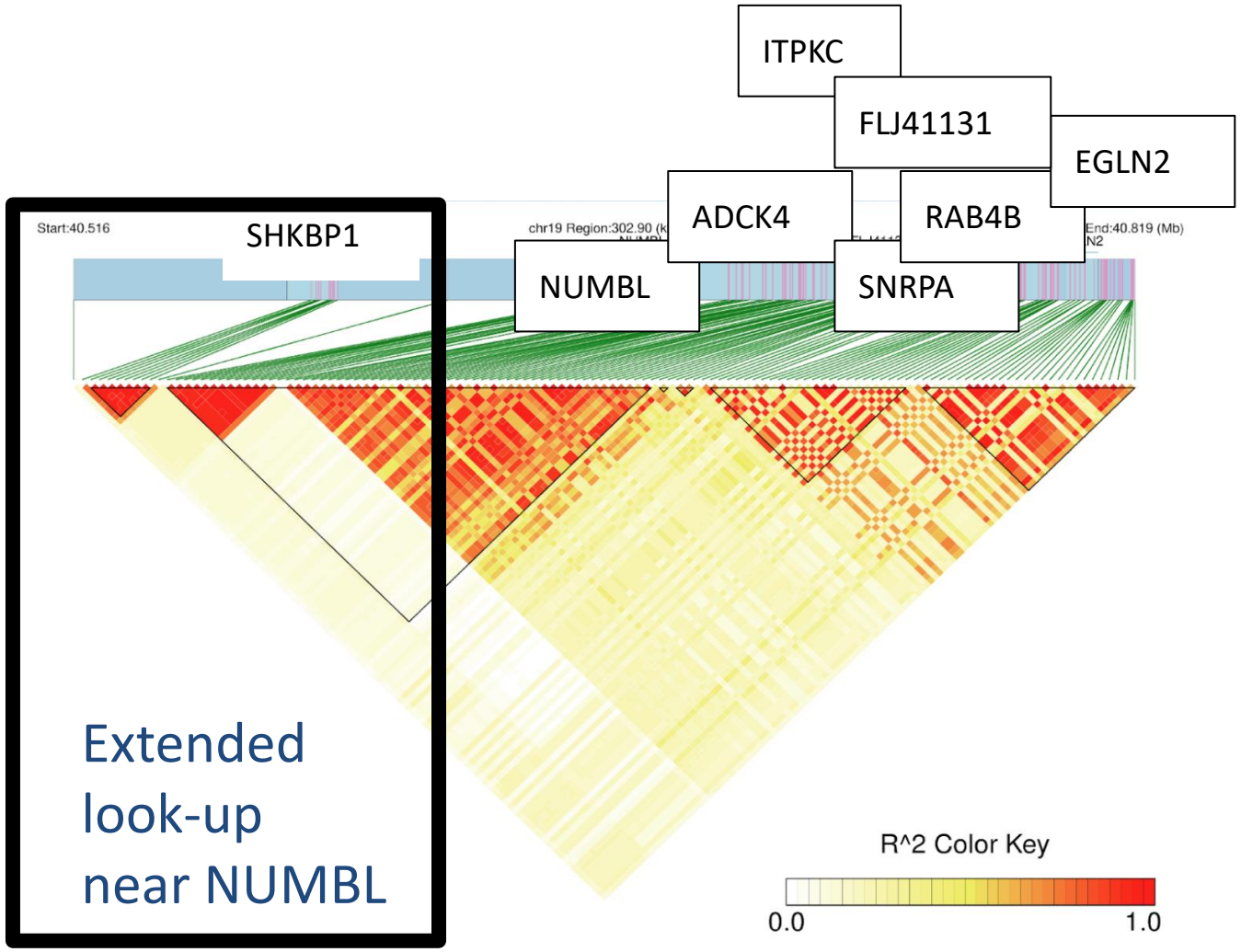
Rypdal M, et al. *Scientific Reports*. 2018

Genetics and Environmental Science: New Frontiers in KD Genetics

GWAS Hispanic

Successfully validated previously discovered variants near ITPKC gene.

Identified novel variants in SHKBP1 gene associated with KD susceptibility.



Genetics and Environmental Science: Genetics and Treatment Resistance

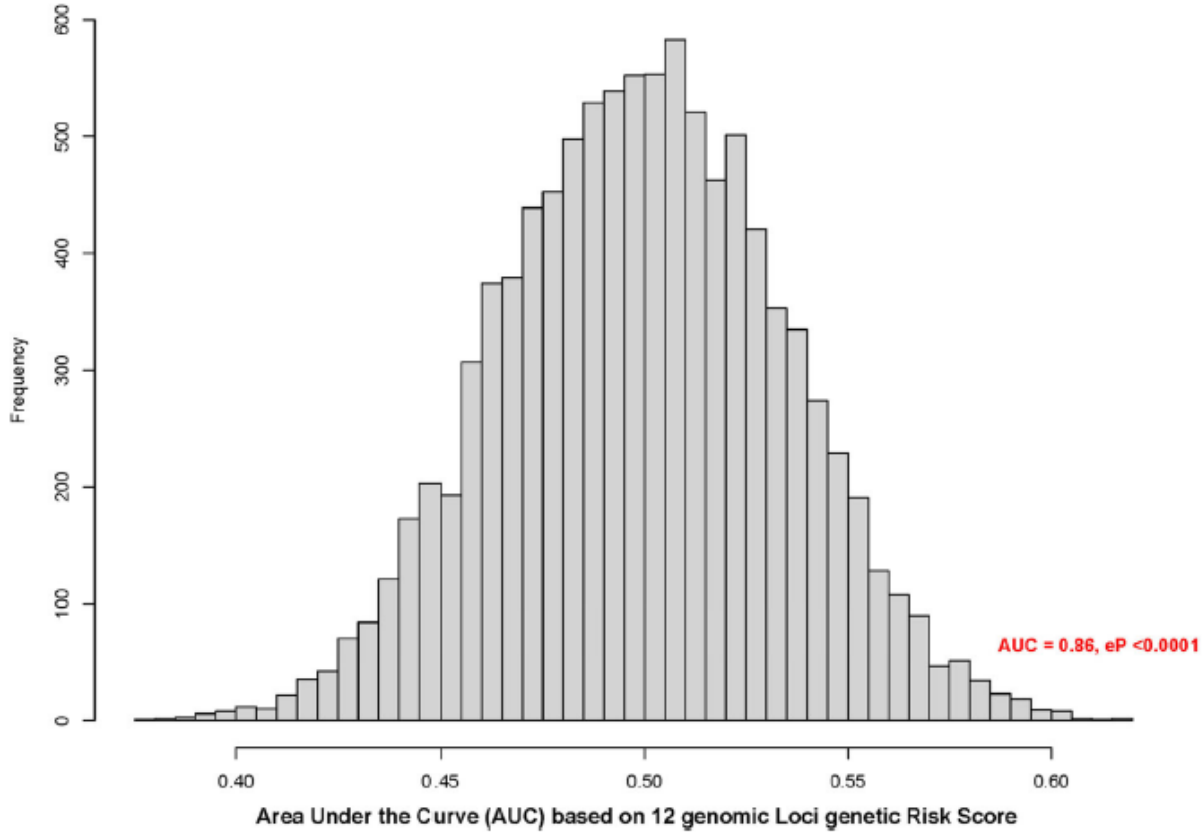
Is there genetic heterogeneity?
Is there genetic association with treatment response and outcome?

Whole Genome Sequencing association analysis of 472 patients with KD
(234 with CAA, 238 without CAA)

Identification of 12 genomic risk loci mapped to 48 genes for CAA z ≥ 5

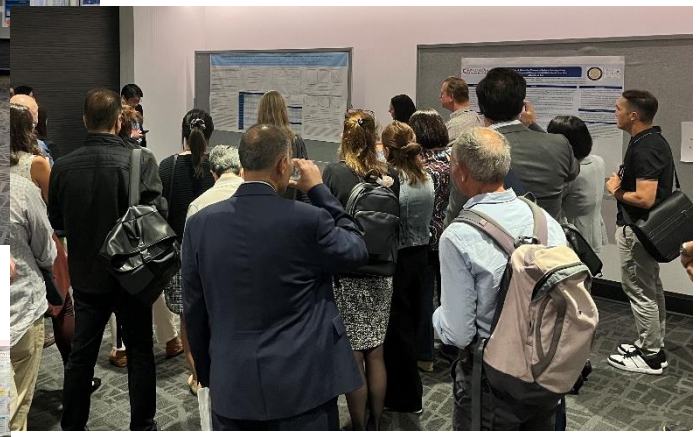
Genetic risk score – AUC 0.86

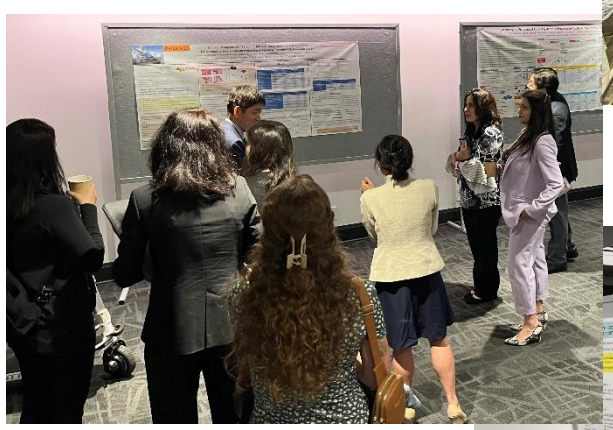
Goal: identify personalized therapeutic approaches

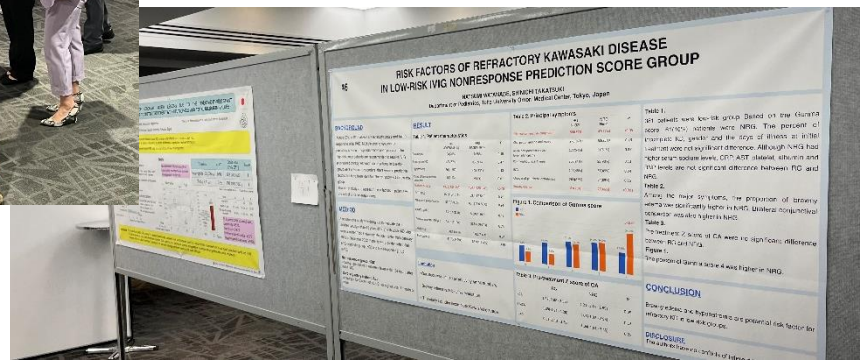


Shrestha S, et al. *NPJ Genomic Medicine*. 2024.

Poster Presentations







Highlights of Poster Presentations

- Importance of patient/family education
- Artificial intelligence models to predict CAA
- Lack of effectiveness of high-dose aspirin
- ARB or ACE inhibitor’s role in CAA regression
- Necessity to develop IVIG-resistance prediction scoring system for infant KD
- Importance of early use of adjunctive therapy to reduce CAA in high-risk infants

Acute KD Imaging

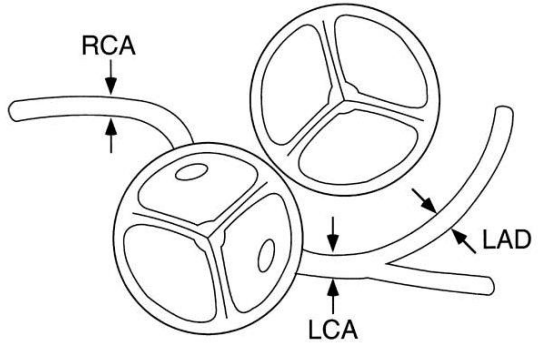
Acute KD Imaging: Echocardiography

High sensitivity and specificity for coronary abnormalities

Importance of accurate measurements and optimizing settings:

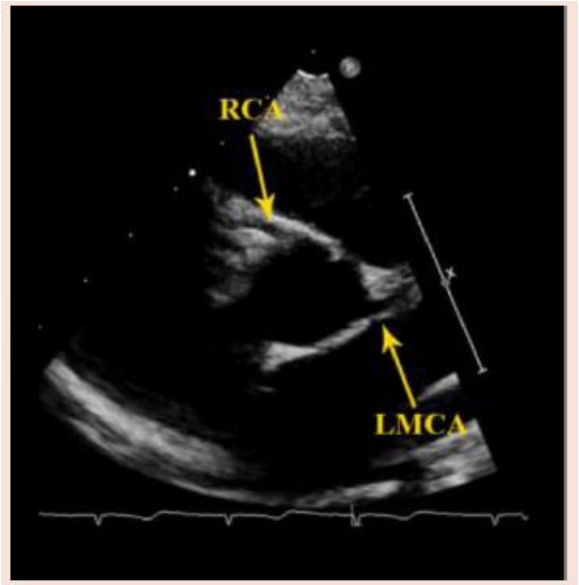
- High frequency probe
- Black/white: lower gain, higher compression
- Color: lower Nyquist color Doppler
- Measurements: inner edge to inner edge

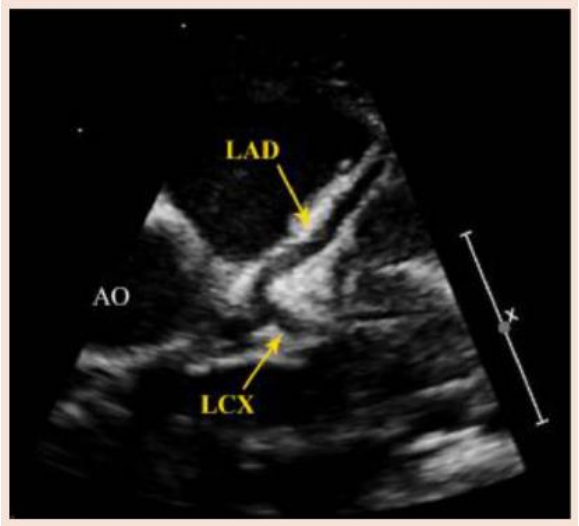
Most common CA involvement: LAD > RCA > LMCA > Cx



de Zorzi A, et al. *Journal of Pediatrics*. 1998.

Benefits of echocardiography beyond the coronaries with subtle myocardial changes via strain assessments





Brown LM, et al. *JASE*. 2015.

Adapted from presentations by Drs. Pei-Ni Jone and Lucy Youngmin Eun

Acute KD Imaging:
Coronary Artery Z-Score Round Table Discussion

Case Presentation

- 3-month-old Caucasian male presenting with:
- Fever x 6 days and clinical features of KD
- Labs: CRP 11.2 mg/dL, ESR 82 mm/hr, platelets 464 thou/µL

	LMCA	LAD	RCA
Diameter (mm)	**2.7**	**2**	**2**
Canada	3.62	2.74	2.14
Japan	3.85	2.51	2.44
PHN, USA	2.55	4	1.71
Boston, USA	2.35	2.47	1.91
Taiwan	3.12	1.77	1.96
Korea	2.67	2.14	2.03
Italy	2.55	3.1	2.6

Z-Score Measurements:

- Normal: <2
- Dilation (ectasia) only: 2 to <2.5
- Small aneurysm: 2.5 to <5
- Medium aneurysm: 5 to <10 and <8 mm
- Large/giant aneurysm: ≥10 or ≥8 mm

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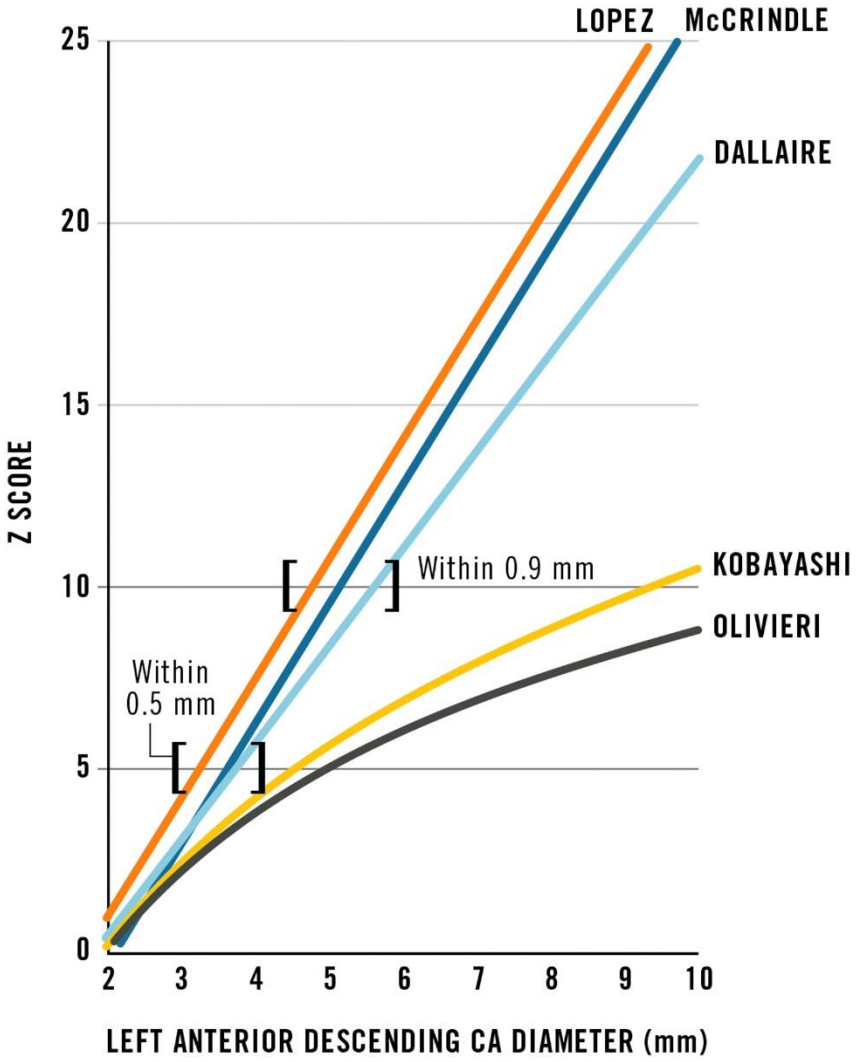
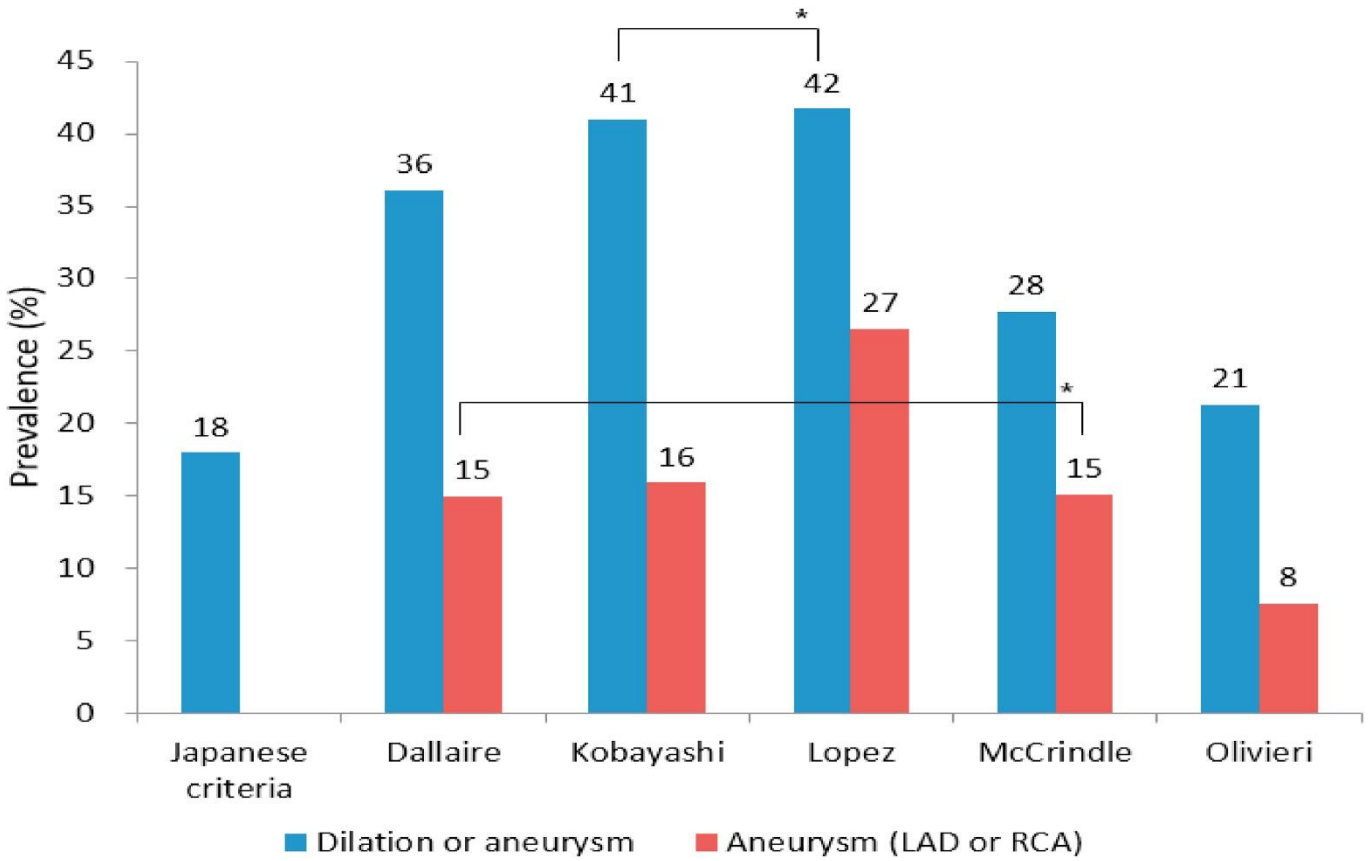
Acute KD Imaging: Variability of Z-scores



Dallaire F, et al. *JASE*. 2021.

Korean national survey of 6,889 KD patients



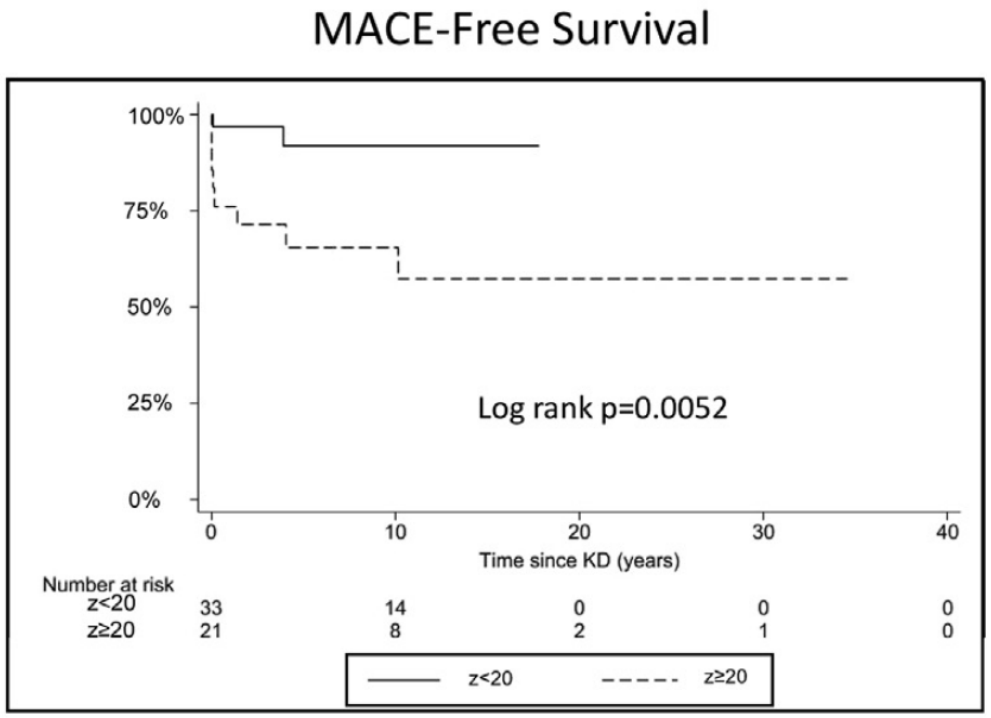
Kim SH, et al. *JASE*. 2021.

Acute KD Imaging: Z-Scores

Larger CAA are associated with higher risk of major adverse events, primarily z-score ≥ 10.

There are different methods of calculating z-scores, reflecting different normative values in diverse patient populations and various methodologies.

Z-scores calculations should not be used interchangeably. Consistency is important.



Elias MD, et al. *Journal of Pediatrics.* 2024.

Thank you and enjoy the conference!

ikds.org

Take Home Messages – Day 2

14th International Kawasaki Disease Symposium

August 28, 2024

Dr. Federica Anselmi
Paediatric Rheumatology
University hospital of Bicetre- Paris
Faculty of Medicine of Paris-Saclay University

Dr. Fujito Numano
Fujito Numano, MD, PhD
Lecturer of Pediatrics
Niigata University Graduate school of Medical and Dental Sciences

Conflict-of-Interest Disclosures

Presenters:	Federica Anselmi Fujito Numano
Any direct financial payments including receipt of honoraria	None
Membership on advisory boards or speakers' bureaus	None
Funded grants or clinical trials	None
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	None

Day 2 Agenda

Young Investigator Oral abstract competition

Bioinformatics and AI

Breakouts

Cardiac imaging CAA follow-up

Re-examining use of ASA and approaches to anticoagulation

Cardiovascular Immunology

Highlights

New insights into KD pathogenesis

KD (early) diagnostic tools

KD is a heterogeneous disease (clusters)

Preventing the CV complications

CV imaging and treatment

Highlights

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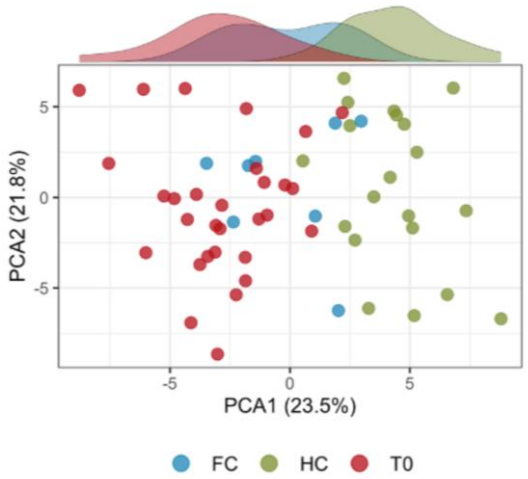
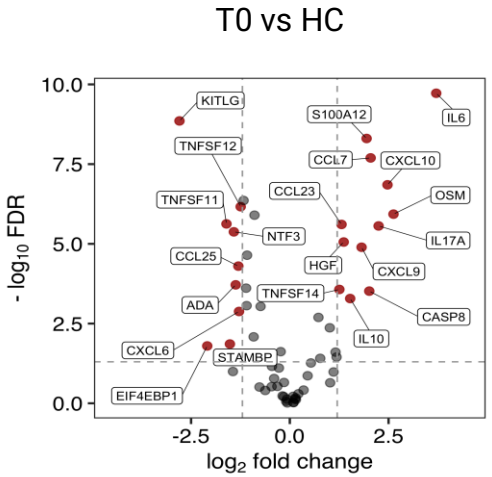
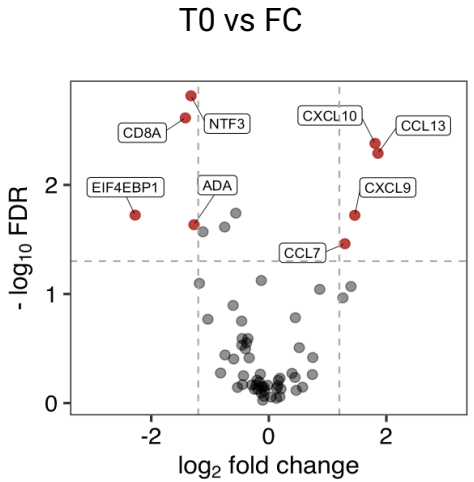
Young Investigator Oral Abstract Competition

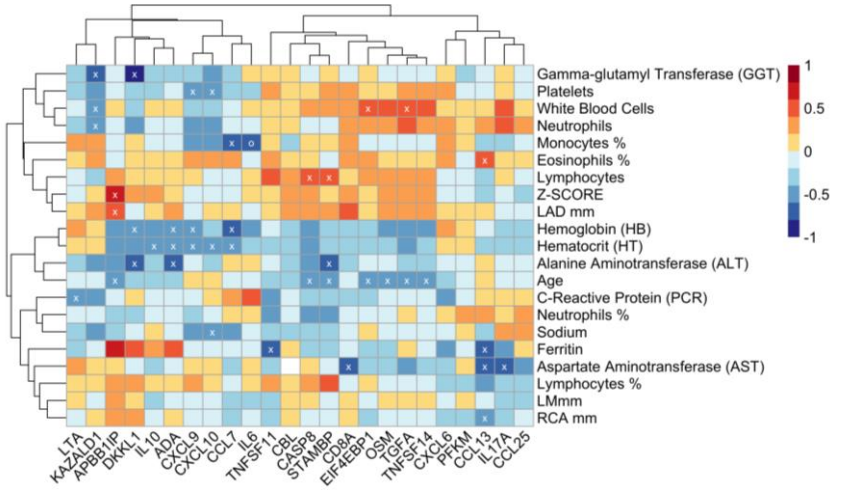
Multi-modal immune dynamics of pre-COVID-19 Kawasaki Disease following Intravenous Immunoglobulin

- Respect febrile controls, inflammation profile in KD is characterized by Th-1 chemokines (CXCL9, CXCL10, CCL7, CCL13)





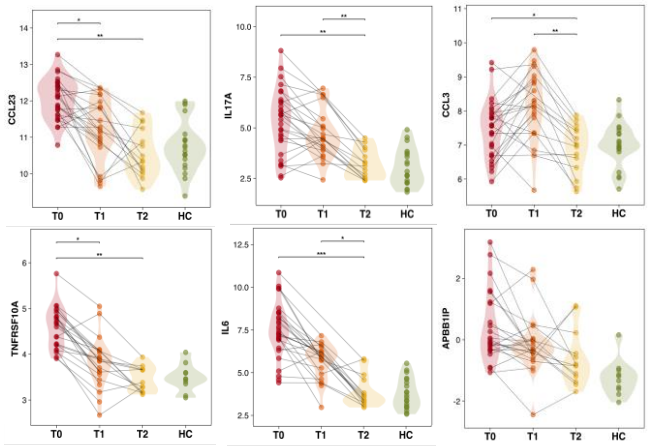




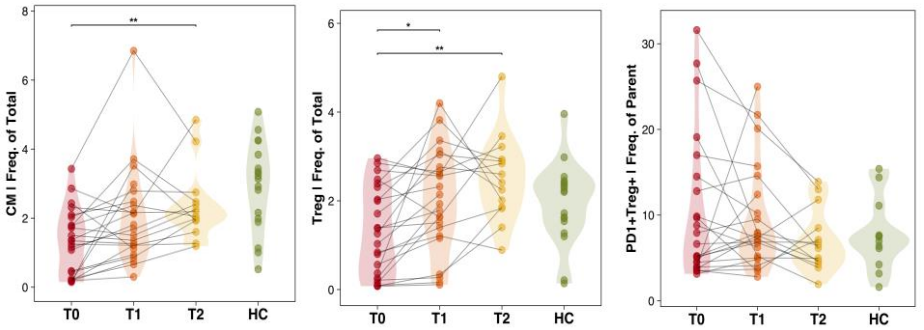
- APBB1IP correlated with higher echocardiogram values and linked to coronary artery involvement.

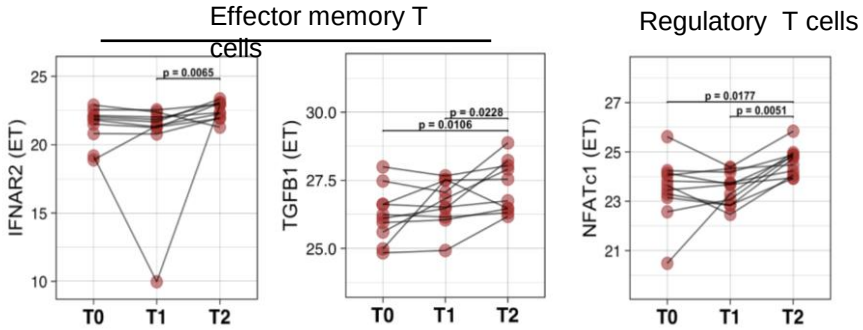
Young Investigator Oral Abstract Competition

Multi-modal immune dynamics of pre-COVID-19 Kawasaki Disease following Intravenous Immunoglobulin

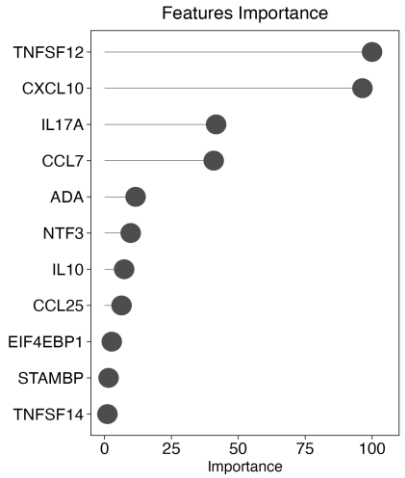


-IVIG modify the levels of proteins (IL-6, IL-17A, L-17C, CXCL11, CXCL10, CXCL9, CCL23, TNF, VEGF9) and modulates Treg cells and their gene expression profile.

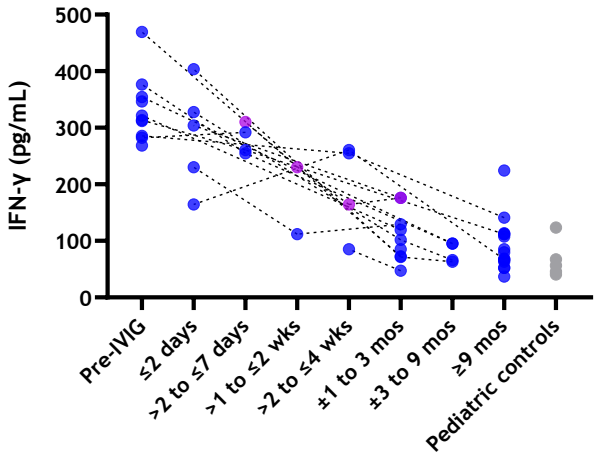


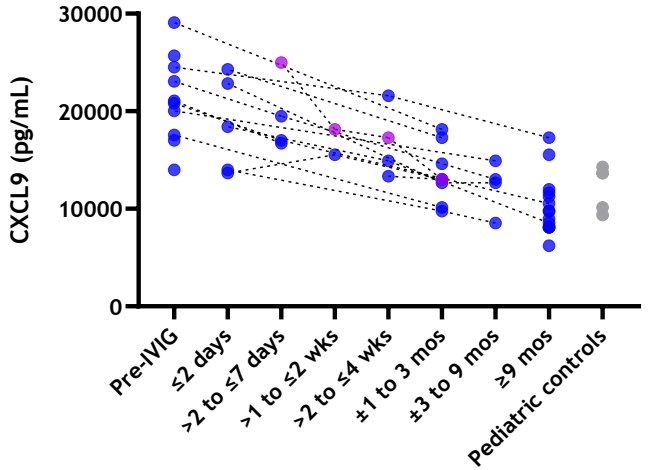


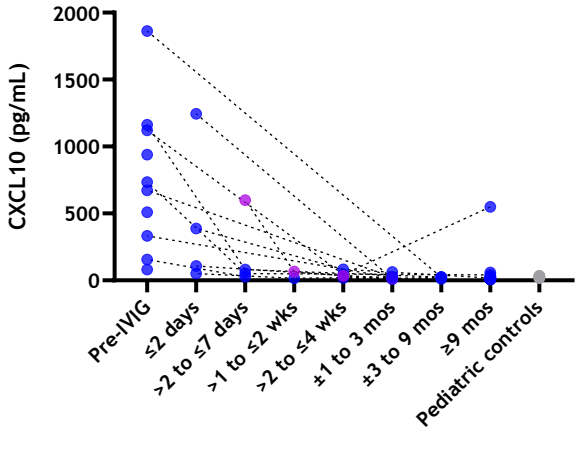
-ML approach identified key proteins that distinguish KD thus offering insights into KD pathogenesis as well as valuable information on prognostic indicators.



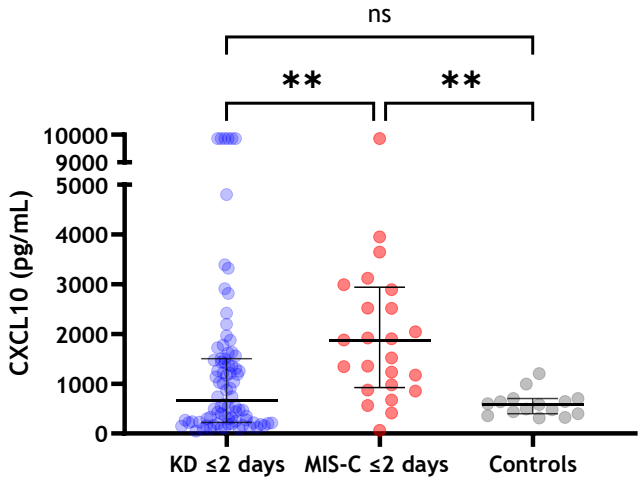
Immunological Biomarkers in KD







CXCL10 higher in MIS-C than KD → correlated with disease severity (ICU admission)

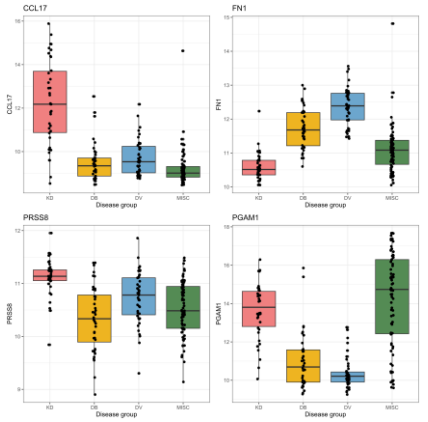


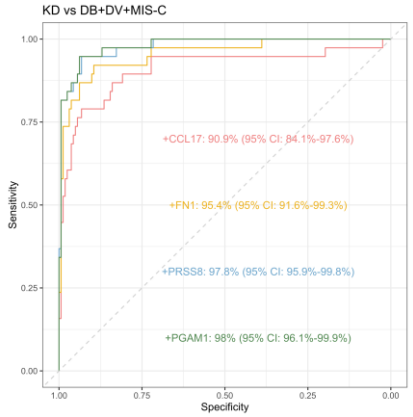
Giant CAA, IVIG resistance, treatment >10 days

Striking difference between KD and MIS-C is the hallmark Vβ21.3 expansion seen in MIS-C and not in KD

Young Investigator Oral Abstract Competition

A Host Protein Signature to Distinguish KD from Other Infectious and Inflammatory Diseases





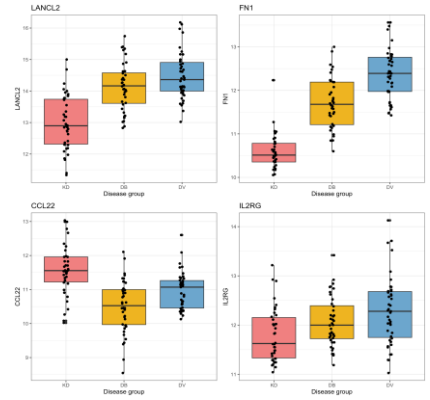
KD vs DB	KD vs DV	KD vs MIS-C
98.8% (CI: 97.1 – 100%)	98.4% (CI: 96.6% - 100%)	97.4% (CI: 94.8 – 100%)

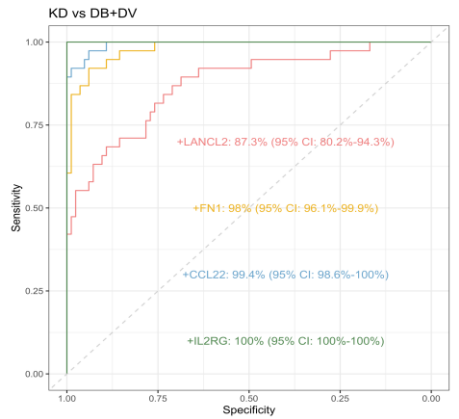
4 proteins can distinguish KD from other pediatric infectious and inflammatory syndromes

Protein	Model	Role in KD
Fibronectin (FN1)	DB+DV+MIS-C (M1); DB+DV (M1)	pathogenesis of coronary artery lesions in KD
C-C Motif Chemokine 17 (CCL17)	DB+DV+MIS-C (M1)	susceptibility and formation of coronary artery aneurysm in KD
Phosphoglycerate Mutase 1 (PGAM1)	DB+DV+MIS-C (M1)	Promotes cardiac fibrosis by affecting cardiac-hypertrophy associated proteins
C-C Motif Chemokine 22 (CCL22)	DB+DV+MIS-C (M3); DB+DV (M1)	Activated in acute KD stimulating cell recruitment; Increased concentration in serum

translation to point-of-care diagnostic test feasible

Adapted from Sophya Yeoh

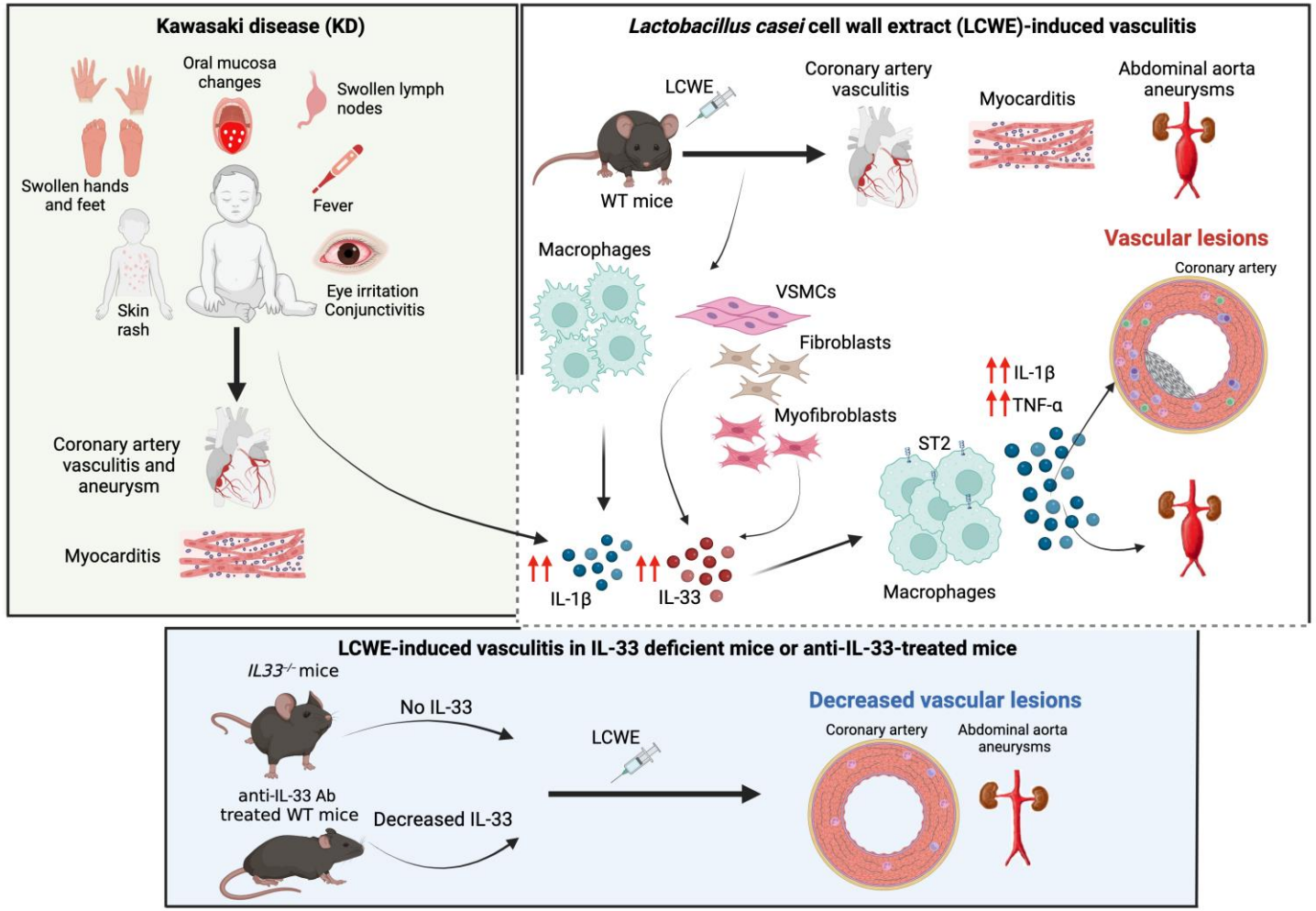




KD vs DB	KD vs DV
100% (95% CI: 100 – 100%)	100% (95% CI: 100% - 100%)

Young Investigator Oral Abstract Competition

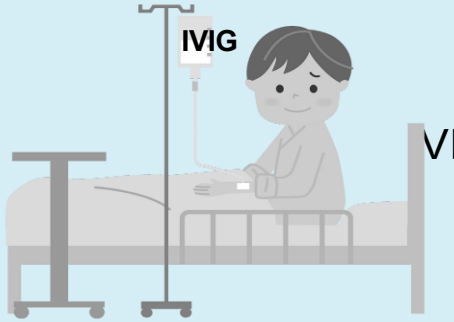
IL-33 promotes cardiovascular lesion development by boosting IL-1β production in a murine model of KD



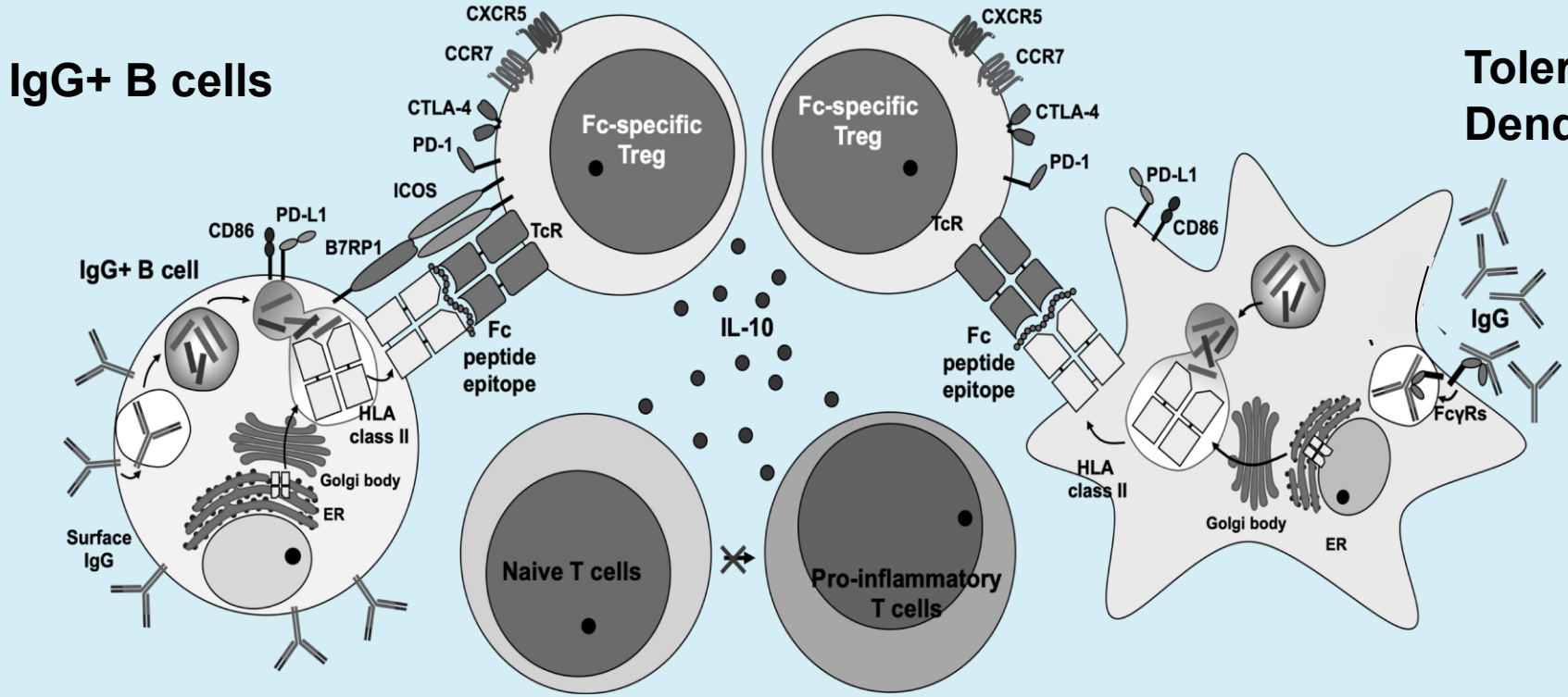
Cedars Sinai
Guerin Children's

Role of regulatory T-cells in pathogenesis and therapeutics of KD

Fc-specific Treg are primed by IgG+ B cells



The antigen processing of IgG is slow and inefficient in KD
VIG therapy provides a sufficient dose o IgG to allow the processing and presentation to Treg of Fc peptides



Highlights

New insights into KD pathogenesis

KD (early) diagnostic tools

KD is a heterogeneous disease (clusters)

Preventing the CV complications

CV imaging and treatment

Young Investigator Oral Abstract Competition

Evaluation of the 2017 AHA Incomplete KD Diagnostic Algorithm and a Data-driven Proposal of Changes

	2017 AHA	Proposed cutoffs
CRP (mg/dl)	≥ 3.0	≥ **5.0**
ESR (mm/hr)	≥ 40	≥ **15**
Platelets (10^3/ml)	≥ 450 (after day 7)	≥ **400** (any day)
Albumin (g/dl)	≤ 3.0	≤ **3.2**
WBC (10^3/μl)	≥ 15	≥ **25**
Urinalysis (WBC/μl)	≥ 50	≥ **50**

		KD	FC	Sens (%)	Spec (%)	PPV (%)	NPV (%)	AUC
AHA 2017 algorithm	Positive	36	10	87.8	75.6	78.3	86.1	0.817
	Negative	5	31					
Proposed cut-offs	Positive	37	2	90.2	95.1	94.9	90.7	0.927
	Negative	4	39					

Hao Wang

Young Investigator Oral Abstract Competition

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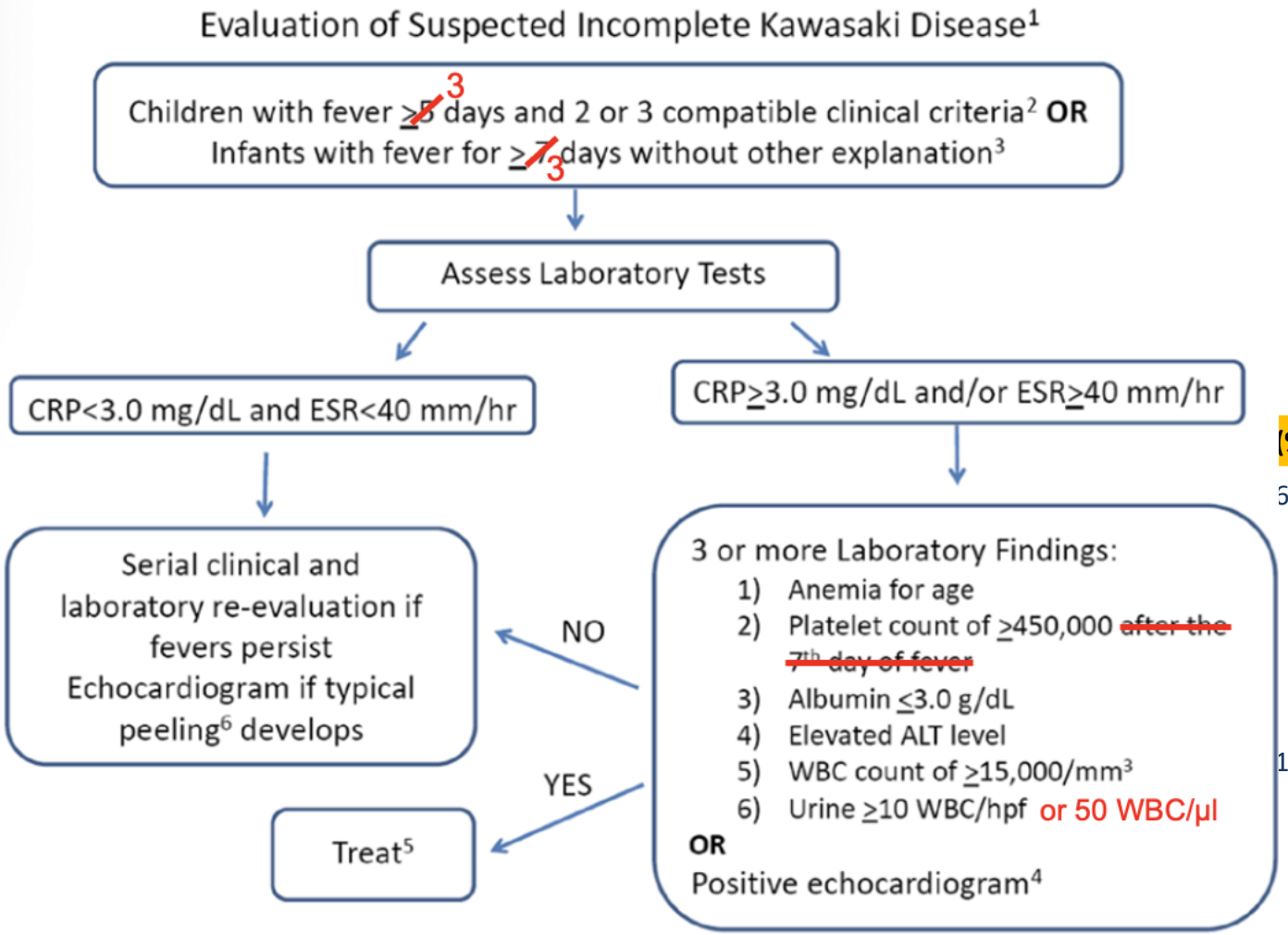


(%)	PPV (%)	NPV (%)	AUC
6	78.3	86.1	0.817
1	94.9	90.7	0.927

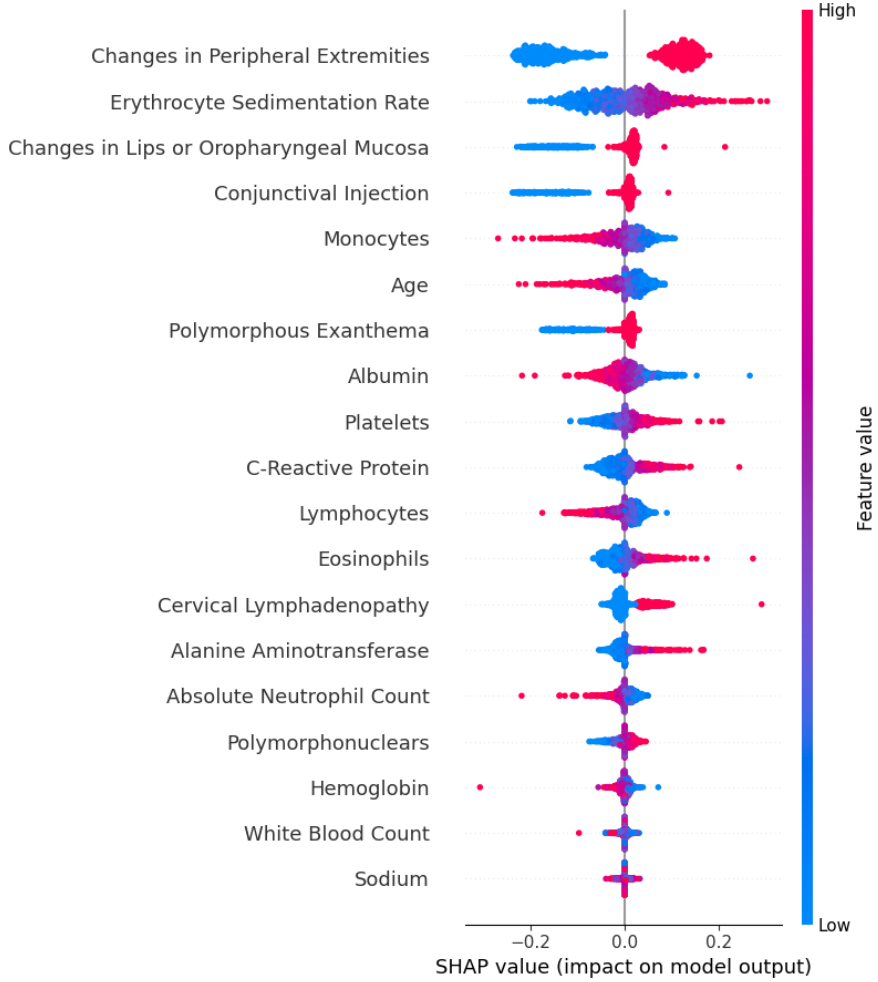
Hao Wang

Bioinformatic and AI: Diagnostic and Management tools

Kawasaki MATCH: A Clinical Decision Support Tool for KD

Most important features of the model correlate with well-characterized KD clinical variables

- Increase in the prevalence of clinical signs
- High ESR
- Low monocyte %
- Younger age



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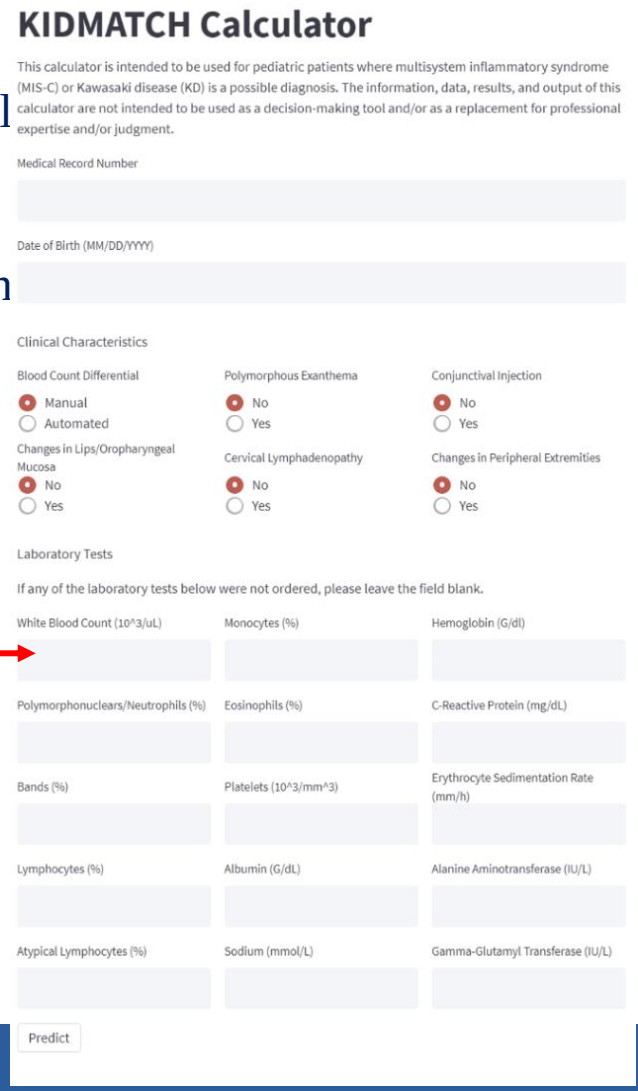
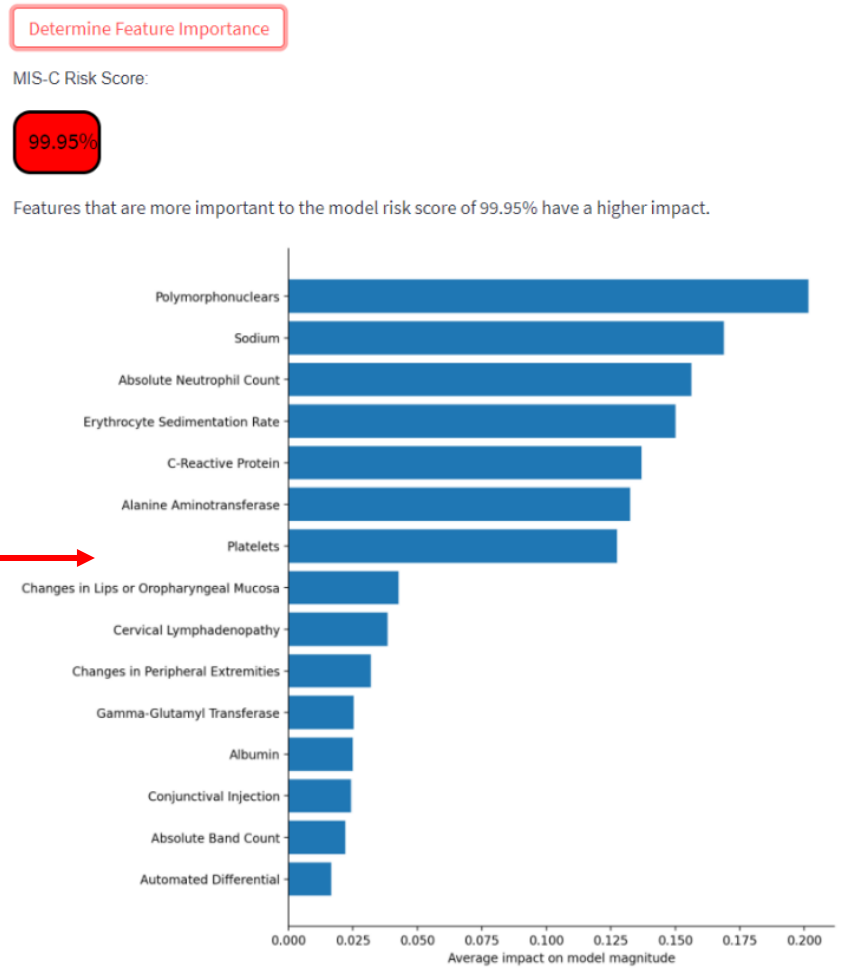




Deployment ecosystem

Patient-facing application

Unique patient code

Patient facing web portal 4C

- Consent
- Patient residence
- Date illness onset

Automated aggregator of spatiotemporal public data

Google Earth | Google Maps | sources

Data aggregation 1D

Environmental data application

Data processing

Feature extraction algorithms

MISKD application

Electronic health record

MSKD staging server 4B

Long-term FU 3+

MISKD CDSS 3D

4A

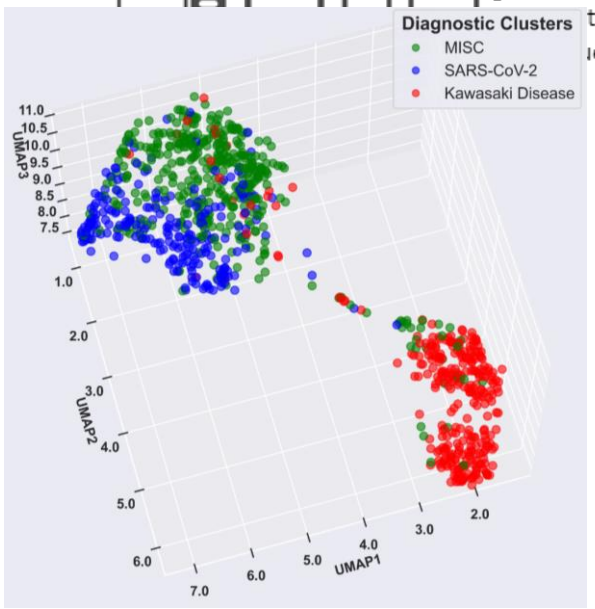
code

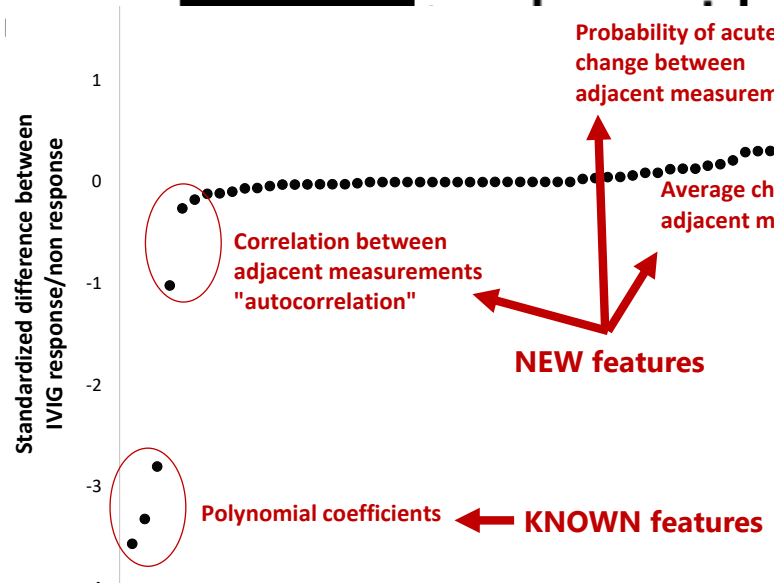
Distributed surveillance and federated learning

surveillance *Bitnobi* 4E

Federated learning *Integrate.ai* 4F

bitnobi





				Validation			
	Prev. MIS-C	Prev. KD	p	AUC	p	Se/Sp	O/E
ICU	58.4%	8.5%	<.001	0.85	<.001	77/78%	4.6%
ARDS	28.7%	4.6%	<.001	0.96	<.001	90/90%	3.5%
Shock	29.7%	3.4%	<.001	0.84	<.001	76/76%	6.2%
EF	24.8%	5.9%	<.001	0.72	<.001	66/66%	6.3%

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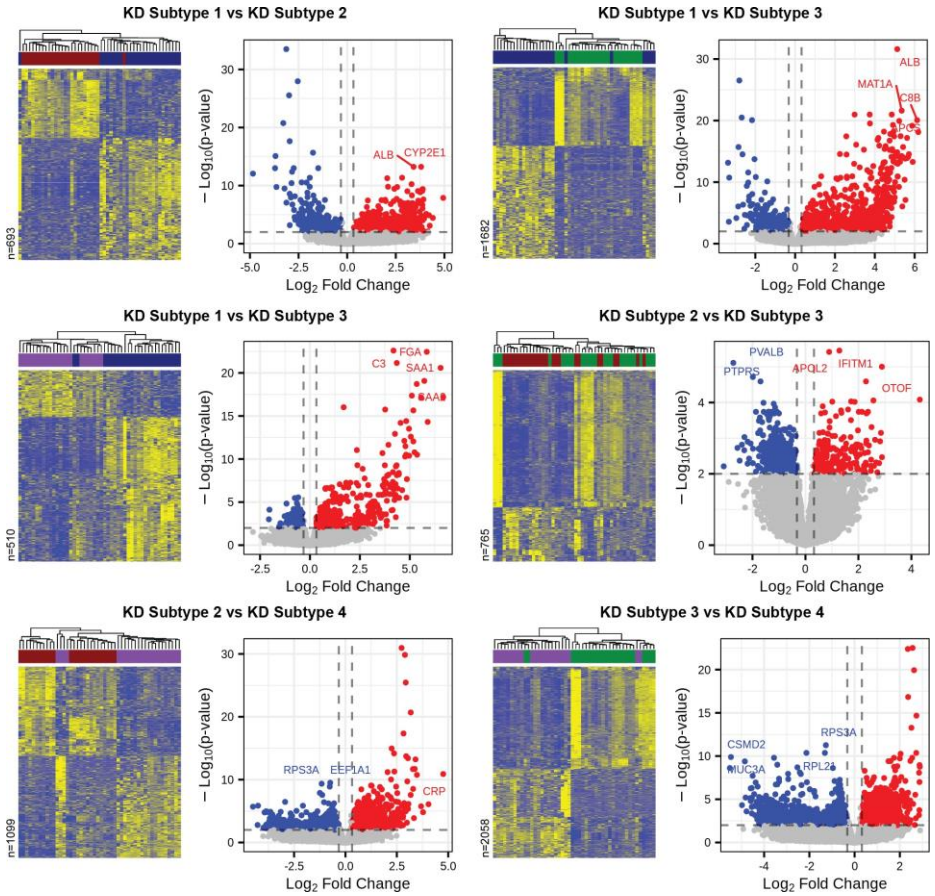
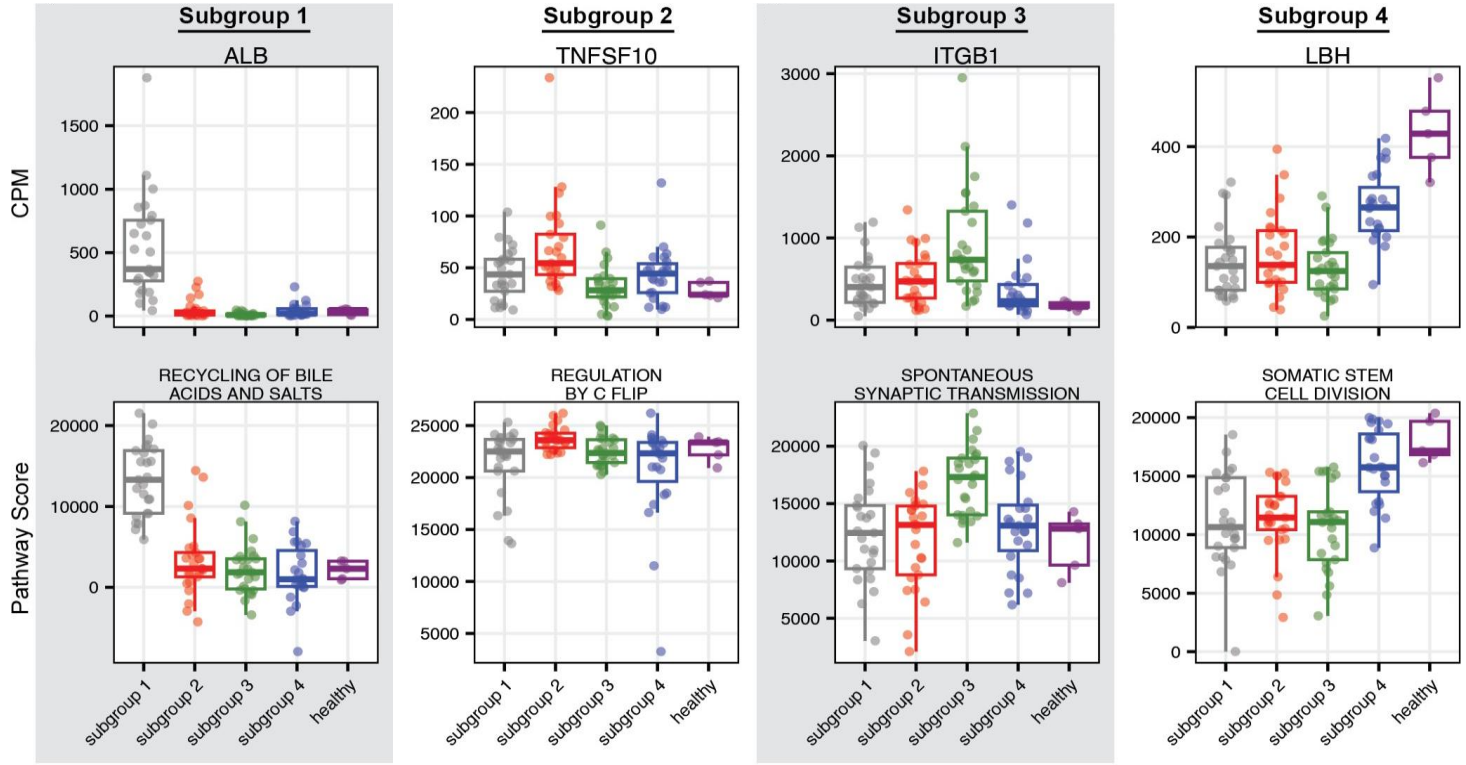
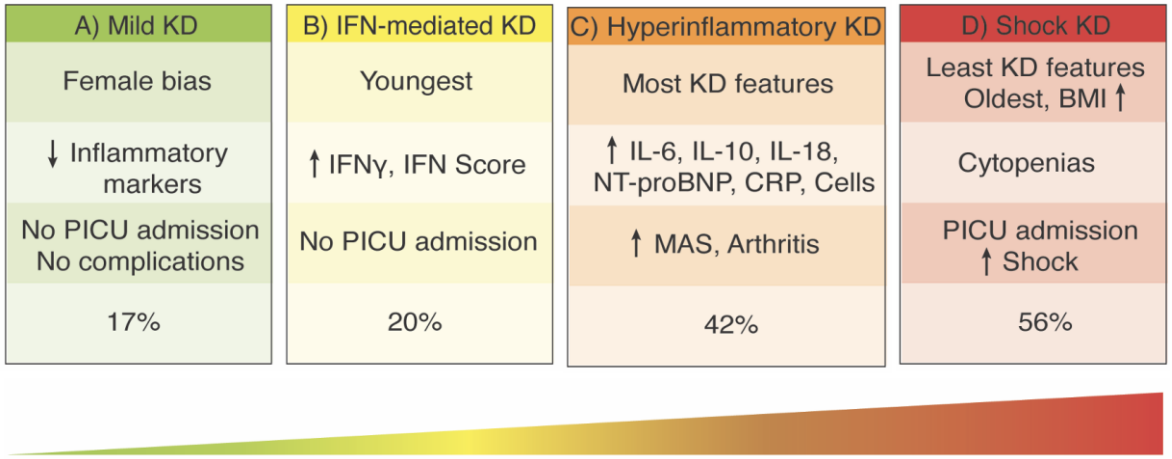
Young Investigator Oral Abstract Competition

Cell-Free RNA Signatures of Kawasaki Disease Subgroups





Data-driven approaches



Characteristic	MIS-C like, n = 671 (34%)		KD-like, n = 1274 (65%)		p
	Severe MIS-C n = 39 (2%)	Mild MIS-C n = 632 (32%)	Classic KD n = 574 (29%)	Severe KD n = 700 (36%)	
Age at presentation (yrs)	7.7	4.9	2.8	4.4	<0.001
Southeast Asian (%)	9%	9%	5%	4%	0.02
Respiratory Symptoms (%)	28%	39%	30%	31%	0.02
Abdominal pain (%)	92%	39%	31%	19%	<0.001
Shock (%)	16%	2%	2%	1%	<0.001
ICU Admission (%)	22%	4%	1%	2%	<0.001
Mean LVEF (%)	54%	58%	62%	62%	<0.001

Patient clusters can be uniquely described by composite signatures based on distinct biological profiles specific disease trajectories and patient outcomes

A proportion of patients diagnosed with KD prior to the COVID-19 pandemic had a clinical profile consistent with subgroups of pandemic-era MIS-C patients.

Pre-pandemic KD patients with a phenotype MIS-C like had a substantially higher prevalence of shock and LV dysfunction.

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Young Investigator Oral Abstract Competition

Predicting coronary artery abnormalities development using coronary Z-score and clinical parameters before the treatment for KD

- Risk factors for the development of CAA differed from those of IVIG resistance, except for younger patient age.

  - ✓ Pre-Zmax ≥ 1.6 (2points)
  - ✓ Albumin ≤ 3.1 g/dL (1point)
  - ✓ Months of Age ≤ 12 (1point)

≥ 2 points : high-risk for CAA.

<CAA development >

	Odd Ratio	[95% CI]
Pre-Zmax	2.443	[1.859-3.246]
Albumin (g/dL)	0.502	[0.265-0.957]
Age (months)	0.979	[0.963-0.993]

<1st IVIG resistance>

	Odd Ratio	[95% CI]
Male sex	1.444	[1.027-2.030]
Neutrophil (%)	1.058	[1.039-1.078]
Platelet (×10⁴/μL)	0.970	[0.952-0.990]
T-bil (mg/dL)	1.545	[1.211-1.971]
Age (months)	0.972	[0.962-0.982]

- A higher baseline Z-score was reported to be associated with the development of CAA from various countries> The ideal cutoff value for Zmax may be < 2.0.

- In addition to patients at high risk of IVIG resistance, those at high risk of developing CAA should also be considered for initial intensive therapy.

Young Investigator Oral Abstract Competition

Diagnostic Value of 99mTc-MIBI Myocardial Perfusion Imaging in Detecting Myocardial Ischemia of Children with Kawasaki Disease and Coronary Artery Lesions

Diagnostic value of the MPI in detecting myocardial ischemia compared to other tests

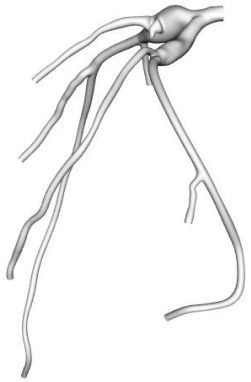
Test	Sensitivity	Specificity	Accuracy	PPV	NPV	Kappa
MPI	79.2% (38/48)	69.0% (89/129)	71.8% (127/177)	48.7% (38/78)	89.9% (89/99)	0.403
CMRI	67.7%* (23/34)	89.7% (78/87)	83.5%* (101/121)	71.9% (23/32)	87.6% (78/89)	0.583
Echocardiogram	25.0%* (12/48)	96.9% (12/129)	77.4% (137/177)	75.0% (12/16)	77.6%** (125/160)	0.277
CEEs	52.1% (25/48)	85.9% (110/128)	76.8% (136/177)	58.1% (25/43)	82.7% (111/134)	0.394

99mTc-MIBI MPI is safe, with an optimal diagnostic sensitivity among noninvasive examinations (CMRI, echo, CEE)

Yiting Gui

Hemodynamic analysis and risk assessment of coronary artery aneurysms and thrombosis in KD

- Hemodynamic parameters derived from CFD revealed **superior predictive performance on thrombus** than current standard metrics based on diameters of CAAs.



• Machine Learning approaches **for real-time prediction of hemodynamics** quantities

• They require data amounts that are **difficult to gather for rare pathologies** such as CAAs

• Data-driven methods available for **generating large populations of plausible CAAs** for training ML models

• The method is validated by medical experts and will allow for **real-time thrombosis risk estimation**

Highlights

New insights into KD pathogenesis

KD (early) diagnostic tools

KD is a heterogeneous disease (clusters)

Preventing the CV complications

CV imaging

I speak in Japanese. Please put on your headset.

THE YUKI LYNN MEMORIAL LECTURE: Establishing WHO Center and Training

Yuki Lynn Takahashi Memorial Lecture: Establishing WHO Centre and training

Allergy Immunology Unit,
Department of Pediatrics,
Advanced Pediatrics Centre,
PGIMER, Chandigarh

WHO Collaborating Centre for Education, Research and Training in Pediatric Immunology

Dr. Surjit Singh
MD; DCH (Lon.); FRCP (Lon.); FRCPCH (Lon.); FAMS

Head, Department of Pediatrics and Chief, Allergy Immunology Unit,
Advanced Pediatrics Centre, PGIMER, Chandigarh, India

WHO Collaborating Centre for Education, Research and Training in Pediatric Immunology
Asia Pacific League of Associations for Rheumatology Centre for Excellence in Rheumatology
Indian Council of Medical Research Collaborating Centre of Excellence in Pediatric Immunology

BREAKOUT SESSIONS:
From Emerging Clinician to Expert

KD shock syndrome (acute management)

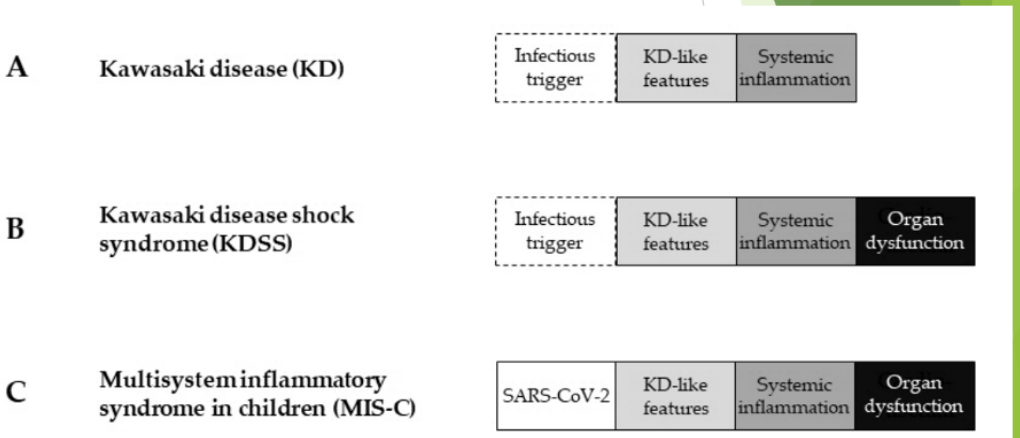
Definition of KDSS

- Sustained systolic hypotension
- Clinical signs of poor perfusion
- Initiate volume expansion or infusion of vasoactive agents or Transfer to an intensive care setting

KDSS incidence

- 2.8% to 5.3%. in the United States.
- Five out of 84 (6 %) in Italy
- 5% in Mexico.
- In Japan (1.1%, 6/552)
- In Korea 0.8% (9/1095)
- 9 patients (1.9%) in Taiwan

Consequently, KDSS is relatively uncommon in Taiwan, leading to a higher rate of initial misdiagnosis and delays in appropriate therapy for KDSS.



Adapted from presentation by Dr. Kun-Lang Wu

Refractory KD

Differential diagnosis for Kawasaki disease

<Diseases causing coronary artery aneurysms>

Inflammatory diseases	Kawasaki disease, Takayasu arteritis, polyarteritis nodosa, giant cell arteritis, IgA vasculitis, eosinophilic polyangiitis granulomatosis, systemic lupus erythematosus, systemic juvenile idiopathic arthritis, Behçet's disease, PFAPA syndrome, Erdheim-Chester disease, IgG4-related disease, ADA2 deficiency, chronic granulomatosis
Infections	Yersinia infection, COVID-19 associated pediatric multi-organ inflammatory syndrome (MIS-C), Infectious mononucleosis (IM), chronic active EB virus infection (CAEBV), Mycoplasma infections, rickettsia infections
Syndromes	Marfan synd.、Noonan synd.、Williams synd.、Ehles-Danlos synd.、Loeys-Dietz synd. etc.
Others	Iatrogenic disease, atherosclerosis, congenital coronary arterial fistula

Asi K, *et al. Pediatr Rheumatol Online J. 2019; 17:3.* Cascio A, *et al. New Microbiol.* 2011; 34: 421-424. .van Doorn HR, *et al. Pediatr Cardiol.* 2006;27 :515-518. Jost ZT, *et al. Eur Heart J Case Rep. 2022; 6: ytac204.* Tang R, *et al. Med Hypotheses.* 2006; 67: 371-4. Toshiro Hara. *Nippon Rinsho.* 2014; 72: 1542-1547. Kang Z, *et al. Front Pediatr.* 2022;9 :781106. Guo Y, *et al. Heliyon.* 2023; 9: e21385.

<Incidence of coronary artery aneurysms>

KD	MIS-C	Juvenile–onset SLE	Systematic JIA	Takayasu arteritis	Polyarteritis nodosa	CAEBV
< 25% (untreated)	**14-48%**	**4.45%**	**< 16%**	**55.6%** (pediatric)	**< 1%**	**8.9%**

Sharma C, *et al. Rheumatol*. 2021; 17: 731-748. Lei C, et al. Can J Cardiol. 2020; 36: 535-542. Gori T. Biomedicines. 2021; 9:622. Wei A, *et al. Orphanet J Rare Dis.* 2021; 16: 50. Liu JJ, *et al. China Med Herald.* 2017;14:76–79. Yeh TT, *et al. J Microbiol Immunol Infect.* 2007; 40: 525–531. Felix A, *et al. Pediatr Rheumatol* Online J. 2022;20: 98. Zhang L, *et al. Pediatr Rheumatol Online J.* 2024; 22: 4. Ozen S, *et al. J Pediatr.* 2004; 145: 517-522. Kasap Cuceoglu M, *et al. Semin Arthritis Rheum.* 2021; 51: 559-564. Canares TL, *et al. Pediatr Rheumatol Online J.* 2012; 10: 1.

In this case, the diagnostic criteria for Kawasaki disease were met. But it was atypical and intractable. Therefore, vasculitis syndrome and JIA were differentiated.

Adapted from presentation by Dr. Kenichiro Yamamura

Differential diagnosis: Is it really KD? (Rash)

Differential Diagnosis

- Viral illnesses (eg adenovirus, enterovirus)
- Scarlet Fever
- Measles
- Toxic Shock Syndrome
- Stevens-Johnson Syndrome
- Staphylococcal Scalded Skin Syndrome
- Rheumatic Fever
- Malaria
- Typhoid
- Rocky Mountain Spotted Fever or other rickettsial infections
- Leptospirosis
- Systemic Juvenile Arthritis
- Drug Reactions
- Mercury Poisoning

Exercise as a daily healthy routine in KD patients

FITT Principle

When giving exercise guidance, the 4 factors, including exercise frequency, intensity, time, & type should be fully considered based on medical history, physical examination, & necessary auxiliary examinations, & should be dealt with from dynamic exercise & static exercise

- Frequency
- Intensity
- Time
- Type

Exercise as a daily healthy routine in KD patients

JCS/JSCS Recommendations for School Activity Level Mild, Moderate, & Intense Exercise

[Revised in 2011]

School Life Management Table (for Elementary School Children)

Name M / F Birth date (years) School Grade Class Date

1. Diagnosis (findings)	2. Level of management Management required: A, B, C, D, E No management required	3. School sport club activity Name of club ( ) Allowed (Note:) · Prohibited	4. Next visit ___ years ____ months later or when symptoms develop	Name of institution: Name of physician: (seal)

[Level of management: A - Requires treatment at home or in hospital, B - Goes to school but must avoid exercise, C - Can do mild exercise, D - Can do moderate exercise, E - Can do intense exercise]

Sport activity / Intensity of exercise				Mild exercise (C, D, E - allowed)	Moderate exercise (D, E - allowed)	Intense exercise (E - allowed)
Type of sport	Basic exercise*	Warming-up exercise Exercise-play to improve athletic ability	Grade 1-2	Balance exercise-play (play consists of different body postures such as lying down, sitting up/down, and standing up)	Exercise-play using apparatus (grabbing, releasing, rotating, rolling or going through the apparatus)	Exercise-play to change location (crawling, running, jumping, and hopping)
		Warming-up exercise Exercise to improve athletic ability	Grade 3-4	Balance exercise (exercise consists of different body postures such as lying down, sitting up/down, standing up, and hopping)	Exercise using apparatus (grabbing, holding, rotating, and releasing the apparatus, and exercise using a rope)	Strength competition (push or pull the partner, or compete strength), combination of basic movements
		Warming-up exercise Strength-training exercise	Grade 5-6	Exercise to improve flexibility (including stretching), light walking	Exercise to improve techniques (Rhythmic exercise and exercise using a ball, hoop or clubs)	Full-body activities within a given time/course (short-rope jumping, long-rope jumping, long-distance running)
	Athletics	Running and jumping exercise-play	Grade 1-2	Walking in different ways, rubber rope jumping	Hopscotch	Full-strength foot race, straight-course relay race, relay race with low obstacles
		Running and jumping exercise	Grade 3-4	Walking and light standing broad jump	Slow jogging, light jumping (standing long/high jump)	Full-strength foot race, round-course relay race, low hurdle race, high/long jump with short running start
		Athletics	Grade 5-6			Full-strength sprint, hurdle race, high jump with running start, long jump with running start
	Ball sports	Games, ball games, tag (for early grades), games using goals or nets, baseball-type games (for middle grades)	Grade 1-2	Target shooting with ball throwing, bouncing and catching	Target shooting with ball kicking and holding, ball kicking, tag, encampment games	Competition-style exercise
			Grade 3-4	Basic ball handling (passing, catching, kicking, dribbling, shooting, and batting)	Simple games (games with basic exercises with modified rules to fit the place and apparatus used)	
		Ball sports	Grade 5-6			
	Apparatus gymnastics	Exercise-play using apparatus	Grade 1-2	Exercise-play using climbing frames	Exercise-play using monkey bars and wall bars	Exercise-play using mat, horizontal bars and vaulting horse
		Apparatus gymnastics using mats, vaulting horse or horizontal bars	Grade 3-4 Grade 5-6	Basic exercises Mat exercise (basic movements such as forward roll, backward roll, handstand against wall, and bridging) Vaulting horse (basic movements such as jumping with legs apart) Horizontal bars (basic movements such as forward roll landing)	Basic techniques Mat exercise (e.g., forward/backward rolls, forward/backward rolls with legs apart, handstand against wall, and handstand with support) Vaulting horse (e.g., jumping with legs apart with short running start, jumping with legs folded, and forward roll on the horse) Horizontal bars (e.g., back hip circle with support, forward roll landing with a leg over the bar, front hip circle, and back hip circle)	Combination of gymnastic movements
	Swimming	Play with water	Grade 1-2	Play with water (foot race, playing train in swimming pool)	Floating and diving (e.g., prone float with hands against the wall, and paper-rock-scissors or staring game in water)	Relay race in the pool, bubbling, and bobbing
		Floating and swimming	**Grade 3-4**	**Floating (e.g., prone float, back float, jelly fish float)** Swimming movements (flutter kicks, frog kicks)	**Floating (e.g., kick and float)** Swimming (e.g., repeated bobbing, etc.)	**Crawl stroke and breaststroke with supportive apparatus**
		Swimming	Grade 5-6			Crawl stroke and breaststroke
	Dance	Rhythmic play	Grade 1-2	Pretend play (e.g, birds, bugs, dinosaurs, and animals)	Pretend play (e.g., airplane, fun-park rides)	Rhythmic play (e.g., bouncing, whirling, twisting, and skipping)
		Expression movement	Grade 3-4 Grade 5-6	Improvised expression movement	Light rhythmic dance, folk dance, simple Japanese folk dance	Combination of variable movements (rock and samba dance) Japanese folk dance with strenuous movements
	Outdoor activities such as play in the snow or on the ice, skiing, skating, and waterfront activities			Playing on snow or ice	Walking with ski plates or skates and waterfront activities	Skiing and skating
Cultural activities				Cultural activities without prolonged activities requiring physical strength	Most cultural activities not described in the right column	Playing instruments requiring physical exertion (such as trumpet, trombone, oboe, bassoon, horn), playing or conducting quick rhythmical music, playing in a marching band
School events and other activities				·Follow the above intensity of exercise during athletic festival, during athletic meetings, ball sports competitions, and exercise tests. ·Students other than those in Category "E" should consult with their school physician or their attending physicians in determining whether they will participate in other special school activities such as class trips, camp schools, seaside schools, and training camp. ·Consult school/attending physicians for the distance of running and swimming (refer to the school curriculum guideline)		

Remarks

Definitions Mild exercise: Physician activities that do not increase respiratory rate in average children at the same age.
Intermediate exercise: Physical activities that increase respiratory rate without causing shortness of breath. Players may talk with partners, if any, during exercise.
Intense exercise: Physical activities that increase respiratory rate and cause shortness of breath.
* Basic exercise: including resistance (isometric) exercise.

[Revised in 2011]

School Life Management Table (for Junior and Senior High School Students)

Name M / F Birth date (years) School Grade Class Date

1. Diagnosis (findings)	2. Level of management Management required: A, B, C, D, E No management required	3. School sport club activity Name of club ( ) Allowed (Note:) · Prohibited	4. Next visit ___ years ____ months later or when symptoms develop	Name of institution: Name of physician: (seal)

[Level of management: A - Requires treatment at home or in hospital, B - Goes to school but must avoid exercise, C - Can do mild exercise, D - Can do moderate exercise, E - Can do intense exercise]

Sport activity / Intensity of exercise				Mild exercise (C, D, E - allowed)	Moderate exercise (D, E - allowed)	Intense exercise (E - allowed)
Type of sport	Basic exercise	Warming-up exercise Strength-training exercise		Light exercise or rhythmic movement to communicate with other students Basic movements (throwing, hitting, catching, kicking, jumping)	Exercise to improve flexibility, techniques, high-force movement, and endurance	Exercise with maximum endurance, speed, and muscle strength
	Apparatus gymnastics	(Mat, vaulting horse, horizontal bar, and balance beam)		Calisthenics, light mat exercise, balance exercise, light jumping	Practice of low-grade technique, running to perform actions such as holding, jumping, and rotation	Performance, competition, combination of actions
	Athletics	(racing, jumping, throwing)		Basic motion, standing broad jump, light throwing, light jumping (must avoid running)	Jogging, short run and jump	Long-distance running, sprint race, competition, time race
	Swimming	(freestyle, breaststroke, backstroke, butterfly)		Easy movement in water, float, prone float, kick and float, etc.	Slow swimming	Competition, swimming marathon, time race, start and turn
	Ball sports	Goal games	Basketball Handball Soccer Rugby	Slow exercise without running	Basic movements (e.g., passing, shooting, dribbling, feinting, lifting, trapping, throwing, kicking, and handling)	Training with footwork (with no close body contact)	Simple games using basic movements (adjust games according to the time, space and apparatus available to practice collaborative playing, and offensive/defensive components)	Time race, applied practice, simplified game, game, competition	Competition
		Net games	Volleyball ping-pong Tennis Badminton		Basic movements (e.g., passing, servicing, receiving, tossing, feinting, stroking, and shots)				
		Baseball-type games	Softball Baseball		Basic movements (e.g., pitching, catching, and batting)				
		golf			Basic movements (light swinging)		Practicing at golf range		
	Martial arts	Judo, kendo, sumo		Etiquette, basic movement (e.g., sukemi, swinging, sabaki)	Practicing simple techniques and forms with modest basic movements			Applied practice, competition	
	Dance	Original dance, folk dance, modern dance		Basic movement (e.g., hand gesture, steps, expressions)	Dance with modest basic movements			Dance recitals	
	Outdoor activity	Play in the snow or on the ice, skiing, skating, camping, climbing, swimming marathon, water-front activities		Playing on water, snow, or ice	Walking with ski plates or skates, slow skiing/skating, hiking on flatlands, playing in the water, etc.			Climbing, swimming marathon, diving, canoeing, boating, surfing, wind surfing, etc.	
Cultural activities				Cultural activities not requiring long-term physical activity	Most cultural activities not described in the right column			Playing instruments requiring physical exertion (such as trumpet, trombone, oboe, bassoon, horn), playing or conducting quick rhythmical music, playing in a marching band	
Cultural activities not requiring long-term physical activity				·Follow the above intensity of exercise during athletic festival, during athletic meetings, ball sports competitions, and exercise tests. ·Students other than those in Category "E" should consult with their school physician or their attending physicians in determining whether they will participate in other special school activities such as class trips, camp schools, seaside schools, and training camp					

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Definitions Mild exercise: Physician activities that do not increase respiratory rate in average children at the same age
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Intense exercise: Physical activities that increase respiratory rate and cause shortness of breath.
* Basic exercise: including resistance (isometric) exercise

Fukazawa R, Kobayashi J, et al; Japanese Circulation Society Joint Working Group. JCS/JSCS 2020 Guideline on Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease. Circ J. 2020 Jul 22;84(8):1348-1407.

Adapted from presentation by Dr. Roni Jacobsen

Chronic life-long phase: What anticoagulant & antiplatelet

Special Considerations

- Warfarin is known to interact with several drugs and certain foods, and it often presents with problematic dosing and maintenance in young children
- Previous studies of warfarin therapy in children with KD and in those who underwent Fontan surgery showed that time in the therapeutic range for warfarin was only 45%-60% , leaving a substantial amount of time with inadequate anticoagulation

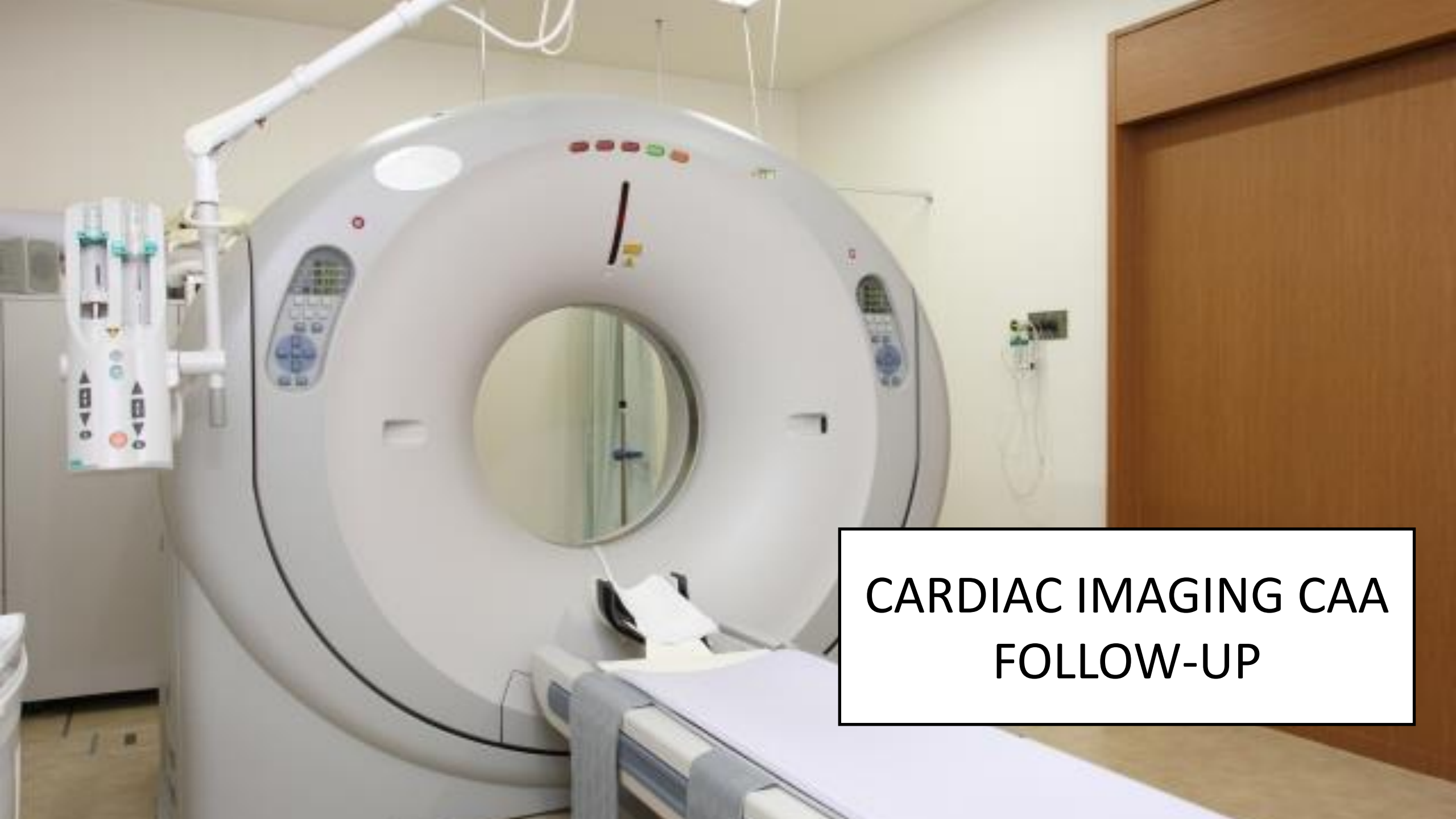
IKD Registry

Chronic life-long phase: What anticoagulant & antiplatelet

Special Considerations

- LMWH has more predictable pharmacokinetics, rapid achievement of a therapeutic level of anticoagulation, and minimal monitoring
- Patients on LMWH require twice-daily subcutaneous injections, which may affect their quality of life
- Long-term therapy with LMWH has been associated with possible decreased bone mineral density and increased risk of fracture in adults, although this effect is not well characterized for pediatric patients

IKD Registry

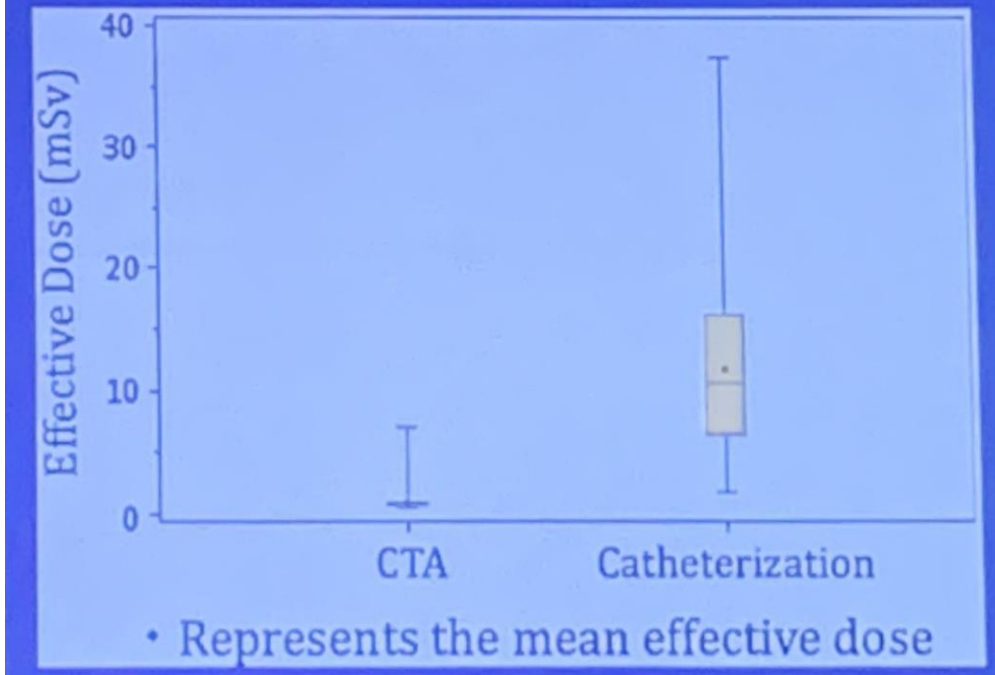


CARDIAC IMAGING CAA FOLLOW-UP

CT coronary imaging in KD

How does CT compare to catheter angiography?

Ann & Robert H. Lurie Children's Hospital of Chicago



- Represents the mean effective dose

Source	Estimated effective dose (mSv)
Natural background radiation	3 mSv/yr
Airline passenger (cross country)	0.04 mSv
Chest X-ray (single view)	up to 0.01 mSv
Chest X-ray (2 view)	up to .1 mSv
Head CT	up to 2 mSv
Chest CT	up to 3 mSv
Abdominal CT	up to 5 mSv

The radiation used in X-rays and CT scans has been compared to background radiation we are exposed to daily. This also is misleading as this refers to whole body dose which is not truly comparable to studies that image only a portion of the body. However, this comparison may be helpful in understanding relative radiation doses to the patient.

Radiation source	Days background radiation
Background	1 day
Chest X-ray (single)	1 day
Head CT	up to 8 months
Abdominal CT	up to 20 months

Stanley Manne Children's Research Institute

Northwestern Medicine Feinberg School of Medicine

Watson et al. 2013 Ped Card

30

Adapted from presentation by Dr. Simon Lee

Imaging surveillance of coronary arteries

Summary of imaging data for KD coronary assessment

Imaging Evaluation of Kawasaki Disease

Pei-Ni Jone [1], Jennifer Romanowicz [2], Lorna Browne [3], LaDonna J Malone [3]

Affiliations + expand

PMID: 35986822 DOI: 10.1007/s11886-022-01768-4

- In the first two years – assessment more likely for symptomatic ischemia
- > two years, most imaging for risk assessment (except medium- giant aneurysms)
- If there was never coronary involvement – no findings on imaging (up to 20 years)
- If there are regressed aneurysm or small aneurysm – vessel wall changes may occur (calcium, abnormal vasoreactivity) but risk of MACE is low
- Large aneurysms do not regress and the long-term chance of intervention/MACE is high
- Echo is not sufficient for stenosis or distal vessel evaluation, may miss aneurysms in distal or circumflex coronary artery
- CMR is age/HR dependent, best for perfusion/tissue characterization but does not see calcium and distal vessels (3T, contrast angiography may change this)
- CCT has low radiation dose in the current era – is good for vessel pathology including coronary calcium in all ages and heart rates

Adapted from presentation by Dr. Kelly Han

MRA imaging – perfusion defect (optional 4D flow in KD) Pros & Cons

The debate continues …..

- While the technique offers unique advantages, these practical constraints often influence its adoption and utilization in clinical practice
- More robust evidence is needed to establish its clinical utility and to guide its integration into routine clinical practice
- Its use is likely to evolve as more evidence accumulates and technology improves
- To address validation gaps, will take time and collaborative efforts to accumulate the necessary evidence

Until then, the use of MRI perfusion imaging in Kawasaki disease remains somewhat controversial and should be decided on a case-by-case basis

Stakes are too high for any delayed or misinterpretation of myocardial ischemia in pediatric patients so until all these limitations are addressed,

MRI Perfusion imaging is not yet ready for Prime time…

NEW YORK MEDICAL COLLEGE School of Medicine | WMCHealth | maria Fareri children's Hospital

Adapted from presentation by Dr. Supriya Jain

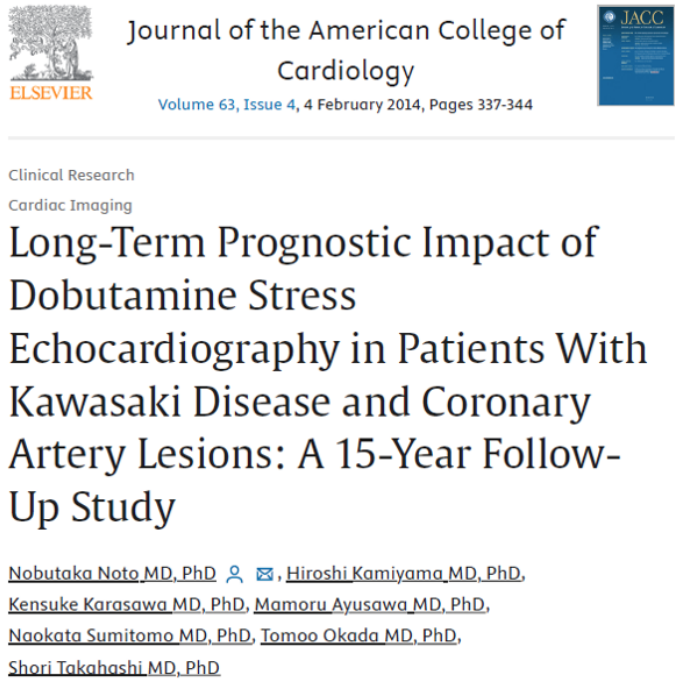
Utility of stress echo in KD patients : Dobutamine stress echo

Adapted from presentation by Dr. Nobutaka Noto

Utility of stress echo in KD patients: Exercise stress echo

"Exercise is More Physiologic"

- Dobutamine creates increased oxygen demand of myocardium
- May be used in those under 7 yrs, who cannot use exercise equipment
- Noto et al. evaluated 50 KD patients compared to angiography demonstrated 19/21 patients, > 50% occlusion of coronaries had positive response to dobutamine stress echocardiography **(Noto et al. JACC 1996)**
- Noto et al. more recently demonstrated that dobutamine stress echo had prognostic value predicting MACE in 15-year follow-up

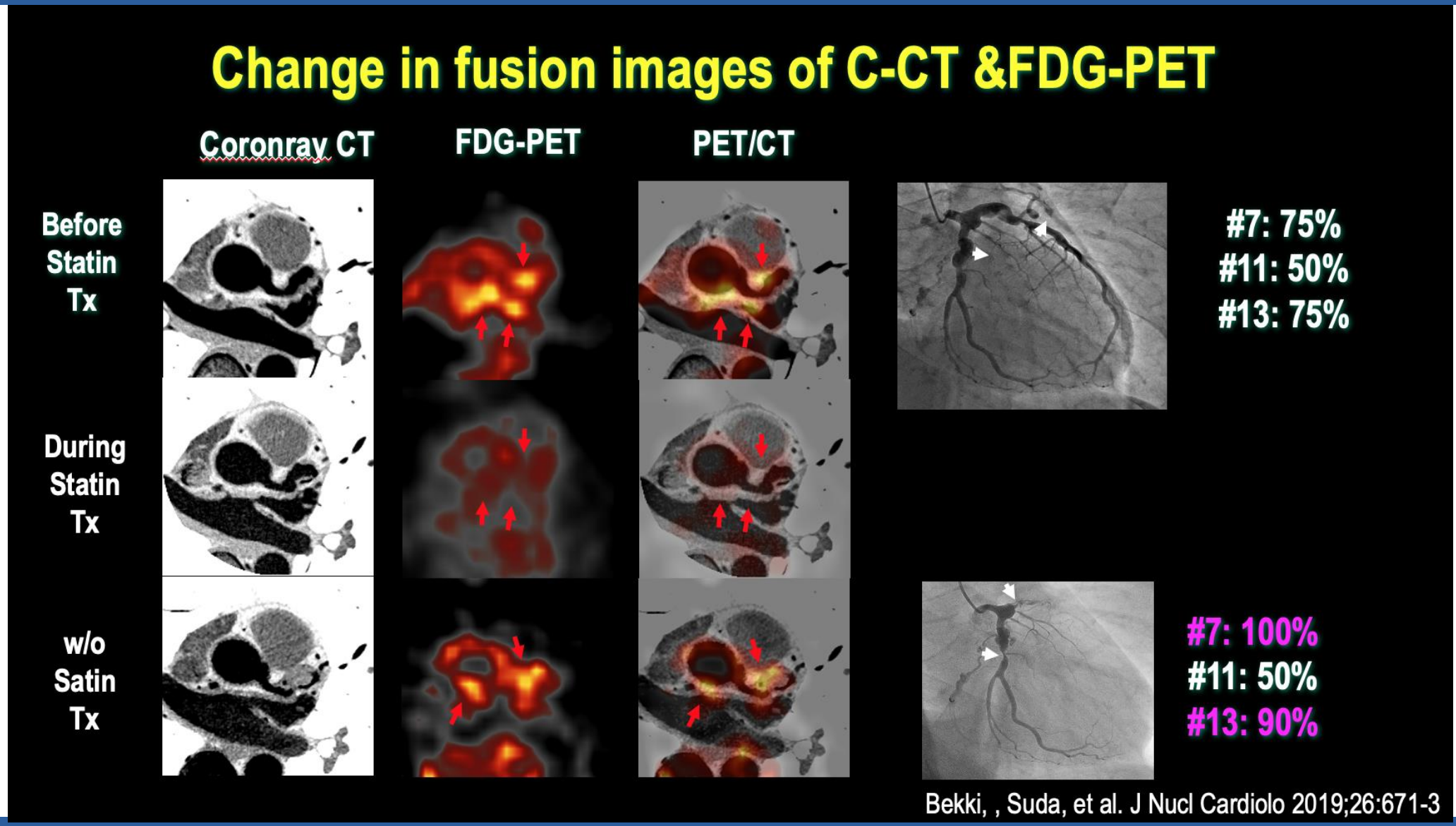

ELSEVIER
Journal of the American College of Cardiology
Volume 63, Issue 4, 4 February 2014, Pages 337-344
JACC
Clinical Research
Cardiac Imaging

Long-Term Prognostic Impact of Dobutamine Stress Echocardiography in Patients With Kawasaki Disease and Coronary Artery Lesions: A 15-Year Follow-Up Study

Nobutaka Noto MD, PhD, Hiroshi Kamiyama MD, PhD, Kensuke Karasawa MD, PhD, Mamoru Ayusawa MD, PhD, Naokata Sumitomo MD, PhD, Tomoo Okada MD, PhD, Shori Takahashi MD, PhD

Adapted from presentation by Dr. Michelle Grenier

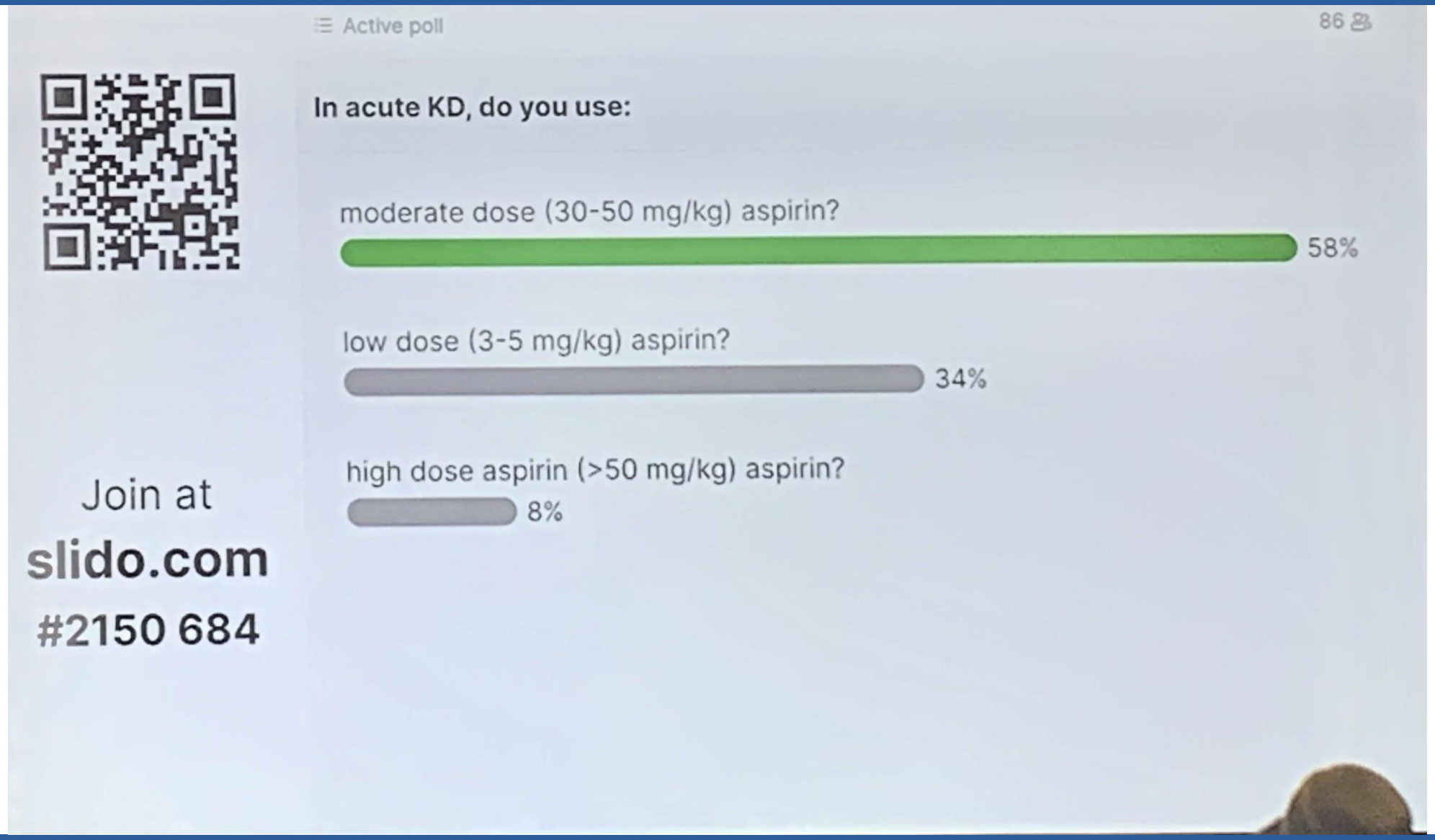
PET nuclear scans of coronary arteries



Adapted from presentation by Dr. Kenji Suda

RE-EXAMINING USE OF ASPIRIN AND APPROACHES TO ANTICOAGULATION

Initial intravenous immunoglobulin therapy without aspirin for acute KD



Initial intravenous immunoglobulin therapy without aspirin for acute KD

CAL occurrence within 1 month

	Regression analysis		Propensity score analysis			
			Matching		IPTW	
	Risk ratio (95% CI)	P-value	Risk ratio (95% CI)	P-value	Risk ratio (95% CI)	P-value
MD	(reference)		(reference)		(reference)	
non-MD	**1.12 (0.83–1.51)**	**0.46**	**1.44 (0.62–3.38)**	**0.40**	**1.19 (0.90–1.56)**	**0.23**

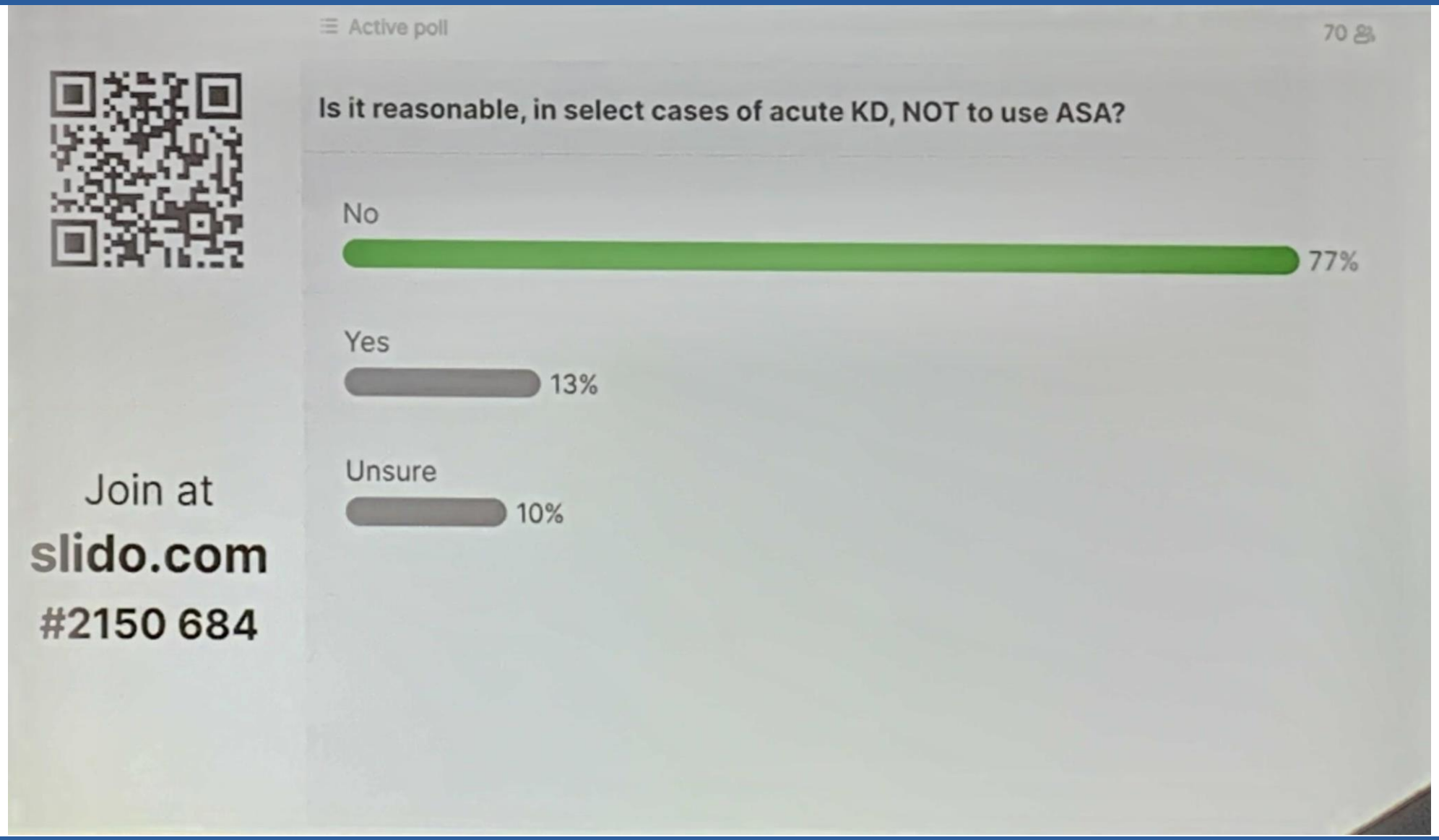
The point estimate of the Risk Ratio for the non-MD group exceeded 1, but the result was not statistically significant.

Limitations:

- It is difficult to verify non-inferiority in observational studies.
- The non-MD group includes cases where ASA was administrated with the initial IVIG, so it is unclear whether only cases without concerns for coronary arteries were extracted.

Adapted from presentation by Dr. Shinsuke Hoshino

Initial intravenous immunoglobulin therapy without aspirin for acute KD



Advantages of DOACs

- Oral formulations (once, twice or 3 times daily)
- Predictable effect
  - Wide therapeutic and safety margin
  - Reduces the need for routine monitoring
- Fixed dosing:
  - Weight based dosing regimen with established pediatric PK and PD
  - Role of DOAC level in dose titration still under evaluation
- Fewer drug-drug interactions

DOACs for prophylaxis and thrombolysis–Challenges for KD patients

DOAC-associated Bleeding

- Activated charcoal – within 6 h
- Non-specific reversal agent*
  - Prothrombin complex concentrates (4F-PCC):

    prefer inactivated > activated PCC (25 to 50 IU/kg, IV; typical initial dose up to 2,000 IU)

Hemodialysis

- Dabigatran (with renal impairment)

**Low to very low quality in systematic review*

Burnet AE, *et al. J Thromb Thrombolysis 2016;41(1):206-32*
Schulman S. Semin Thromb Hemost 2017;43(8):886-92

Thank you for your attention and enjoy the conference!

Take Home Messages – Day 3

14th International Kawasaki Disease Symposium

August 29, 2024

Rakesh Kumar Pilania MD, DM
Post Graduate Institute of Medical Education and Research, Chandigarh, India

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Conflict-of-Interest Disclosures

Presenters:	
Any direct financial payments including receipt of honoraria	None
Membership on advisory boards or speakers' bureaus	None
Funded grants or clinical trials	None
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	None

Day 3 Summary

IVIG and Novel Therapies

Impact of Missed or Delayed Diagnosis

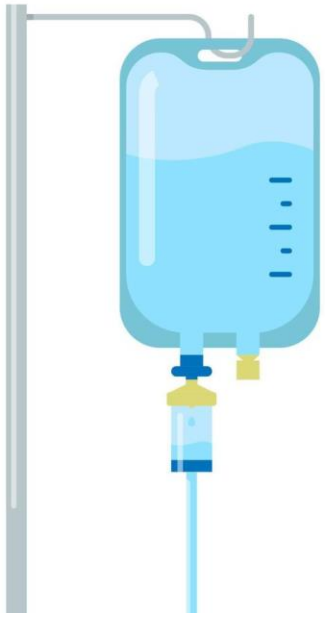
Richard Rowe Memorial Lecture

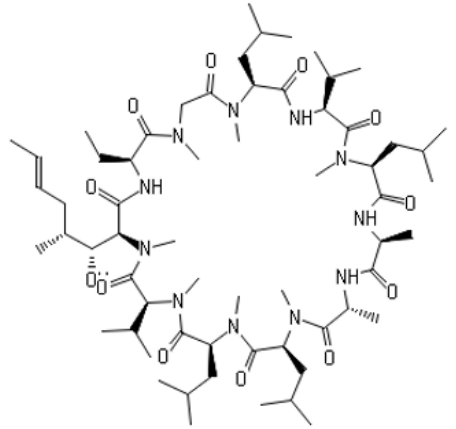
Acute Coronary Syndrome in KD

Transition of Care and Canvas for the Future

Solving Worldwide Gaps in KD Care

IVIG and Novel Therapies

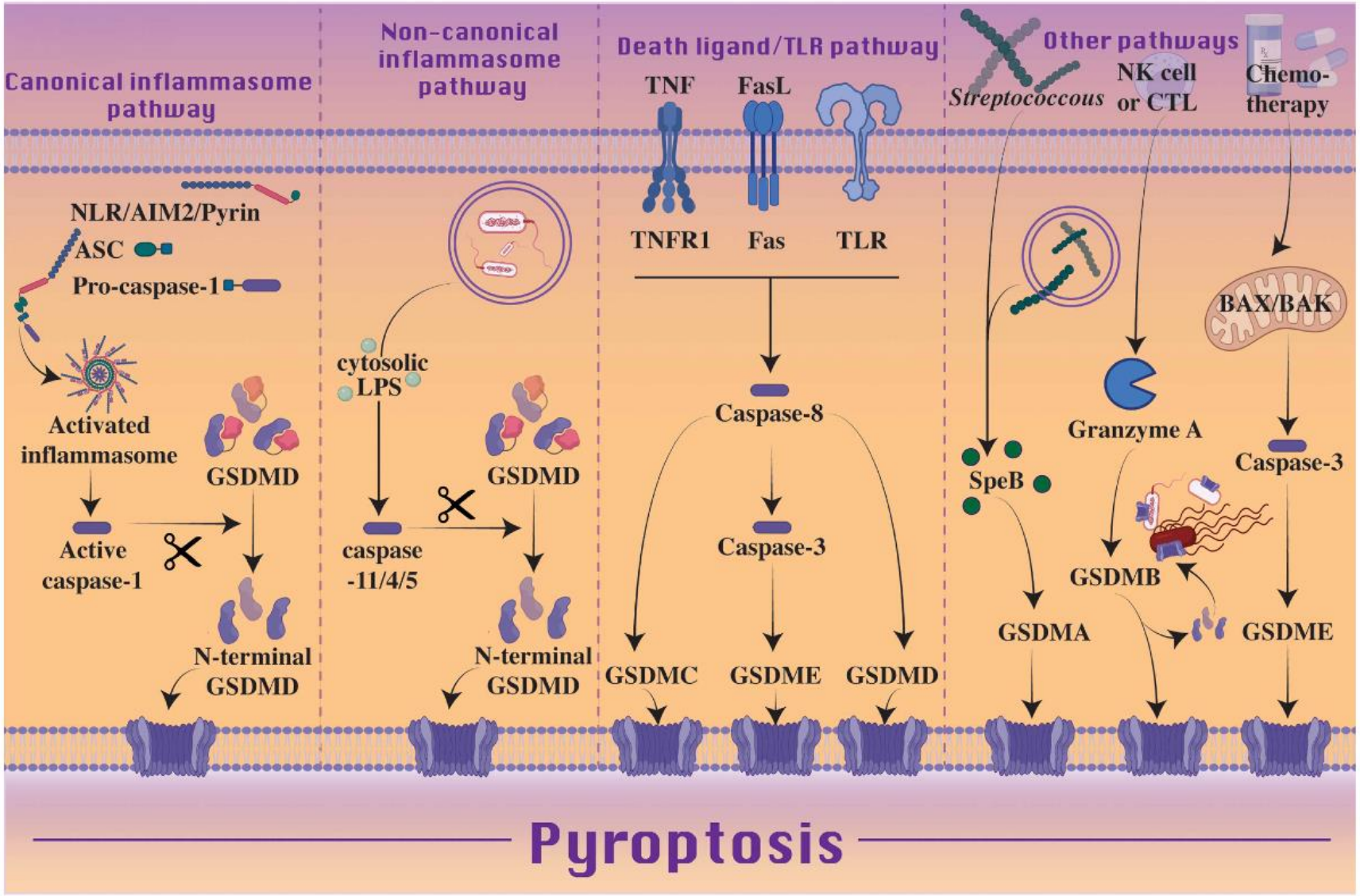




Too Long, Didn't Watch

Statins	Steroids	Anakinra	Infliximab	Cyclosporine
Helpful	Helpful	Helpful	Helpful	Helpful

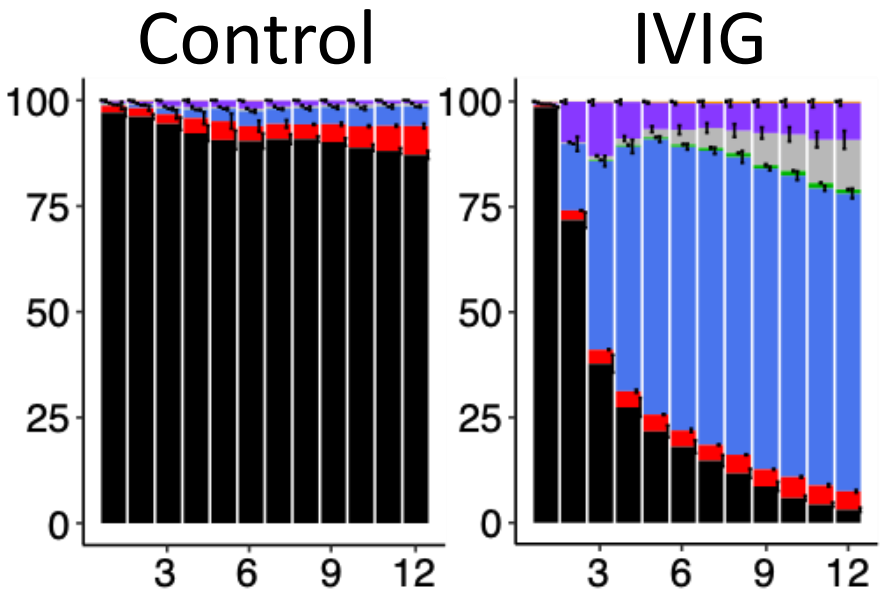
IVIG and Mechanism of Action



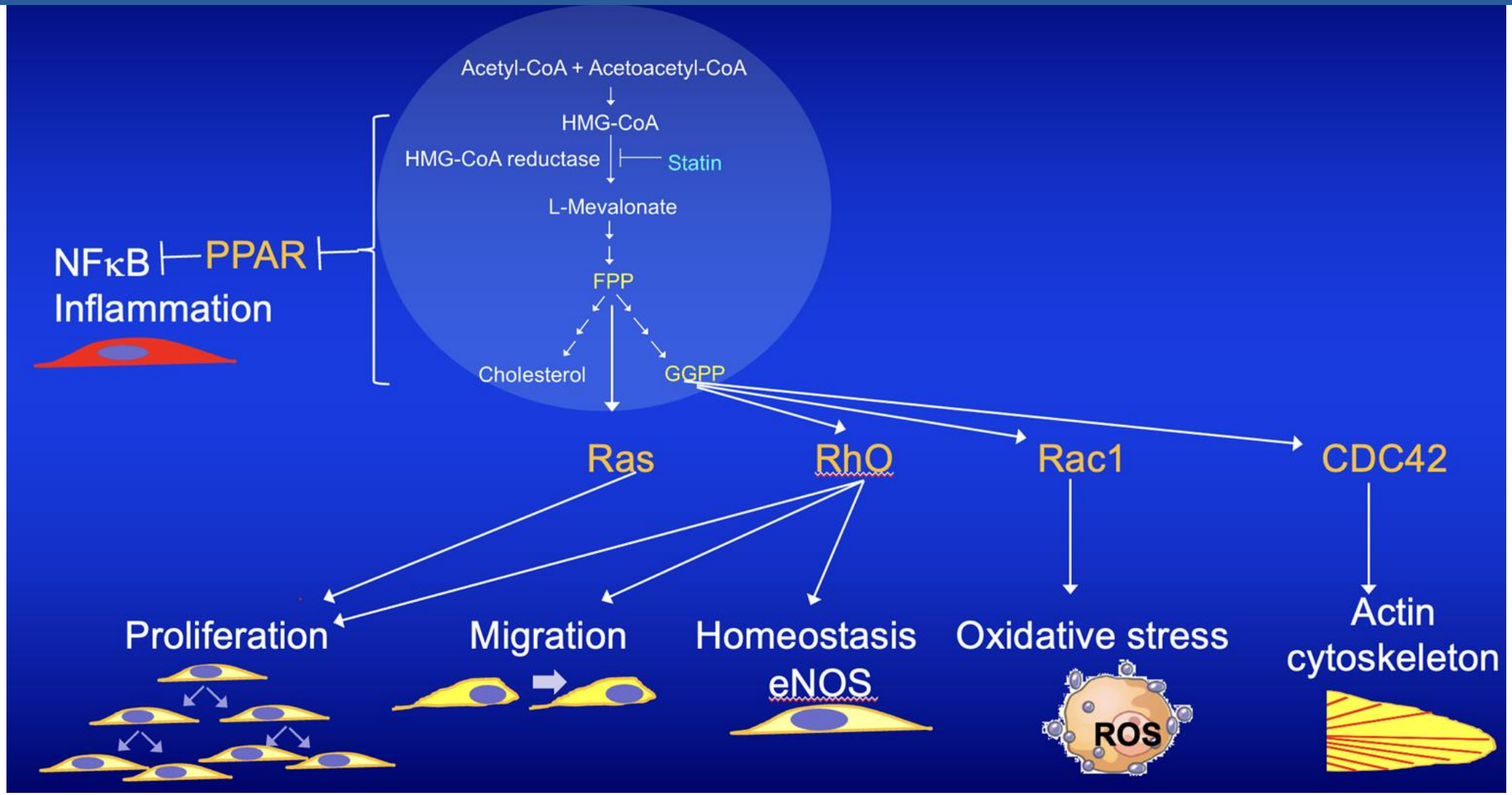
Adapted from presentation by Dr. Ben Croker

IVIG and Mechanism of Action

- **Steady state**: apoptotic neutrophils are cleared (10^{11}/day)
- **Disease**: apoptotic neutrophils are not cleared, and proceed to extrude nuclear DNA, histones, citrullinated proteins, proteases, and form cytoplasts
  - Anti-microbial event
  - Amplifier of innate and adaptive immunity
  - Source of autoantigen

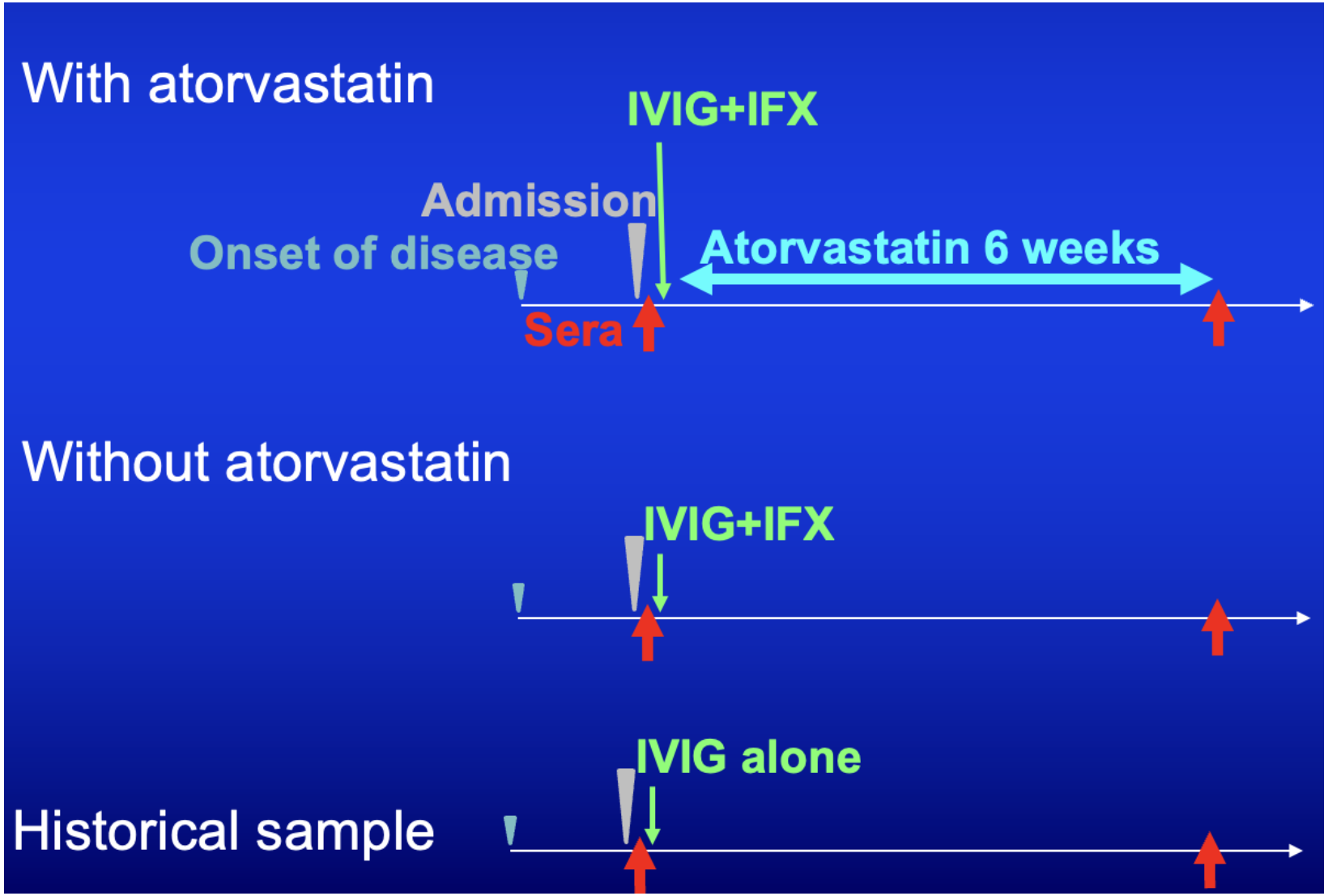


Statins and Endothelial Health



Adapted from presentation by Dr. Chisato Shimizu

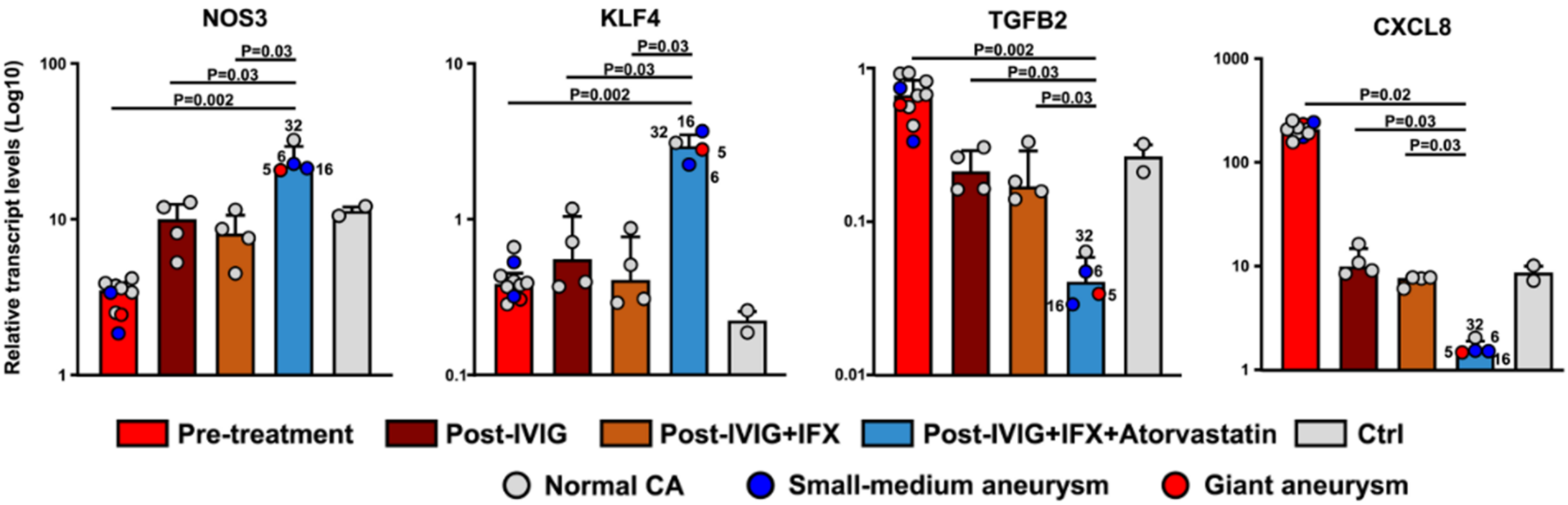
Statins and Endothelial Health



Shimizu. JAHA: 2022

Adapted from presentation by Dr. Chisato Shimizu

Statins and Endothelial Health

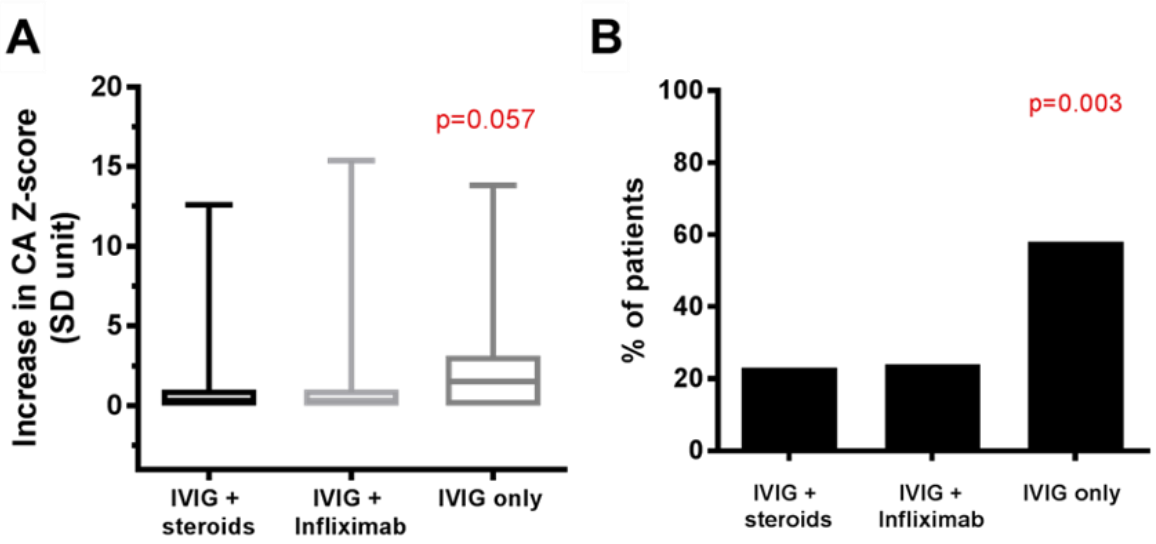


Adapted from presentation by Dr. Chisato Shimizu

Adjunctive Treatment with Steroids

Retrospective study in patients with CA z-score > 2.5 at diagnosis comparing 3 centers: IVIG alone vs. IVIG + steroids vs. IVIG +infliximab

Treatment resistance rates:	IVIG alone	IVIG + infliximab	IVIG + steroids	p-value
	21%	14%	0%	0.02



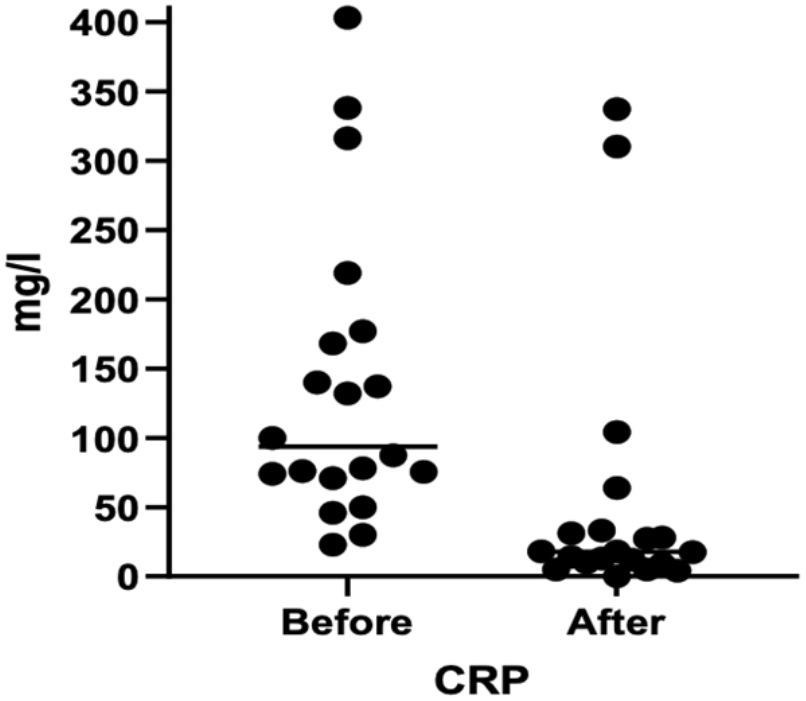
[E] **High risk* criteria:**

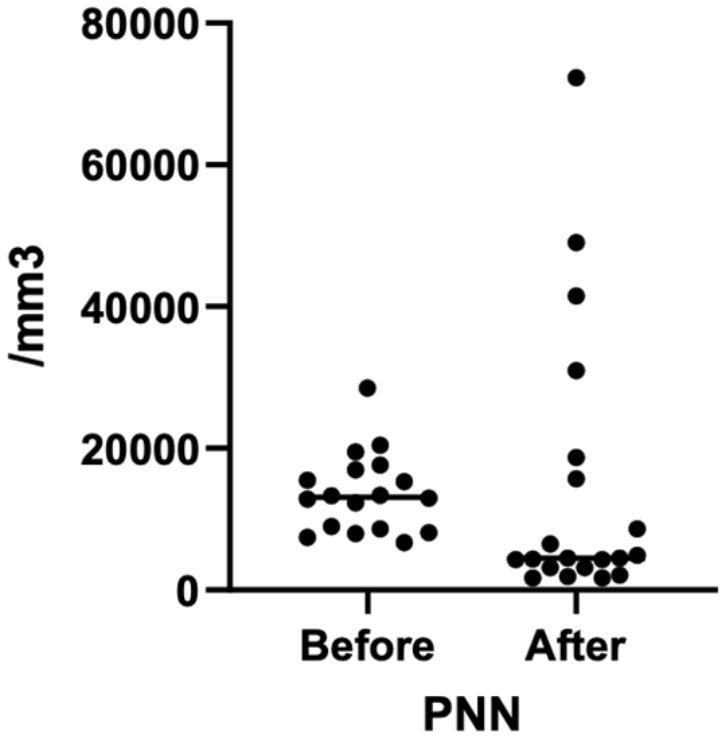
- ≤ 6 months of age
- LAD or RCA coronary artery z score ≥ 2.5 on baseline echo
- Kawasaki Shock syndrome [cardiovascular collapse and hypotension requiring volume expanders, vasoactive agents or transfer to the ICU]
- Macrophage Activation Syndrome (physician diagnosis)
- Other (expert physician's judgment; e.g. 2nd episode of KD)

**Monitoring for high-risk patients: frequent clinical and laboratory monitoring as per Rheumatology; Echo Q2-3 days until stable CA dimensions or as determined by Cardiology*

Use of Anakinra in Kawasaki Disease

Biologic data before and after anakinra: 24 patients.





Value the day of anakinra is started and the day it is stopped: 19 patients with concomittant CT)

Infliximab for Intensification of Primary Therapy

Standard treatment: IVIG 2 g/kg IV and aspirin

2004

IVIG 2 g/kg IV and aspirin

Adding **5 mg/kg infliximab** for patients with CAA at diagnosis

2014

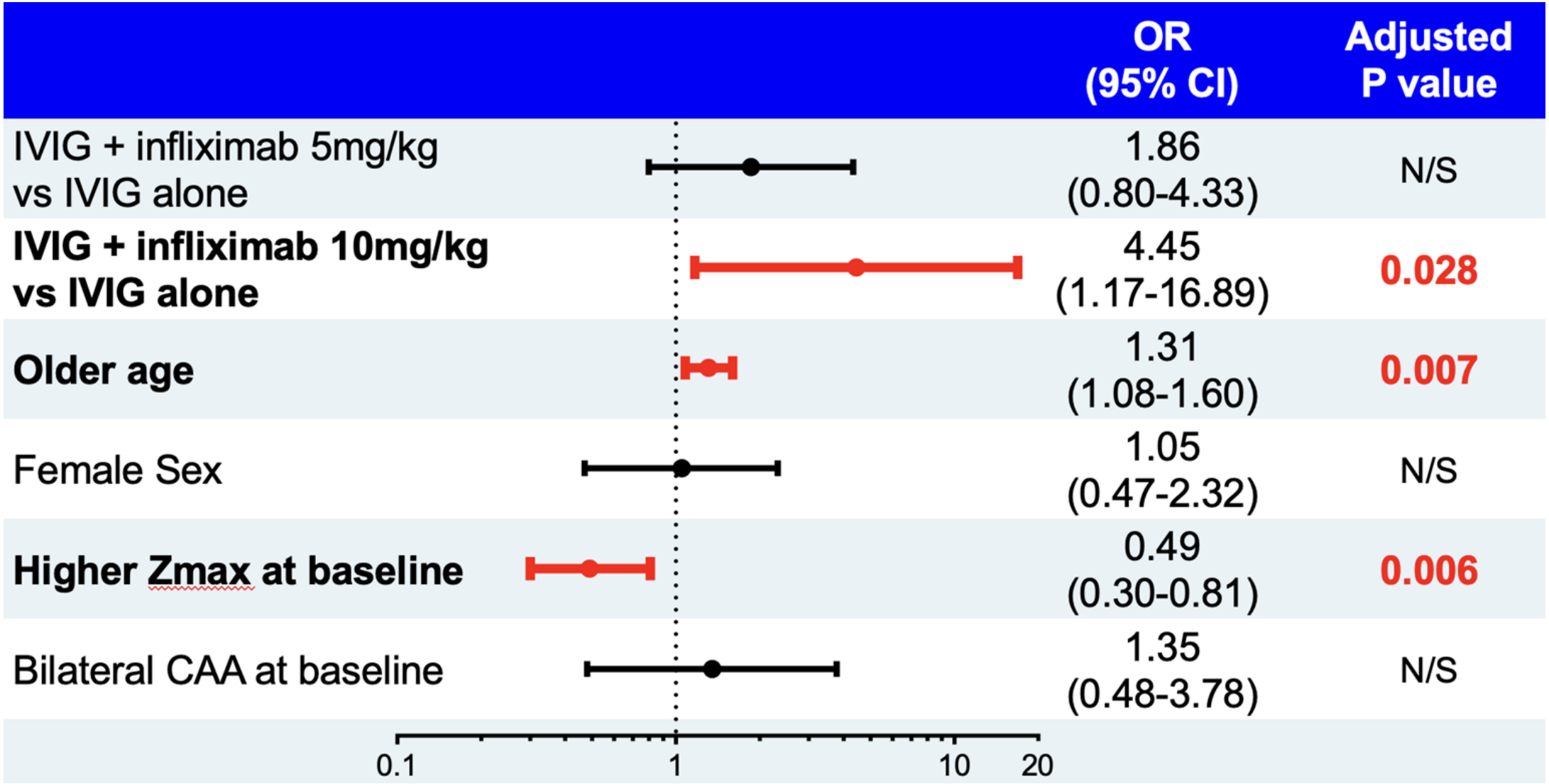
IVIG 2 g/kg IV and aspirin

Adding **10 mg/kg infliximab** for patients with CAA at diagnosis

- The dose of aspirin was 80–100 mg/kg/day until 2013, changed into 30–50 mg/kg/day.
- Aspirin was reduced to 3–5 mg/kg/day at discharge.

Adapted from presentation by Dr. Koichi Miyata

Infliximab for Intensification of Primary Therapy



Adapted from presentation by Dr. Koichi Miyata

Infliximab for Treatment Resistant Kawasaki Disease

Primary outcome measure:

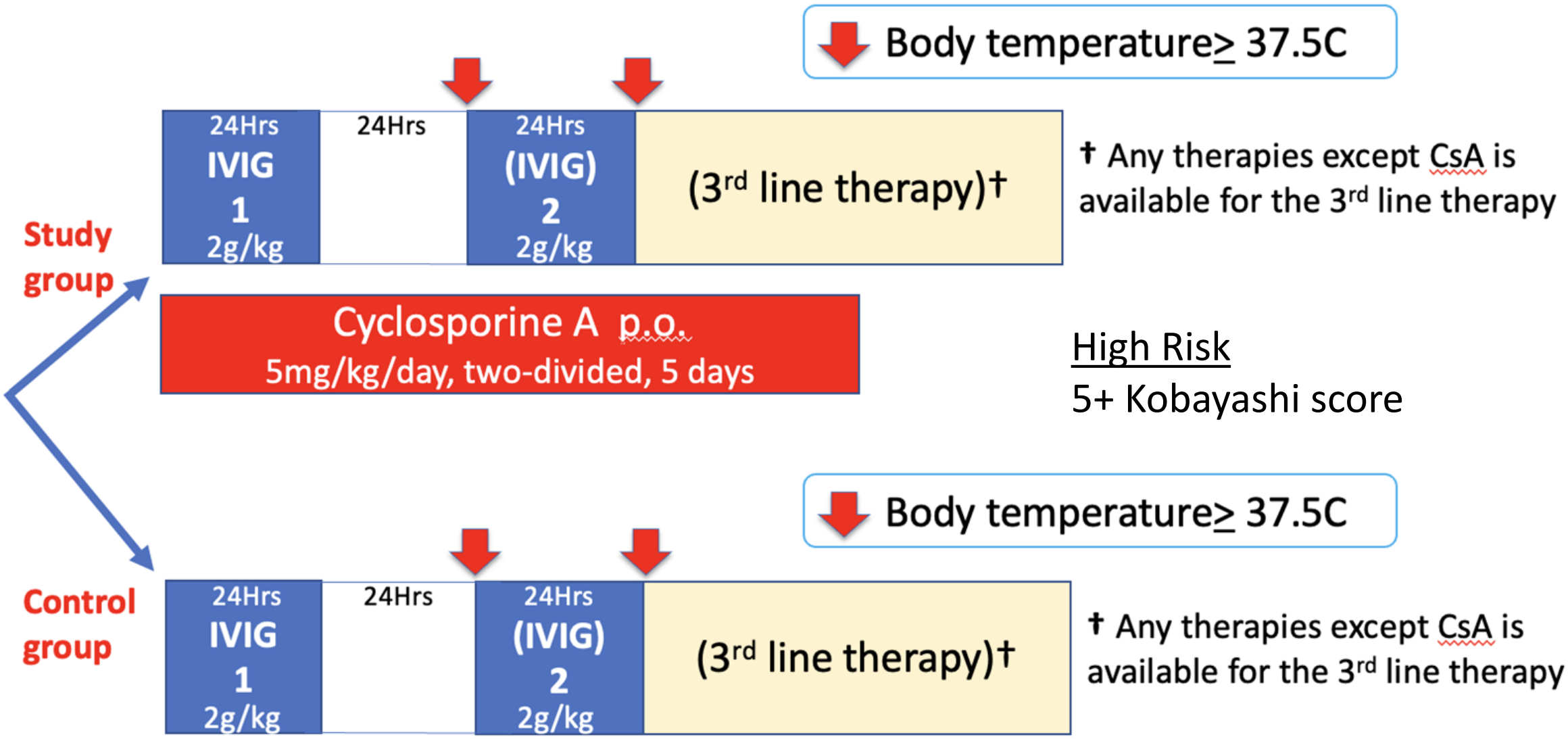
Afebrile at 24h after initiation of study treatment with no return of fever

- Infliximab: 40/52 (77%)
- 2nd IVIG: 25/49 (51%)

p=0.0076

Adapted from presentation by Dr. Adriana Tremoulet

Cyclosporine A in Kawasaki Disease



Adapted from presentation by Dr. Nobuyuki Kakimoto

Cyclosporine A in Kawasaki Disease

	IVIG+CsA (n=86)	IVIG (n=87)	p	95%CI
The incidence of CAAs	14%	31%	0.010	0.46 (0.21 – 0.86)

Mantel-Haenszel analysis

CAAs in
1 segments: 12
2 segments: 0
3 segments: 0

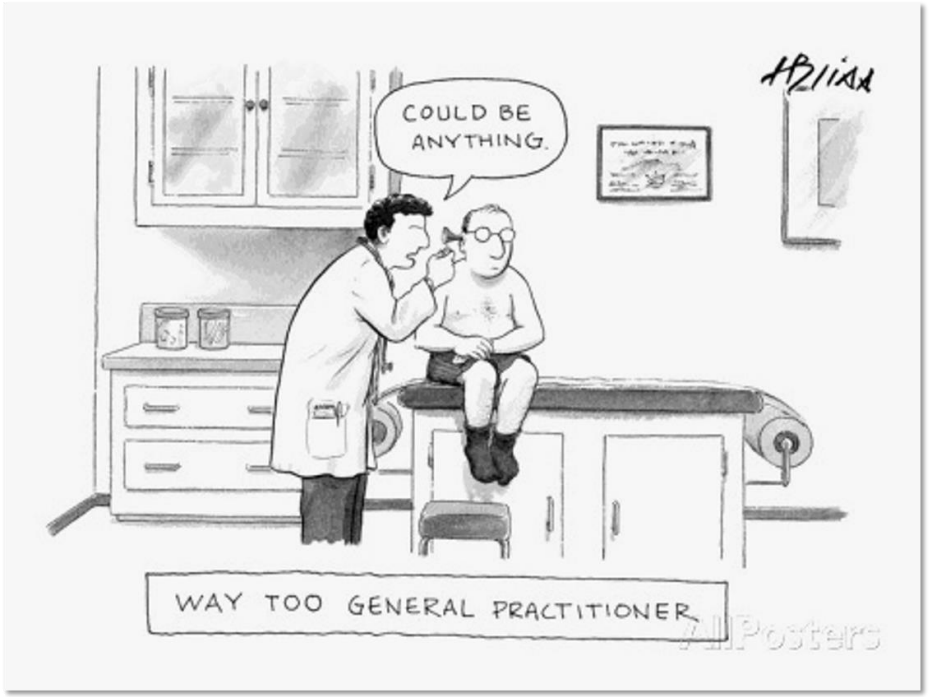
CAAs in
1 segments: 20
2 segments: 4
3 segments: 3

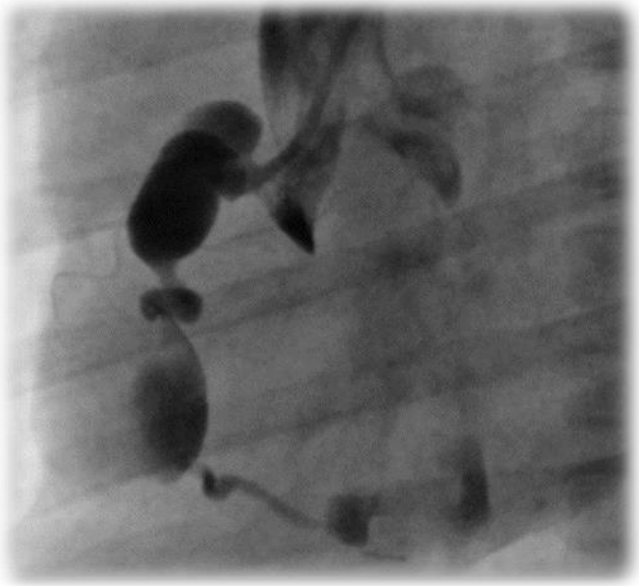
Hamada H, et al. ***Lancet***, 2019

Cyclosporine A in Kawasaki Disease

Concurrent use of steroids and Cyclosporine A in KD may increase risk of serious adverse events.

Impact of Delayed or Missed Diagnosis





Impact of Delayed or Missed Diagnosis

without IVIG 25 %

with IVIG 4%

with IVIG
< 6 mths > 50 %

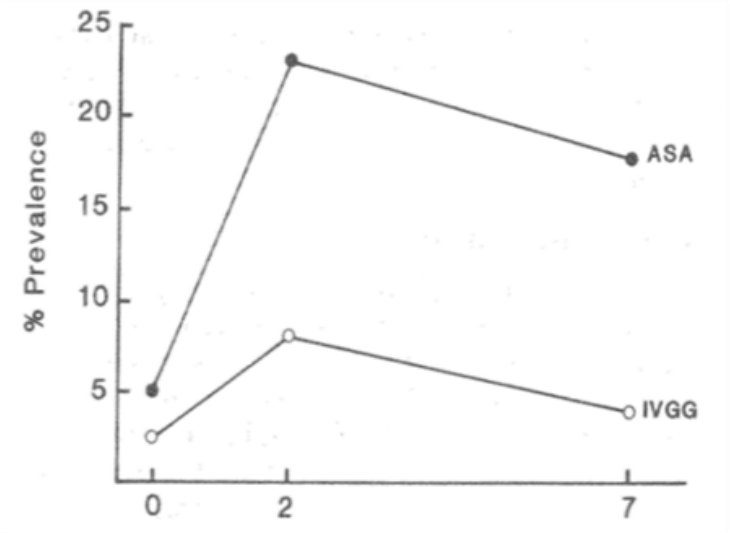


Table II. Coronary artery abnormalities in subjects with KD treated in the first 10 days of illness*

	<6 mo old (CHOC and RCHSD) n = 76	≥6 mo old (RCHSD only) n = 545	P value
Baseline coronary artery status, n (%)			<.001
Normal	43 (56.6)	439 (80.6)	
Dilated	27 (35.5)	91 (16.7)	
Aneurysm	5 (6.6)	14 (2.6)	
Giant aneurysm	1 (1.3)	1 (0.2)	

Complications confined to large CAA ≥10

Prognosis good, low fatality rates

Adapted from presentation by Dr. Toni Hospach

Diagnostic Pearls of Kawasaki Disease

Infections and Kawasaki Disease: Implications for Coronary Artery Outcome

Susanne M. Benseler, MD*‡; Brian W. McCrindle, MD, MPH, FRCPC*‡§; Earl D. Silverman, MD, FRCPC*‡; Pascal N. Tyrrell, Msc*‡; Joseph Wong,*‡; and Rae S.M. Yeung, MD, PhD, FRCPC*‡

33% of KD patients had at least one confirmed infection at time of KD diagnosis

FEVER – typically "unresponsive to antipyretics" in KD

KD excluded if genuine pathogen cultured/identified from sterile site

A positive respiratory viral PCR usually compatible with KD diagnosis

A positive GAS throat swab is compatible with KD diagnosis

Adapted from presentation by Dr. David Burgner

Think about KD in Children with Fever and

- Unwilling or unable to walk
- Culture negative “urinary tract infection” (initially diagnosed on basis of fever and urine WBC)
- Unexplained aseptic meningitis
- Culture negative shock
- Age <6 months with prolonged fever and irritability
- Prolonged fever and cervical adenitis
- Other clues:
  - Eosinophilia
  - Inflamed BCG site
- There are KD subgroups

Key Characteristics of KD subgroups

- **Liver**
  - Elevated ALT, GGT, bilirubin
  - Lowest CAA rate
  - Highest IVIG resistance rates
- **Band**
  - Highest band neutrophil count
  - Highest KD shock rate
- **Node**
  - Cervical LAD
  - Highest markers of inflammation (ESR, CRP, WBC, plt)
  - Lowest hemoglobin z-scores
- **Young**
  - Young age at onset
  - Highest CAA rate
  - Lowest IVIG resistance rates

Dr. Richard Lowe Memorial Lecture

14th International Kawasaki Disease Symposium (IKDS)
August 26th – 29th, 2024 | Montreal, Canada | Hotel Bonaventure
ikds.org

https://www.ajconline.org/article/0002-9149(88)90900-9/pdf

Richard Rowe Memorial Lecture

Disaster in Kawasaki Disease

- Rupture of Coronary Artery Aneurysm -

Mamoru Ayusawa MD., PhD.
Faculty of Health and Medical Science,
Kanagawa Institute of Technology
Department of Pediatrics and Child Health,
Nihon University School of Medicine

Cases with ruptured aneurysm and fatal outcomes

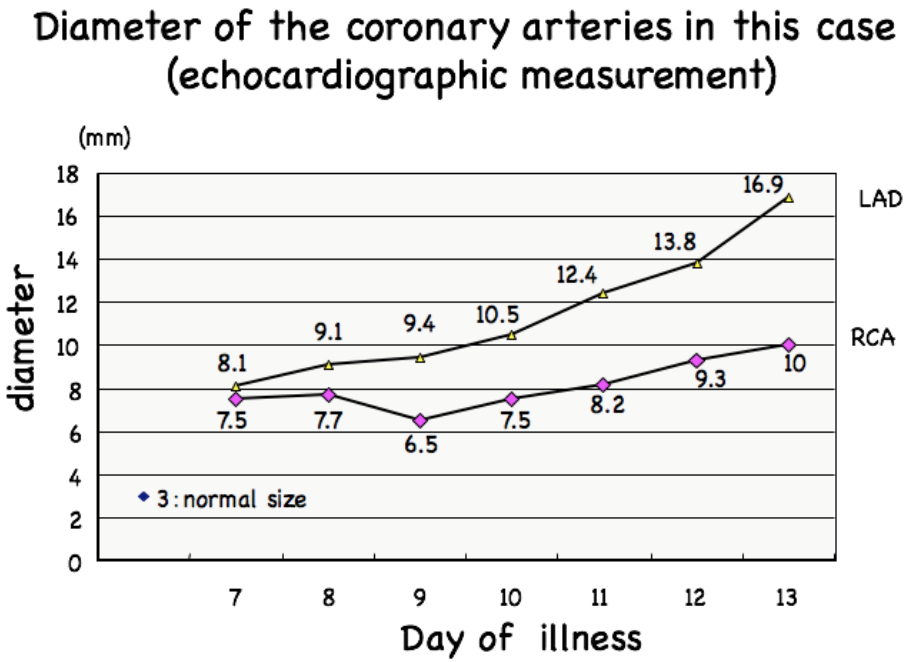
'Disaster'

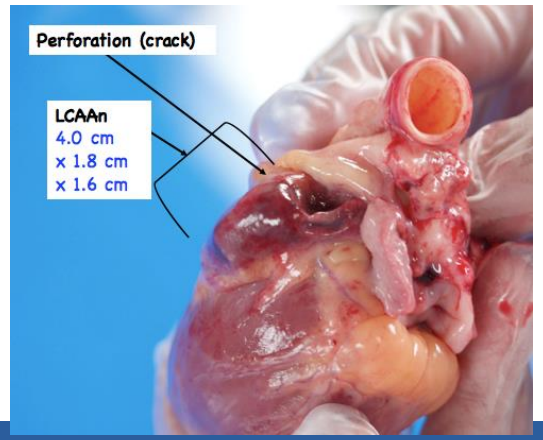
- Very Rare
- Suddenly encounter
- Difficult to predict
- Fatal, and traumatic
- No good strategy for the present

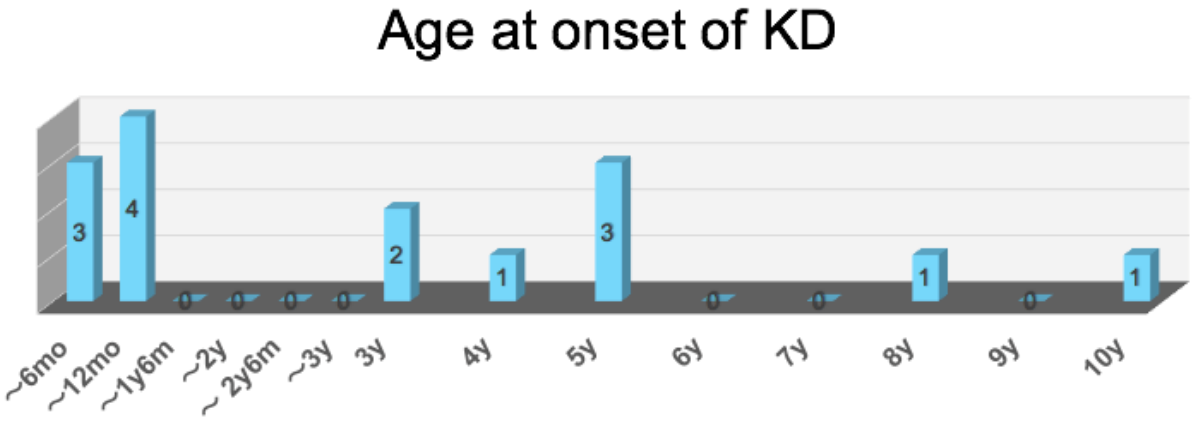
- These are typically 'Supergiant aneurysms' - CAAn grew >10 mm in diameter rapidly within 10-15 days

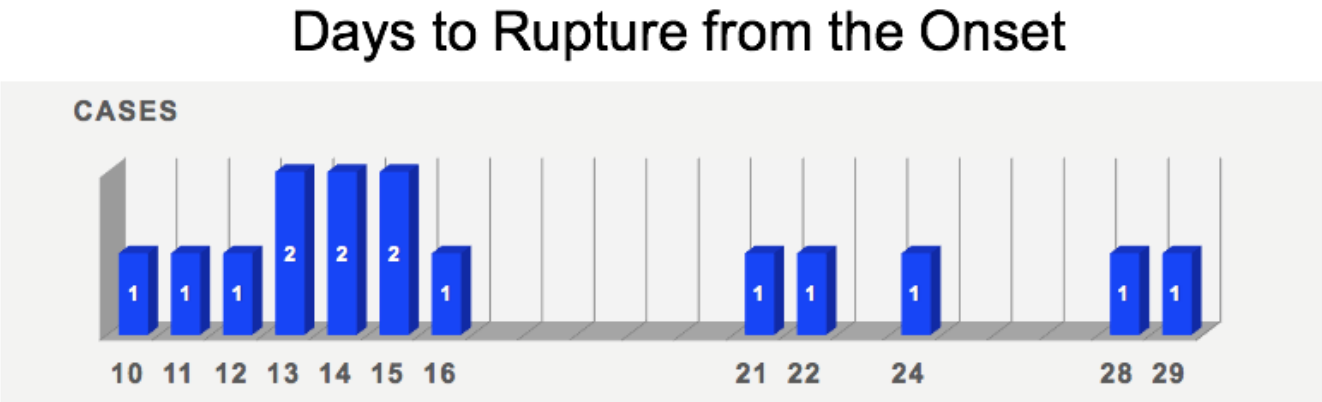
Adapted from presentation by Dr. Mamoru Ayusawa

Rupture of coronary aneurysms









Adapted from presentation by Dr. Mamoru Ayusawa

Rupture of coronary aneurysms

- *Prevention / prediction is the most important key*
- Early diagnosis and treatment
- Treatment intensification
- Need a simulation of intensive care for ≧10mm coronary aneurysm in your hospital if you care severe KD patients
  - Sedative drugs, beta blockers and calcium antagonists
  - Blood pressure optimization

We need to identify the super giants

Acute Coronary Syndrome in KD

Invasive angiography survey data from European

Aprox. 200 patients / 63 % male

Aprox. 280 Cardiac Catherisations (CC)

CAA rate: 2010	37.5%
2022	75%
2024	90%

- Younger patients have higher chances of regression
- More number aneurysms >>> more likely to have regression of largest aneurysm / also to develop stenosis
- Length of aneurysm does not much affect development of stenosis
- Saccular are associated greater chances of sequelae

Acute Coronary Syndrome in KD

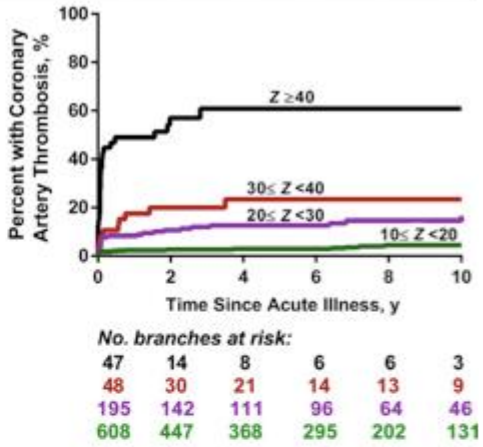
Who are at risk for ACS

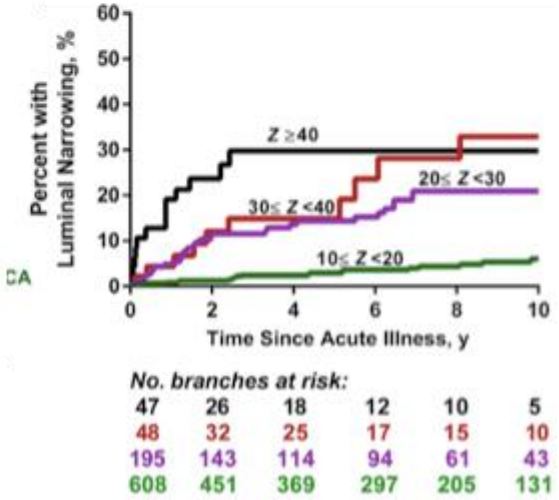
Risk of thrombosis

- LAD aneurysm
- Aneurysm ≥ 8 mm
- Most frequently in first 90 days after diagnosis

Medium-Term Complications Associated with Coronary Artery Aneurysms After Kawasaki Disease

IKD Registry



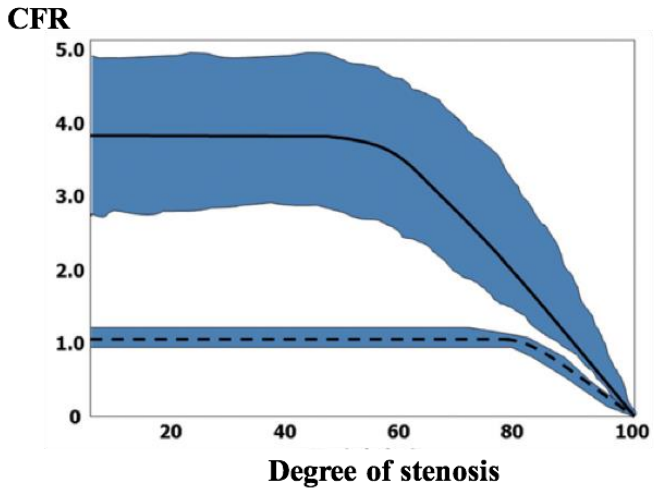


Adapted from presentation by Dr. Simon Lee

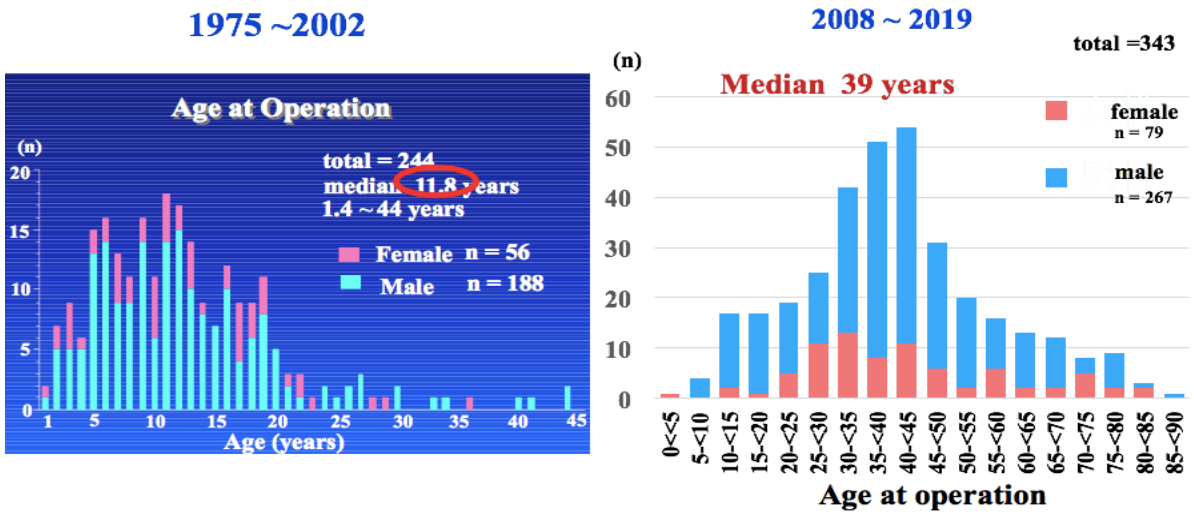
Acute Coronary Syndrome in KD

The Japan Experience: CABG in KD

Relation between stenosis and Coronary flow reserve



Changes in age at operation in Japan

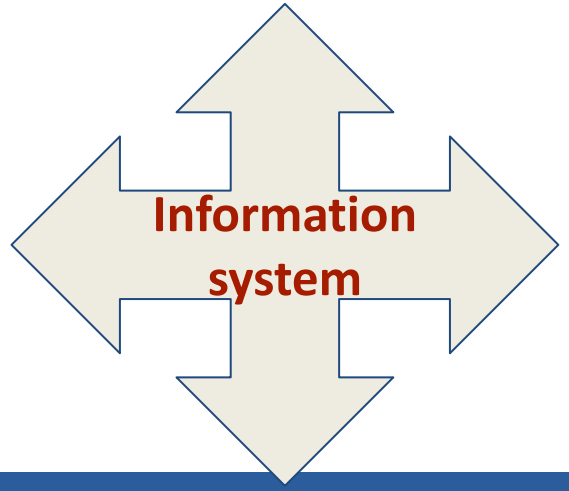


Coronary flow reserve is decreased after 85% stenosis

- Indication and timing of CABG need to be optimized
- Should be performed as an elective procedure with preserved LV function

Multi-disciplinary decision making model

Clear communication system in place



Adapted from presentation by Annette Baker

Transition of Care and Canvas for Future

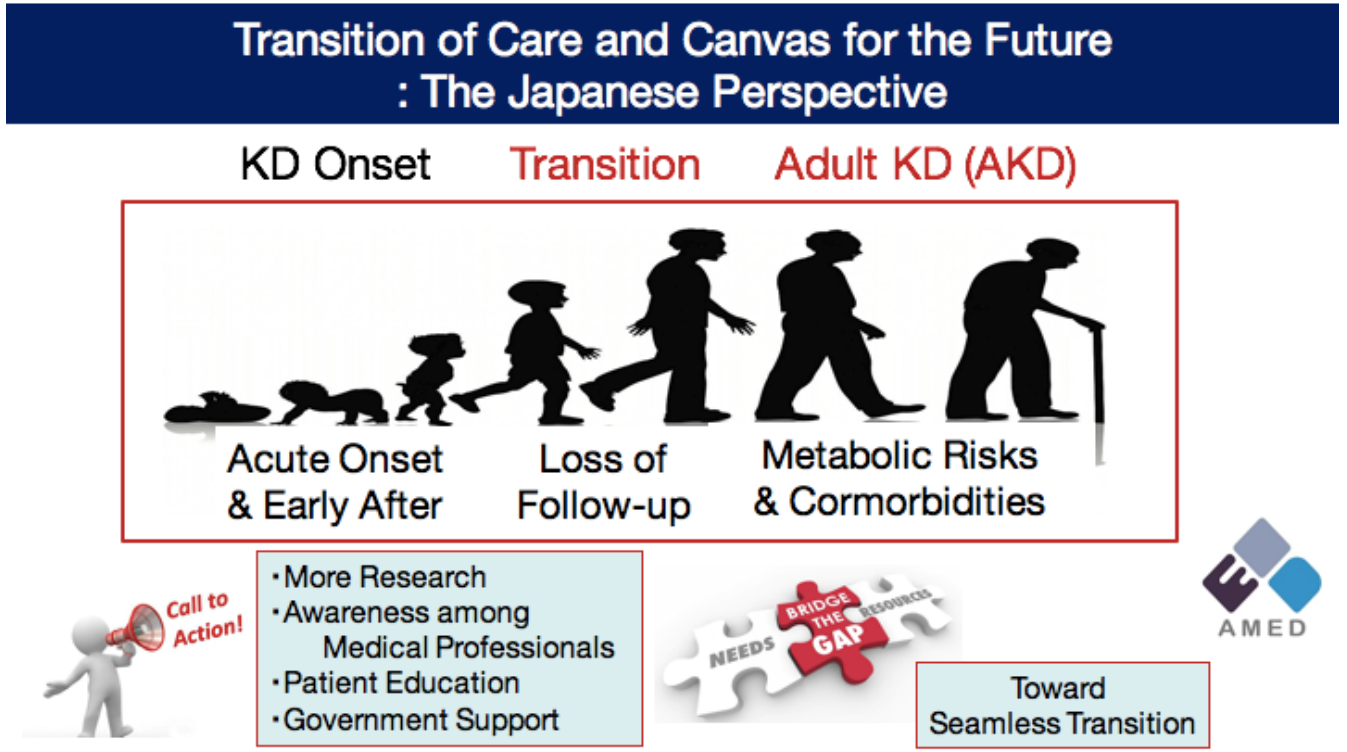
Why it is essential

Loss to follow-up

Needs are different

Females with KD and CALs

Patients once adult they want to be treated as adult



Adapted from presentation by Drs. Ayusawa and Mitani

Transition of Care and Canvas for Future

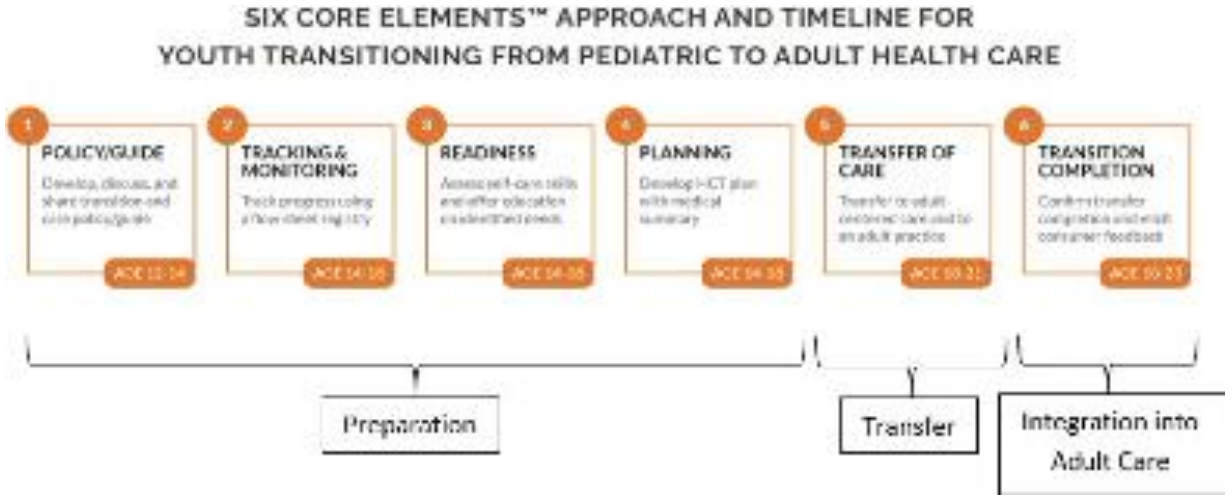
Journal of the American Heart Association

AHA SCIENTIFIC STATEMENT

Falling Through the Cracks: The Current Gap in the Health Care Transition of Patients With Kawasaki Disease

A Scientific Statement From the American Heart Association

Nagib Dahdah, MD, MBA; Samuel C. Kung, MD, MAS; Kevin G. Friedman, MD; Ariane Marelli, MD, MPH, FAHA; John B. Gordon, MD; Ermias D. Belay, MD; Annette L. Baker, RN, MSN, CPNP, FAHA; Dhruv S. Kazi, MD, MSc, MS, FAHA; Patience H. White, MD, MA; Adriana H. Tremoulet, MD, MAS, FAHA; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young, and the Council on Arteriosclerosis, Thrombosis and Vascular Biology



Medical summary

Empowerment of the patients

Patient engagement

Patient education

Health Passport

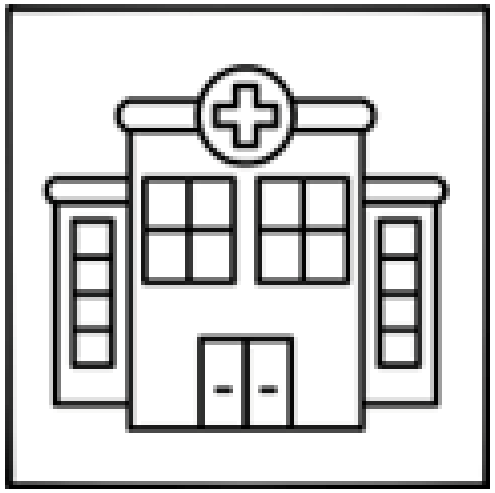
Adapted from presentation by Dr. Tremoulet

Transition of care

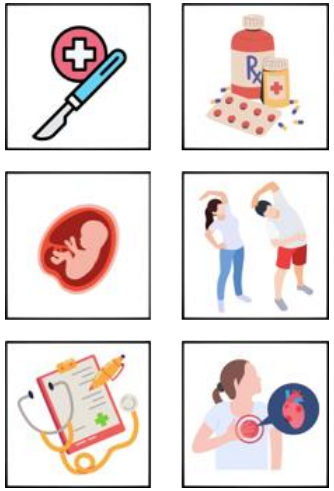
DEBATE: Who is going to see you once you are adult

Pediatric cardiologist

Adult cardiologist

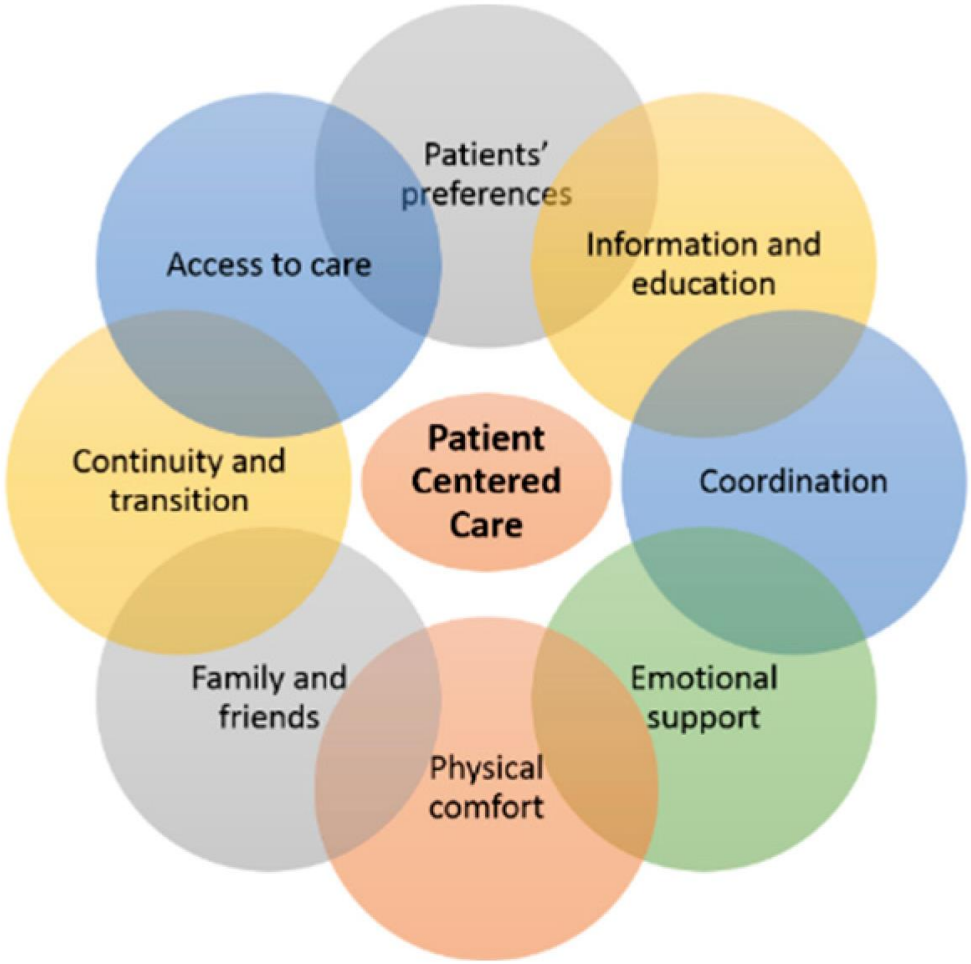


Transition from Pediatric to Adult cardiologist is essential



KD with CAA warrants life-long expert care

Most unique and critical perspective



Patient perspective

Adapted from patient perspective presentation

Solving Worldwide Gaps in KD Care

Guideline Issues and Gaps (Expert Opinion)

Guideline Issues	Guideline Gaps
• Update with latest evidence (in process) • Integrate different guidelines into cohesive approach • Clarify utility and predictive value of scoring systems • Develop approach to infants < 6 months • Clarify the role of the following mediations: salicylates, anticoagulants, statins • Management of fever and CAA at diagnosis	• Dissemination, education and training across specialties. • Increase guideline awareness across primary providers • Develop practical and easy-to-recall protocols • Long-term follow-up and transition to adult services • Standardize reporting of echo CA dimensions

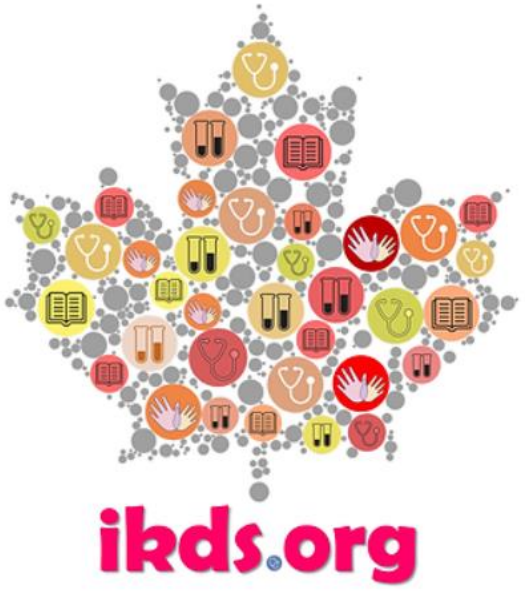
Adapted from presentation by Dr. Teresa Giani

Guideline Issues and Gaps (Roundtable)

Guideline Issues	Guideline Gaps
• **Update with latest evidence (in process)** • **Integrate different guidelines into cohesive approach** • **Clarify utility and predictive value of scoring systems** • Develop approach to infants < 6 months • Clarify the role of the following mediations: salicylates, anticoagulants, statins • Management of fever and CAA at diagnosis • Guidelines in different languages	• **Dissemination, education and training across specialties.** • **Increase guideline awareness across primary providers** • **Develop practical and easy-to-recall protocols** • Long-term follow-up and transition to adult services • Standardize reporting of echo CA dimensions

Adapted from presentation by Dr. Teresa Giani

Thank you and
enjoy the final day of the conference!



Take Home Headlines: Consolidated knowledge & new trajectories

14th International Kawasaki Disease Symposium

August 29th, 2024

Audrey Dionne MD
Boston Children's Hospital

Frederica Anselmi MD, Fujito Numano MD, PhD, Alan Wang MD, Matthew Elias MD,
Rakesh Kumar Pilania MBBS, Luisa Berenise Gamez-Gonzalez MD

Conflict-of-Interest Disclosures

Presenter:	
Any direct financial payments including receipt of honoraria	None
Membership on advisory boards or speakers' bureaus	None
Funded grants or clinical trials	Pfizer, Boston Scientific (unrelated Kawasaki disease)
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	None

Take Home Messages – Day 1
14th International Kawasaki Disease Symposium

August 27, 2024

Dra. Luisa Berenise Gámez González
Pediatric Immunology
Professor of Immunology, Faculty of Medicine Chihuahua's University
Hospital Infantil de Especialidades de Chihuahua

Matthew D. Elias, MD
Clinical Associate Professor of Pediatrics
Attending Physician, Division of Cardiology
Co-Medical Director,
Cardiology Kawasaki Disease Program
The Children's Hospital of Philadelphia

Take Home Messages – Day 2
14th International Kawasaki Disease Symposium

August 28, 2024

Dr. Federica Anselmi
Paediatric Rheumatology
University hospital of Bicetre- Paris Faculty of Medicine of Paris-Saclay University

Dr Fujito Numano
Fujito Numano, MD, PhD
Lecturer of Pediatrics
Niigata University Graduate school of Medical and Dental Sciences

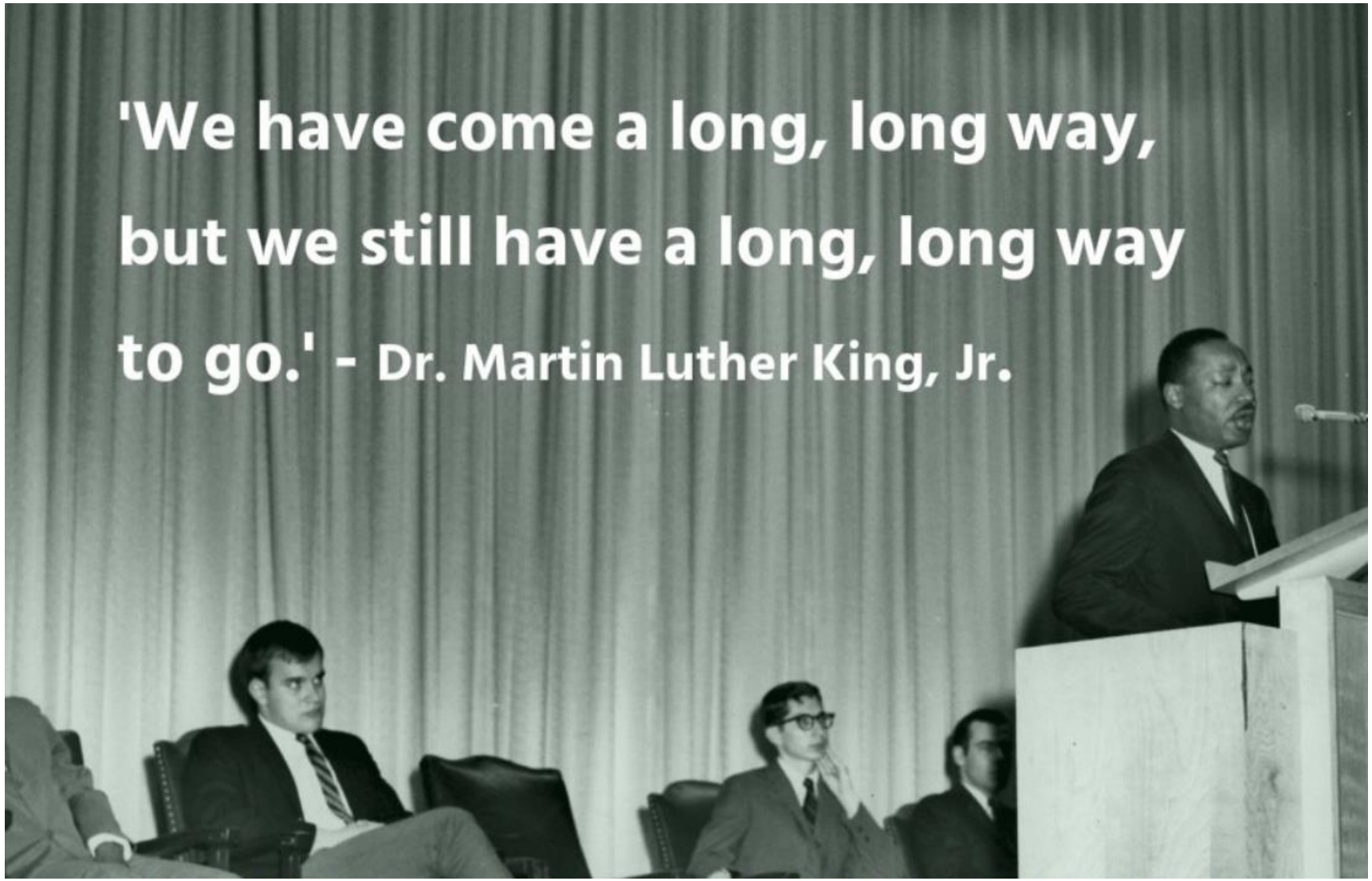
Take Home Messages – Day 3
14th International Kawasaki Disease Symposium

August 29, 2024

Rakesh Kumar Pilania MD, DM
Post Graduate Institute of Medical Education and Research, Chandigarh, India

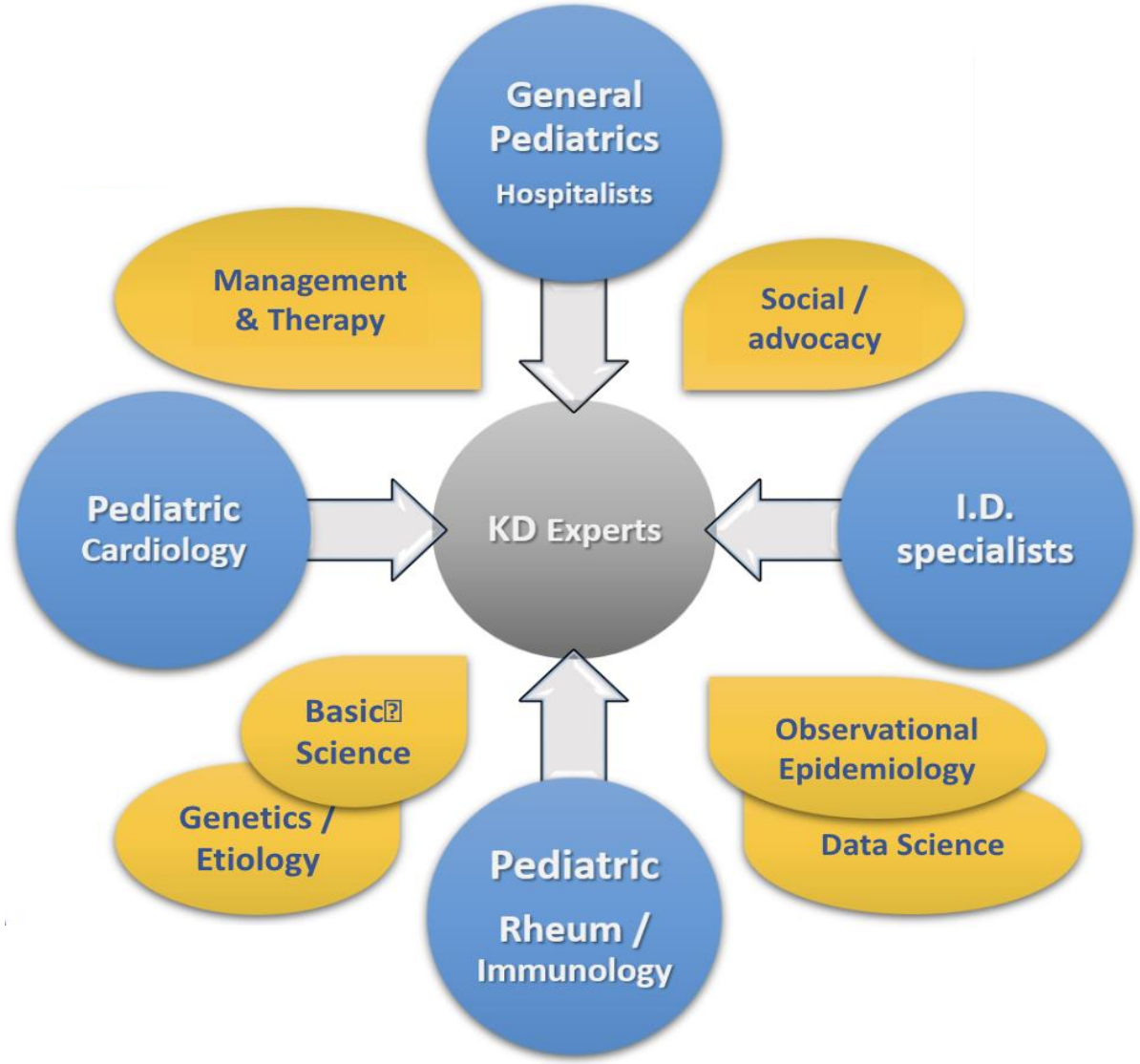
Alan Wang MD
Ann & Robert H. Lurie Children's Hospital of Chicago, USA

Daily wrap-up


'We have come a long, long way,
but we still have a long, long way
to go.' - Dr. Martin Luther King, Jr.

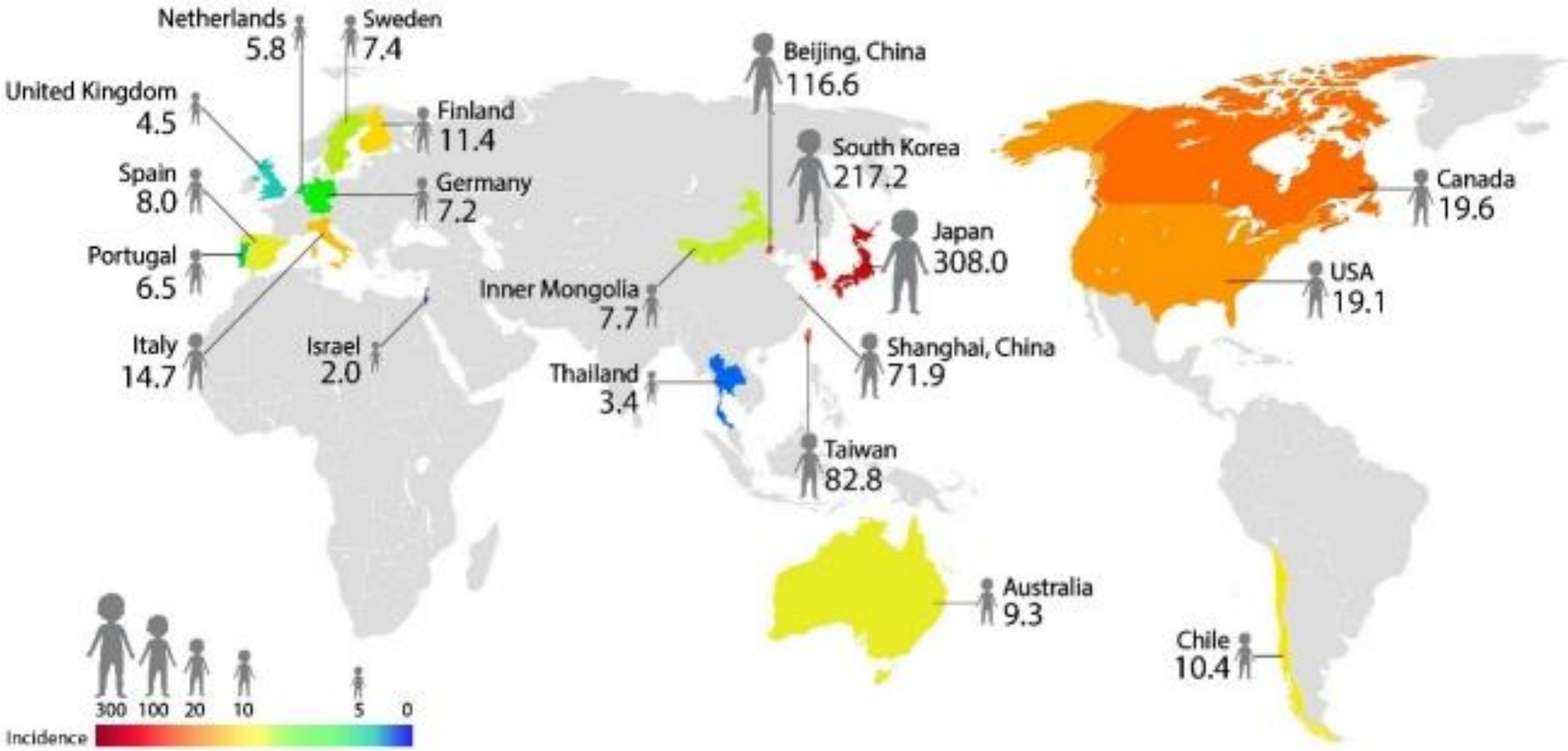
Collaboration

Multidisciplinary



Adapted from Dahdah

International



Gi Beom Kim. Clinical and Experimental Pediatrics. 2019

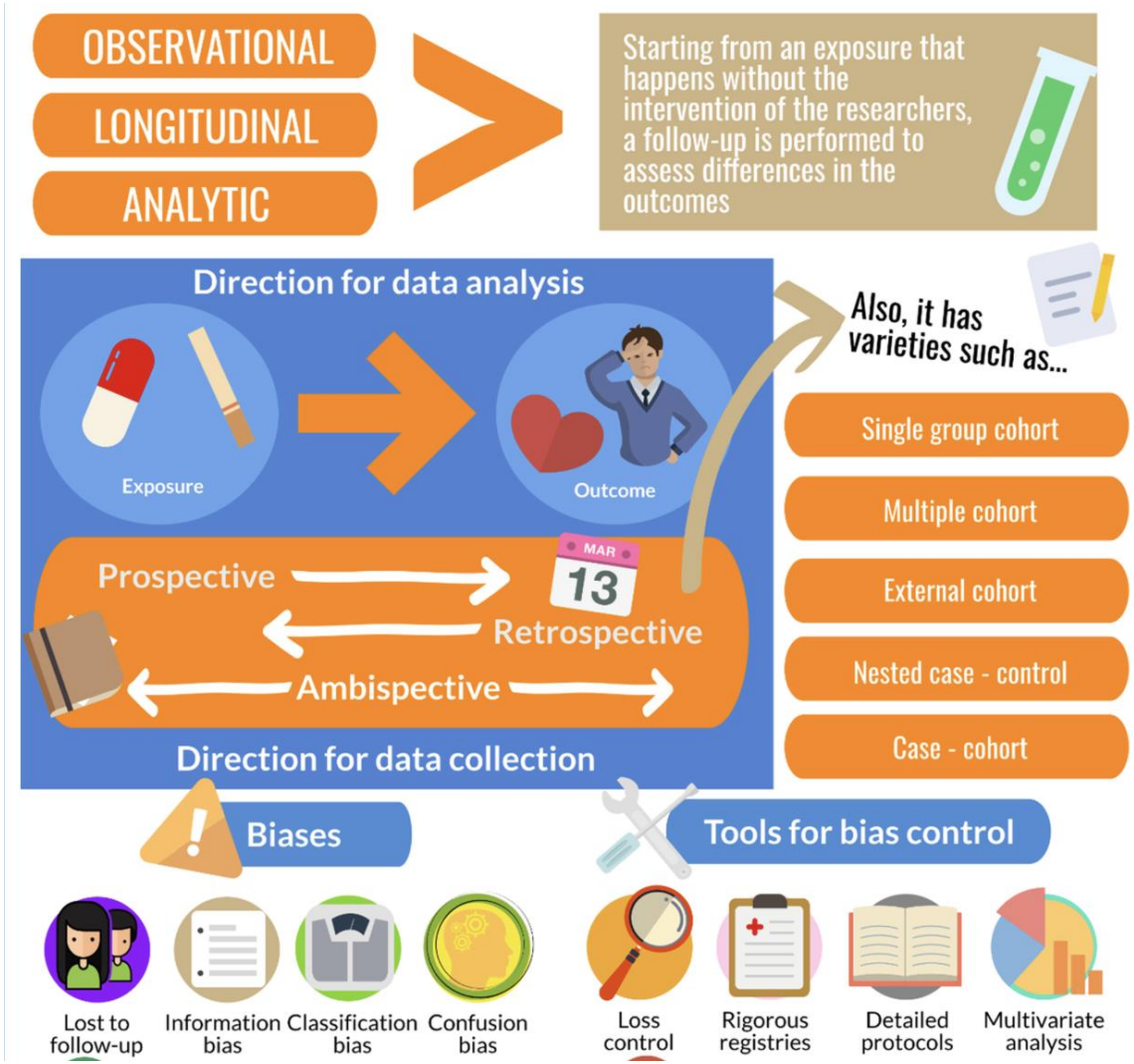
Working together

Groups – Country / Region	Year	Countries	Institutions	Members
Nationwide Survey of Epidemiology of KD in South Korea (guidance of the Korean Society of KD) | ***South Korea***	1991	1	90	10-20
Registro Regionale della Malattia di Kawasaki Emilia Romagna | ***Italy***	2002	1	10	10-20
Japan Kawasaki Disease Genome Consortium (JKDGC) | ***Japan***	2009	1	40	20-50
Kawasaki Study Group | ***Netherland***	2012	1	18	10-20
REKAMLATINA (Red de Enfermedad de Kawasaki en América Latina) | ***Latin-America***	2013	20	86	100 +
International Kawasaki Disease Registry (IKDR) | ***N-Am / International***	2013	8	51	20-50
SOCIETI | ***UK***	2015	1	10	20-50
KAWARACE | ***Spain***	2015	1	95	100 +
Kawasaki Disease Comparative Effectiveness (KIDCARE) trial | ***USA***	2016	1	30	20-50
Asia Pacific Kawasaki Disease Association | ***Eastern Asia / South-Pacific***	2016	14	30	50-100
Genetic Prediction of KD Treatment Resistance (GENESYS) | ***USA / North-Am***	2018	2	6	10-20
Indian Society of Kawasaki Disease | ***India***	2018	1	10	50-100
Cardiac Catheterization in Kawasaki Disease registry (CCinKD registry) |***Germany / Europe***	2019	6	16	20-50
JIR COHORT KD (KAWANET) and MIS-C | ***Europe***	2019	11	87	20-50
AMED Study Group | ***Japan***	2020	1	150	50-100
Cape Town Kawasaki Group | ***South Africa***	2020	1	2	10-20
COVASAKI network | ***Italy***	2020	1	18	20-50
KAWARABI (Kawasaki Disease Arab Initiative) | ***MENA***	2021	14	24	20-50
Kawasaki disease Sweden (SwedKD) | ***Sweden***	2021	1	1	10-20
Collaborated Surveillance by 4 Associations Working for Pediatric Critical Medicine (JMKsurvey) | ***Japan***	2022	1	50	10-20

Working together

Working Together to Get Numbers

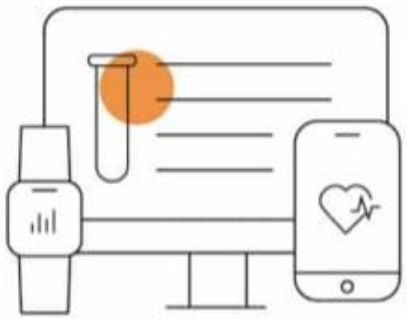
Observational Studies



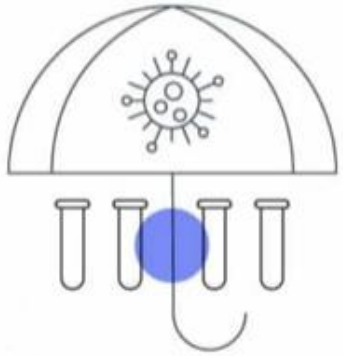
‘The most dangerous pharse in language is ‘We’ve always done it that way

-Admiral Grace Hopper

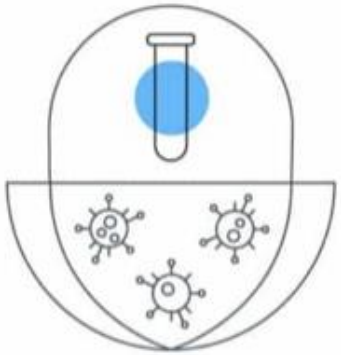
Re-think Clinical Trial Designs



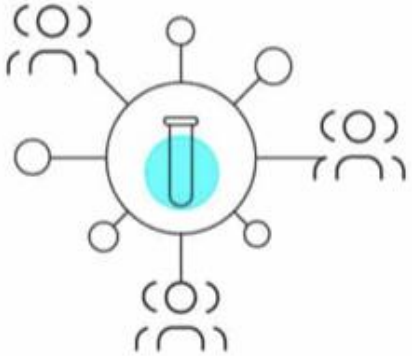
Synthetic control arms



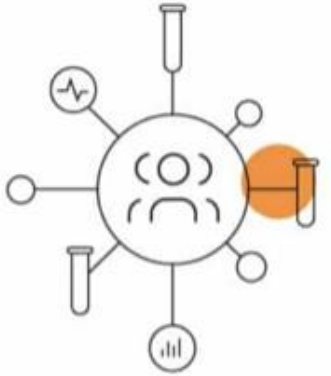
Umbrella studies



Basket (or bucket) trials

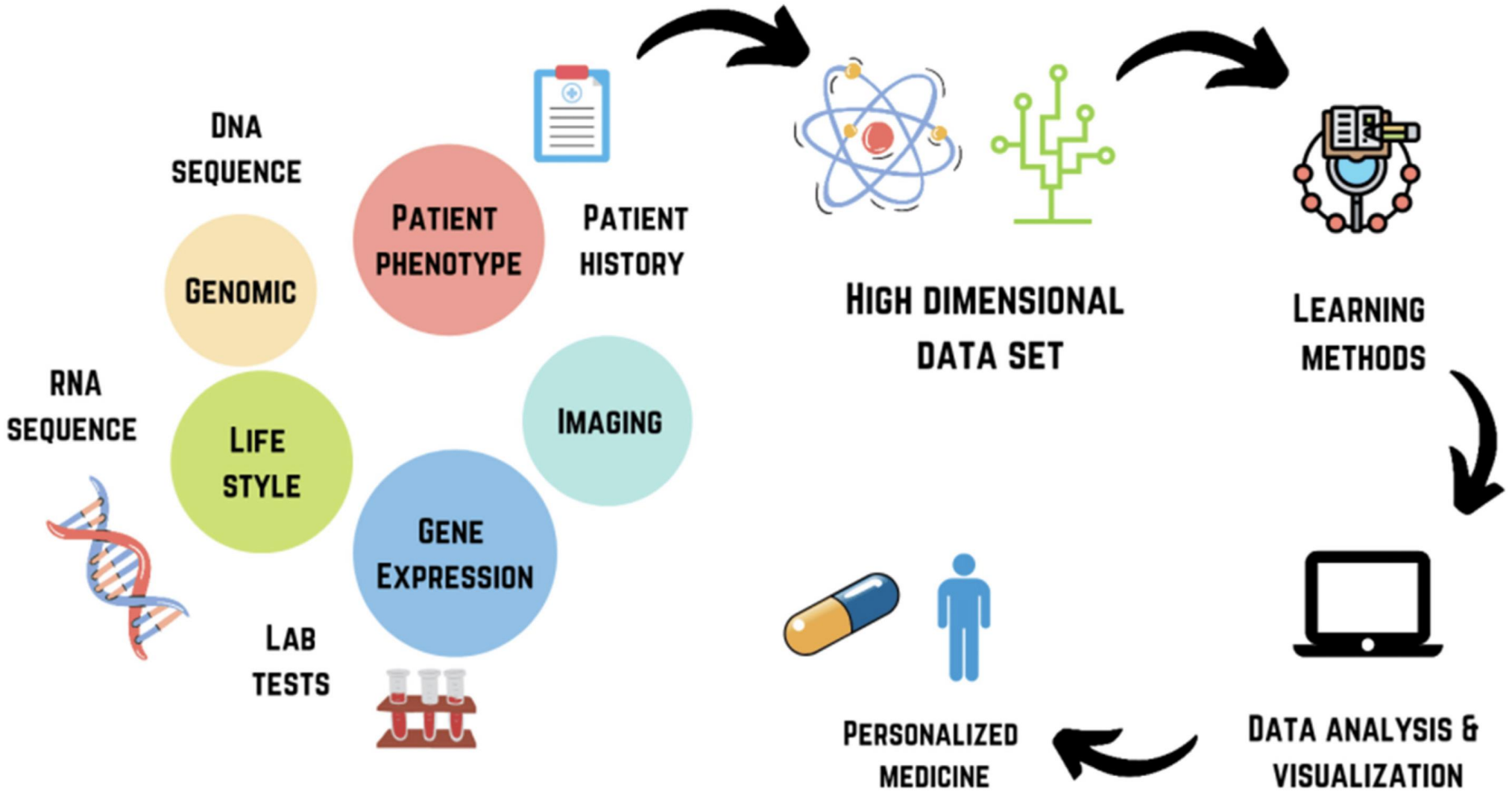


Platform studies



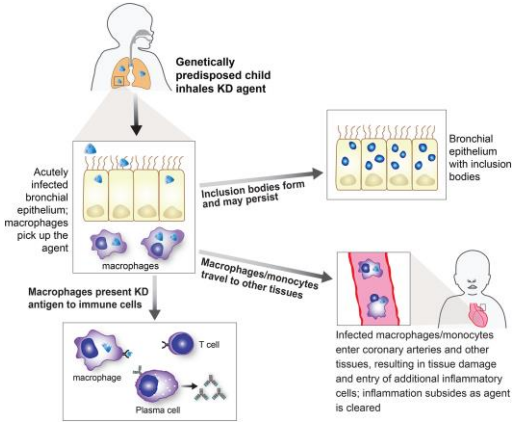
Master Observational Trials (MOTs)

Bioinformatics and Artificial Intelligence



Gaps in knowledge

Etiology



Treatment

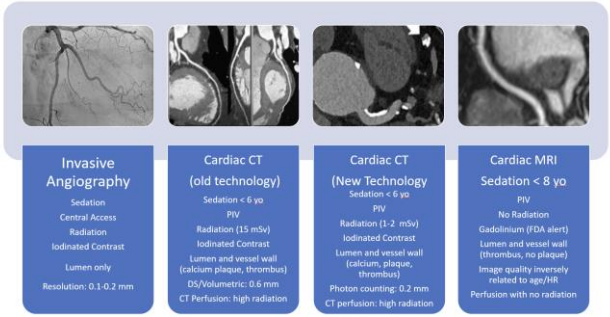
Adjunctive Therapy for high risk KD patients

Which agent to use?

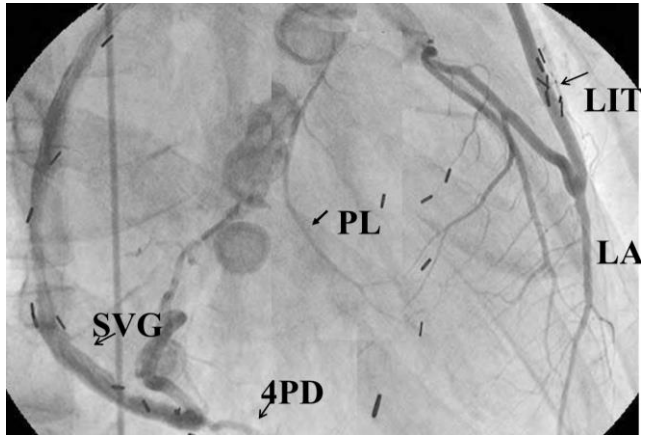
i. 2nd dose of IVIG (2 g/kg)**
ii. Infliximab (10 mg/kg)
iii. Steroids
iv. Cyclosporine
v. Cytoxan
vi. Other (anikinra, etanercept, plasmapheresis)

** risk for hemolytic anemia

Imaging surveillance CAA



Revascularization



Genetics

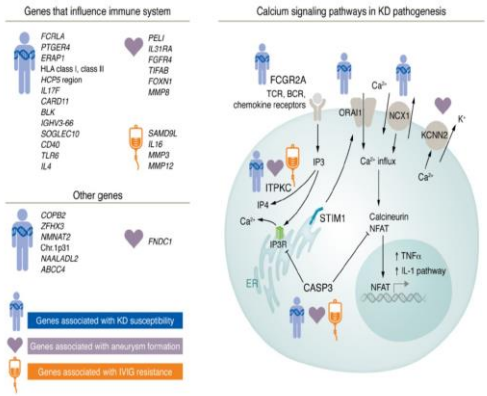


Figure 3. Pathways and genes influencing KD susceptibility and outcome. Figure concept and design are courtesy of Chisato Shimizu.

Anticoagulation

Safety Profile: Phase 3 Pediatric DOAC Prophylaxis Trials 641

	Rivaroxaban UNIVERSE ♥	Apixaban SAXOPHONE ♥ (KD = 16)	Edoxaban ENNOBLE-ATE ♥ (KD = 24)	Edoxaban ENNOBLE-ATE ♥ (Extension)	Apixaban PREVAPIX-ALL
Adult dose equivalence	10 mg, Q day (↓)	5 mg, BID (↑)	60 mg, Q day (↑)	60 mg, Q day (↑)	2.5 mg, BID (↓)
Number of patients	112	129	109	144	256
Age in years (median)	4	8	8	8	7
Δt on DOACs (months)	12	12	3	9	1
Bleeding (overall)	2%	<1%	None	<1%	<1%
	6%	<1%	<1%	<1%	4%
	33%	36%	NA	NA	NA

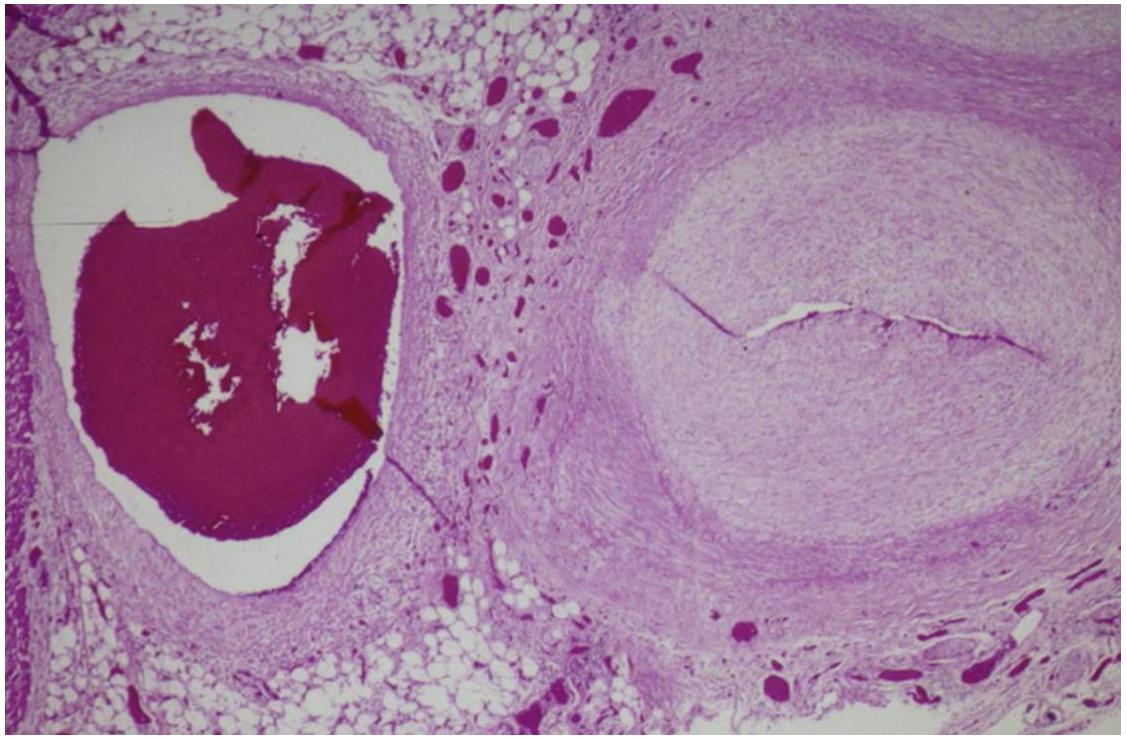
Legends: KD, Kawasaki disease; mg, milligram; BID, twice a day; Q day, once a day; VTE, venous thromboembolism; Δt, time interval; DOAC, direct oral anticoagulant; NA, not available

Assessment of ischemia

	Stress Echo	Stress CMR	CCTA	Stress SPECT	Stress PET
Advantage	Low cost Wide availability versatility	Myocardial fibrosis tissue characterization Ischemia, viability function	Widely available Coronary anatomy plaque, perivascular inflammation, coronary calcification	Quantitative Established	Quantitative Absolute Coronary flow
Disadvantage	Good image Quality needed Operator dependence	Limited availability Implantable devices Claustrophobia Gadolinium contrast needed	Moderate radiation exposure Nephrotoxic iodine contrast	High radiation exposure High cost	Moderate radiation exposure High cost

(Picano et al. Eur Heart J Cardiovasc Imaging 2024, revised)

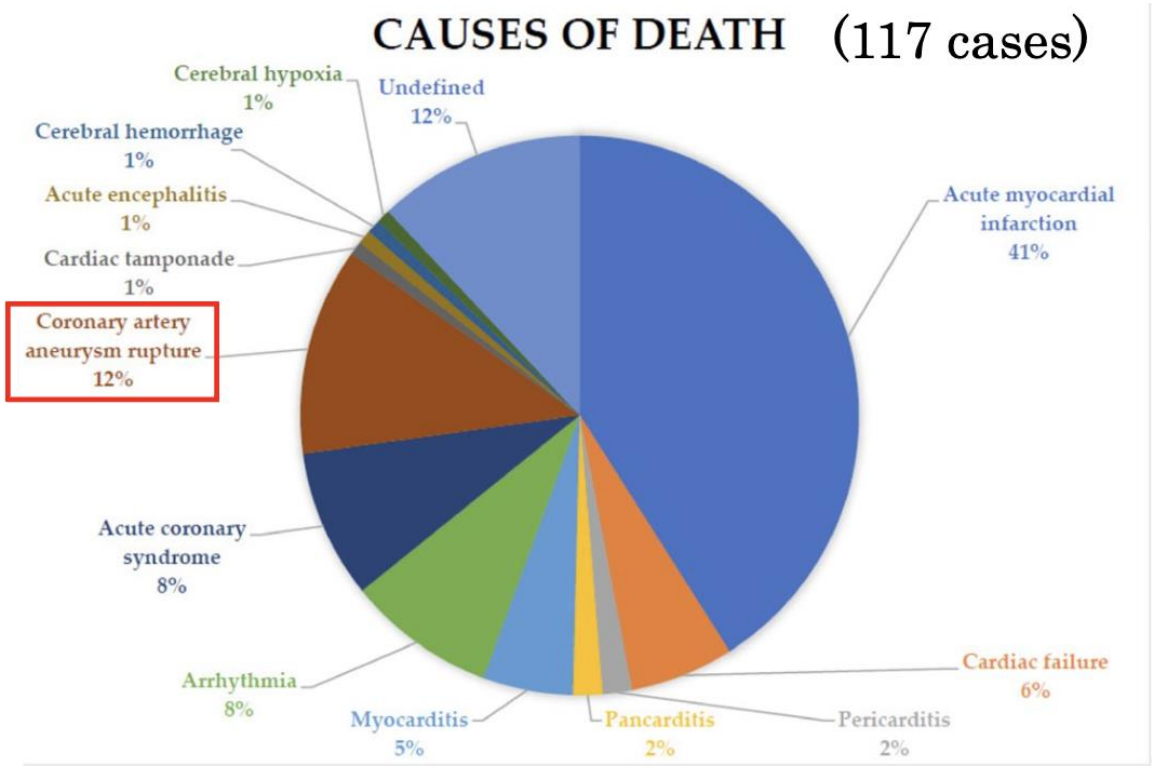
Correlation with Outcomes



Artide

Autoptic Findings in Cases of Sudden Death Due to Kawasaki Disease

Giacomo Visi [1], Federica Spina [1], Fabio Del Duca [2], Alice Chiara Manetti [3], Aniello Maiese [1,*], Raffaele La Russa [4], Paola Frati [2] and Vittorio Fineschi [2]



Adapted from Ayusawa

Transition of Care















14th International Kawasaki Disease Symposium (IKDS)

Montreal, Canada
Hotel Bonaventure