ADULT CONGENITAL HEART DISEASE

ACHD

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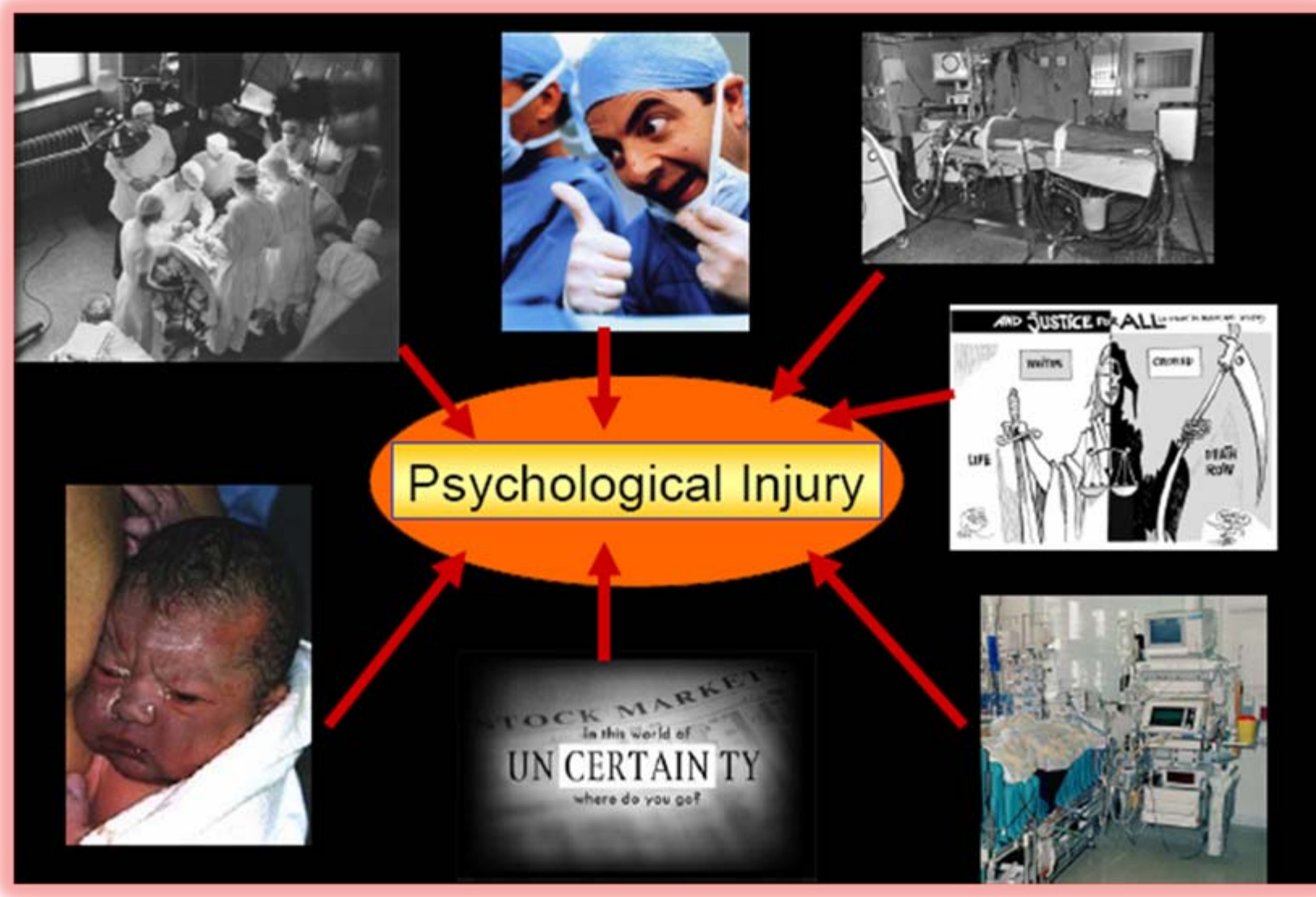

Psychological Injury
AND JUSTICE FOR ALL
LIFE
DEATH ROW
STOCK MARKET
In this World of
UNCERTAINTY
where do you go?

From the beginning…

A Brief History of ACHD

- Joseph K. Perloff

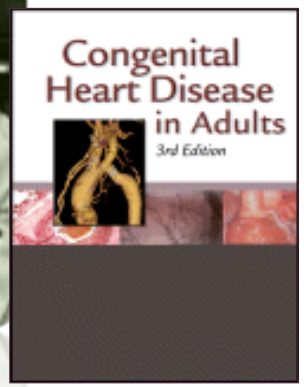
- Jane Somerville

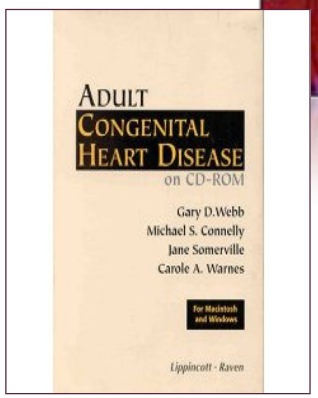
- John Morch

ACHD in North America – Transcending Borders

THE LEGACY OF FOUNDERS. FROM CHD TO ACHD

- 1975 and 1977: The birth of units specializing in Adult Congenital Heart Disease (ACHD)
- Royal Brompton Hospital, Imperial College of Medicine (London, UK)
- UCLA School of Medicine (USA)

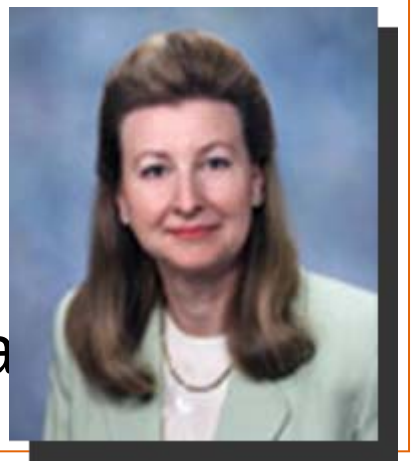




SUCCESSORS

- 1983 University of Toronto Congenital Cardiac Centre for Adult (TCCCA)
  - 1959 (Drs. Morch, Evans)

- Mayo Clinic Adult Congenital Cardiac Clinic



- Boston, Cleveland, London, Chiba

A Brief History of ACHD

The Canadian Adult Congenital Heart (CACH) Network – founded 1991

ACHD in North America – Transcending Borders

ACHD in the US

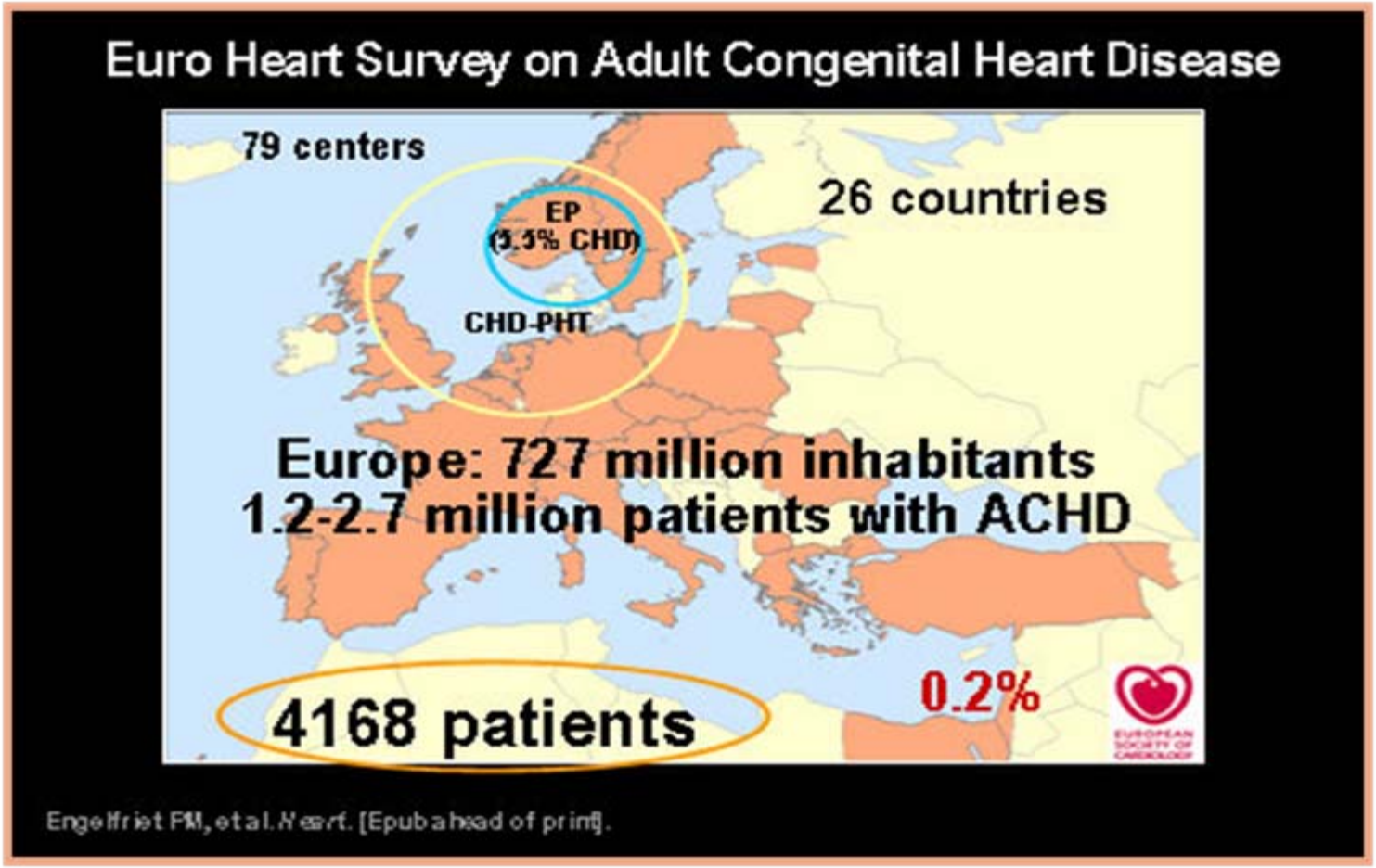
Recent Developments in ACHD

The impressive growth of

American ACHD Clinics.

ACHD in North America – Transcending Borders

EUROPE


Euro Heart Survey on Adult Congenital Heart Disease
79 centers
26 countries
EP
(3.5% CHD)
CHD-PHT
Europe: 727 million inhabitants
1.2-2.7 million patients with ACHD
4168 patients
0.2%
Engelfriet PM, et al. Heart. [Epub ahead of print].

Scope of the problem. Epidemiology

ACHD

		Year			
Country	Population	80's	2000	2008	2020
United States	320, 000 000	300, 000	800, 000	1, 000 000	1, 400 000
United Kingdom	60, 000 000		150, 000 (2005)		
Canada	32, 000 000		180,000	11,000 7,000 active (Toronto CCA)	
Israel	7, 500 000			~ 3,000 (ACHD Unit, Rabin)	

Scope of the problem. Epidemiology

1. Each year approximately 40,000 newborn with congenital heart disease (CHD) in the US
2. Moderate to severe CHD, 6/ 1.000 live birth
3. Approximately 3 - 5/ 1.000 need some kind of cardiac care during their life*
4. Almost 1 in 150 young adults will have some form of CHD in the next decade

* Bicuspid aortic valve 19/ 1,000; tiny VSD 75/ 1,000

Number of patients
Regional ACHD centers

	6 largest national ACHD centers					
	Toronto	Brompton	Boston	UCLA	Mayo	Cleveland
Active patients 2004	7,000	5,000	3,200	2,500	2,000	1,700
Median (pts/center)	2,850					

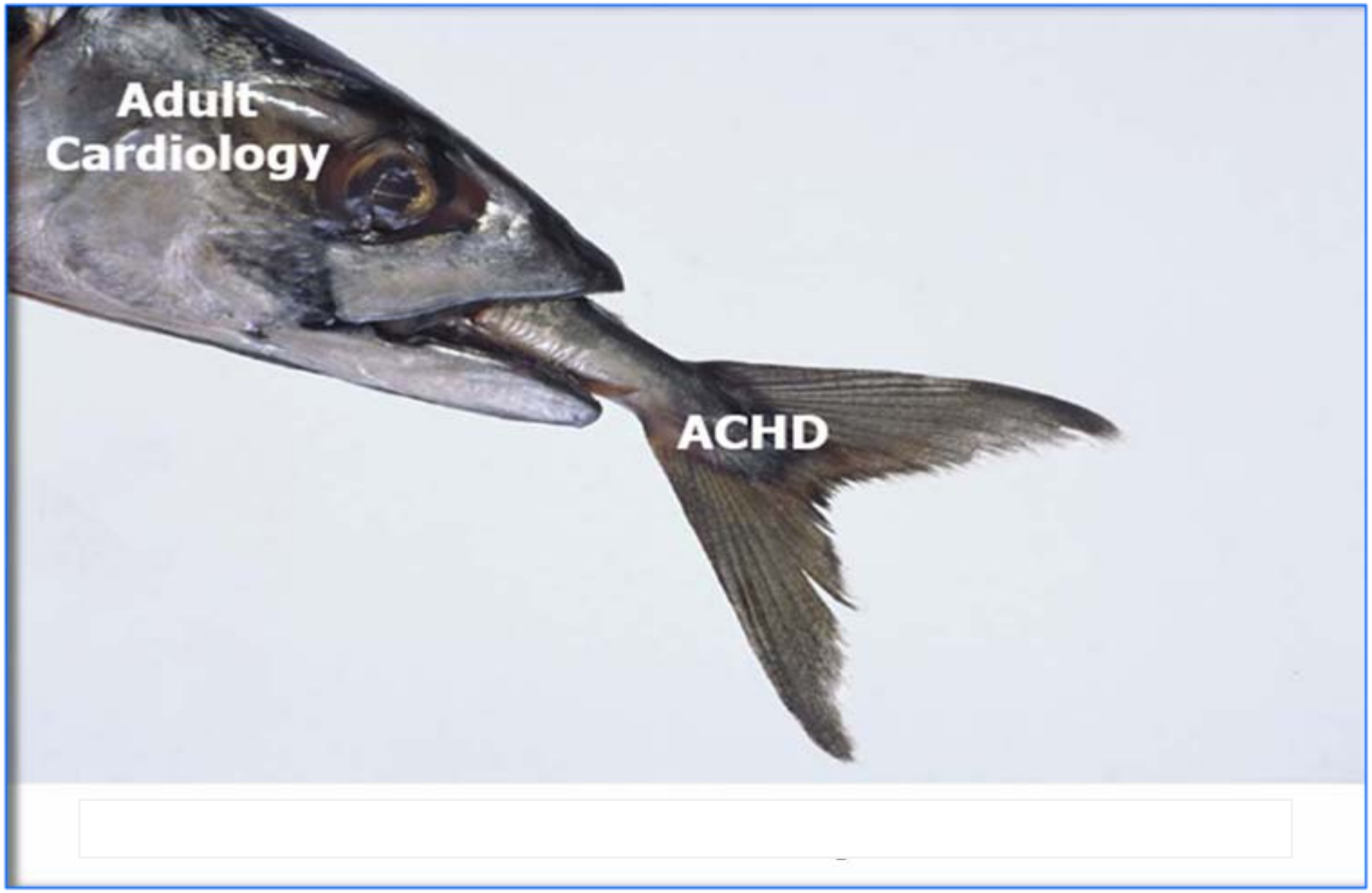
Niwa K. et al. International Journal of Cardiology 2004;96:211

Maude Unit

Courtesy Dr. A. Marelli, Quebeck

Adult Cardiology vs. ACHD

Adult Cardiology vs. ACHD



Question 1

- Combined incidence of congenital heart defects (CHD)?
- Prevalence of CHD in adults/ kids?
- First time diagnosis of CHD in adults (%) ?
- Survival of pts with CHD ?
- Mortality: overall; surgical; sudden death?
- Recurrence rate of CHD: parents, siblings?
- Sex distribution of CHD: overall; type specific lesions?
- Genetic associations of CHD?
- Most frequent CHD: adults; kids?
- Specific lesions

INCIDENCE OF CONGENITAL HEART DISEASE (CHD)

- CHD is the most common group of human birth defects
- Combined incidence of CHD in humans

Live birth	~ 0.4 – 0.8% (4-8/ 1000)
Spontaneously aborted fetuses	~ 10%

J.A. Towbin, J.Belmont, 2000; Wulfsberg EA et al.,1991; Ferencz et al.,1985

Question 2

- Combined incidence of congenital heart defects?
- Prevalence of CHD in adults/ kids?
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- Survival of pts with CHD ?
- Mortality: overall; surgical; sudden death?
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- Most frequent CHD: adults; kids?
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- Most studies on CHD frequency refer to birth prevalence with variable reported rates

- Prevalence of CHD has been determined in general population of Quebec (Canada) using 18 years data (23-25% of population)

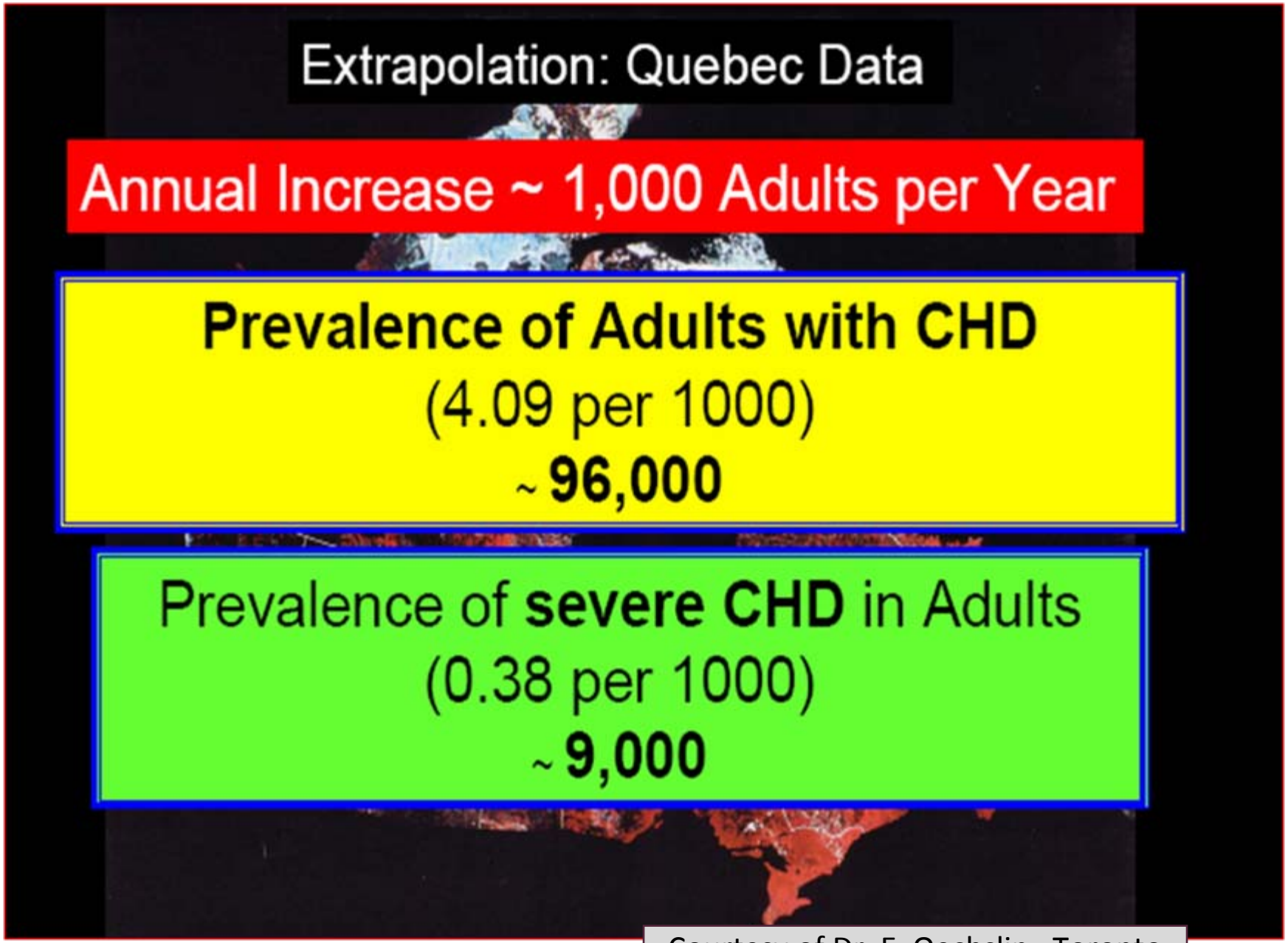
Observed **prevalence**:
11.89/1000 children and **4.09/1000 adults**

A. Marelli et al., Circulation 2007

Prevalence of severe and other CHD in the year 2000

	Adults alive in 2000		Children alive in 2000	
	N (%)	Per 1000 adults	N (%)	Per 1000 children
All CHD	23563 (100)	4.09	18979(100)	11.89
Severe lesions				
TOF or TA	1001	0.17	778	0.49
Transposition	834	0.14	914	0.57
Univentricular	235	0.04	424	0.27
All severe	2205 (9)	0.38	2316 (12)	0.45
Other lesions				
ASD	5076	0.88	6205	3.89
VSD	4486	0.78	6709	4.20
PDA	103	0.02	493	0.31

A. Marelli et al., Circulation 2007



Courtesy of Dr. E. Oechslin , Toronto

OVERALL PREVALENCE OF CONGENITAL HEART DEFECTS VARIES BY RACE AND ETHNICITY

1. Non - Hispanic White 14.4 /1000 live births

2. Non - Hispanic Black 12.8 /1000 live births

3. Others (American Indian, Pacific Asian) 12.5 /1000 live births

4. Hispanics 8.8 /1000 live births

3075 congenital CV malformations of 2303 children from a birth population of 235,230

Tania Mangones et al., IJC, 2010

Question 3

- Combined incidence of congenital heart defects?
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- Mortality: overall; surgical; sudden death?
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- Genetic associations of CHD?
- Most frequent CHD: adults; kids?
- Specific lesions

DIAGNOSIS OF CHD

1. Approx. 60% in babies
2. Children, 30%
3. **Adults, 10%**

Question 4

- Combined incidence of congenital heart defects?
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- Mortality: overall; surgical; sudden death?
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- Most frequent CHD: adults; kids?
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Complex Congenital Heart Disease

Year of birth	Survival rate
1940-1959	10%
1960 – 1979	50%
1980 - 1989	80%*
1990 – 2000s	**85 – 95%**

Warnes et al., JACC, 2001 (modified)

GROWING POPULATION OF ADULT PATIENTS WITH CHD

40s – 70 s

80% - 90% kids

10% - 20% adults

90s – 2000

50% kids

50% adults

Next decade or two

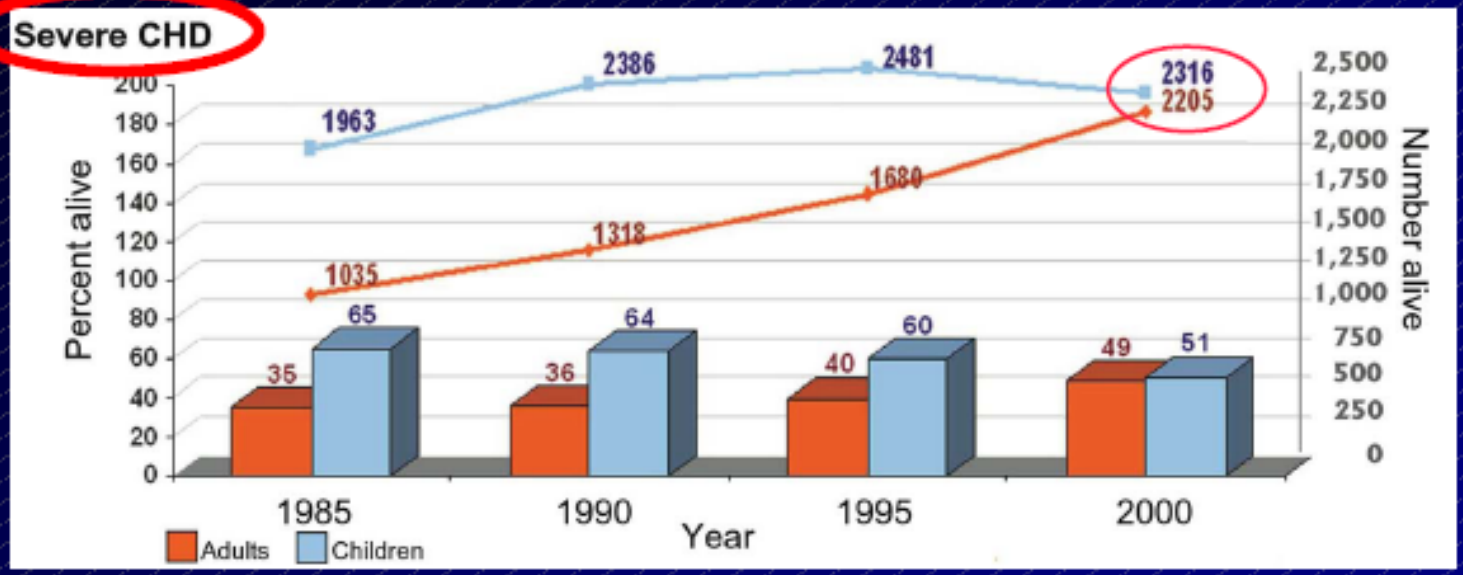
40% kids

60% adults

Today

all CHD, adults/ kids 55/ 45%; severe CHD 49/51%

Changing Age Distribution of Severe CHD 1985 - 2000

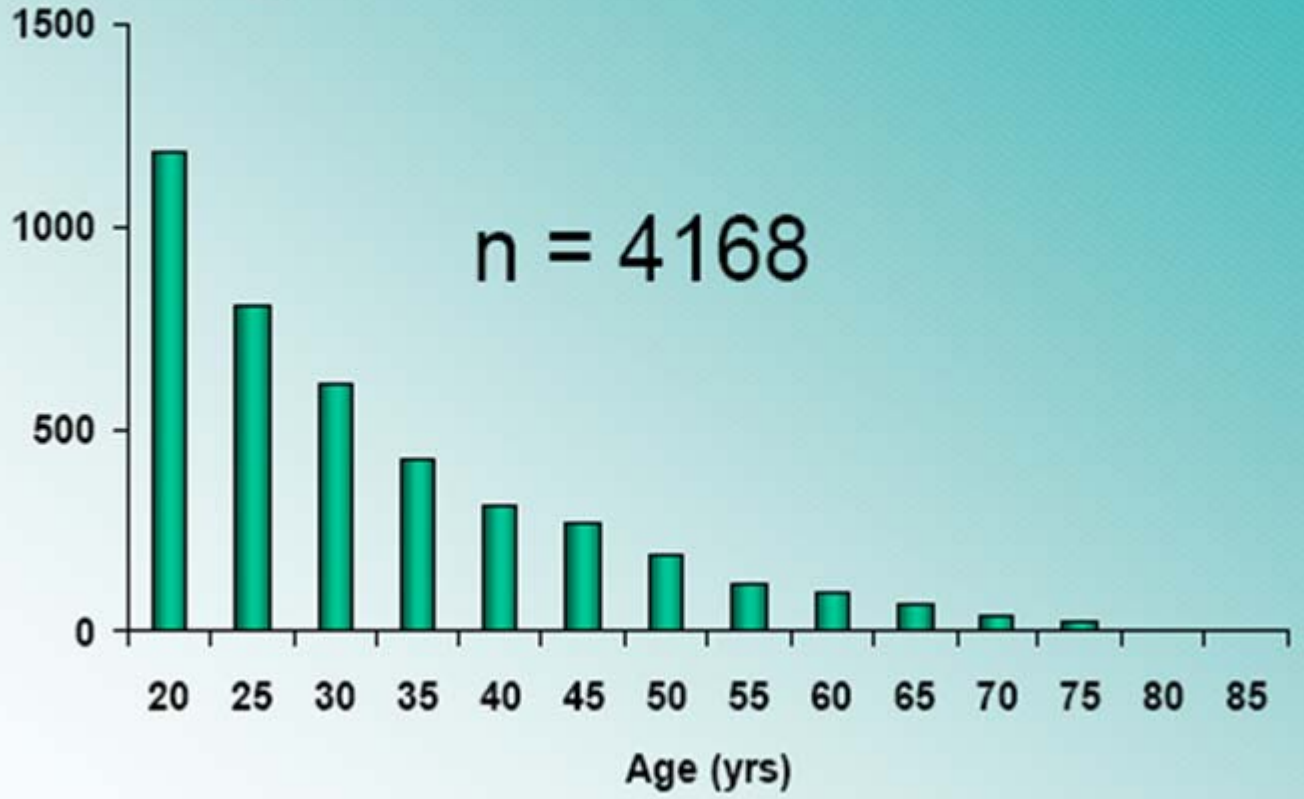


Toronto

Marelli AJ, et al. Circulation 2007; 115: 163-172

Courtesy of Dr. E. Oechslin , Toronto

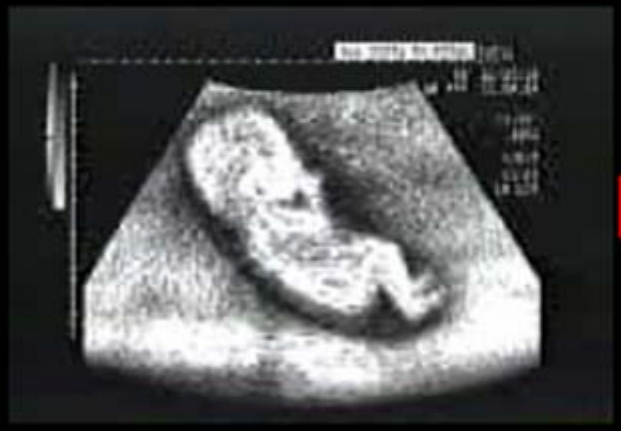
Age Distribution

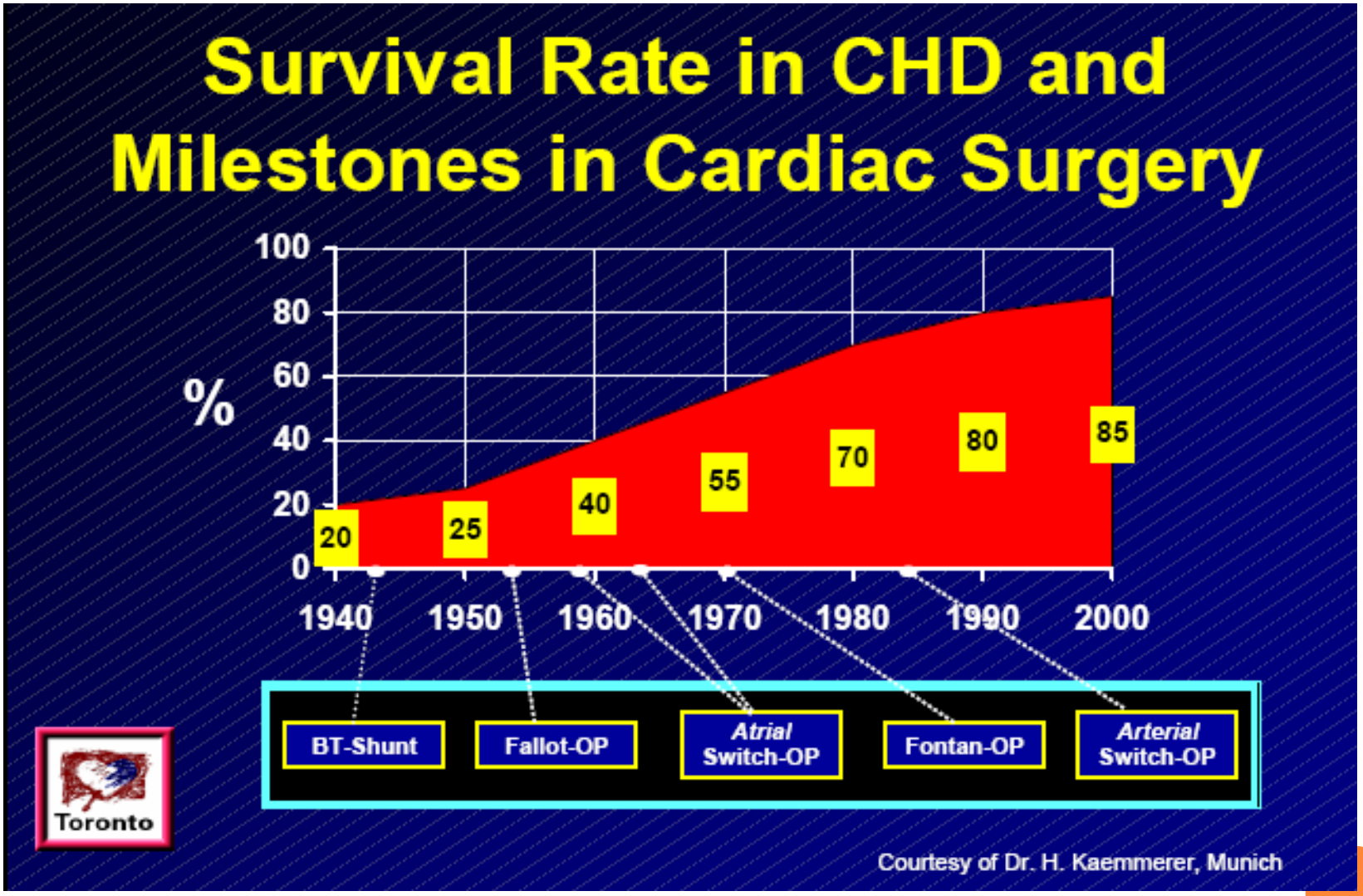


Euro Heart Survey on Adult Congenital Heart Disease

EUROPEAN SOCIETY OF CARDIOLOGY

CHD is a Continuum from Fetal Life until Adulthood




Survival Rate in CHD and Milestones in Cardiac Surgery
%
100
80
60
40
20
0
20
25
40
55
70
80
85
1940
1950
1960
1970
1980
1990
2000
BT-Shunt
Fallot-OP
Atrial Switch-OP
Fontan-OP
Arterial Switch-OP
Toronto
Courtesy of Dr. H. Kaemmerer, Munich

Question 5

- Combined incidence of congenital heart defects?
- Prevalence of CHD in adults/ kids?
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EuroHeart Survey. Mortality

	n	Number of death		5 yr mortality	
		CV	Non CV	Kaplan Meier estimate (%)	95% CI (%)
ASD sec.	882	5	4	1.1	0.3, 1.9
VSD	628	6	2	1.6	0.5, 2.7
TOF	811	8	3	1.3	0.5, 2.1
Coarctation	551	2	1	0.7	0.0, 1.4
TGA	363	9	0	3.0	1.0, 4.9
Marfan syndrome	287	3	2	1.7	0.0, 3.3
Fontan circulation	198	12	4	8.2	4.0, 12.3
Cyanotic defects	390	44	10	12.6	9.1, 16.0
Overall	4110	89	29	**3.0**	2.4, 3.5

EHJ, 2006

EuroHeart Survey.

ACHD Mortality

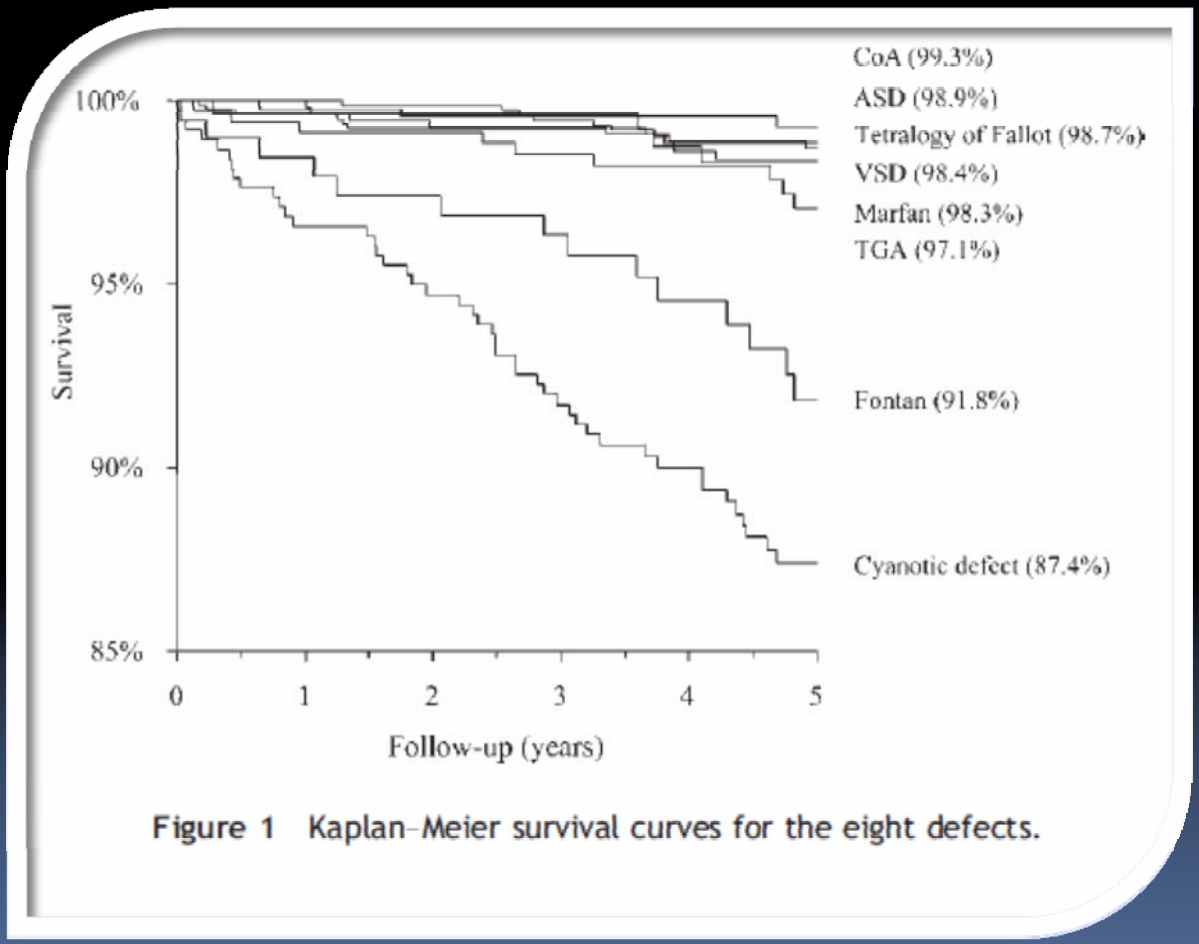


Figure 1 Kaplan–Meier survival curves for the eight defects.

EHJ, 2006

Clinical activity and cardiac surgery

	UCLA	Toronto	Cleveland	Boston	Mayo	Royal Brompton
Settings	Adult	Adult	A. & ped.	A & ped.	Adult	Adult
Adm./yr*	350	660	100	180	300	450
Pregn./ yr	23	60	30	15	18	80
Surgery						
Oper./yr	170	150	50	70	100	100
Re-do	80%	35%	25%	29%	56%	60%
Postop. mort.	**2%**	**1.5%**	**2%**	**1.5%**	**3%**	**1.5%**

* Ratio: # hospit./ total # of pts followed, averaged 10%

K. Niwa et. al., IJC, 2004

Surgery is corrective, if.....

- ...? tricular function ? normal
- ...life expeta ? is no ? al!
- ...there is no ? ed for therapeutic me ? res during follow-up! ?

Toronto

Volume 97, Number 1 January 1989

The Journal of THORACIC AND CARDIOVASCULAR SURGERY

J THORAC CARDIOVASC SURG 1989;97:1-9

Honored Guest's Address

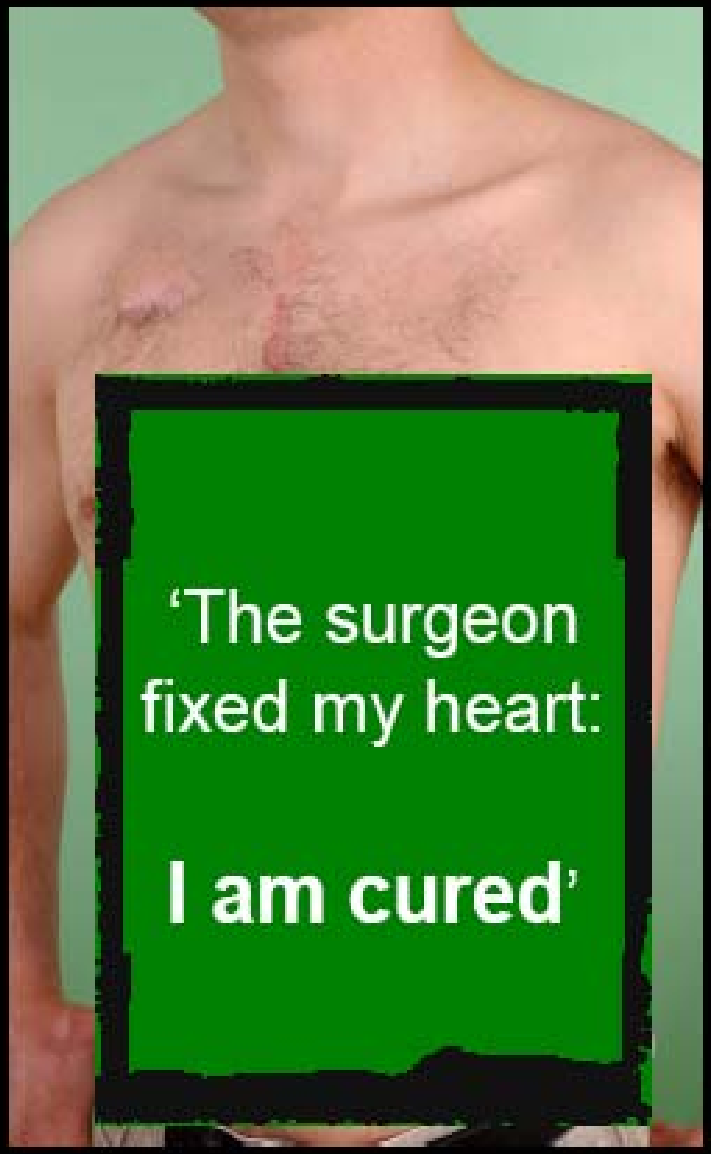
Do we really correct congenital heart defects?

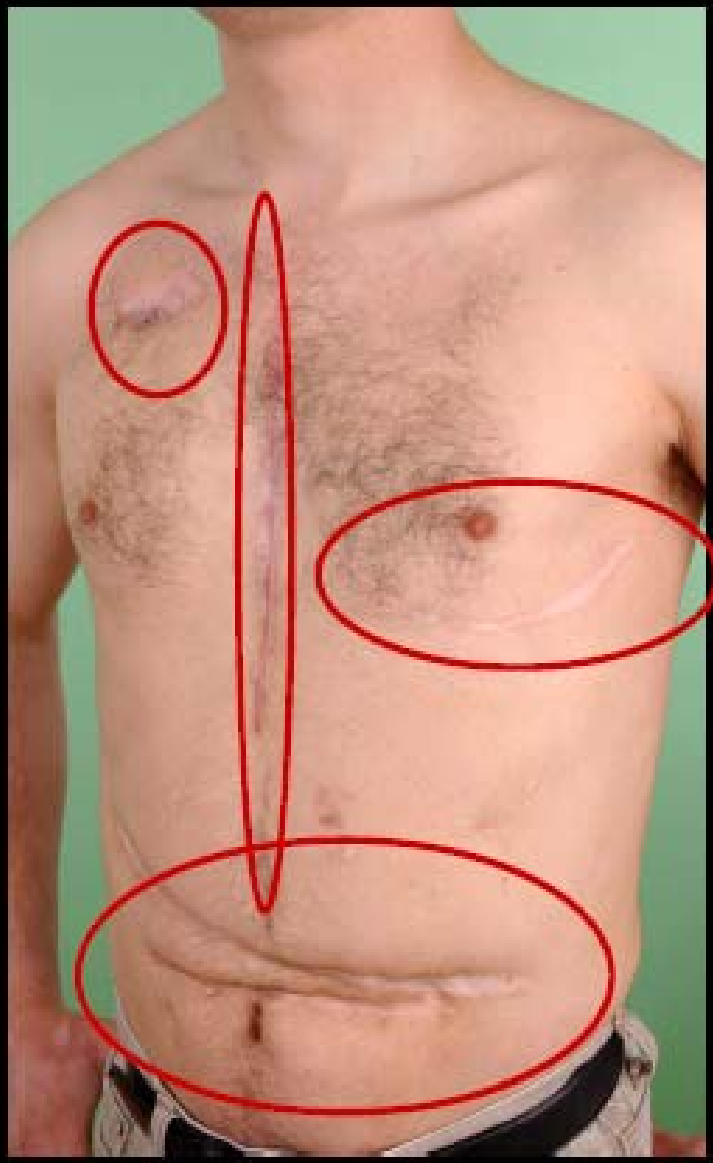
J. Stark, FRCS, FACS, FACC, *London, England*

Corrective Surgery....

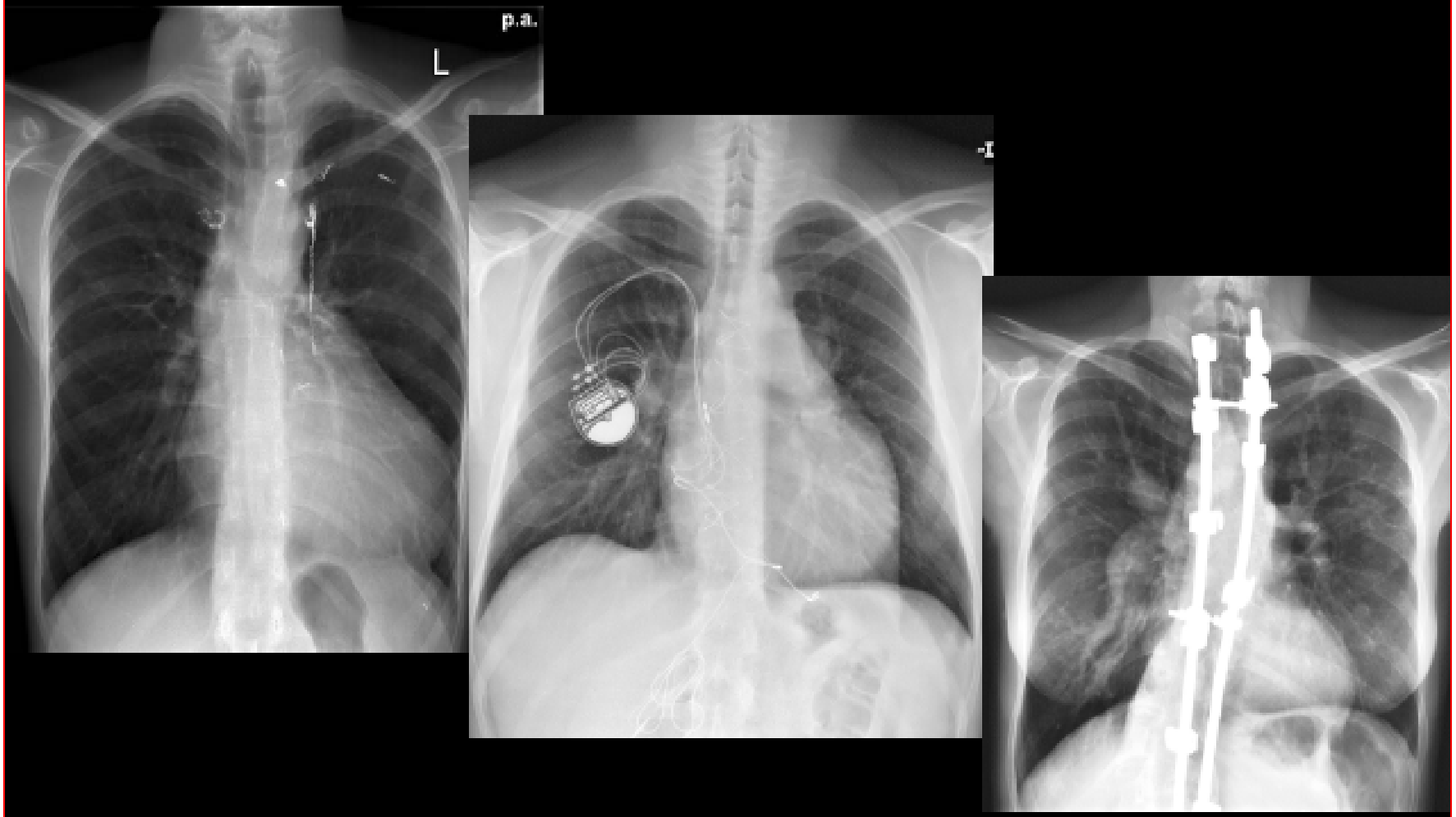
- Atrial septal defect
- Ventricular septal defect
- Patent ductus arteriosus

... if treated during childhood!!

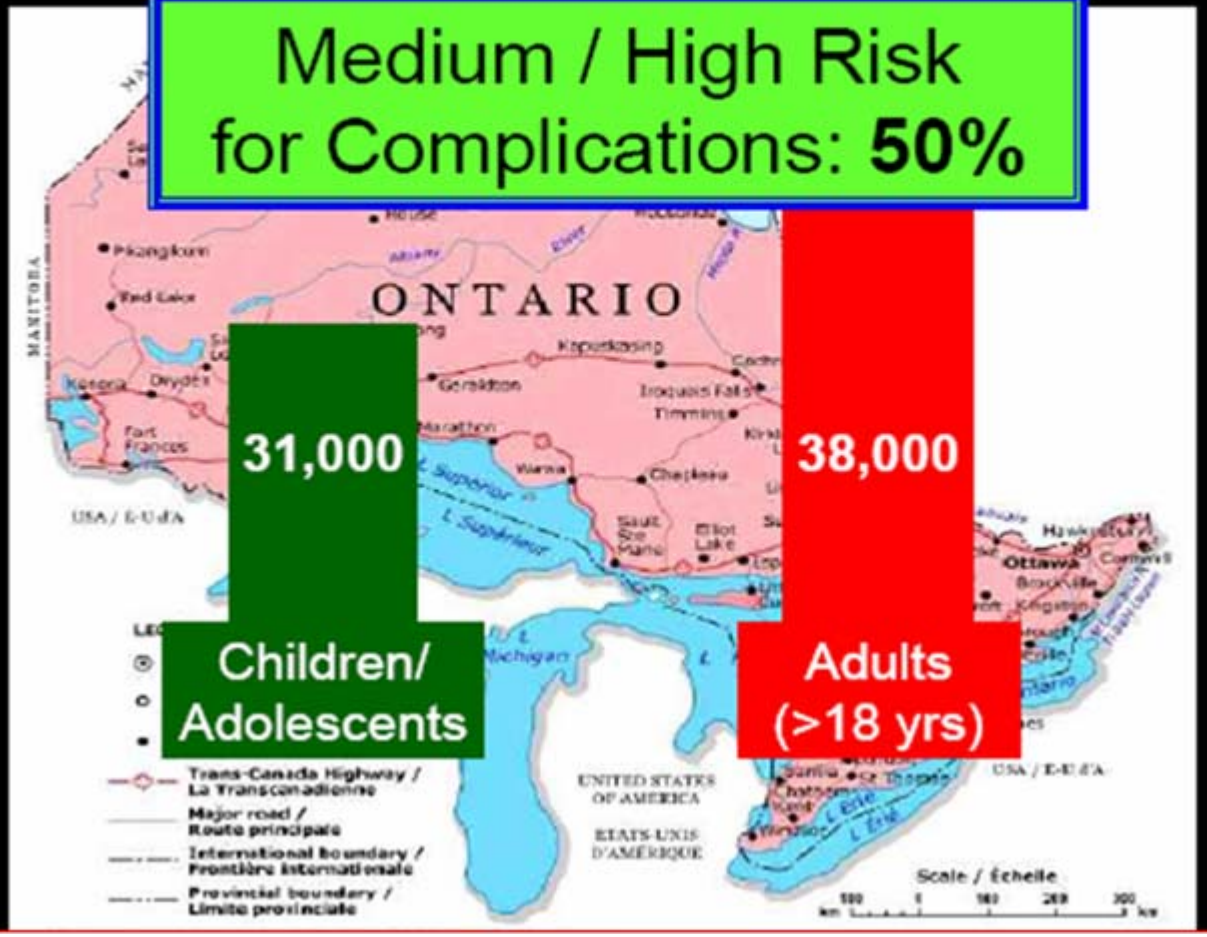

'The surgeon
fixed my heart:
I am cured'



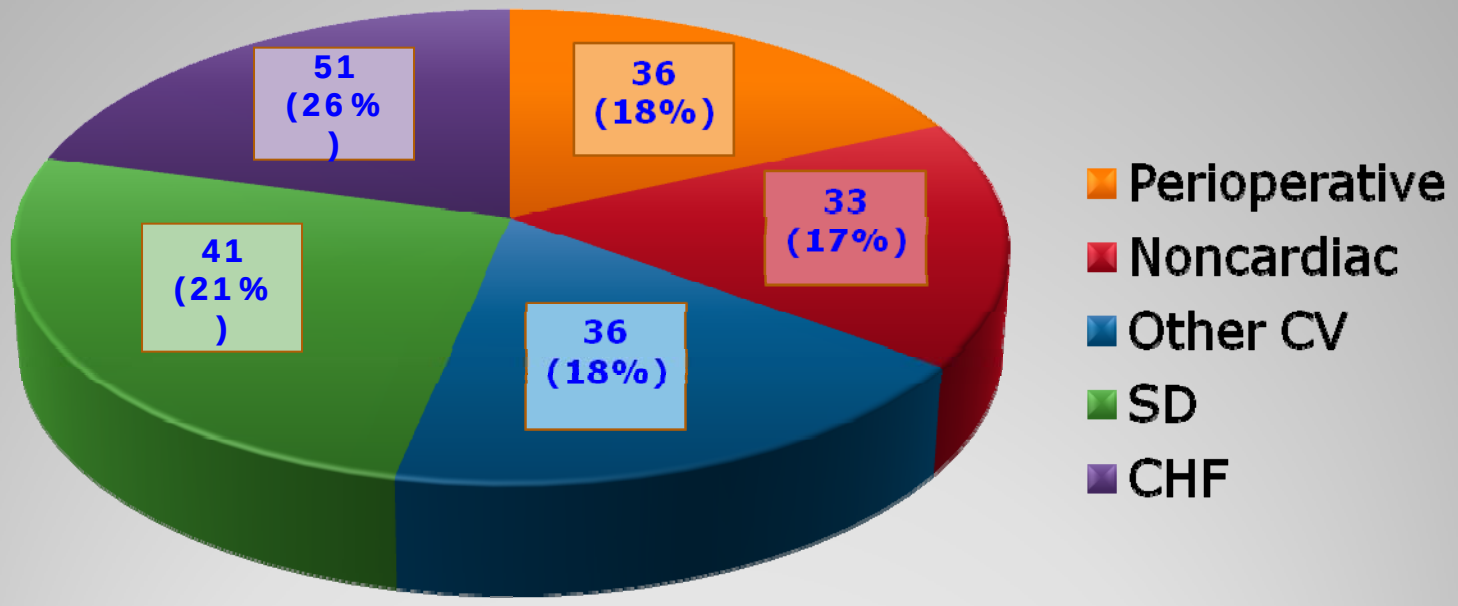
Hardware……



CHD Patients in Ontario

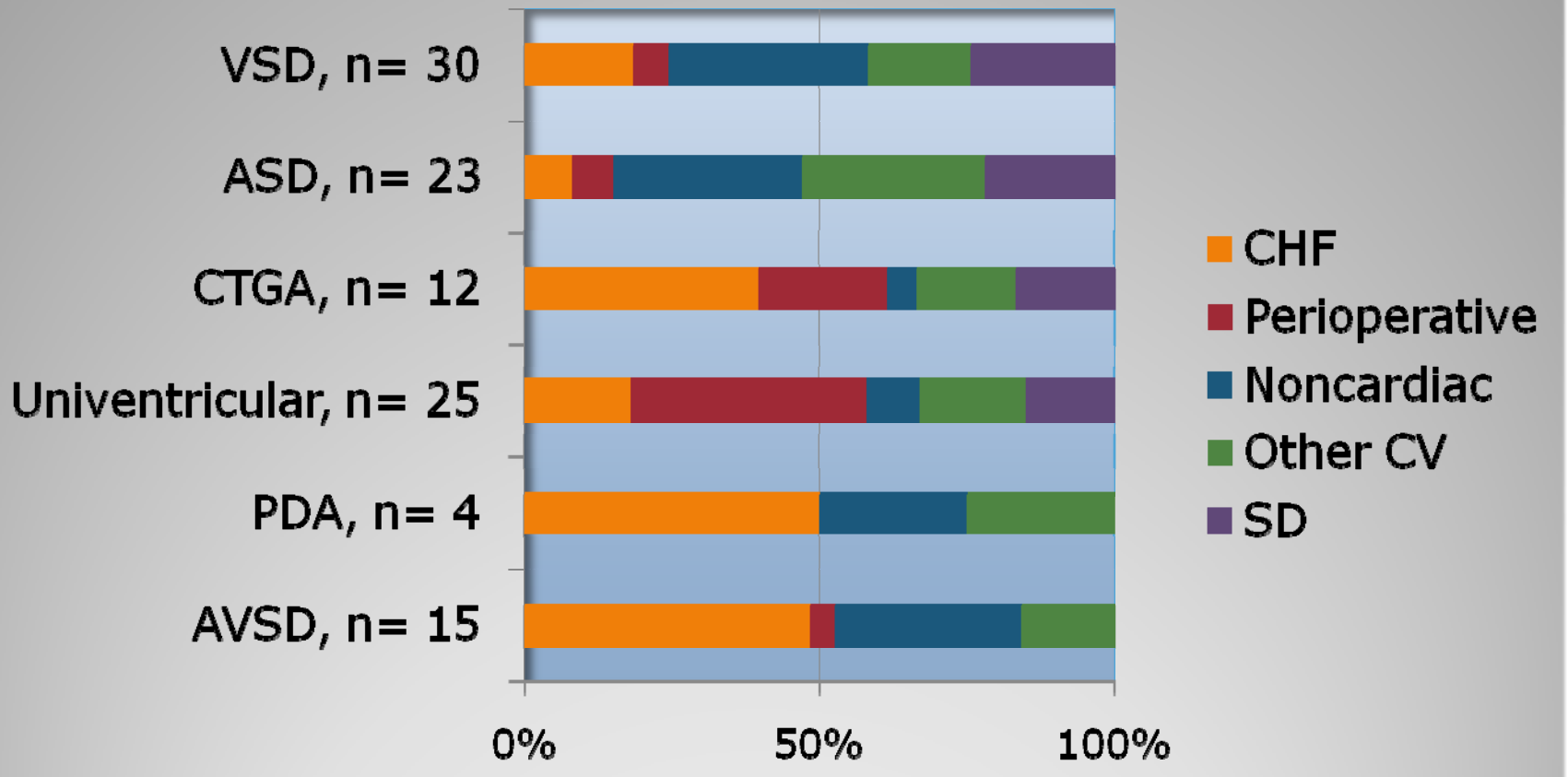


Courtesy of Dr. E. Oechslin , Toronto



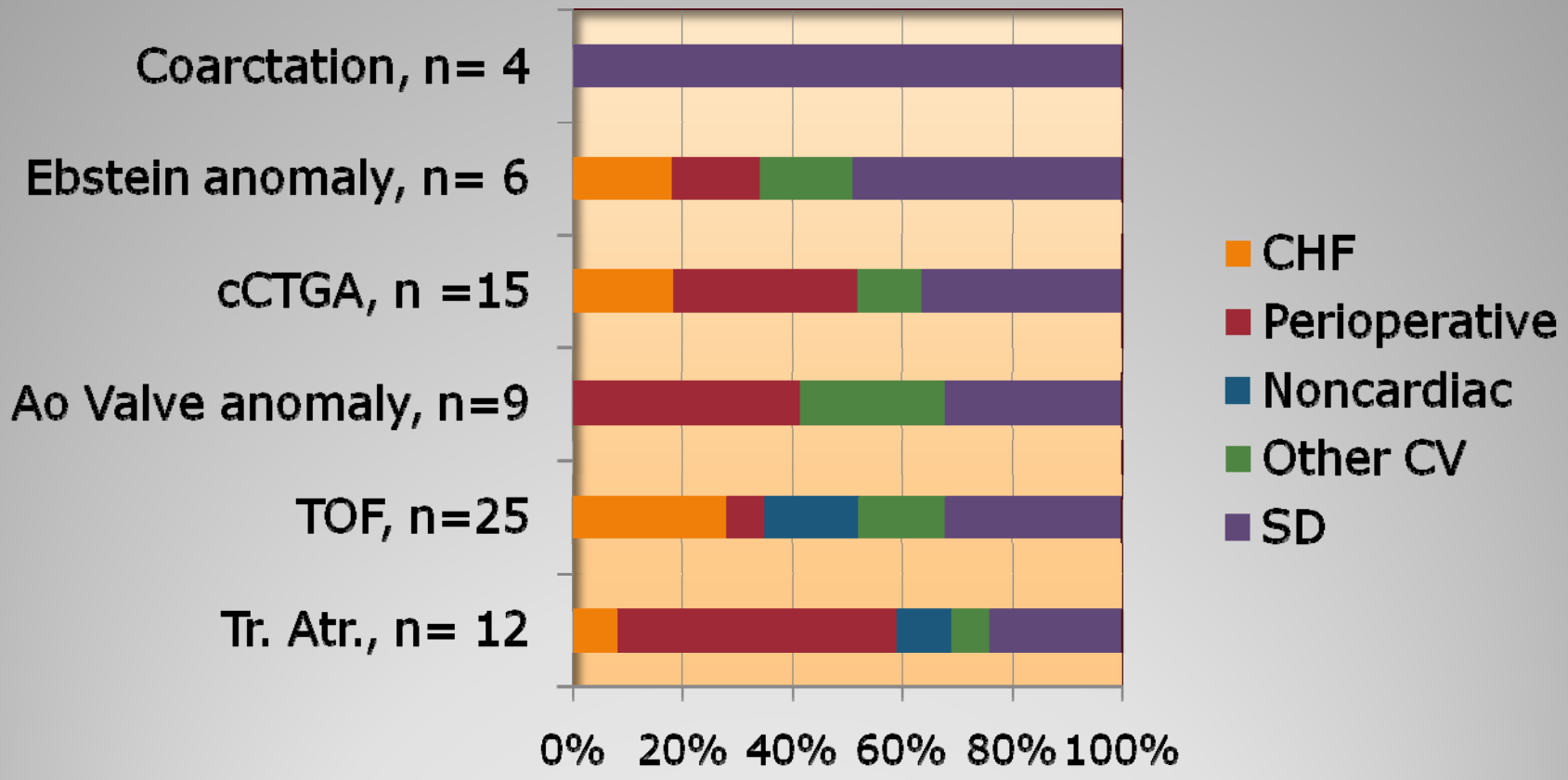
Mechanism of death
(197 deceased pts, 1981- 1996)

E. Oechslin et. al., AJC, 2000



Mechanism of Death by Diagnosis

E. Oechslin et. al., AJC, 2000



Mechanism of Death by Diagnosis

E. Oechslin et. al., AJC, 2000

Sudden Cardiac Death in ACHD

- Late SCD (after CHD surgery)
- 0.9/1000 patient – years (significantly higher than in general population)

1. Arrhythmic events
2. Embolic events
3. Acute ventricular failure
4. Aneurysm rupture
5. Eisenmenger syndrome

L. Harris, S. Belaji (in M. Gatzoulis et al.) ACHD, 2003

Event rate of SCD in ACHD

2.2/1000; 90% of cases

1. TOF
2. CTGA
3. Coarctation (LVH)
4. Aortic stenosis

- Residual stenosis
- Coronary emboli
- Cerebral emboli
- IE

0.14/1000

- Left to right shunt lesions
- Pulmonary valve stenosis

L. Harris, S. Belaji (in M. Gatzoulis et al.) ACHD, 2003

Circumstances of death in ACHD

Pts (n)	Pts.-yrs	Death, n (%)
8,595	26,500	231 (2.7)

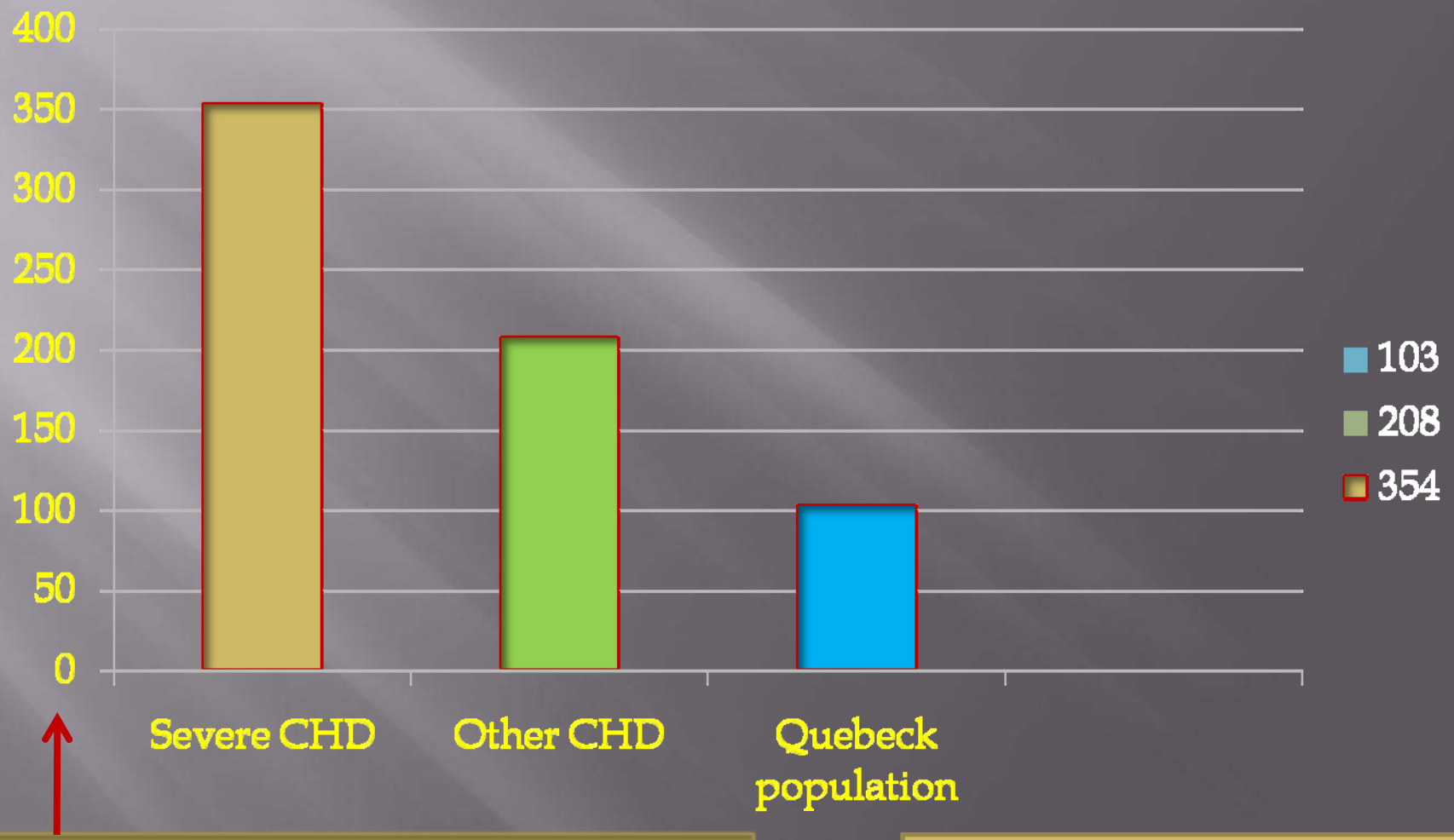
Main causes (%)	Out of hospital (%)	Season
- HF - 26% - SCD - 22%	35 (rural 55 vs. urban 32)	Fall – slightly higher (NS)

Sudden CV death (%)	During exercise (%)	Out of hospital (%)
~ 40%	8%	62%

Non-sudden CV death –18% out of hospital

Zomer AC et al., IJC, 2010

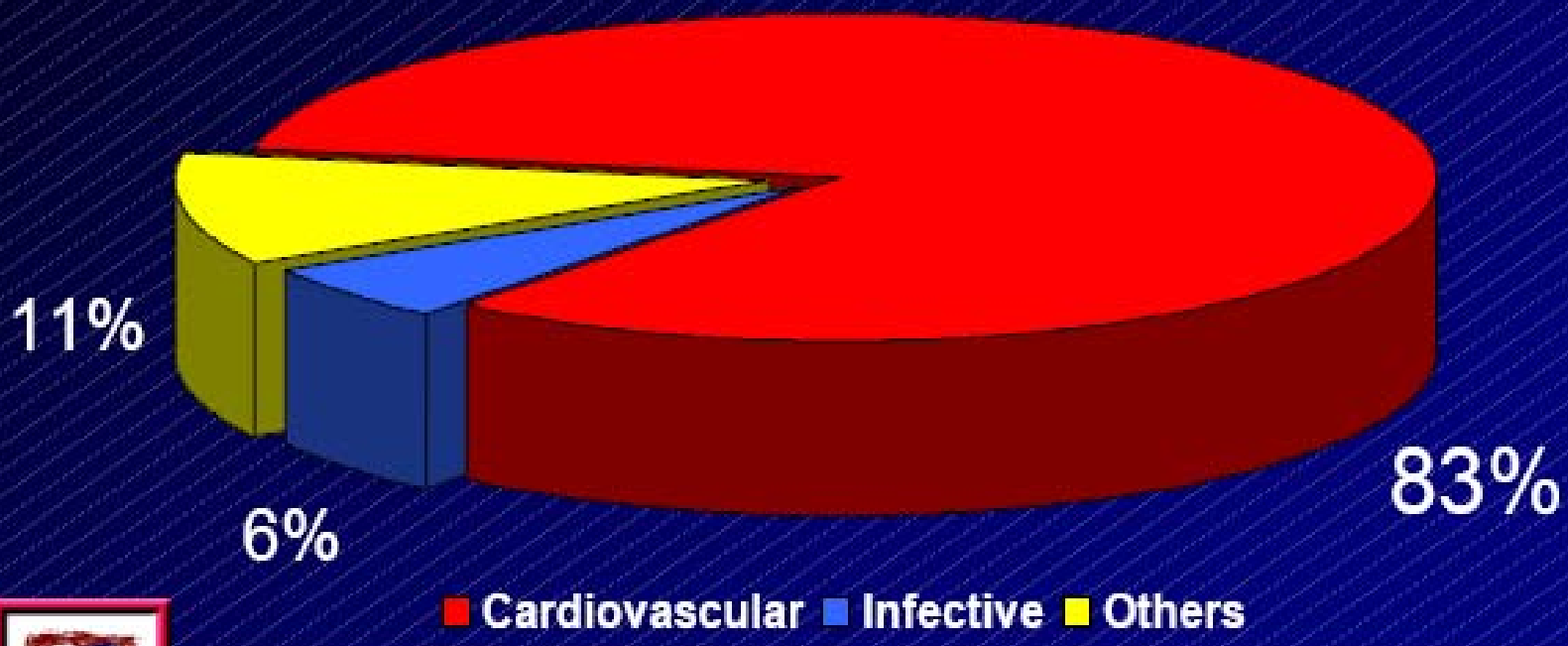
One – year Hospitalization Rate



Hospitalizations per 100 pts, 1999 - 2000

A.S. Mackie, Am J Card, 2007

Emergencies

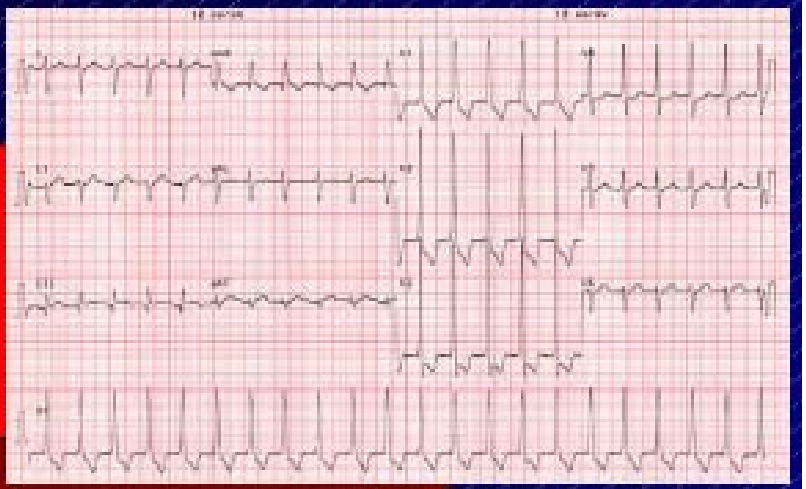


Toronto

Kaemmerer H, Oechslin E, ... Hess J. J Thorac Cardiovasc Surg 2003; 126:1048-52

Courtesy of Dr. E. Oechslin , Toronto

Cardiovascular Emergencies



- Arrhythmias
- Heart failure
- Syncope
- Cerebral ischemia
- Other cardiovascular
- Infections
- Others

Toronto

Kaemmerer H, Oechslin E, ... Hess J. J Thorac Cardiovasc Surg 2003; 126:1048-52

Courtesy of Dr. E. Oechslin , Toronto

Arrhythmias – ACHD patients

Rhythm disturbance	Associated lesion
Bradycardias	
SN dx	CTGA – Mustard
	CTGA - Senning
	Fontan
	Sinus venosus defect
	Heterotaxy syndrome
AVB	AV septal defects
	cCTGA
Surgically/ interventionaly induced AVB	VSD
	SA stenosis
	AVVR

ACC/ AHA ACHD Guidelines, 2008

Arrhythmias – ACHD patients

Rhythm disturbance	
Tachycardias	
WPW	Ebstein anomaly
	cCTGA
IART (atrial flutter)	CTGA – Mustard
	CTGA – Senning
	Fontan
	TOF
AFib	MV disease
	AS
	TOF
	Post palliation – single ventricle
VT	TOF

ACC/ AHA ACHD Guidelines, 2008

Question 6

- Combined incidence of congenital heart defects?
- Prevalence of CHD in adults/ kids?
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CHD RECURRENCE RISK*

Baltimore – Washington Infant Study (BWIS)

	Siblings (%) with CHD	One affected child
All forms of CHD	3 - 5	-
Subgroup of patients - Lt. sided obstructive lesions - PAS - Ebstein's anomaly	4.5 – 13.8	-
Recurrence risk of CHD	-	At least x3 baseline risk

Huhta James C. et al., 2006

RISK OF RECURRENT DISEASE IN OFFSPRING OF PARENTS WITH CHD

Lesion	Mother affected		Father affected	
	Risk of transmission (%)	Number of cases	Risk of transmission (%)	Number of cases
AVSD	11.6	5/43	4.3	1/23
AS	8.0	36/248	3.8	18/469
Coarctation	6.3	14/222	3.0	9/299
ASD	6.1	59/969	3.5	16/451
VSD	6.0	44/731	3.6	26/717
PS	5.3	24/453	3.5	14/396
PDA	4.1	39/828	2.0	5/245
TOF	2.0	6/301	1.4	5/362
Total	**5.8**	222/3795	**3.1**	93/2961

Nora JJ, JACC 1994; 23: 1468 – 71

EuroHeart Survey.
Percentage of women with at least one full term pregnancy

Pathology	Ever pregnant		General Dutch Population %
	%	N observed	
ASD sec.	50	232/462	46
VSD	40	111/281	38
TOF	36	129/354	36
Coarctation	40	76/191	38
TGA	30	41/137	33
Marfan syndrome	36	50/137	42
Fontan circulation	2	2/88	31
Cyanotic defect	18	42/238	43
Overall	36	683/1888	40

EHJ, 2006

Predictors of maternal cardiac complications (newly identified predictors in bold)

Variable	Odds ratio	p
History of arrhythmias	4.3	0.0011
Other (cardiac) medication before pregnancy	4.2	<0.0001
NYHA functional class	2.2	0.0298
LVOT obstruction	12.9	<0.0001
Systemic AV valve regurgitation (moderate/severe)	**2.0**	**0.0427**
Pulmonary AV valve regurgitation (moderate/severe)	**2.3**	**0.0287**
Mechanical valve prosthesis	**74.7**	**0.014**
Cyanotic heart disease	**3.0**	**<0.0001**

LVOT=Left ventricular outflow tract

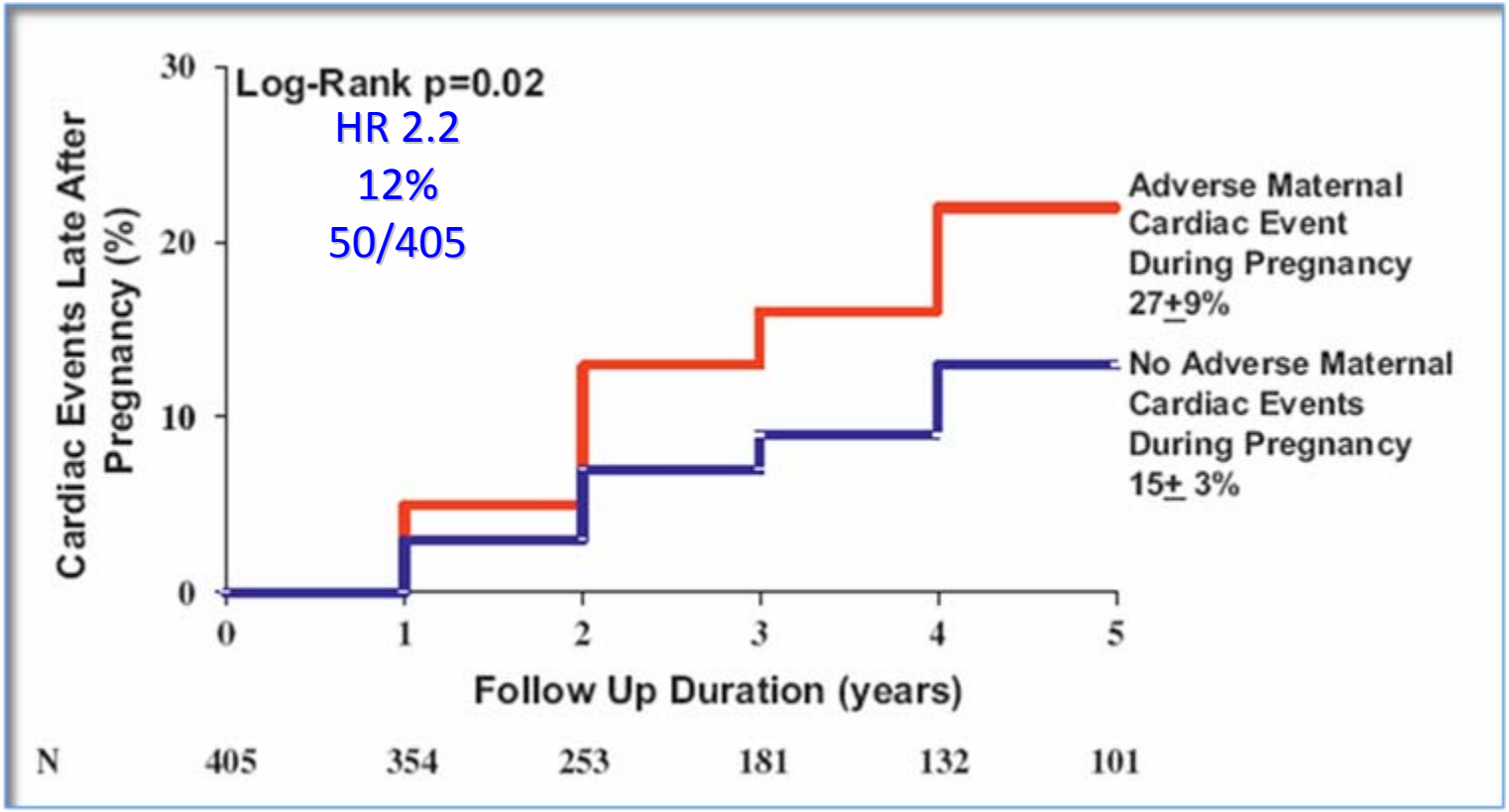
Drenthen W et al. European Society of Cardiology Congress 2007; September 1-5, 2007; Vienna, Austria.

Predictors of neonatal complications

Variable	Odds ratio	p
Twin or multiple gestation	5.4	0.0014
Smoking during pregnancy	1.7	0.0070
Cyanotic heart disease	**2.0**	**0.0003**
Mechanical valve prosthesis	**13.9**	**0.0331**
Other (cardiac) medication before pregnancy	**2.2**	**0.0009**

Drenthen W et al. European Society of Cardiology Congress 2007; September 1-5, 2007; Vienna, Austria.

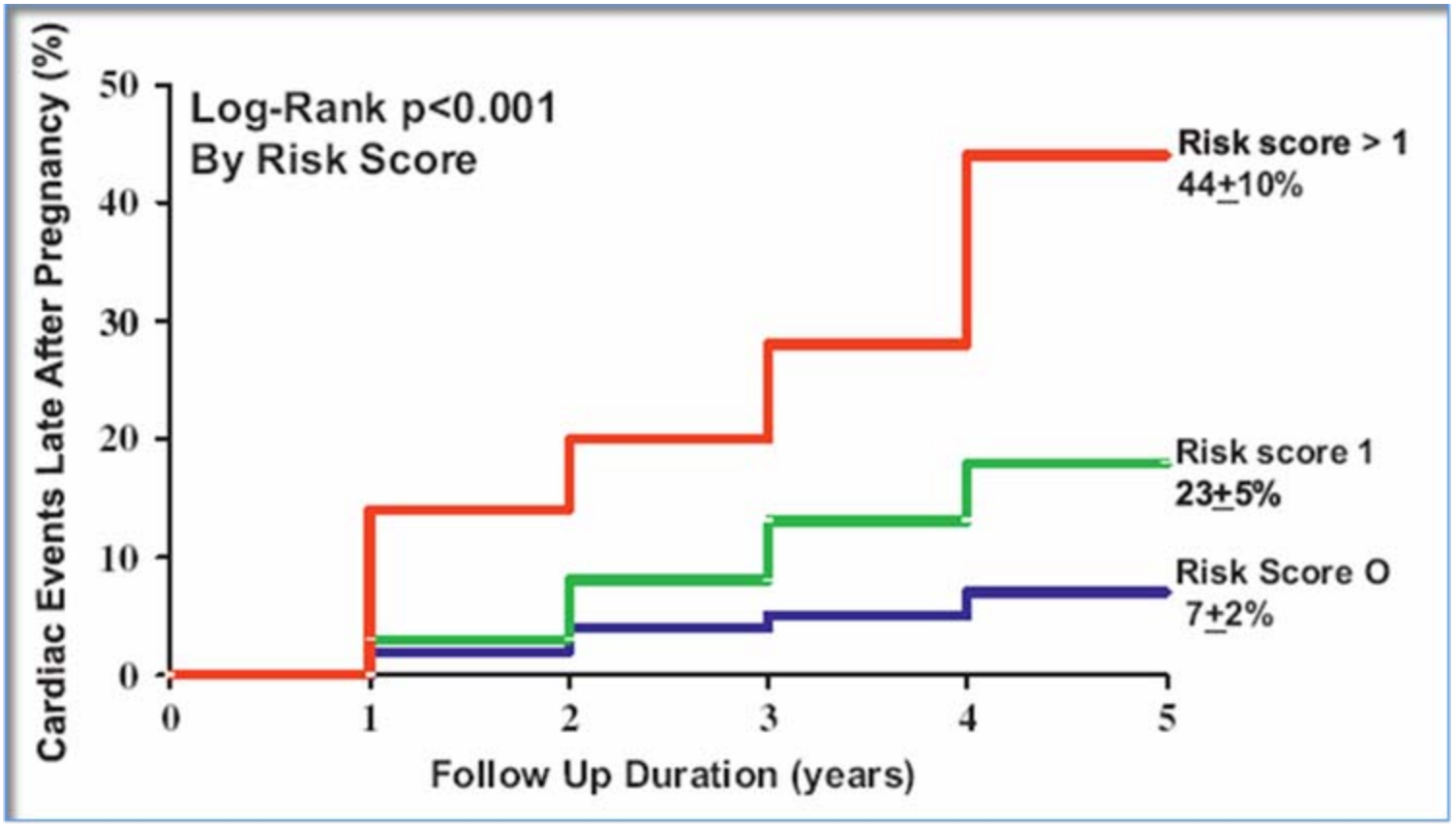
Incidence of adverse cardiac events late after pregnancy according to pregnancy - related adverse cardiac events



Adverse cardiac events: cardiac death, cardiac arrest, pulmonary edema, sustained symptomatic tachyarrhythmia and/or bradyarrhythmia required treatment or stroke/ TIA

Heart, 2010

Incidence of adverse cardiac events late after pregnancy according to maternal risk score



Risk predictors:
NYHA>2/resting cyanosis; subaortic/ subpulmonary ventricular dysfunction and/or severe PR; left heart obstruction; cardiac events during or before pregnancy

Heart, 2010

Absolute contraindications for pregnancy

- Eisenmenger syndrome (30% - 50% maternal mortality)
  Termination of pregnancy is safer, preferably with cardiac anesthesia
- Complex cyanotic CHD
- Marfan syndrome with dilated aortic root
- Severe aortic stenosis
- Untreated/ severe coarctation
- Systemic ventricular dysfunction

Eur Heart J 2003

QUESTION 7

- Combined incidence of congenital heart defects?
- Prevalence of CHD in adults/ kids?
- First time diagnosis of CHD in adults (%) ?
- Survival of pts with CHD ?
- Mortality: overall; surgical; sudden death?
- Recurrence rate of CHD: parents, siblings?
- Sex distribution of CHD: overall; type specific lesions?
- Genetic associations of CHD?
- Most frequent CHD: adults; kids?
- Specific lesions

MEN VS. WOMEN

- Dutch Registry - CONCOR
- 7414 pts
- Average age of pts: 34 y.o men, 36 y.o women

Odds ratios of outcomes in women compared with men

Outcome	Odds ratio (95% CI)
Death	0.79 (0.57–1.09)
Pulmonary hypertension	1.33 (1.07–1.65)
Systemic hypertension	1.08 (0.88–1.33)
Aortic outcomes	0.67 (0.50–0.90)
Cerebrovascular vascular accident/transient ischemic attack	0.88 (0.66–1.18)
Endocarditis	0.53 (0.40–0.70)
Pacemaker	0.91 (0.73–1.14)
Implantable cardioverter defibrillator	0.45 (0.26–0.80)
Arrhythmia	0.88 (0.77–1.02)

Verheugt CL et al. *Circulation* 2008; available at: http://circ.ahajournals.org.

SEX DISTRIBUTION OF CHD

Female		Prevalence of CHD		
57%		Female	Male	P
All CHD	1985	4.83/1000	3.94/1000	
	2000	4.55/1000	3.61/1000	< 0.0001
Severe CHD	1985	0.25/1000	0.16/1000	
	2000	0.41/1000	0.35/ 1000	0.0001

A. Marelli et al., Circulation 2007

Sex distribution of specific lesion

	2000		p	1985		p
Shunt lesions	**Female**	**Male**		Female	Male	
ASD, VSD, PDA, AVSD	**2.13/ 1000**	1.46/ 1000	< 0.0001	1.59	0.93	< 0.0001
Transp. complex	0.03/ 1000	**0.05/ 1000**	0.01	0.11	0.19	< 0.0001
Coarct.	0.05	**0.08**	< 0.001	0.16	0.01	< 0.0001

A. Marelli et al., Circulation 2007

Smoking and CHD

- Largest case control study in the US, tracking 5,000 cases of CHD and the same number of controls in 10 states
- 35,000 – 40,000 infants born every year in the US with CHD
- If all women of reproductive age stop smoking there will be (–) 2,000 kids born with CHD

Smoking and CHD

- Women who are smoking during early pregnancy are 60% more likely to have babies with CHD [(than those who do not smoke (OR 1.6)]
- Smokers 80% more likely to have babies with septal or right sided defects
- Of women who had kids with CHD, 34% reported they smoked some time from the month prior to conception thru the end of the first trimester (comp. to 25% of women whose children did not have heart problems)

Maternal Diabetes Mellitus and CHD

- DM is known to have a teratogenic effect on the cardiovascular system
- Reported risk of malformation in published studies is 1.7% to 4.0%, but a prospective population-based study of live born infants of diabetic mothers has not previously been reported.
- Recently published study, comparing the prevalence of structural cardiovascular malformations in live babies born to mothers with preexisting diabetes with those born to nondiabetic mothers.

Maternal Diabetes Mellitus and CHD

- Information from all live births between 1995 and 2000 in the former Northern Health Region of England
- 192,618 babies were born, of whom 609 had diabetic mothers
- Congenital structural defects of the heart, including transposed arteries, were found in 22 of the babies with diabetic mothers (3.6%) and in 1417 babies with mothers without diabetes (0.74%)
- The odds ratio for a CV malformation with maternal diabetes was 5.0 (95% CI 3.3 to 7.8).

Maternal Diabetes Mellitus and CHD

- More than X3 excess of the following heart malformations in babies of diabetic mothers:

1. Transposition of the great arteries (TGA)
2. Truncus arteriosus (TA)
3. Tricuspid atresia (TrA)

- The X5 excess of cardiovascular malformations overall
- Implies that these specific malformations are perhaps at least 15 times more prevalent [in babies born to diabetic mothers] than in offspring of nondiabetic pregnancies

Question 8

- Combined incidence of congenital heart defects?
- Prevalence of CHD in adults/ kids?
- First time diagnosis of CHD in adults (%) ?
- Survival of pts with CHD ?
- Mortality: overall; surgical; sudden death?
- Recurrence rate of CHD: parents, siblings?
- Sex distribution of CHD: overall; type specific lesions?
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- Most frequent CHD: adults; kids?
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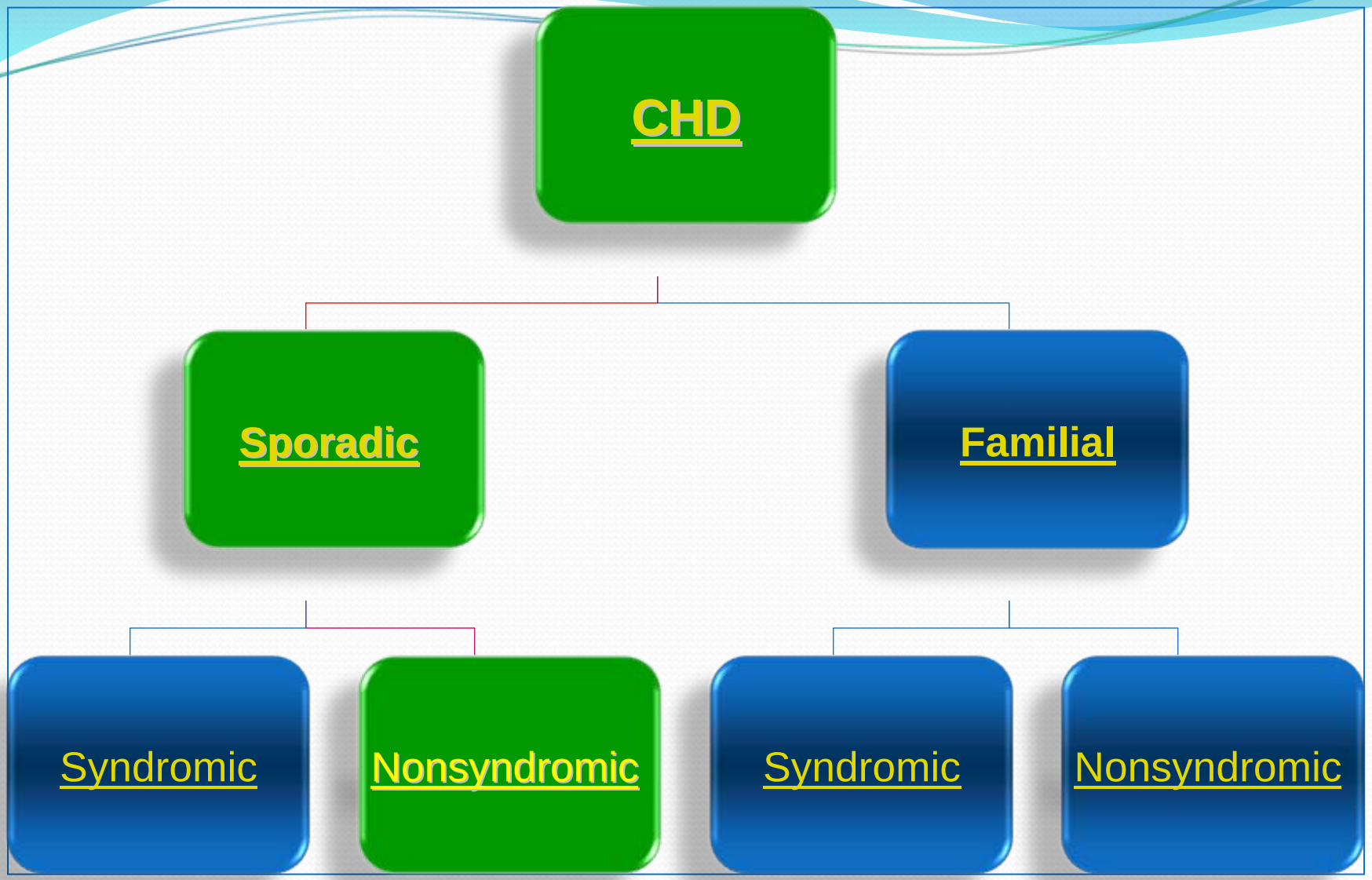
PREVALENCE OF GENETIC PROBLEMS IN CHD

Chromosomal abnormalities	4-8% of CHD
Singe gene syndromes (AD, AR, X-linked; high recurrent rate)	1-3% of CHD
Known teratogens	1-2% of CHD
Multifactorial (probably)	87 – 94%

Deletions, missense mutations, duplications within a gene

Jeffrey A. Towbin, John Belmont, 2000; Wulfsberg EA et al.,1991
Mary S. Minette and David J. Zahn, 2006


CHD
Sporadic
Familial
Syndromic
Nonsyndromic
Syndromic
Nonsyndromic

HEART FAILURE IN ACHD PATIENTS

Typical ACHD substrates for late heart failure in ACHD patients

1. Severe AS/ AR BAV and variants, subvalvular or supravalvular pathology, superimposed coarctation
2. Severe congenital mitral stenosis/ regurgitation
3. Uncorrected ASD/ AVSD
4. cCTGA
5. CTGA (after correction)
6. TOF with early – era surgery, long standing shunt, or severe PR
7. Single- ventricle physiology
8. Fontan

ACC/ AHA ACHD Guidelines, 2008

HEART FAILURE IN ACHD PATIENTS

Other possible pathogenetic factors for heart failure in ACHD patients

1. Prolonged cyanosis
2. Prolonged pressure/ volume overload
3. Poor myocardial intraoperative preservation
4. Large ventricular septal patch or incision/ scar
5. Residual obstruction/ shunts
6. Arrhythmias
7. Obesity

ACC/ AHA ACHD Guidelines, 2008

CONTRIBUTORS TO OR "TIP THE BALANCE" TOWARD DEVELOPMENT OF HEART FAILURE

Other possible factors for heart failure development in ACHD patients

1. Acquired valvular disease
2. CAD
3. Systemic hypertension
4. DM
5. IE
6. Pregnancy
7. Chronic lung disease
8. Chemotherapy/ mediastinal irradiation
9. Illicit drug
10. Acquired renal/ liver disease
11. Sleep apnea
12. Thyroid problems

ACC/ AHA ACHD Guidelines, 2008

NON- CARDIAC SURGERY

1. Thorough evaluation before anticipated surgery
2. Consultation with ACHD expert & cardiac anesthesiologist
3. Moderate & high-risk patients, non-cardiac surgery (even minor) at experienced ACHD center

- Significant residual defects
- Fontan physiology
- Severe pulmonary hypertension, including Eisenmenger
- Cyanotic CHD
- Congestive heart failure
- Valve disease
- Arrhythmias

ACC/ AHA ACHD Guidelines, 2008

Noncardiac Surgery

High risk
Pulmonary hypertension, primary or secondary
Cyanotic congenital heart disease New York Heart Association class III or IV
Severe systemic ventricular dysfunction (ejection fraction less than 35%)
Severe left-sided heart obstructive lesions
Moderate risk
Prosthetic valve or conduit
Intracardiac shunt
Moderate left-sided heart obstruction
Moderate systemic ventricular dysfunction

ACC/ AHA ACHD Guidelines, 2008

Heart/ Lung Transplantation

1. Pts with uncorrectable or previously repaired or palliated CHD associated with significant pulmonary vascular disease (ex. single ventricle physiology)
2. Simple cardiac defect (ASD, VSD, PDA) can often be repaired at lung Tx
3. Combined heart – lung TX is most appropriate in the presence of more complex intracardiac abnormalities
4. Chronic cyanosis – fatal hemorrhagic complications
5. Complex anatomy/ vascular problems/ access
6. Previous thoracotomies (less problematic)

ACC/ AHA ACHD Guidelines, 2008

Heart/ Lung Transplantation

- Survival after heart Tx

1. Predicted post Tx half – life (median survival) for the entire cohort of pediatric and adult heart recipients is 10 yrs with a half- life of 13 yrs for those who survive the first yr
2. Having an ACHD as an indication for Tx increases the risk during the first yr by 2 – fold

- Survival after lung Tx: approx. 75% at 1 yr, 60% at 2 yrs

1. Actuarial survival at 10 yrs after heart/ lung Tx is 20%
2. The outcome for heart/ lung Tx is similar to that for lung Tx

ACC/ AHA ACHD Guidelines, 2008

Eisenmenger physiology. Cyanosis

1. Patients with Eisenmenger physiology/ cyanosis should avoid situations that could predispose them to clinical deterioration
- Pregnancy contraindicated
- Dehydration
- Moderate and severe strenuous exercise (particularly isometric exercise)
- Acute exposure to excessive heat
- Exposure to altitudes greater than 5,000 feet
- Phlebotomy. Iron deficiency
- Prolonged flights - precaution measures

ACC/ AHA ACHD Guidelines, 2008

INFECTIVE ENDOCARDITIS

Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable

Condition	Congenital Specific Condition*
Previous infective endocarditis	Unrepaired cyanotic CHD, including palliative shunts and conduits
Prosthetic cardiac valve or prosthetic material used for cardiac valve repair	Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
	Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibit endothelialization
	Cardiac transplant recipients who develop cardiac valvulopathy

ACC/ AHA ACHD Guidelines, 2008
AHA Guidelines 2007
ACC/AHA Guidelines 2008

QUESTION 9

- Combined incidence of congenital heart defects?
- Prevalence of CHD in adults/ kids?
- First time diagnosis of CHD in adults (%) ?
- Survival of pts with CHD ?
- Mortality: overall; surgical; sudden death?
- Recurrence rate of CHD: parents, siblings?
- Sex distribution of CHD: overall; type specific lesions?
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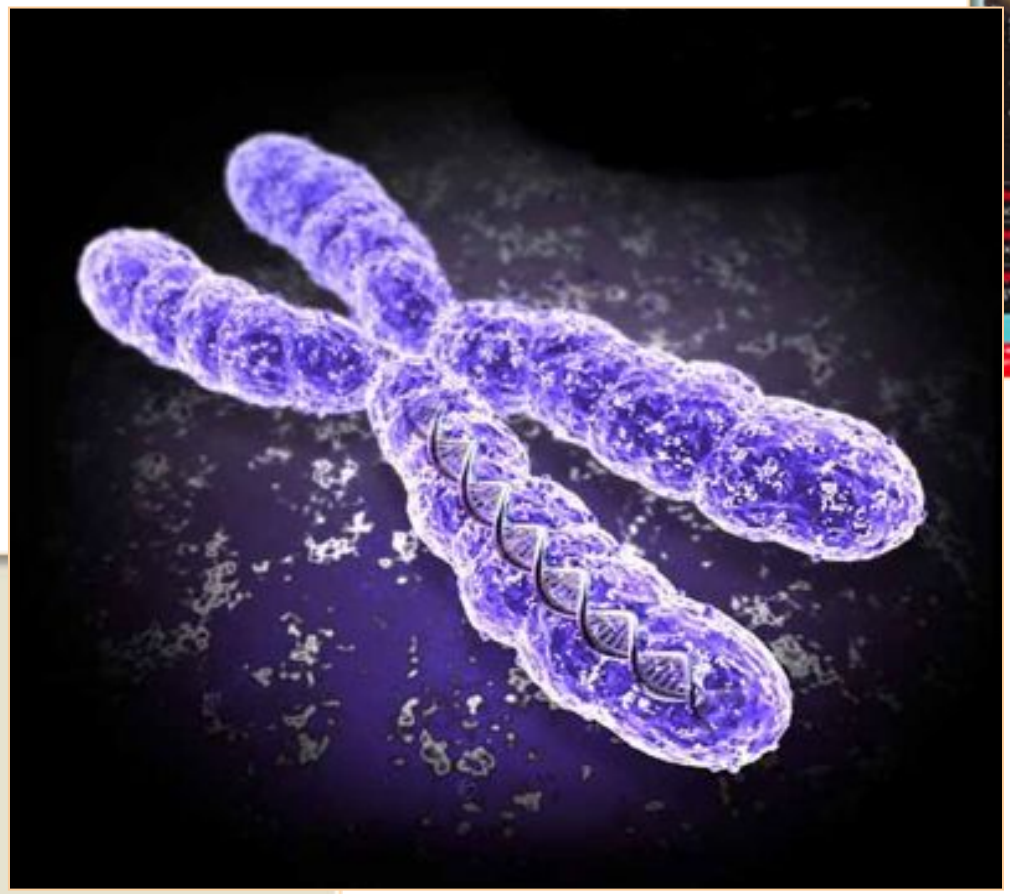
- Most frequent CHD: adults; kids?
- Specific lesions

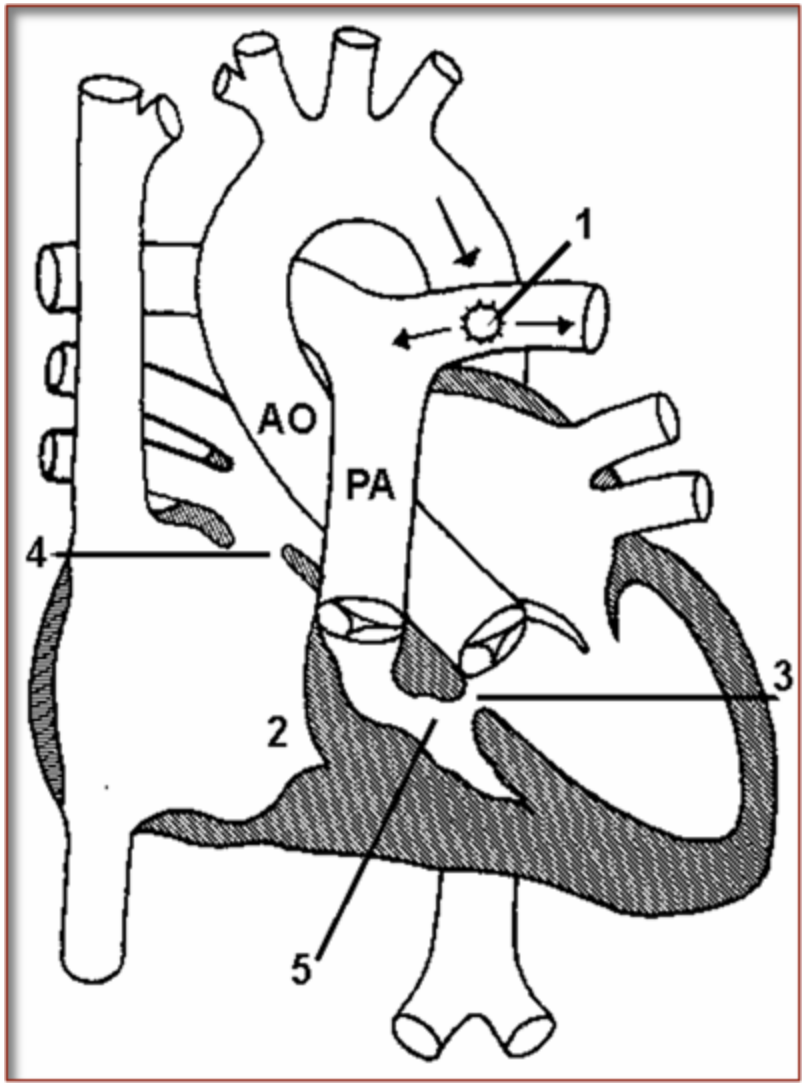
Classification system

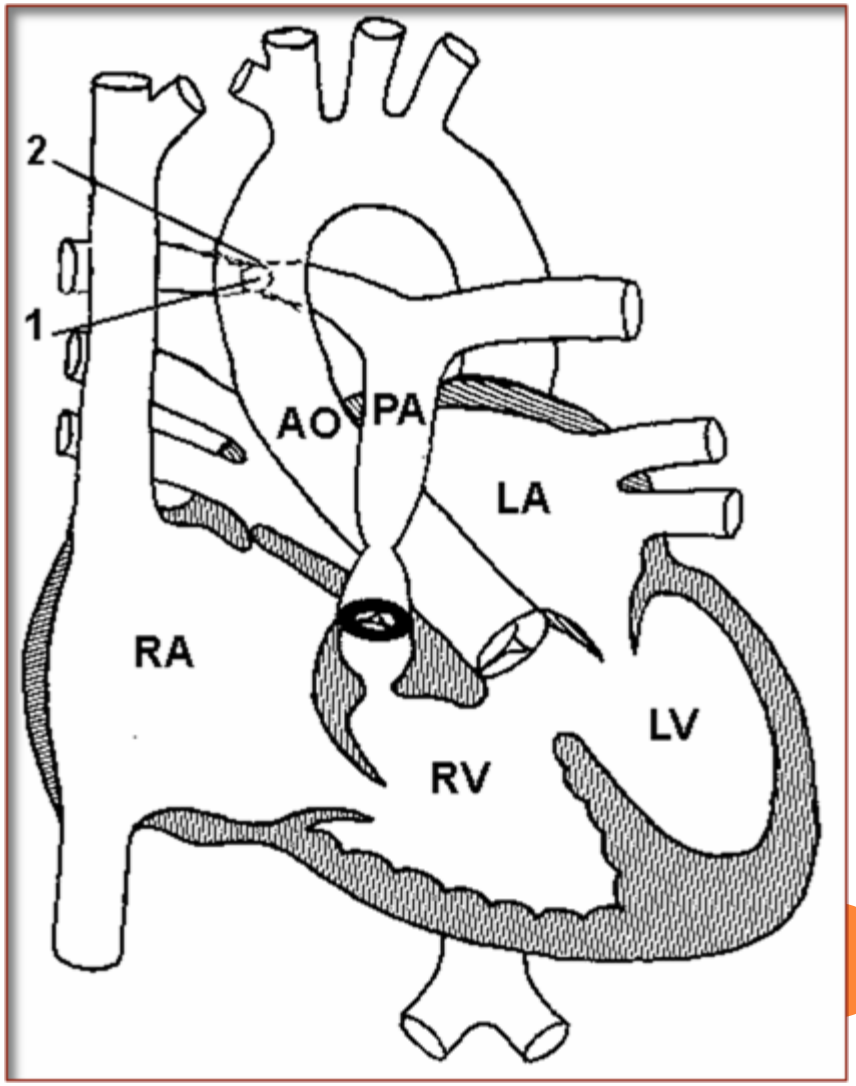
Physiology	Morphology/ ACHD types		Coronary	
Acyanotic	Shunts	ASD, VSD,PDA, AVSD	ALCAPA	
Cyanotic	Left sided	LVOTO	CAFist.	
Eisenmenger	Right sided	RVOTO		
Systemic RV	Conotruncal			
Fontan	Ebstein anomaly			
Single ventricle variants	"Situs anomalies"			
Simple or complex	Vascular			
Repaired/ palliated/unrepaired				


nature
The first human chromosome sequence

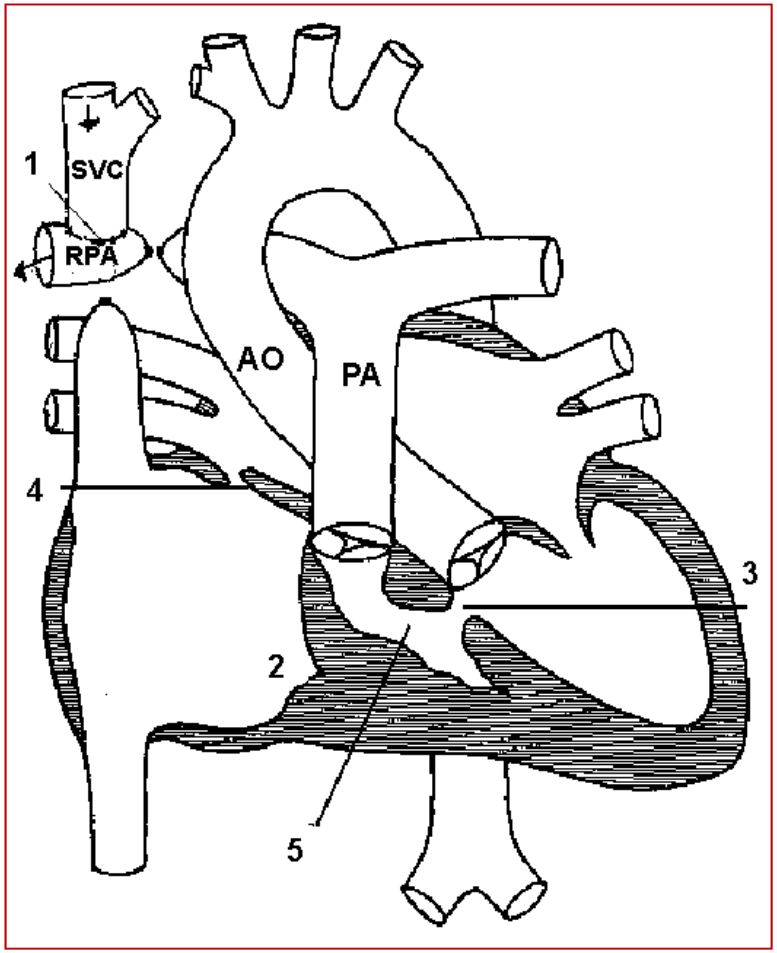


SHUNT? WHAT ELSE?





Shunt? What else?



Cyanosis …

Cyanosis	Upper extremities	Lower extremities	Examples
Differential	Red	Blue	- Coarctation - Interrupted aortic arch
Reversed differential	Blue	Red	-DORV (Taussig - Bing anomaly) - CTGA

Differential cyanosis:

- Lt arm mild cyanosis (unoxygenated blood to LSA)
- Right arm cyanosis (PA to right PDA)

Reversed differential cyanosis:

DORT V (TB):

- LV blood → subpulmonary VSD → PA → PDA → DA

CTGA (PDA, intact IVS):

- Blood from PA → aorta thru PDA (distal to the LSA)

Summary

- *Mortality and morbidity are shifting* away from the young and towards the adult
- *Workload* is increasing

Impact on Health Care System!

Summary

- The *demographics* of CHD population have changed:
  - Increasing number of adults with CHD
- *Distribution* of CHD:
  - Prevalence of pts with *severe CHD* is increasing more rapidly in adults than in children
  - Equalizing numbers of adults and children with severe CHD

Toronto

Congenital Heart Disease

- Heterogeneous population – the patient profile is changing
- Most pts are not ‚fixed‘
  - Life-long risk for complications
- Expert care with knowledge and expertise in:
  - Anatomy and phsyiology
  - Long-term outcome
- Multi-disciplinary team approach in designated centres

CONGENITAL HEART DISEASE (CHD) IT IS A STORY ABOUT:

- Structural heart problems with unique morphology and physiology

1. Shunts
2. Fine balance between pulmonary (& systemic) blood flow
3. Morphological right ventricle (RV) in systemic position
4. Systolic and diastolic RV dysfunction
5. Frequent multiple associated lesions, even relatively simple

- Sometimes (infrequent), associated genetic/ familial syndromes (including non - cardiac problems)
- Continuum of disease, from fetal life into adult age with regular adult problems (cardiac and non-cardiac) on top of baseline CHD
- Significantly modified natural history by multiple surgical/ interventional procedures (with very good results, but nearly never totally repaired/completely healed)

CONGENITAL HEART DISEASE (CHD) IT IS A STORY ABOUT:

- Continuously growing adult population
- Good survival rate but substantial morbidity and mortality, especially in pts with moderate/ high risk and complex lesions (including non-cardiac ones)

1. CHF
2. Cyanosis
3. Pulmonary arterial hypertension
4. Arrhythmias/ EP treatment
5. Infective endocarditis
6. Non - cardiac interventions

- Reasonably good tolerance of pregnancy, in general
- Not negligible recurrence risk

Patients with ***named conditions or operations*** are **complex**

Specialized centre

Toronto

ACHD TSUNAMI:
Catch The WAVE!

- Arrhythmias
- Heart Failure
- Pulmonary Hypertension
- Re-Intervention
- Psychosocial Issues
- Reproduction
- Premature Death


OMIM
Online Mendelian Inheritance in Man
Johns
Hopkins
University

CATCH 22

- **C**ardiac disease
- **A**bnormal facies
- **T**hymic hypoplasia
- **C**left palate
- **H**ypocalcemia
- **22**q11 del. (mid 1990's)

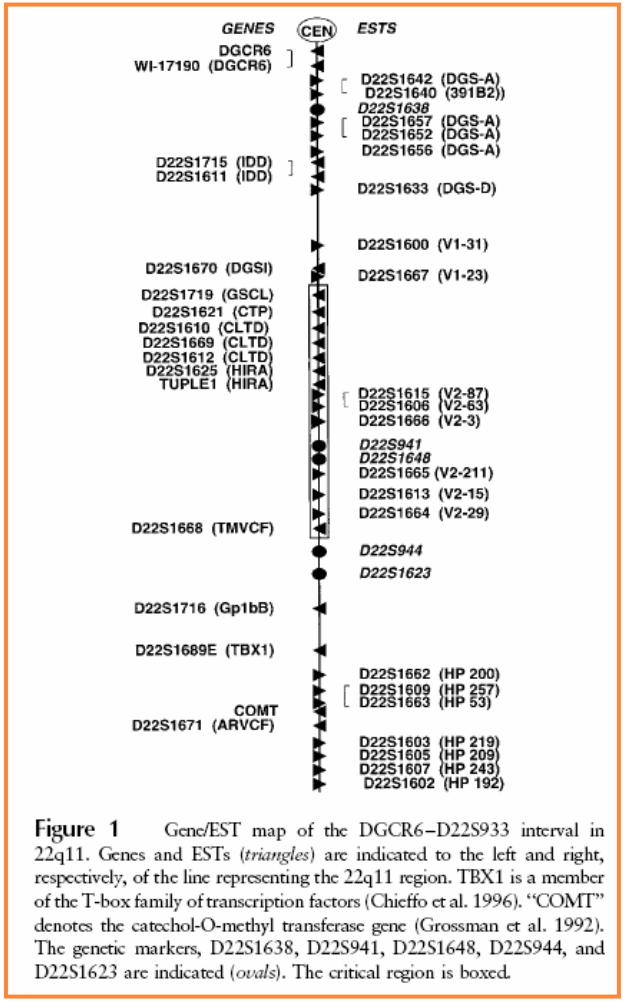


Figure 1 Gene/EST map of the DGCR6–D22S933 interval in 22q11. Genes and ESTs (*triangles*) are indicated to the left and right, respectively, of the line representing the 22q11 region. TBX1 is a member of the T-box family of transcription factors (Chieffo et al. 1996). "COMT" denotes the catechol-O-methyl transferase gene (Grossman et al. 1992). The genetic markers, D22S1638, D22S941, D22S1648, D22S944, and D22S1623 are indicated (*ovals*). The critical region is boxed.

C Carlson 1997

MULTIPLE NAMES - THE SAME SYNDROME

- IAA, TA, TOF & parathyroid and thymic hypoplasia: classic findings of DiGeorge syndrome (DGS)

- Conotruncal defects (esp. with misalignment VSD) & velopharyngeal insufficiency,learning difficulties: more common in velo-cardio-facial syndrome (VCFS) and conotruncal anomaly face syndrome (CAFS)

- Cayler cardiofacial, Opitz G/BBB, Shprintzen, Sedlackova (sydromes) etc.

22Q11.2DEL

- 90% pts with full "DGS phenotype"
- 70% pts with "VCFS"
- 15% pts with isolated conotruncal defect

?

- De novo cases approx. 90%
- Inherited – approx. 10% (parents more mildly affected than kids and CHD are rare)
- Recurrence risk approx. 50% (AD)

DIAGNOSIS

- Microdeletion of 22q 11 (submicroscopic)
  - 1.5 – 3 MB deletion: dozens of genes and multiple repeated sequences

- No single gene mutation as a case of the syndrome

- FISH test highly specific
  - Approx. 90% pts - FISH positive
  - Subgroup (approx. 10%) pts - FISH negative

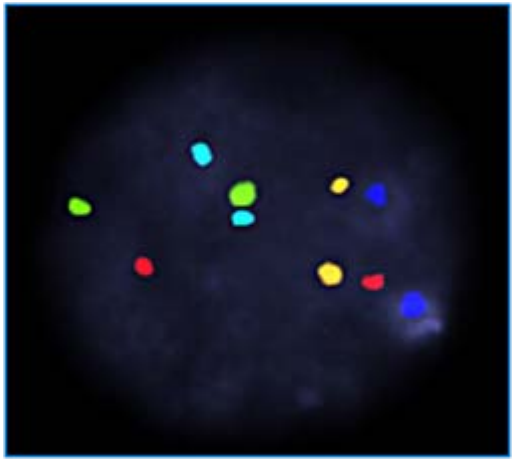
    * small amount of deletion or (an)other syhdrome/s

An example of a normal FISH test for a balanced structural rearrangement

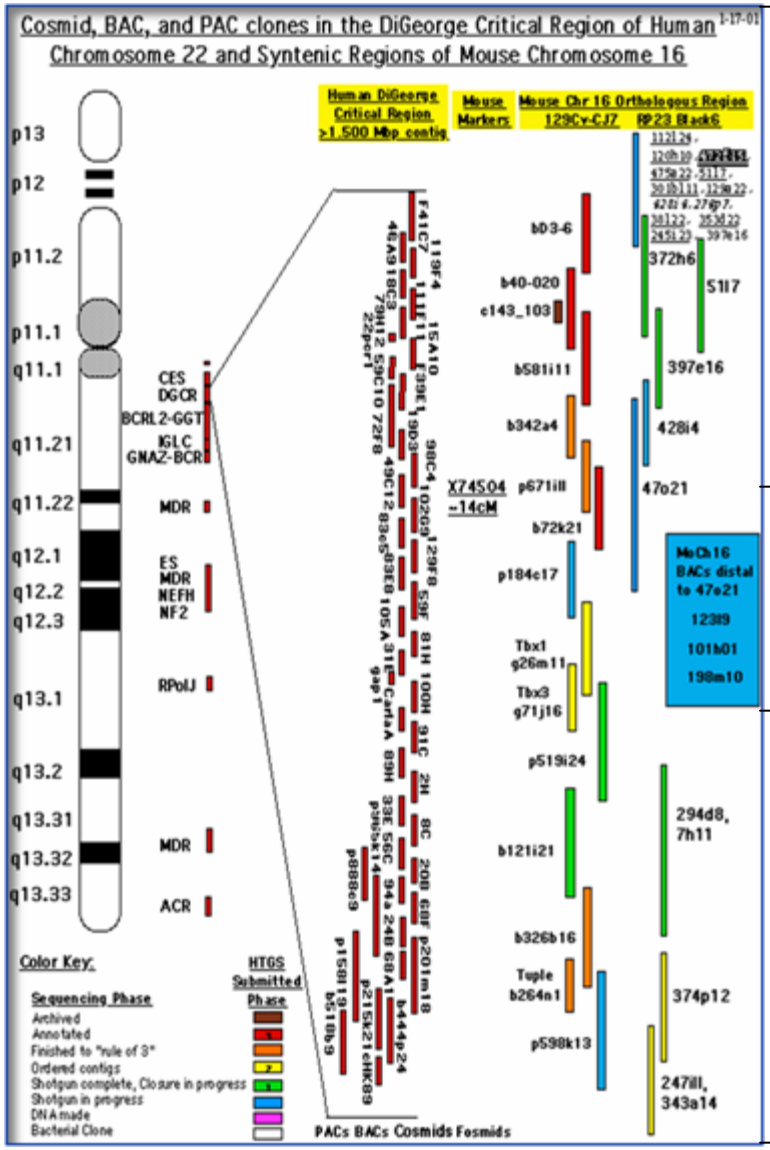
Chromosome 4 telomere - red

Chromosome 22 - yellow

Chromosome 22 telomere - green



www.givf.com



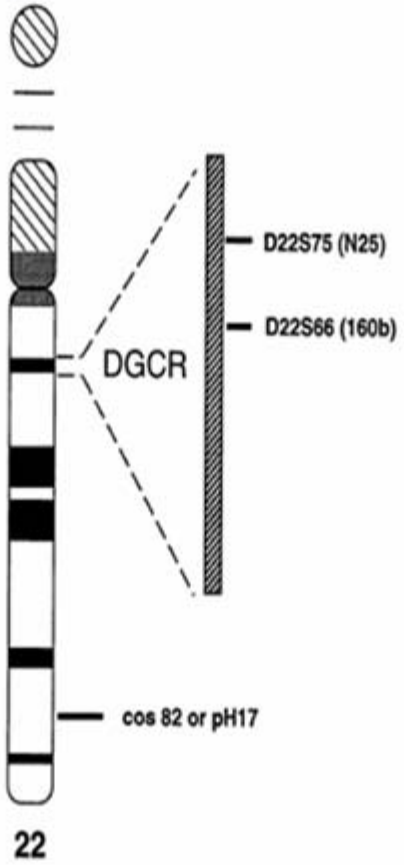


Figure 1. Idiogram of chromosome 22 illustrating the commonly deleted region (DGCR, hatched box) and the approximate location of the probes used for deletion analysis. Probes for loci D22S75 (N25) and D22S66 (160b) lie within the DGCR. Cos 82 and pH17, the control probes, map to the distal long arm of chromosome 22.

Elizabeth Goldmuntz et al., 1998

TESTS FOR DIAGNOSIS OF 22Q11 DEL

Test method	Mutations detected	Mutation detection rate	Test availability
FISH	Deletion 22q11.2 DGCR	> 95%	Clinical testing
Direct DNA	Smaller 22q11 del or point mutation	< 5%	Research only

Mutation analysis, scanning sequence analysis, molecular genetic testing

OMIM. PubMed

SCREENING FOR 22Q11 DEL

- CHD – conotruncal
- Learning difficulties or mental retardation
- Characteristic facies
- Hypernasal speech and/or palatal abnormalities
- History of immune problem (thymic problem)
- History of hypoparathyroidism/ hypocalcemia

A. Bassett, E. Chow, 1999

OTHER CONGENITAL PROBLEMS IN 22Q11 DEL

- Blood disorders: bleeding, coagulopathies
- Immune disorders: infections
- Parathyroid: hypocalcemia
- Renal
- Hernias
- Talipes
- Orthopedic
- ENT
- Ophthalmologic
- Mental retardation/ Learning diffic./ Speech dist./ Developmental…

Modified from A. Bassett, E. Chow, 1999

WHICH ADULT SHOULD BE SCREENED?

Commonly associated cardiovascular lesions	Extracardiac manifestations
TOF	Psychiatry history
PA-VSD	Mental retardation
TA	Nonverbal learning disability
IAA (typeB)	Dysmorphic facial features
Isolated arch anomalies	History of cleft palate
	Hypernasal speech
	Hypocalcemia

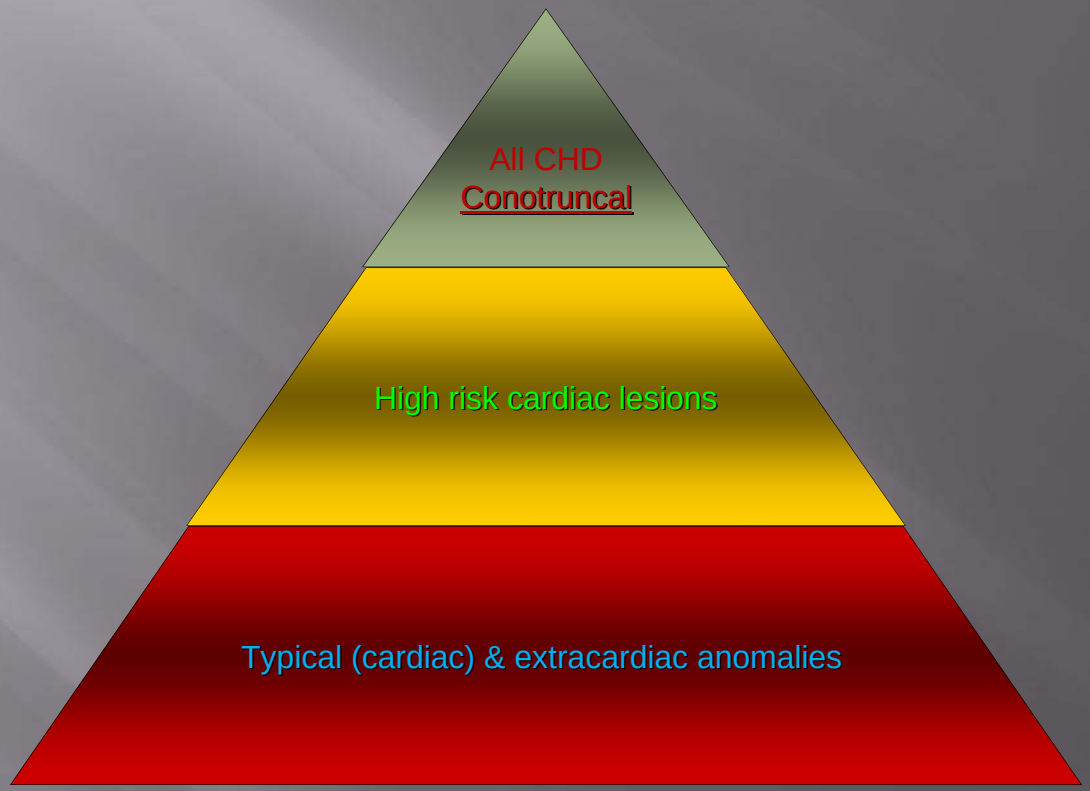
Modified from Luc M Beauchesne et al., 2005

WHICH ADULTS SHOULD BE SCREENED?

- Conotruncal heart defects (TOF & co)
- Global dysmorphic facies
- Voice abnormalities (eg. hypernasality)
- History of learning difficulties
- Young age (esp.< 30 y.o.)

Personal communication. Dr. A. Bassett, 2006

Who should be screened?



Modified from Luc M Beauchesne et al., 2005

CONCLUSIONS

- The incidence and prevalence of 22q 11del syndrome ranging from 1:2000 to 1:6000
- Significant clinical overlap with other genetic syndromes; genetic testing important in some cases (22q11del)
- Multisystemic disease required multidisciplinary team involved in the care of this population
- Important implications for surgical treatment and management
- Awareness required


nature
The first human chromosome sequence

Guidelines

1. ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease (JACC, 2008)

2. Canadian Cardiovascular Society (CCS) 2009 Consensus Conference on the management of adults with congenital heart disease. (Canadian Journal of Cardiology, 2010)

3. Proceedings of the 32-nd Bethesda Conference: Care of the Adult with Congenital Heart Disease (JACC, 2001)

4. ESC Guidelines for the Management of Grown Up Congenital Heart Disease (new version 2010). (EHJ, 2010)

Guidelines

1. Congenital Cardiac Defects Committee of the AHA Section on Cardiovascular Disease in the Young. Collaborative care for adults with congenital heart disease, Circulation, 2002)

2. Report of British Cardiac Society Working Party. GUCH disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK (Heart, 2002)

3. Report of the NHLBI Working Group on Research in Adult Congenital Heart Disease (JACC, 2006)

Guidelines

1. Canadian CCS Consensus on Pediatric and Adult Congenital Heart Transplantation (2004)

2. AHA Scientific Statement … Indications for Heart Transplantation in Pediatric Heart Disease (Circulation, 2007)

3. 2008 Focused Update Incorporated into the ACC/ AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease

Management of Congenital Valvular Heart Disease in Adolescents and oung Adults; Management of Valvular Disease in Pregnancy

Questions? Uncertainties?

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