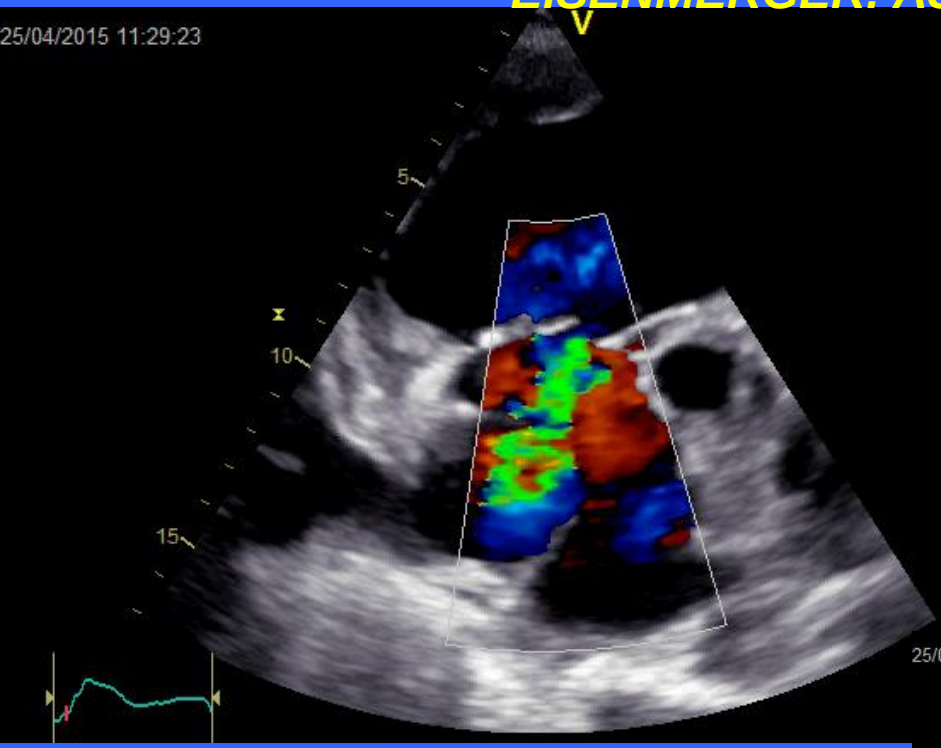
ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΜΕΛΕΤΗΣ ΤΗΣ ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ
1ο ΠΑΝΕΛΛΗΝΙΟ ΣΥΝΕΔΡΙΟ
ΠΝΕΥΜΟΝΙΚΗΣ ΥΠΕΡΤΑΣΗΣ

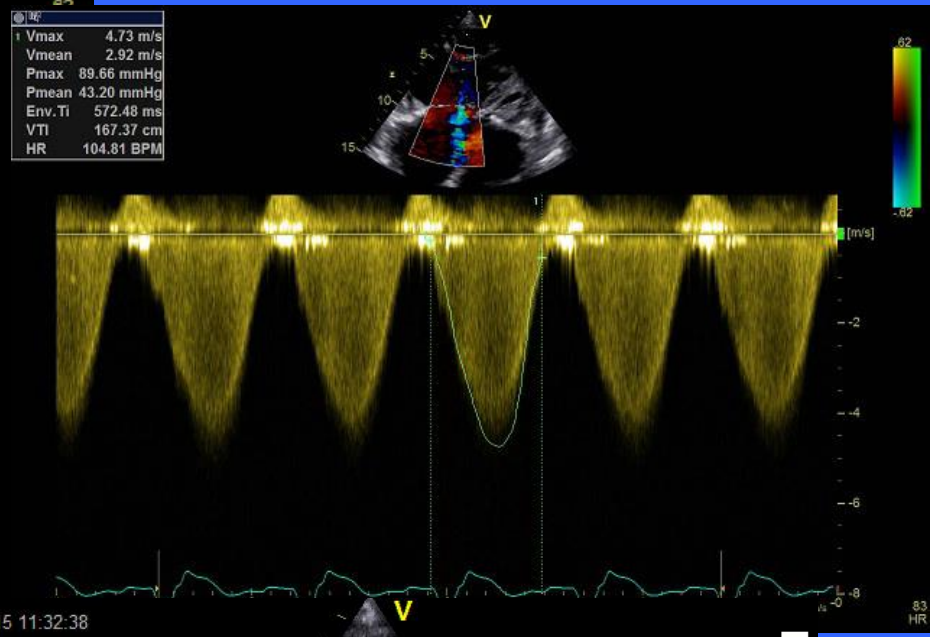
CAUSES OF DEATH IN PAH

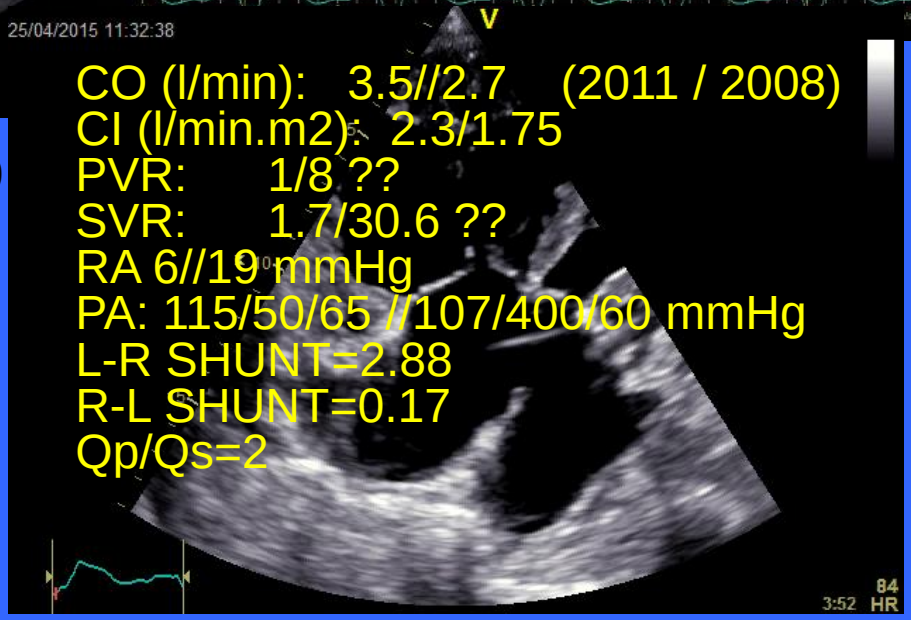
THE 2017 PERSPECTIVE

G. D. ATHANASSOPOULOS

EISENMERGER: ASD PRIMUM, 69 y old







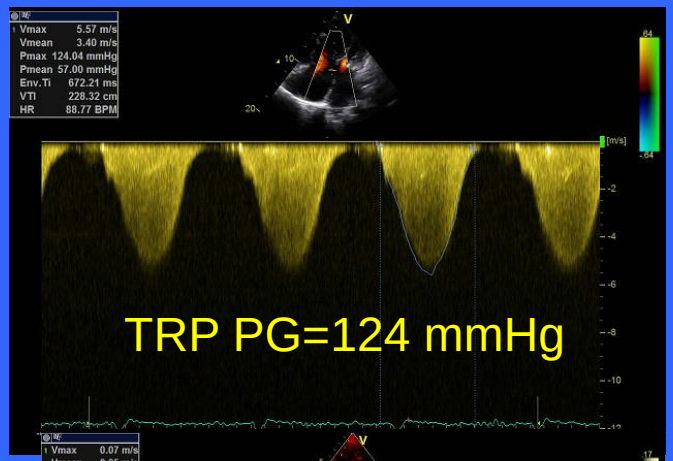
ASD PRIMUM 69 Y/ W, FUP SINCE 2009
AF/PACE 2013,
COUMADIN 2013, INR=2
BOSENTAN 2009,
ILOPROST INHALED 2014
DIURETICS 2009

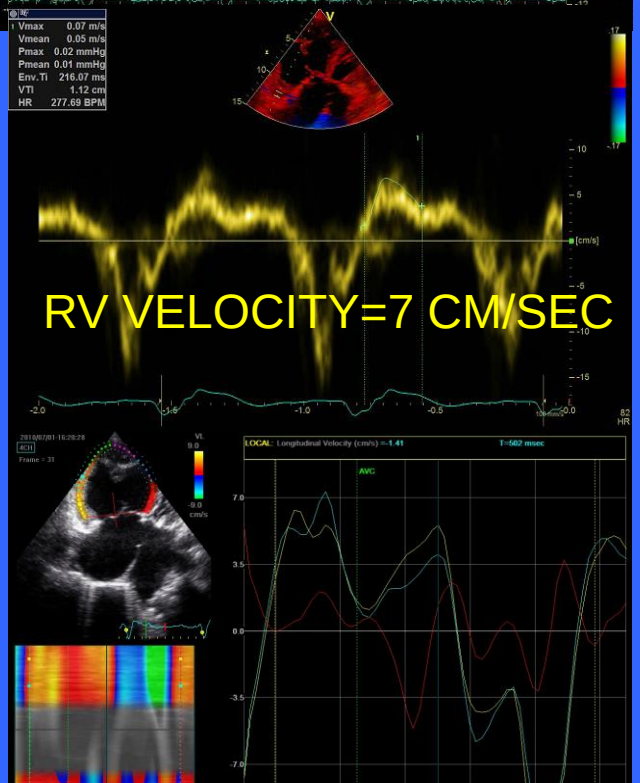
ARTHROPLASTY (GENERAL ANESTHESIA 2013!!!)

CO (l/min): 3.5//2.7 (2011 / 2008)
CI (l/min.m2): 2.3/1.75
PVR: 1/8 ??
SVR: 1.7/30.6 ??
RA 6//19 mmHg
PA: 115/50/65 //107/400/60 mmHg
L-R SHUNT=2.88
R-L SHUNT=0.17
Qp/Qs=2

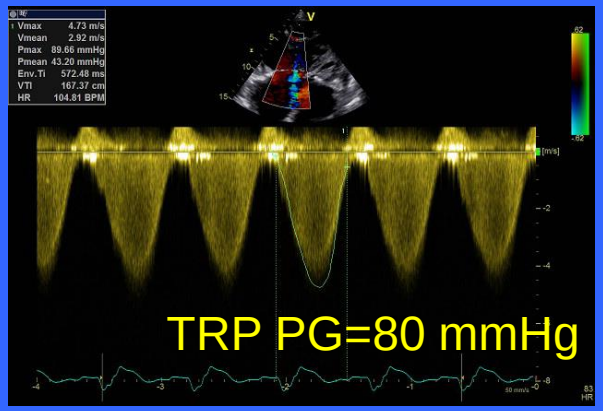
EISENMERGER: ASD PRIMUM, 69 y old

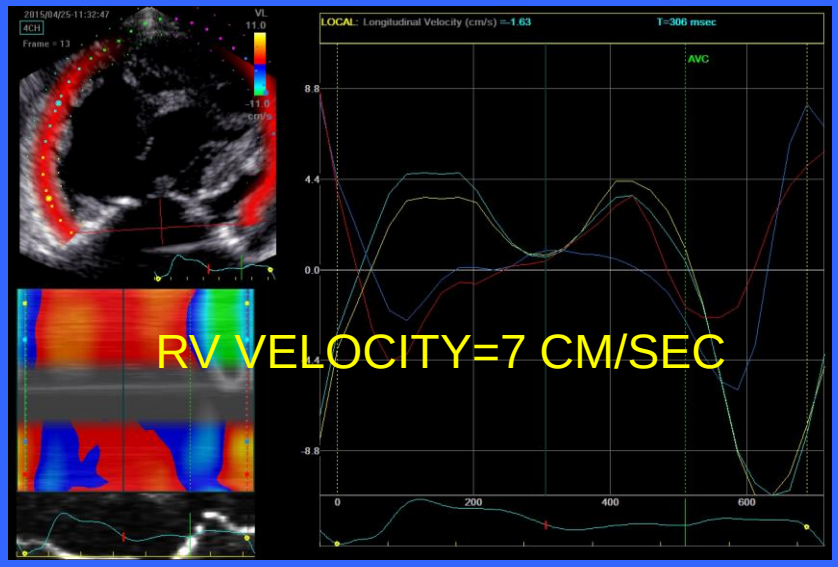
2010: WHO III





2016: WHO III/II

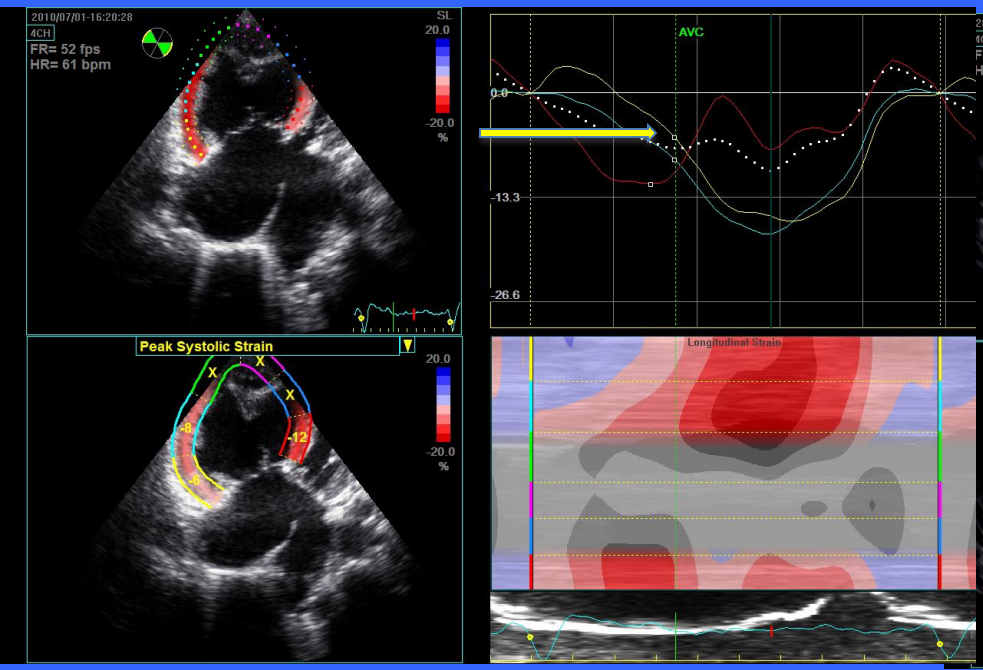


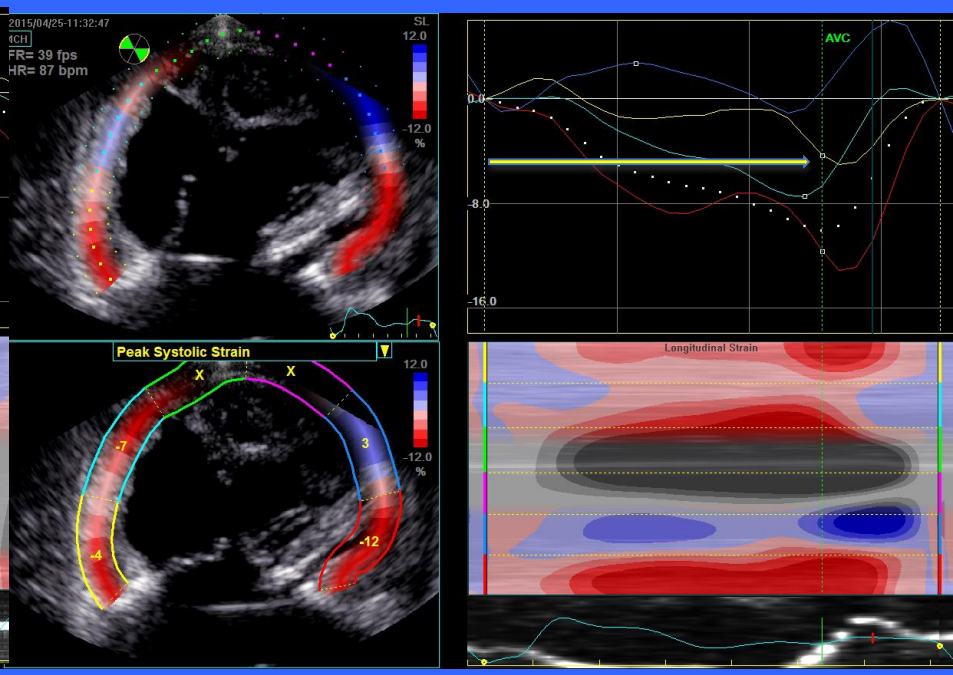


EISENMERGER: ASD PRIMUM, 69 y old

2010: WHO III
RV STRAIN
BASE: -6%

2015: WHO III/II
RV STRAIN
BASE: -4%





EISENMERGER PATIENT 1

- 69 Y F, PRIMUM ASD
- Short stay (2-3 days) in hospital for IV furosemide 03/2015, 04/2016, 11/2016 due to peripheral oedema

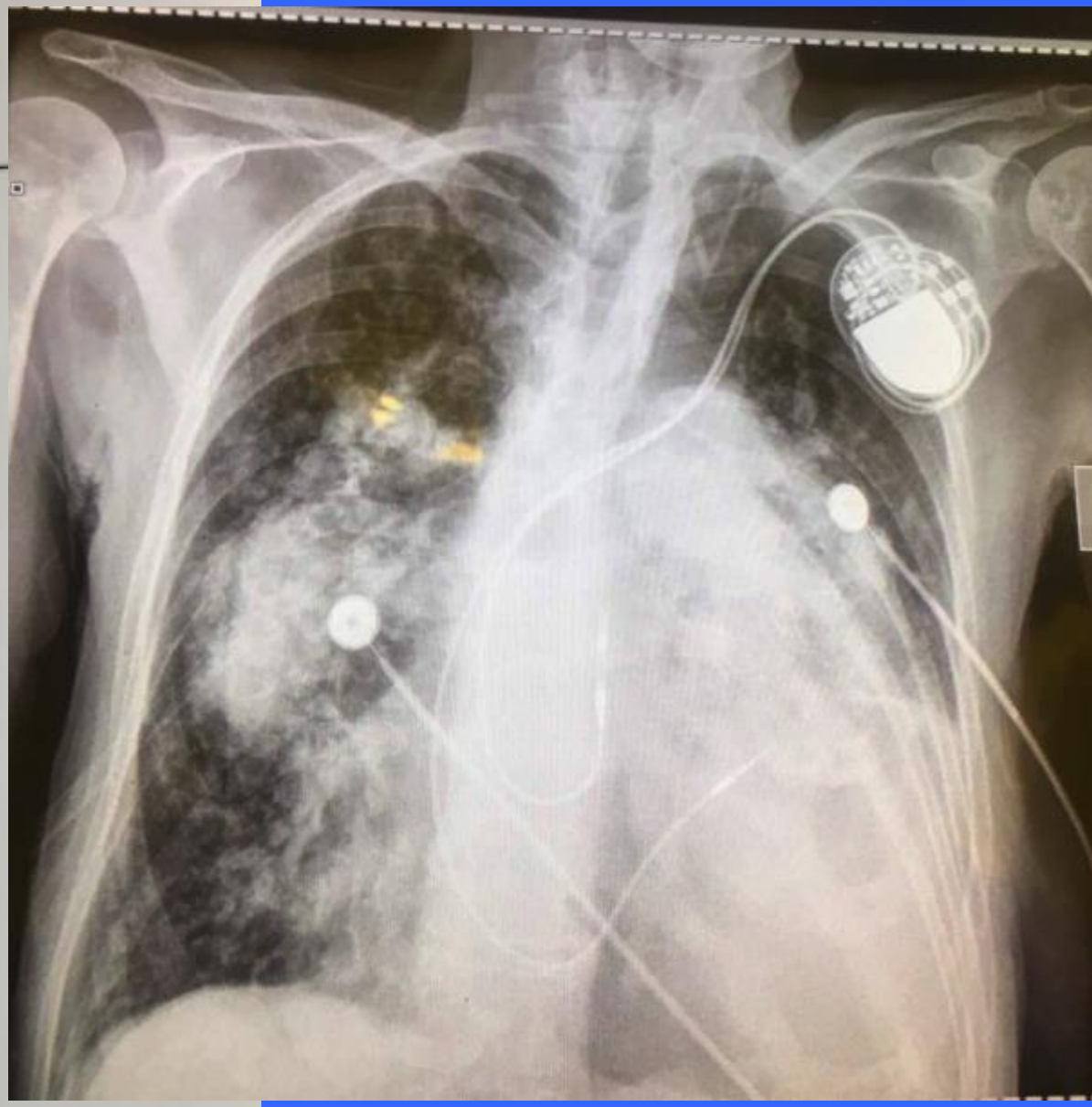
- 02/2017:
- Respiratory infection 3 (?) days before/Empiric antibiosis (GP)
- Due to dizziness, fainting presented to emergency OCSC

- On the way for admission respiratory arrest
  - (purulent material detected in intubation)

ABL835 I902-754R2339N0006 09:43 PM 21-Feb-17
PATIENT REPORT Syringe - S 195uL Sample # 1538

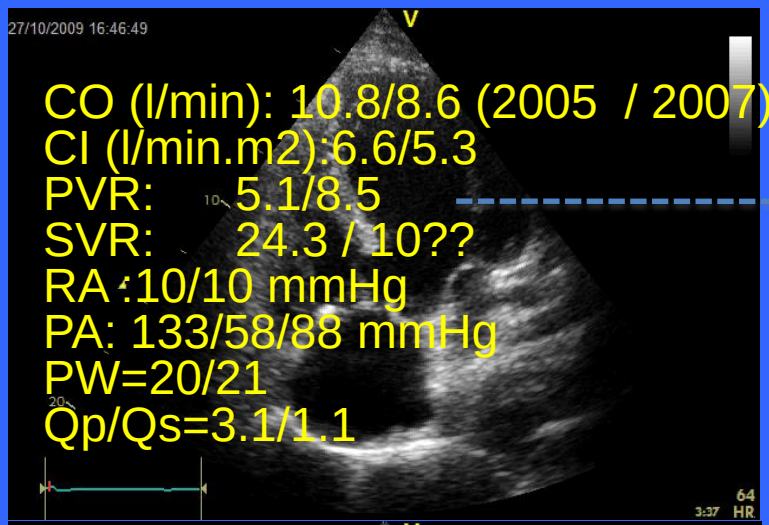
Identifications
Patient ID
Patient Last Name
Patient First Name
Sample type Not specified
T 37.0 °C

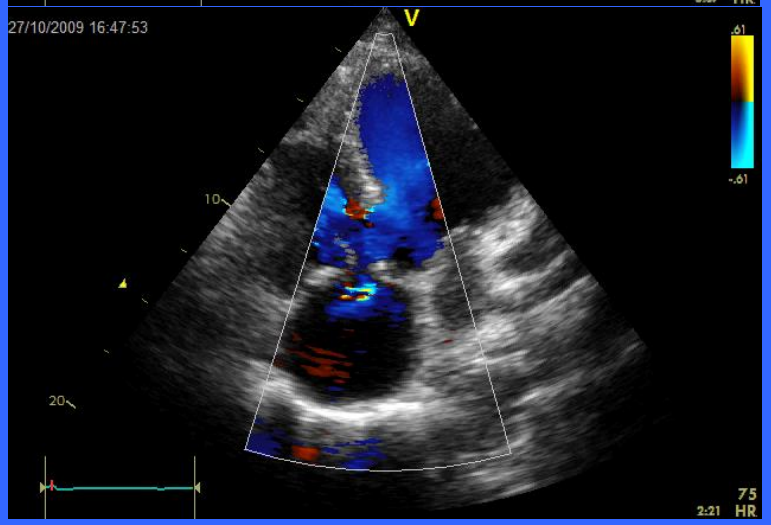
pH	7.216	
pCO_2	89.7	mmHg
pO_2	44.3	mmHg
ctHb	19.5	g/dL
Hct_c	59.5	%
sO_2	63.8	%
FO_2Hb	62.6	%
FCOHb	1.1	%
FHHb	35.5	%
cK^+	4.3	mmol/L
cNa^+	137	mmol/L
cCa^{2+}	1.01	mmol/L
cCl^-	94	mmol/L
cGlu	212	mg/dL
pH(T)	7.216	
$pCO_2(T)$	89.7	mmHg
$pO_2(T)$	44.3	mmHg
ctO_2c	17.1	Vol%
$p50_c$	36.28	mmHg
$cBase(Ecf,ox)_c$	7.1	mmol/L
$cHCO_3^-(P,st)_c$	25.0	mmol/L
$mOsm_c$	286.4	mmol/kg



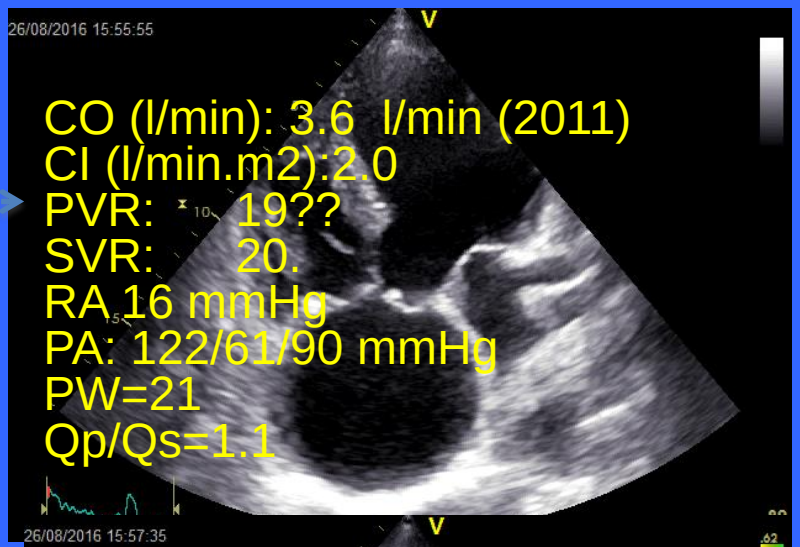
EISENMERGER VSD 45 y old FEMALE

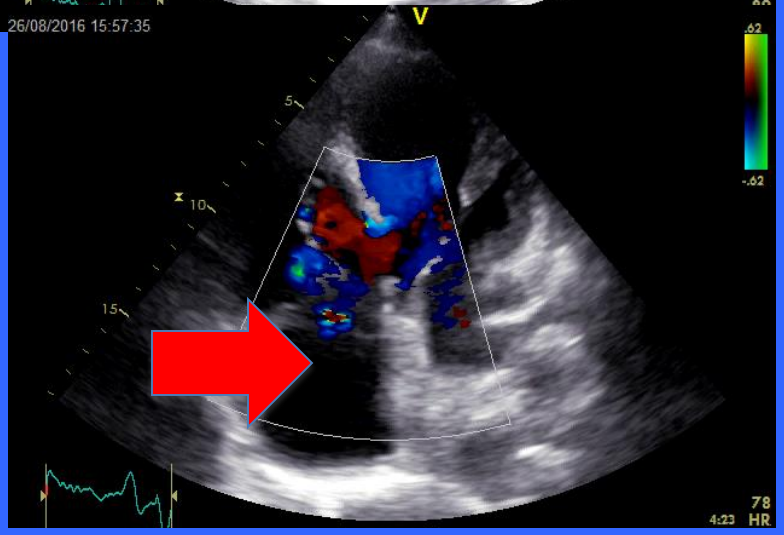
2009: WHO II





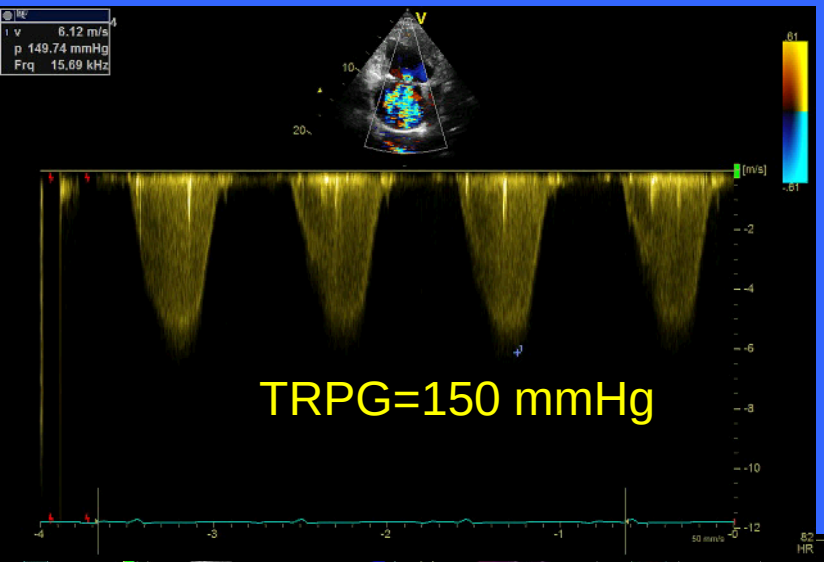
2016: WHO II

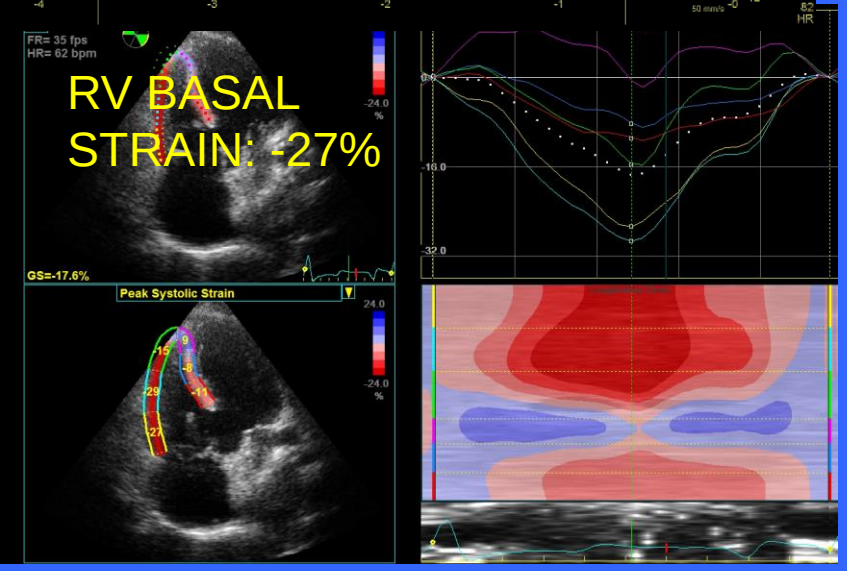




EISENMERGER VSD 45 y old FEMALE

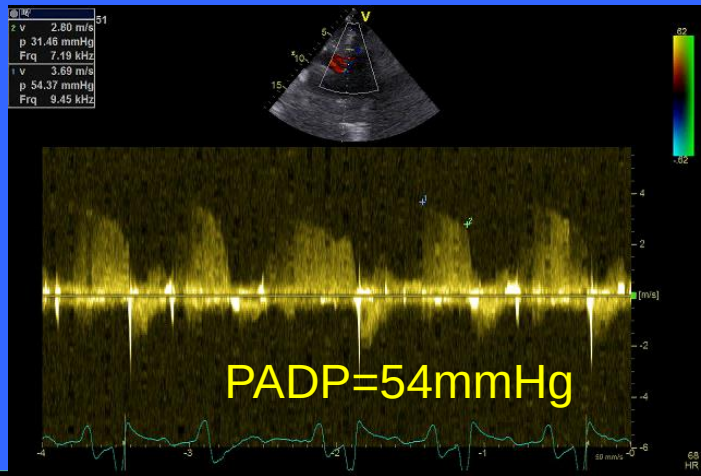
2009: WHO II

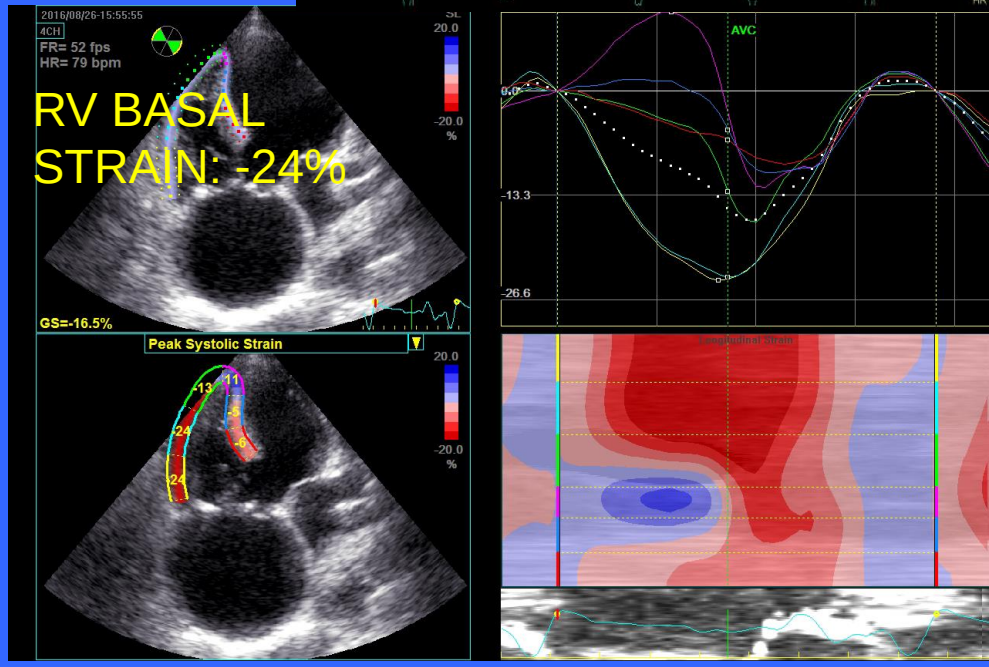




Bosentan 2003
Tadalafil 2015
Coumadin 2014
INR=2
Bisoprolol 2010

2016: WHO II





EISENMERGER PATIENT 2

- 46 Y F, VSD
- WHO II STABLE up to 12/2016 LAST VISIT
- 02/2017:
- RESPIRATORY INFECTION
  - PROLONGED HOSPITALIZATION ABROAD
  - DECOMPENSATED RIGHT HEART FAILURE
- ACUTE RENAL FALURE

European Heart Journal (2017) **0**, 1–8
doi:10.1093/eurheartj/ehx201

CLINICAL RESEARCH
Congenital heart disease

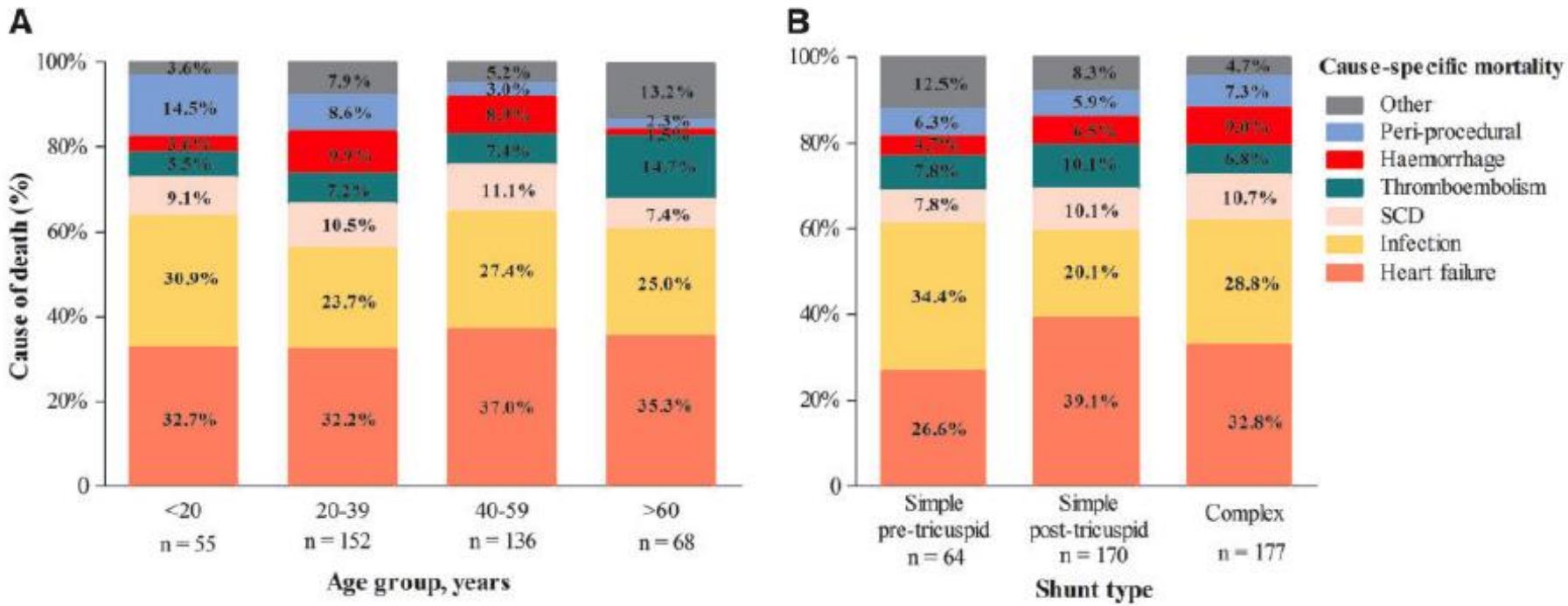
Past and current cause-specific mortality in Eisenmenger syndrome

Cause of death	All deceased[a] *N* (% all causes) (% known causes of death)	'Early' era[b] *N* (% all causes) (% known causes of death)	'Late' era[c] *N* (% all causes) (% known causes of death)	*P*-value 'Early' vs. 'late'
Cause-specific mortality				
Heart failure	141 (25.3) (34.3)	65 (21.9) (29.7)	76 (29.1) (39.6)	0.032[d]
Infection	108 (19.2) (26.3)	54 (18.2) (24.7)	54 (20.7) (28.1)	0.477
Sudden cardiac death/arrhythmia	41 (7.3) (10.0)	21 (7.1) (9.6)	20 (7.7) (10.5)	0.766
Thromboembolism	34 (6.1) (8.3)	25 (8.4) (11.4)	9 (3.4) (4.7)	0.014[d]
Haemorrhage	30 (5.4) (7.3)	19 (6.4) (8.7)	11 (4.2) (5.8)	0.258
Non-cardiac peri-procedural	14 (2.5) (3.4)	12 (4.0) (5.5)	2 (0.8) (1.0)	0.014[d]
Cardiac peri-procedural	13 (2.3) (3.2)	12 (4.0) (5.5)	1 (0.4) (0.5)	0.004[d]
Other	30 (5.4) (7.3)	11 (3.7) (5.0)	19 (7.3) (9.9)	0.056
Unknown	147 (26.5)	78 (26.3)	69 (26.4)	0.882

European Heart Journal (2017) **0**, 1–8
doi:10.1093/eurheartj/ehx201

CLINICAL RESEARCH
Congenital heart disease

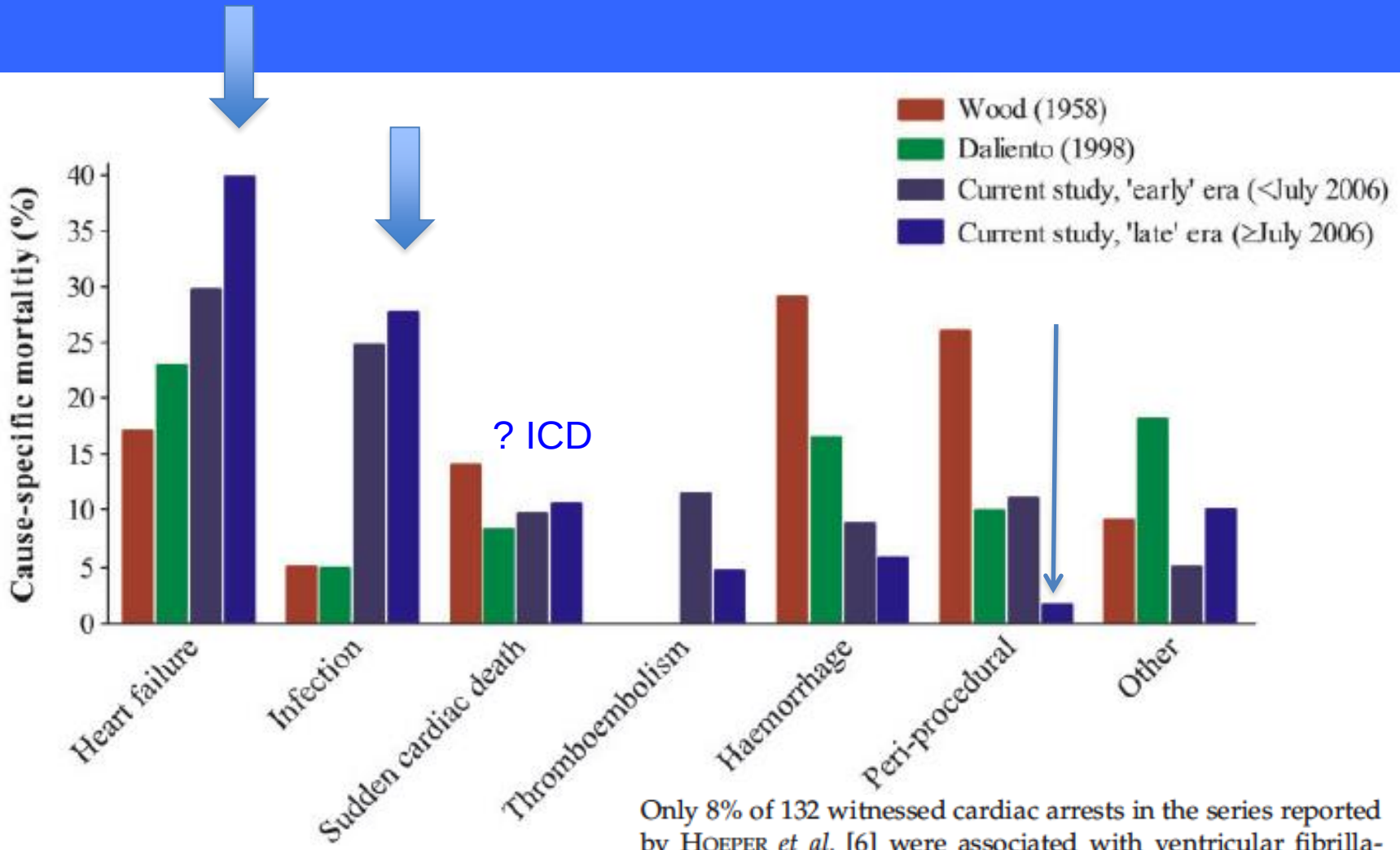
Past and current cause-specific mortality in Eisenmenger syndrome



European Heart Journal (2017) **0**, 1–8
doi:10.1093/eurheartj/ehx201

CLINICAL RESEARCH
Congenital heart disease

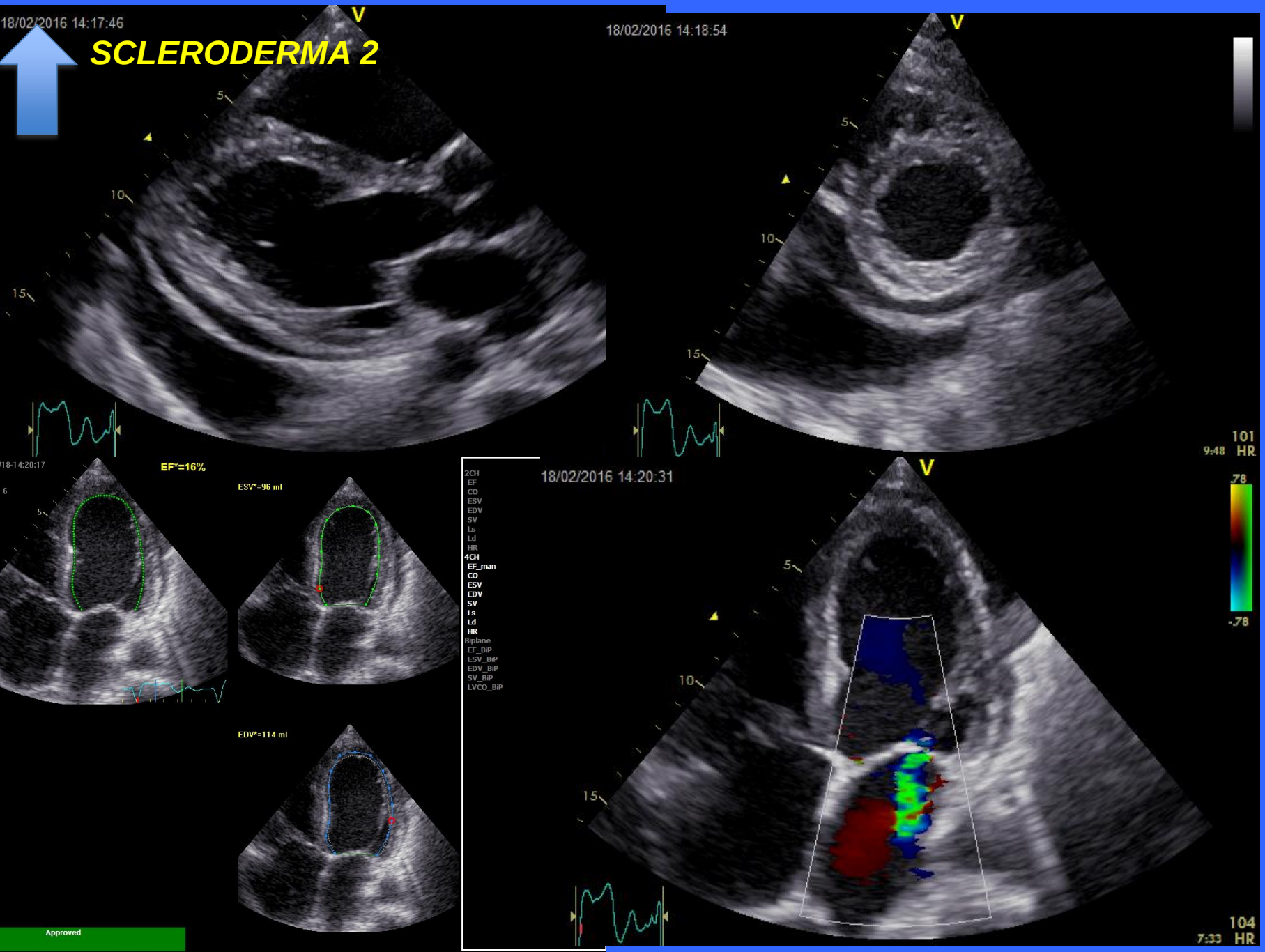
Past and current cause-specific mortality in Eisenmenger syndrome

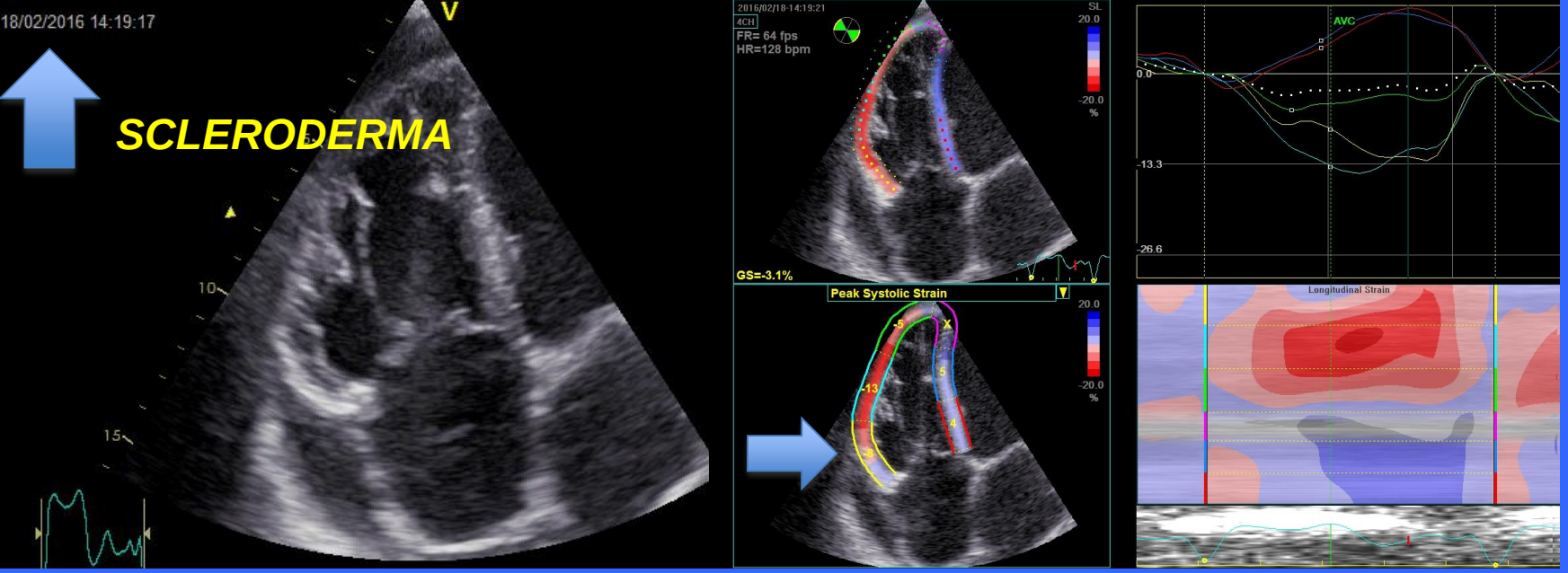


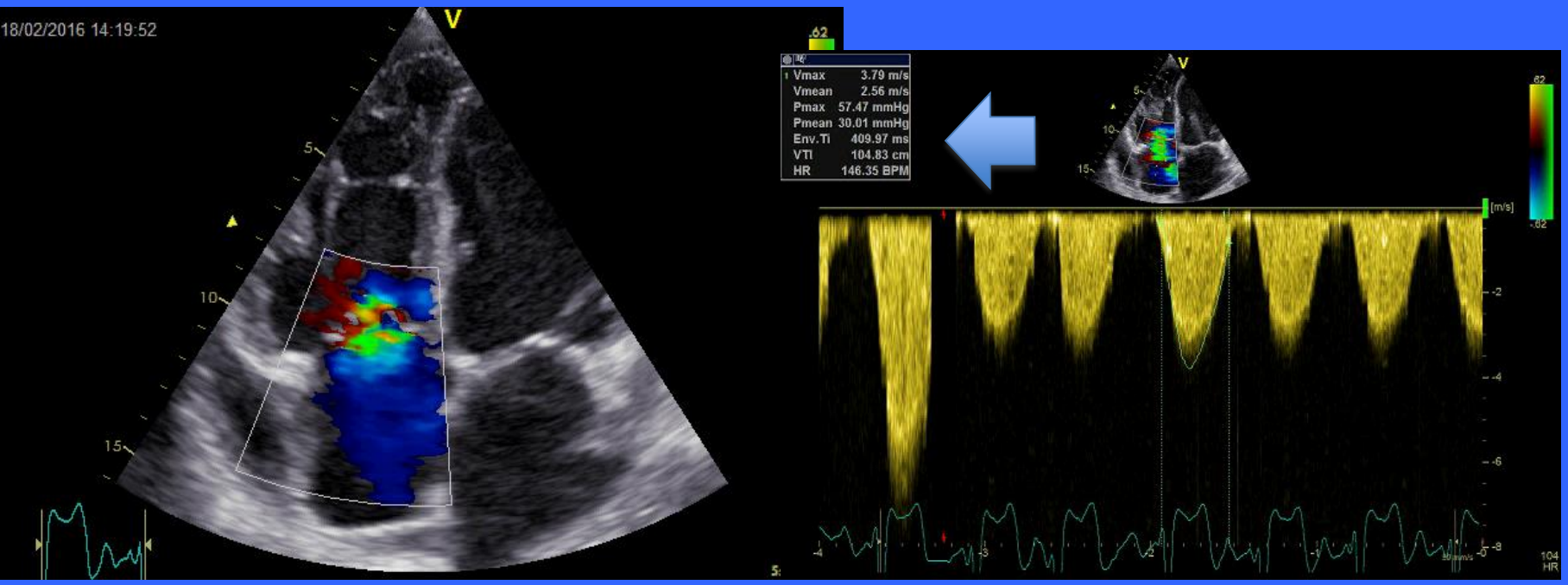
Only 8% of 132 witnessed cardiac arrests in the series reported by HOEPER *et al.* [6] were associated with ventricular fibrilla-

SCLERODERMA PATIENT

- 62 y F, OCSC Fup since 2013
- Initially NYHA III/IV
- LVEF 20%, meanPA 56 mmHg, PVR 8 wood, PW-25 mmHg (2013 cath)
- On Carvedilol 6.25 1x3, furosemide 60 (bosentan disc/hepatic enz), ambrisentan 10, tadalafil 20
- NYHA II/III
- LVEF 20%, mean PA 41 mmHg, PVR 6 Wood, PW 17mmHg (2015 cath)
- Impressive improvement in ulcer/skin plasticity
- LAST VISIT 02/ 2016
- 03/2016: Pneumonia/SEPTIC SHOCK


SCLERODERMA 2
18/02/2016 14:17:46
18/02/2016 14:18:54
EF*=16%
ESV*=96 ml
EDV*=114 ml
18/02/2016 14:20:31
2CH
EF
CO
ESV
EDV
SV
Ls
Ld
HR
4CH
EF_man
CO
ESV
EDV
SV
Ls
Ld
HR
Biplane
EF_BiP
ESV_BiP
EDV_BiP
SV_BiP
LVCO_BiP
101
HR
104
HR
Approved


18/02/2016 14:19:17
SCLERODERMA
2016/02/18-14:19:21
4CH
FR= 64 fps
HR=128 bpm
GS=-3.1%
Peak Systolic Strain
AVC
Longitudinal Strain


18/02/2016 14:19:52
Vmax 3.79 m/s
Vmean 2.56 m/s
Pmax 57.47 mmHg
Pmean 30.01 mmHg
Env.Ti 409.97 ms
VTI 104.83 cm
HR 146.35 BPM
[m/s]

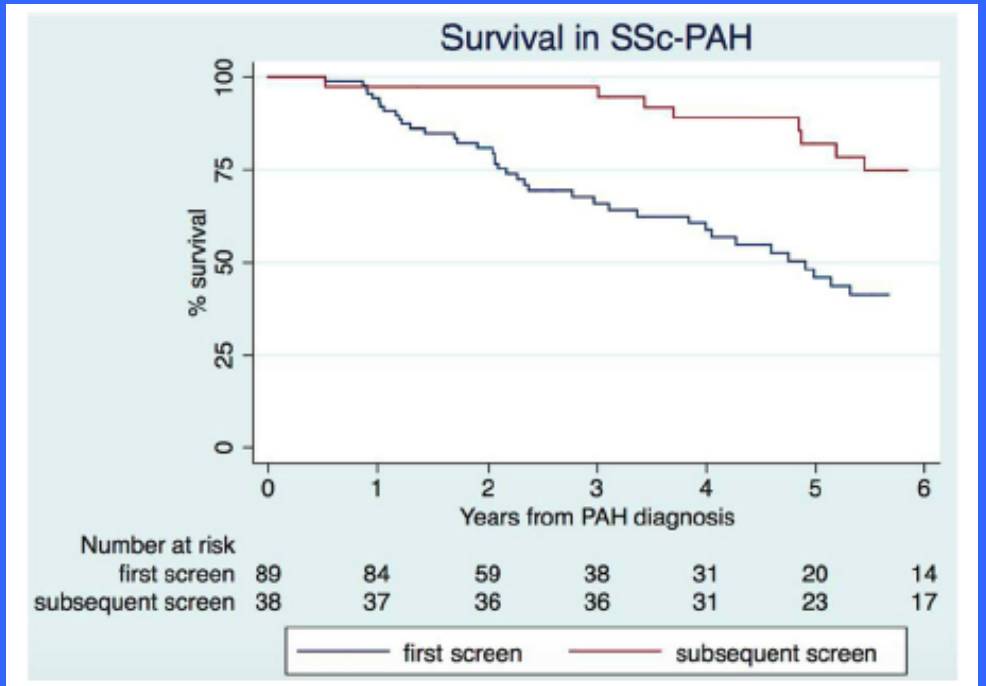
Morrisroe et al. Arthritis Research & Therapy (2017) 19:42
DOI 10.1186/s13075-017-1250-z

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Epidemiology and disease characteristics of systemic sclerosis-related pulmonary arterial hypertension: results from a real-life screening programme

Results: Among 1636 patients with SSc, 194 (11.9%) had PAH proven by right-heart catheter. Of these, 160 were detected by screening. The annual incidence of PAH was 1.4%. Patients with PAH diagnosed on subsequent screens, compared with patients in whom PAH was diagnosed on first screen, were more likely to have diffuse SSc ($p = 0.03$), be in a better World Health Organisation (WHO) Functional Class at PAH diagnosis ($p = 0.01$) and have less advanced PAH evidenced by higher mean six-minute walk distance ($p = 0.03$), lower mean pulmonary arterial pressure ($p = 0.009$), lower mean pulmonary vascular resistance ($p = 0.006$) and fewer non-trivial pericardial effusions ($p = 0.03$). Adherence to annual PAH screening using an ECHO-based algorithm was poor among Australian rheumatologists, with less than half screening their patients with SSc of more than ten years disease duration.



Medicine®
OBSERVATIONAL STUDY
OPEN

Registry of the Spanish Network for Systemic Sclerosis

Survival, Prognostic Factors, and Causes of Death

TABLE 4. Risk Factors for Reduced Survival in Systemic Sclerosis Patients by Cox Univariate Analysis

Risk Factor	HR	HR (95% CI)	*P*
dcSSc	4.046	(2.793–5.862)	<0.0001
Male	1.882	(1.215–2.915)	0.005
Age at disease onset ≥65	11.063	(5.961–20.532)	<0.0001
Digital ulcers	1.518	(1.066–2.160)	0.020
ILD	3.229	(2.190–4.761)	<0.0001
PH	3.211	(2.259–4.566)	<0.0001
Heart involvement	3.421	(2.335–5.012	<0.0001
SRC	5.921	(3.412–10.275)	<0.0001
ATA positive	1.820	(1.180–2.807)	0.007
ACA negative	1.773	(1.189–2.644)	0.005

ACA = anticentromere antibodies, ATA = antitopoisomerase I antibodies, CI = confidence interval, dcSSc = diffuse cutaneous systemic sclerosis, HR = hazard ratio, ILD = interstitial lung disease, PH = pulmonary hypertension, SCR = scleroderma renal crisis.

Medicine
OBSERVATIONAL STUDY
OPEN

Registry of the Spanish Network for Systemic Sclerosis

Survival, Prognostic Factors, and Causes of Death

TABLE 2. Causes of Death in 138 Spanish Systemic Sclerosis Patients

Causes, n (%)	lcSSc 69 (50.0)	dcSSc 63 (45.7)	ssSSc 6 (4.3)	Total SSc 138
SSc-related				76 (55.0)
PH	17 (24.7)	5 (8.0)	1 (16.0)	23 (16.6)
PH + ILD	6 (8.6)	9 (14.3)	2 (33.3)	17 (12.3)
ILD	5 (7.2)	13 (20.0)	0 (0)	18 (13.0)
SRC	3 (4.3)	9 (14.3)	0 (0)	12 (8.7)
Ischemic cardiopathy	0 (0)	1 (1.6)	2 (33.3)	3 (2.1)
PBC	3 (4.3)	0 (0)	0 (0)	3 (2.1)
Non-SSc–related				44 (31.8)
Cancer	8 (11.5)	7 (11.1)	1 (16.0)	16 (11.6)
Heart failure	8 (11.5)	4 (6.3)	0 (0)	12 (8.7)
Septicemia	2 (3.0)	1 (1.6)	0 (0)	3 (2.1)
Other causes	5 (7.5)	8 (12.7)	0 (0)	13 (9.4)
Unknown causes	12 (17.0)	6 (9.5)	0 (0)	18 (13.0)

Clin Exp Rheumatol. 2017 Feb 6. [Epub ahead of print]

ry

Changes in the pattern of death of 987 patients with systemic sclerosis from 1990 to 2009 from the nationwide Spanish Scleroderma Registry (RESCLE).

CONCLUSIONS: SSc-related causes of death were decreasing over time and, among them, pulmonary involvement was the leading cause of death in both decades. The ratio of renal causes decreased since 1990 at the time that the ratio of cardiac causes increased.

CHEST

Pulmonary Hypertension Surveillance

United States, 2001 to 2010

Mary G. George, MD; Linda J. Schieb, MSPH; Carma Ayala, PhD; Anjali Talwalkar, MD; and Shaleah Levant, MPH

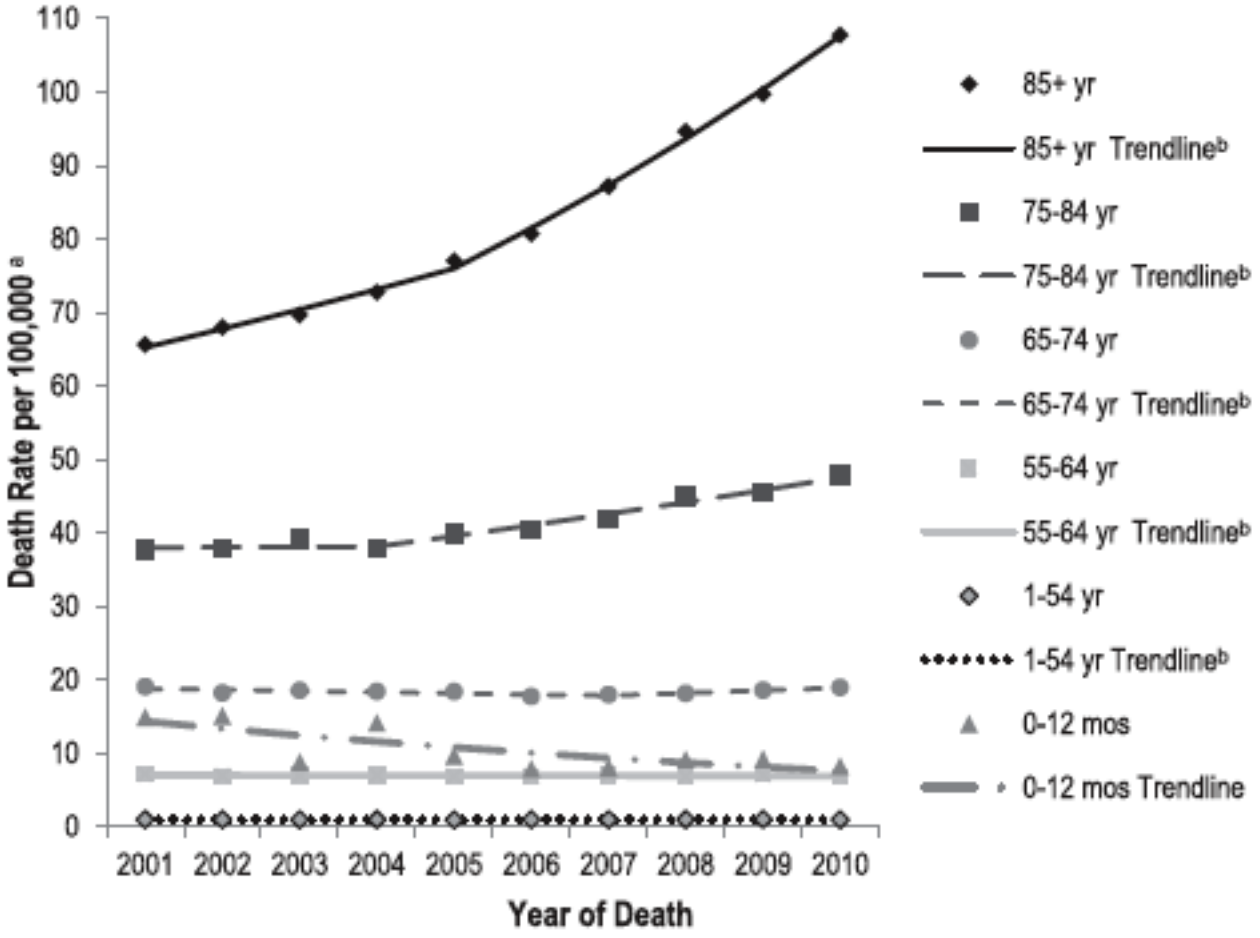


Figure 4 – *Age-specific death rates for pulmonary hypertension as a contributing cause of death and trend lines among individuals of all ages,*

ICD for Mortality	
ICD-10 2001	ICD-10 2003
I27. Other pulmonary heart disease	I27. Other pulmonary heart disease
I27.0. Primary pulmonary hypertension	I27.0. Primary pulmonary hypertension
I27.1. Kyphoscoliotic heart disease	I27.1. Kyphoscoliotic heart disease
	I27.2. Other secondary pulmonary hypertension
I27.8. Other specified pulmonary heart diseases	I27.8. Other specified pulmonary heart diseases
I27.9. Pulmonary heart disease, unspecified	I27.9. Pulmonary heart disease, unspecified

CHEST

Pulmonary Hypertension Surveillance

United States, 2001 to 2010

Mary G. George, MD; Linda J. Schieb, MSPH; Carma Ayala, PhD; Anjali Talwalkar, MD; and Shaleah Levant, MPH

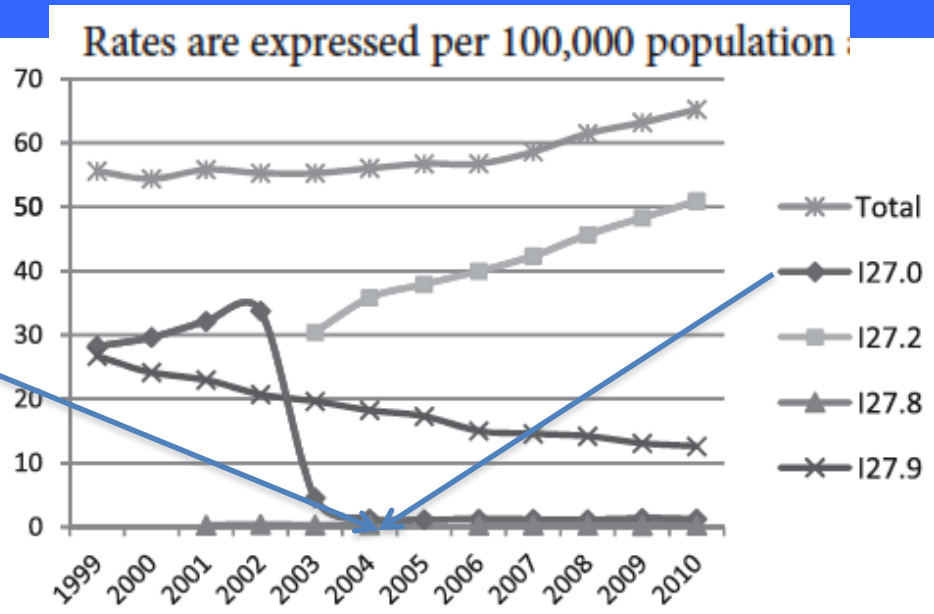


Figure 1 – International Classification of Diseases *coding for pulmonary hypertension mortality: United States, 2001-2010. I27.0 = primary pulmonary hypertension; I27.2 = other secondary pulmonary hypertension; I27.8 = other specified pulmonary heart diseases; and I27.9 = pulmonary heart disease, unspecified. Data are from the Multiple Cause of Death Files, 1999-2010, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. (Reprinted from the Centers for Disease Control and Preven-*

Pulmonary Hypertension Surveillance --- United States, 1980--2002

TABLE 9. Percentage of selected causes of death reported as the underlying cause of death among decedents aged <45 years with pulmonary hypertension reported as any contributing cause of death, by period — United States, 1980–2002

Underlying cause of death reported on death certificate (ICD-9/ICD-10 codes*)	1980–1984 (N = 5,672)	1985–1989 (N = 6,741)	1990–1994 (N = 7,338)	1995–1999 (N = 7,861)	2000–2002 (N = 4,725)
Pulmonary hypertension (416.0, 416.8, 416.9/I27.0, I27.8, I27.9)	29.8%	32.7%	36.4%	39.1%	39.8%
Congenital malformations, deformations, and chromosomal abnormalities (740–759/Q00–Q99)	20.9%	21.4%	23.0%	22.3%	21.7%
Complications of pregnancy, childbirth, and the puerperium (640–676/O10–O99), or conditions originating in the perinatal period (760–771.2, 771.4–779/P00–P96)	17.3%	19.6%	12.8%	10.3%	10.5%
All cardiovascular diseases, excluding pulmonary hypertension (390–415, 416.1, 417–448/I00–I26, I27.1, I28–I78)	5.4%	5.6%	6.3%	6.8%	6.2%
All other respiratory diseases (460–478, 495, 500–519/J00–J06, J20–J22, J60–J99)	4.1%	3.5%	3.4%	3.4%	4.2%
Chronic lower respiratory diseases (490–494, 496/J40–J47)	5.2%	3.2%	2.6%	2.5%	2.7%
Systemic lupus erythematosus (710.0/M32), systemic sclerosis (710.1/M34), dermatomyositis (710.3–710.4/M33), sicca syndrome (710.2/M35), rheumatoid arthritis (714.0–714.2/M05–M06), and juvenile arthritis (714.3/M08–M09)	2.1%	2.7%	3.6%	3.7%	2.4%
Influenza and pneumonia (480–487/J10–J18)	1.1%	1.0%	0.9%	1.0%	0.6%
All other causes	14.1%	10.3%	11.0%	10.9%	11.9%

* *International Classification of Diseases, Ninth Revision* (ICD-9) codes 416.0, 416.8, or 416.9 for deaths during 1980–1998 and *International Classification of Diseases, Tenth Revision* (ICD–10) codes I27.0, I27.8, or I27.9 for deaths during 1999–2002.

Pulmonary Hypertension Surveillance --- United States, 1980--2002

The findings in this report indicate that, during 1980--2002, death rates and hospitalization rates for pulmonary hypertension as either any contributing cause of death or as any-listed hospital diagnosis increased. The number of pulmonary hypertension--related deaths and number of hospitalizations also increased, particularly among women, blacks, and older adults. Nevertheless, death rates were higher for men than women during the 2 decades, and hospitalization rates were higher for men than women until 1995. A geographic clustering of the highest Medicare hospitalization rates and highest death rates for pulmonary hypertension was observed in the western United States (in Colorado, Idaho, Montana, and Wyoming) and a second clustering in the Appalachian region (in DC, Maryland, Pennsylvania, Virginia, and West Virginia). In addition, reporting of pulmonary hypertension as the underlying cause of death increased, and reporting pulmonary hypertension as the principal diagnosis decreased during 1980--2002. Among all decedents and all persons hospitalized with pulmonary hypertension, the reporting of chronic lower respiratory disease (including chronic obstructive pulmonary disease) as the underlying cause of death or principal hospital diagnosis declined, and reporting heart failure as the principal diagnosis on the hospital record increased for all age groups.

Increases in reporting pulmonary hypertension as any-listed diagnosis on hospital records might indicate an actual increase in the number of patients or, more likely, a greater increased awareness among physicians to evaluate and diagnose pulmonary hypertension. In 1996, studies suggested a link between appetite suppressants and increases in primary pulmonary hypertension (*28--30*), which probably created greater public and professional interest in the disease, particularly in terms of cases among women. Hospitalization rates for pulmonary hypertension began increasing among both men and women during the early 1990s at the same time that use of appetite suppressants was prevalent (*31*); however, the major increases in hospitalization rates with pulmonary hypertension as any-listed diagnosis seem to have occurred among older women than among younger and middle-aged women who were more likely to take suppressants (*32*).

As the reporting of chronic lower respiratory disease as the underlying cause of death and principal hospital diagnosis declined, heart failure as the principal diagnosis on hospital records and the reporting of pulmonary hypertension as the underlying cause of death on death certificates increased. Changes in the reporting of pulmonary hypertension as the underlying cause of death might be related to changes in medical opinion and interpretation of certification

CHEST

Pulmonary Hypertension Surveillance

United States, 2001 to 2010

Mary G. George, MD; Linda J. Schieb, MSPH; Carma Ayala, PhD; Anjali Talwalkar, MD; and Shaleah Levant, MPH

Disease Category: ICD-10 Codes	2001		2010		AAPC
	Rate/100,000	% of Total PH Deaths	Rate/100,000	% of Total PH Deaths	
Diseases of the circulatory system					
Pulmonary hypertension: I27.0, I27.2, I27.8, I27.9	1.63	29.3	1.95	30.2	1.5
Coronary heart disease: I20-I25	0.48	8.8	0.66	10.3	3.8[a]
Valvular heart disease, nonrheumatic: I34-I38	0.14	2.6	0.25	4.1	6.7[a]
Aortic stenosis: I06.0, I35.0, I35.2	0.04	0.9	0.10	1.6	10.8[a]
Hypertension: I10-I15	0.04	1.0	0.10	1.6	9.2[a]
Rheumatic heart disease: I00-I09	0.07	1.4	0.10	1.5	3.2[a]
Pulmonary embolism: I26	0.07	1.3	0.04	0.7	−7.2[a]
Heart failure: I50	0.03	0.6	0.02	0.4	−3.6[a]
Other cardiovascular/cerebrovascular disease: I27.1, I28-I33, I40-I49, I51-I78	0.21	3.6	0.23	3.7	2.0
Respiratory disorder or infection					
Chronic lower respiratory disease: J40-J47	1.46	26.2	1.24	19.0	−1.3[a]
Emphysema only: J43	0.24	4.2	0.08	1.4	−8.7[a]
Interstitial lung disease: J84	0.24	4.5	0.31	4.9	4.5[a]
Influenza and pneumonia: J09-J18	0.04	0.9	0.07	1.2	5.5[a]
All other respiratory diseases: J00-06, J20-J39, J60-J70, J85-J98	0.08	1.7	0.12	1.9	3.3[a]
Autoimmune diseases: M5-M6, M8, M30-35	0.07	1.3	0.16	2.4	10.9[a]
Congenital malformations, deformation, and	0.17	3.0	0.11	1.6	−5.2[a]

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.023

Pulmonary Arterial Hypertension

Epidemiology and Registries

Registry (Ref. #)	Study Cohort	Incidence/Prevalence	Predominant Etiologies of PAH
U.S. NIH (17,18)	IPAH	NA	NA
U.S. PHC (19)	Group 1 PH, age >18 yrs	NA	IPAH, 48%; CTD-PAH, 30%; CHD-PAH, 11%
Scottish-SMR (20)	Group 1 PH (IPAH, CHD-PAH, and CTD-PAH), age 16–65 yrs	PAH, 7.6/26 cases/MAI; IPAH, 2.6/9 cases/MAI	IPAH, 47%; CTD-PAH, 30%; CHD-PAH, 23%
French (9,21,22)	Group 1 PH, age >18 yrs	PAH, 2.4/15 cases/MAI; IPAH, 1.0/5.9 cases/MAI	IPAH, 39%; CTD-PAH, 15% (SSc, 76%); CHD-PAH, 11%
Chinese (23)	IPAH and HPAH	NA	NA
U.S. REVEAL (8,24–33)	Group 1 PH	PAH, 2.0/10.6 cases/MAI IPAH, 0.9 cases/MAI	IPAH, 46%; CTD-PAH, 25% (SSc, 62%); CHD-PAH, 10%
Spanish (34)	Group 1 PH and CTEPH, age >14 yrs	PAH, 3.2/16 cases/MAI; IPAH, 1.2/4.6 cases/MAI	IPAH, 30%; CTD-PAH, 15% (SSc 61%); CHD-PAH, 16%
UK (6,35)	IPAH, HPAH, and anorexigen-associated PAH	1.1/6.6 cases/MI	NA
New Chinese Registry (36,37)	Group 1 PH, age >18 yrs	NA	CHD-PAH, 43%; IPAH, 35%; CTD-PAH, 19% (SLE, 51%; SSc, 9%)
Mayo (38)	Group 1 PH	NA	IPAH, HPAH 56%; CTD-PAH, 24%, other, 20%
Compera (39)	IPAH, age >18 yrs	NA	IPAH, 100%

Prognostic Equations for Probability of Survival in PAH

Registry (Ref. #)	Equation	C Index
U.S. NIH* (17)	$P(t) = H(t)A(x,y,z)$	0.588
French† (21)	$P(t;x,y,z) = H(t)A(x,y,z)$	0.57
PHC‡ (19)	$P(t) = e - A(x,y,z)t$	Not calculated
REVEAL§ (27)	$P(\text{1-year}) = S0(1)\exp(Z'\beta^{\gamma})$	0.772

*$H(t) = 0.88 - 0.14t + 0.01t^2$; $A(x,y,z) = e^{(0.007325x + 0.0526y - 0.3275z)}$, where x = mean pulmonary artery pressure; y = mean right-sided atrial pressure; and z = cardiac index. †$H(t)$ = baseline survival = $e(a + b \cdot t)$, where a and b are parameters estimated from the multivariate Cox proportional hazards model, and t is the time from diagnosis measured in years; $A(x,y,z)$ = where x is the distance walked (m) at diagnosis, $y = 1$ if female, $y = 0$ if male, and z is the cardiac output (l/min) at diagnosis; $A(x,y,z) = e^{(-(c \cdot x + d \cdot y + e \cdot z))}$, where c and d were parameters obtained from the Cox proportional hazards model. ‡$P(t)$ is the probability of survival, t is the time interval in years, $A(x,y,z) = e(-1.270 - 0.0148x + 0.0402y - 0.361z)$, x = mean pulmonary artery pressure, y = mean right atrial pressure, z = cardiac index. §$S0(1)$ is the baseline survivor function (0.9698), $Z'\beta$ is the linear component, and γ is the shrinkage coefficient (0.939).

Multivariate Predictors of Survival

Journal of the American College of Cardiology
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Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
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Pulmonary Arterial Hypertension

Epidemiology and Registries

Category	Increase Risk	Decrease Risk
Demographics	Sex (male) and age interaction (>65 yrs) (9,27,33,40) Age (6,19) Male (6,9,27,34) Etiology: CTD, (6,19,27,34,37,40) PoPH, (6,34,40); HPAH, (27,40); PVOD (6,34)	
Functional capacity	Higher NYHA/WHO class (23,40,19,27,34,37) Lower 6MWD (6,9,27,40)	Lower NYHA/WHO class (19,27) Higher 6MWD (6,9,27)
Laboratory and biomarkers	Higher BNP or NT-proBNP (27,40) Higher creatinine (27,40)	Lower BNP or NT-proBNP (27)
Imaging	Echo: pericardial effusion (27,37,40)	
Lung function studies	Lower predicted DLCO (27,37,40)	Higher predicted DLCO (27,40)
Hemodynamics	Higher mRAP (6,19,27,34,40) Lower CO or CI (6,9,34) Higher PVR or PVRI (27,40)	Higher CO or CI (19)

Causes and Circumstances of Death in Pulmonary Arterial Hypertension

Adriano R. Tonelli[1], Vineesha Arelli[1], Omar A. Minai[1], Jennie Newman[1], Nancy Bair[1], Gustavo A. Heresi[1], and Raed A. Dweik[1]

[1]Department of Pulmonary, Allergy and Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio

Am J Respir Crit Care Med Vol 188, Iss. 3, pp 365–369, Aug 1, 2013

TABLE 1. PATIENTS' CHARACTERISTICS

	Mean ± SD or N (%
N	84
Age at the time of death, yr	58 ± 14
Female sex (%)	61 (73)
Race (%)	
White	72 (86)
African American	12 (14)
BMI, kg/m^2	30.3 ± 9
Interval between last clinic visit and death, mo	2.2 (3)
NYHA functional class at last visit	
I	1 (1)
II	6 (7)
III	30 (36)
IV	47 (56)
Right heart failure	78 (93)
Patients on O_2	29 (35)
O_2 flow (L/min)	4.1 (2)
D_{LCO} (% of predicted)*	49 ± 22
Interval between last 6-min walk test and death, mo	7.9 ± 9
Last 6-min walk test	
Distance walked, m	284 ± 116
Distance walked % of predicted†	53.4 ± 19
Interval between last echocardiogram and death, mo	1.5 ± 3
Echocardiogram	
LVEF, %	57.9 ± 9
RVSP, mm Hg	82.4 ± 20
RV function, %	
Normal	9 (11)
Mild	4 (5)
Moderate	16 (19)
Severe	55 (65)
RV dilation, %	
Normal	9 (11)
Mild	5 (6)
Moderate	16 (19)
Severe	54 (64)
Pericardial effusion, %‡	24 (29)
Interval between last RHC and death, yr	2.6 ± 3
RHC	
RA pressure, mm Hg	12.8 ± 7
PA mean pressure, mm Hg	51.7 ± 13
PAOP, mm Hg	12.3 ± 5
CI, L/min/m^2	2.4 ± 1
PVR, Wood units	9.7 ± 5
Sv_{O_2}, %	62.5 ± 8

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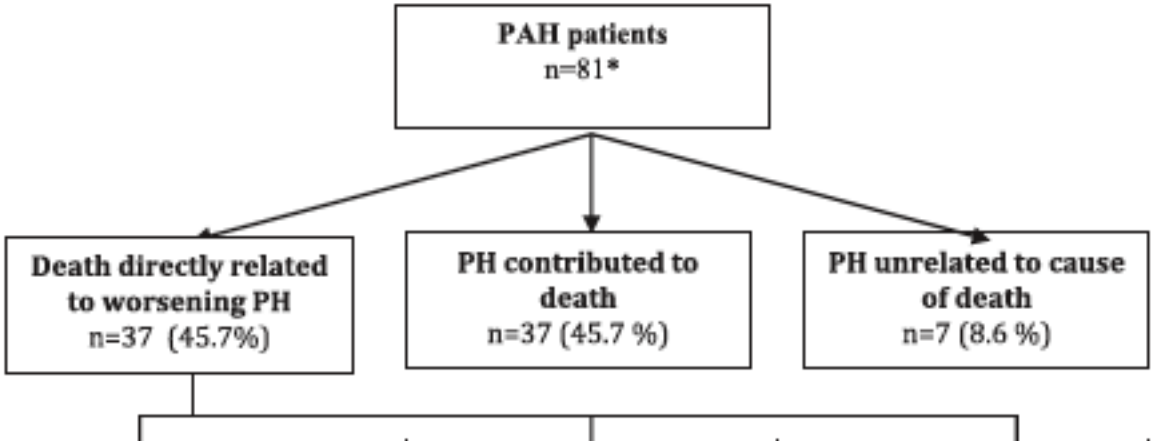
CAUSES OF DEATH	
N	84
PH contribution to death	
Death directly related to PH	37 (44)
PH contributed to death	37 (44)
PH was not related to death	7 (8.3)
Missing	3 (3.6)
Specific causes of death	
Right heart failure/sudden death	37 (44)
Respiratory (non-PH)	14 (16.7)
Pulmonary embolism	0 (0)
Severe sepsis/septic shock	6 (7.1)
Acute renal failure	5 (6.0)
Cardiovascular	7 (8.3)
Neoplasia	8 (9.5)
Miscellaneous	3 (3.6)
Missing	4 (4.8)



	NYHA I/II n=1 (2.7 %)	NYHA III n=13 (35.1 %)	NYHA IV n=23 (62.2 %)
More than 1 PH-specific therapy		9 (69 %)	15 (65 %)
IV/SQ prostacyclin analogs		9 (69 %)	18 (78 %)
IV/SQ prostacyclin analogs or combination Tx		13 (100 %)	21 (91 %)
Reasons for not receiving IV/SQ prostacyclin analogs		- Concomitant ILD (2 p) - Dementia (1 p) - Frequent catheter related infections (1 p)	- Commorbidities with poor prognosis (1 p) - Development of pulmonary edema (1 p) - Psychiatric disease (1 p) - Advanced age without family support (1p) - Refusal (1p)
Listed for Lung Transplant		1 (8 %)	3 (13 %)

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Place of Death	N (%)
N	81*
Out of the hospital	16 (19.8)
RNF, SNF, ER, OR	16 (19.8)
ICU	42 (51.9)
Palliative care	7 (8.6)
Place of inpatient deaths†	
Cleveland Clinic	45 (78)
Outside hospital	13 (22)

Causes and Circumstances of Death in Pulmonary Arterial Hypertension

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Limited data exist concerning the causes of death in patients with PAH in the literature in part because of the difficulties in accurately identifying the specific reason for the patient's demise. This complexity is reflected in our study by need of a third reviewer to achieve consensus in approximately a quarter of our patients with PAH. Even though PH contributed to death in most of our patients we found that progressive right ventricular failure or sudden death was the sole cause of death in a smaller group of patients (44%). The Patient Registry for the Characterization of Primary Pulmonary Hypertension by the NHLBI reported in 1991 the cause of death in 106 patients with idiopathic PAH, before the availability of PH-specific therapies (7). In this multicenter registry, causes of death were right ventricular failure or sudden death in 73% and others in 27% (medications adverse effects, surgery, pneumonia, and cerebrovascular accidents) (7). Similarly, a retrospective nationwide survey in Japan between the years 1980 and 1990 (139 deaths) revealed that in 84.2% of the patients death was considered to be related to PH. In a recent study, focused on the emergency treatments for PAH, the reported causes of death were right ventricular failure or sudden death in 50%, and a variety of other causes in the other half of the patients (8).

Eur Respir Rev 2010; 19: 117, 204–211
DOI: 10.1183/09059180.00004910

REVIEW

Optimising the management of pulmonary arterial hypertension patients: emergency treatments

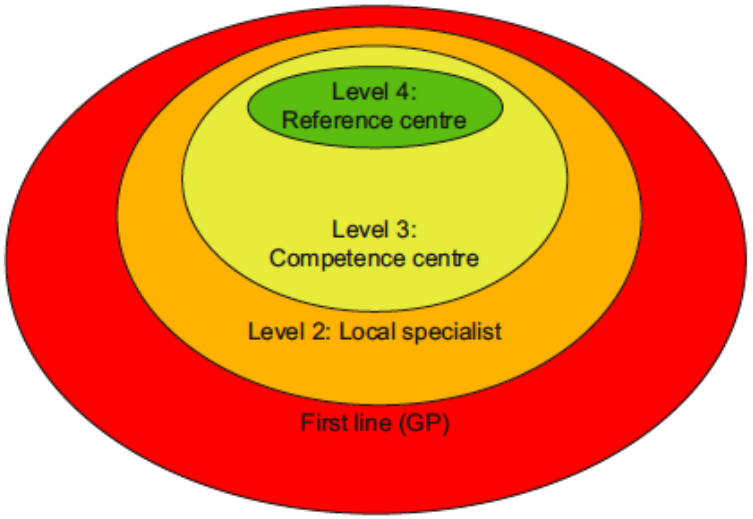

TABLE 1 Causes of death in 99 patients with pulmonary arterial hypertension in UZ Leuven, Belgium

Sudden death	18
Pulmonary hypertension crisis	1
Respiratory failure	2
Pneumonia	3
Massive haemoptysis	1
Liver failure	3
Atrial septostomy	1
Acute pulmonary embolism	1
Ischaemic colitis	1
Medication withdrawal	1
Right ventricular failure	32
Hyperthyroidism	1
Sepsis	8
Bleeding (other)	2
Intracranial bleeding	2
Liver transplantation	1
Anaesthesia	2
Cancer	3
Myocardial infarction	1
Unknown	15

ACUTE RIGHT HEART FAILURE IN PAH

Acute episodes of heart failure, sometimes called "PAH exacerbations", have been recently described by SZTRYMF spectively studied 46 consecutive patients with acute right ventricular failure requiring intensive care unit (ICU) hospitalisation and catecholamine therapy. 52% had idiopathic PAH, 33% associated PAH, 15% distal chronic thromboembolic pulmonary hypertension (CTEPH), and 50% were treated with intravenous epoprostenol. Mortality reached 41%. Predictors

Sztrymf B, Souza R, Bertoletti L, *et al*. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 35: 1286–1293.

Pulmonary hypertension in the ICU

WHO group 1

Known unstable or newly diagnosed PAH

New diagnosis

Initiate PAH-specific treatment

PAH crisis

Stabilisation: dobutamine or milrinone, iNO, aggressive diuresis

Additional therapy: prostanoids, sildenafil, bosentan

Failure of therapy: consider urgent atrial septostomy and/or transplantation

Triggering factors for right heart failure

- PAH-specific therapy withdrawal
- Diuretics withdrawal
- Infection (septicaemia, pneumonia, *etc.*)
- Cardiac arrhythmia
- Acute pulmonary embolism
- Hyperthyroidism
- Pregnancy

Causes and Circumstances of Death in Pulmonary Arterial Hypertension

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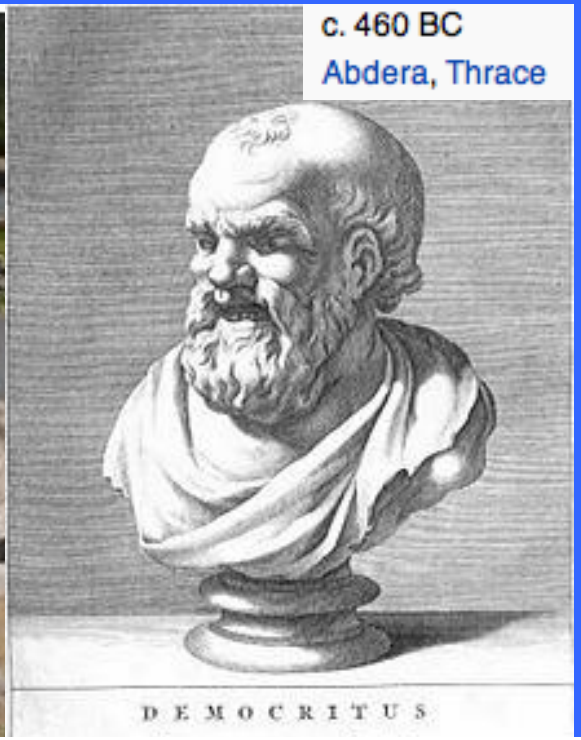
An important aspect of our study is that less than half of patients with PAH (45%) had advanced healthcare directives, a lower than ideal percentage in a population with a severe and ultimately fatal disease. CPR and mechanical ventilation were provided to about a third of patients and vasopressors in half of them despite unproved beneficial effect in this population. A retrospective multicenter study on the frequency and results of CPR in PAH showed that CPR was attempted in 26% of these patients who had circulatory arrest, mostly in healthcare settings and the medical ICU, and only 6% of those in whom CPR was attempted survived more than 3 months (10). These findings suggest that a more proactive approach that includes talking about end-of-life decisions may be required in this patient population.

CAUSE OF DEATH IN PAH ???

AN ETERNIAL CONCEPT:
FOCUSED INFORMATION IS A PREREQUISITE FOR APPLIED PRUDENCY



The knowledge of truth, according to Democritus, is difficult, since the perception through the senses is subjective. As from the same senses derive different impressions for each individual, then through the sense-impressions we cannot judge the truth. We can only interpret the sense data through the intellect and grasp the truth, because the truth is at the bottom.

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.023

Pulmonary Arterial Hypertension

Epidemiology and Registries

A potential explanation for the change of phenotype may be the increased awareness for PAH in the modern management era, as effective therapies are now available. Because PPH was considered a rare disease that affected young women at the time of the initial U.S.-NIH registry, it is likely that older patients and men were often not considered for the diagnosis at that time. Other factors contributing to biased enrollment include lack of awareness of this registry among nonexperts in the community and unavailability of widespread screening tools such as Doppler echocardiography. Nowadays, PAH may indeed be detected more frequently in elderly patients, as the population of most Western countries is aging. However, one should also be cautious about possible misclassifications between PAH and non-PAH PH (particularly post-capillary PH due to heart failure with preserved ejection fraction [HFpEF]), which may occur, particularly in elderly patients as a consequence of uncertainties in the current definitions and difficulties in the measurement of the pulmonary arterial wedge pressure.

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.023

Registries from China and other developing countries demonstrate demographics and characteristics similar to the early studies of the U.S. NIH Registry (23), suggesting that some differences in phenotype are related to the healthcare environment rather than to different expressions of the disease. Nonetheless, specific sources of systematic bias in PAH registries include the following: 1) changes in the classification of PH that have led to the inclusion of a varying spectrum of patients in modern registries; 2) changing interest in PH by academic physicians producing more development and dissemination of information; 3) increased awareness of PH by clinicians due to availability and marketing of effective therapy, with associated education from pharmaceutical representatives (42); 4) easier access to medical information by patients who may then influence their referral to specialized care; and 5) widespread use of noninvasive techniques (Doppler echocardiography), which allow for disease detection even in the absence of previous suspicion, thereby leading to a perception of increased disease prevalence (43). Thus, it appears that the changing phenotype of patients with PH in modern registries is potentially influenced by factors that are independent of the disease itself.

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Pulmonary Arterial Hypertension

Epidemiology and Registries

At-risk population cohorts. Unless all patients who have PH within a population are enrolled in a registry, estimates of incidence or prevalence of disease in a pre-specified population are not possible. To understand the chances of PH developing in a population requires that the population at risk be observed systematically over time to detect the occurrence of PH. Examples of populations of interest in whom the risk of the development of PH makes systematic data collection likely to yield clinically useful information include patients with known *BMPR2* mutations, with ≥ 2 family members with PH, with systemic sclerosis, with cirrhosis and portal hypertension, with past or present methamphetamine use, with mean pulmonary artery pressure of 20 to 25 mm Hg, or with PH observed only during exercise.

[Special Features **CDC PH Surveillance**]

CHEST

Pulmonary Hypertension Surveillance

United States, 2001 to 2010

Mary G. George, MD; Linda J. Schieb, MSPH; Carma Ayala, PhD; Anjali Talwalkar, MD; and Shaleah Levant, MPH

Classification
1. Pulmonary arterial hypertension
1.1. Idiopathic
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1 endoglin (with or without hereditary hemorrhagic telangiectasia
1.2.3. Unknown
1.3. Drug and toxin induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Shistosomiasis
1.4.6. Chronic hemolytic anemia
1.5. Persistent pulmonary hypertension of the newborn
1.6. Pulmonary venoocclusive disease

CHEST

Pulmonary Hypertension Surveillance
United States, 2001 to 2010

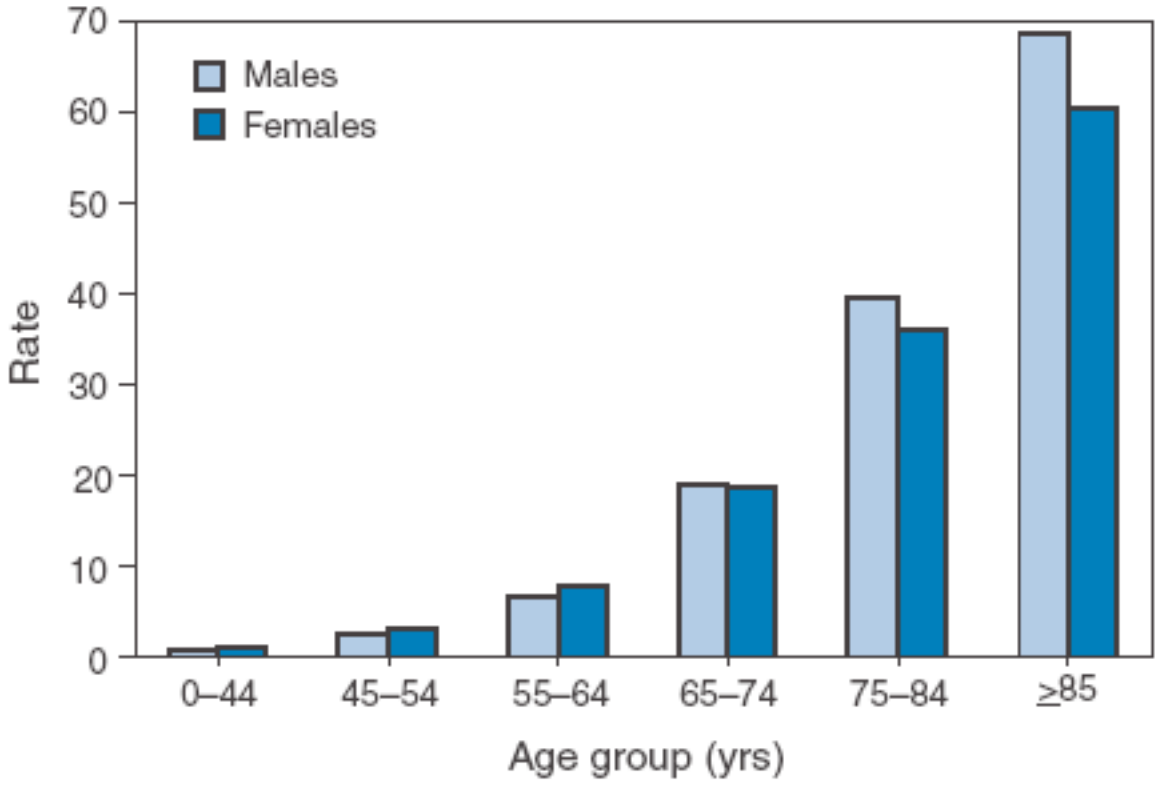
Mary G. George, MD; Linda J. Schieb, MSPH; Carma Ayala, PhD; Anjali Talwalkar, MD; and Shaleah Levant, MPH

The findings in our report indicate significant increases in death rates associated with PH for women, men, all racial/ethnic groups, and especially among those aged 75 years and older. Considering all PH deaths from 2001 to 2010, we identified significant decreases from PH associated with chronic lower respiratory disease (including emphysema specifically), conditions arising in the perinatal period, congenital malformations, and pulmonary embolism. At the same time, we identified increases from 2001 to 2010 in death rates for PH associated with aortic stenosis, hypertension, coronary heart disease, autoimmune diseases, diabetes, renal disease, and chronic liver disease. Given that PH mortality due

Death rates associated with PH for women from 2001 to 2010 were consistently higher than those for men. These sex differences are consistent with data from the REVEAL Registry, in which the patients were more likely to be women.[18] Women have higher rates of connective tissue disease than do men.[22] The French National Pulmonary Hypertension registry found that women have higher rates of idiopathic and inherited PH compared with men.[23] In the REVEAL Registry, which includes only patients with PAH, it was found that roughly one-half of patients with PAH had idiopathic PAH and one-half had associated PAH, with connective tissue disease accounting for roughly 25% of the patients in the registry.[24] With current ICD-10 mortality codes, there are challenges in separating PAH as idiopathic vs associated (Fig 1, Table 2). Indeed, most causes of death from PH in the multiple cause of death files are listed as "other secondary PH" or "PH, not otherwise specified." Few cases are listed as "primary PH." In a retrospective cohort study of

Pulmonary Hypertension Surveillance --- United States, 1980--2002

FIGURE 4. Age-specific death rate* among decedents with pulmonary hypertension as any contributing cause of death, by sex and age group — United States, 2000–2002



* Per 100,000 population.

Pulmonary Hypertension Surveillance --- United States, 1980--2002

TABLE 9. Percentage of selected causes of death reported as the underlying cause of death among decedents aged <45 years with pulmonary hypertension reported as any contributing cause of death, by period — United States, 1980–2002

Underlying cause of death reported on death certificate (ICD-9/ICD-10 codes*)	1980–1984 (N = 5,672)	1985–1989 (N = 6,741)	1990–1994 (N = 7,338)	1995–1999 (N = 7,861)	2000–2002 (N = 4,725)
Pulmonary hypertension (416.0, 416.8, 416.9/I27.0, I27.8, I27.9)	29.8%	32.7%	36.4%	39.1%	39.8%
Congenital malformations, deformations, and chromosomal abnormalities (740–759/Q00–Q99)	20.9%	21.4%	23.0%	22.3%	21.7%
Complications of pregnancy, childbirth, and the puerperium (640–676/O10–O99), or conditions originating in the perinatal period (760–771.2, 771.4–779/P00–P96)	17.3%	19.6%	12.8%	10.3%	10.5%
All cardiovascular diseases, excluding pulmonary hypertension (390–415, 416.1, 417–448/I00–I26, I27.1, I28–I78)	5.4%	5.6%	6.3%	6.8%	6.2%
All other respiratory diseases (460–478, 495, 500–519/J00–J06, J20–J22, J60–J99)	4.1%	3.5%	3.4%	3.4%	4.2%
Chronic lower respiratory diseases (490–494, 496/J40–J47)	5.2%	3.2%	2.6%	2.5%	2.7%
Systemic lupus erythematosus (710.0/M32), systemic sclerosis (710.1/M34), dermatomyositis (710.3–710.4/M33), sicca syndrome (710.2/M35), rheumatoid arthritis (714.0–714.2/M05–M06), and juvenile arthritis (714.3/M08–M09)	2.1%	2.7%	3.6%	3.7%	2.4%
Influenza and pneumonia (480–487/J10–J18)	1.1%	1.0%	0.9%	1.0%	0.6%
All other causes	14.1%	10.3%	11.0%	10.9%	11.9%

* *International Classification of Diseases, Ninth Revision* (ICD-9) codes 416.0, 416.8, or 416.9 for deaths during 1980–1998 and *International Classification of Diseases, Tenth Revision* (ICD–10) codes I27.0, I27.8, or I27.9 for deaths during 1999–2002.

Although the immediate cause of death listed on the death certificate typically contains terms such as cardiac arrest and respiratory failure, the factors leading to these consequences and the circumstances surrounding the events are sometimes less clear. How does a patient with a chronic disease die? In PAH, a major determinant of outcome is RV function (7). Despite this observation, the direct cause of death in PAH may not always be clear. Moreover, because PAH drugs have now changed the course of the disease, probably improving mortality (8), it is now reasonable to postulate that the direct cause of death for some PAH patients might not be RV failure. Rather, as they live longer, some PAH patients might be dying from an underlying comorbidity, or from an altogether unrelated condition. This has certainly been the case over time with HIV infection (9), a condition that was previously rapidly progressive and fatal, with limited treatment options.

Several national PAH registries have reported mortality figures for the treated PAH population; however, none have sought to report the direct causes of and contributors to death in these

that a combination of factors contribute to death in PAH, rather than progressive right heart failure or sudden death on their own. Although we do not have a large registry from which to compile PAH death causality before and after PAH treatment availabil-

study, the fact that less than half of the patients in Tonelli and colleagues' study died directly from progressive right heart failure/sudden death suggests that PAH treatments and/or improved PAH awareness may have begun to allow PAH patients to live long enough to die of alternative causes. Several national PAH registries examining survival in the modern treatment era suggest that this may be the case (2–4). Thus, with continued

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Causes and Circumstances of Death in Pulmonary Arterial Hypertension

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Am J Respir Crit Care Med Vol 188, Iss. 3, pp 365–369, Aug 1, 2013

	Number of Patients with Information Available	N (%)
Advanced directives	73	33 (45)
DNR	83	45 (54)
CPR	71	22 (31)
Comfort care	82	42 (51)
Mechanical ventilation	83	33 (40)
IV prostacyclin analogs initiation*	84	11 (13)
Vasopressors	69	35 (51)
ECMO	84	1 (1)
Lung transplant listing	84	2 (2)

Definition of abbreviations: CPR = cardiopulmonary resuscitation; DNR = do not resuscitate; ECMO = extracorporeal membrane oxygenation; IV = intravenous.

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Preliminary reports from the REVEAL registry have suggested under-treatment of patients with PAH either when they progress from NYHA functional class III to class IV or before death (13, 14). These findings suggest that a large proportion of patients who could have benefited from parenteral therapy or a combination of PH-specific therapies did not receive them (13, 14). We investigated this hypothesis in our cohort of patients and found that this is not the case in our center. In our cohort, all but one patient received some form of PH-specific therapy and more than half of them (57.2%) were on dual or triple combination therapy at the time of death. Seventy percent of patients with PAH that died of right heart failure received parenteral prostanoid therapy. The 30% of patients who did not receive parenteral prostanoids had valid reasons for this decision, such as refusal of parenteral therapy or being poor candidates for this therapy. Based on our findings, it is the view of the authors that most patients that are appropriate candidates for parenteral prostanoid therapy are receiving this treatment at our institution.

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Medications	Mean ± SD or N (%)
N	84
Class of PH-specific therapies	
PDE-5 inhibitors	63 (75)
ERA	33 (39)
Inhaled prostacyclin analogs	8 (10)
IV or SQ prostacyclin analogs	42 (50)
Combination of PH-specific therapies	
No PH therapies	1 (1.2)
Single PH therapy	35 (41.7)
Dual PH therapy	35 (41.7)
Triple PH therapy	13 (15.5)
Number of PH therapies	1.7 ± 0.7

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 25, Suppl D, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.10.023

Pulmonary Arterial Hypertension

Epidemiology and Registries

Registry (Ref. #)	Study Cohort	Study Design and Time Period	No. of Centers	No. of Patients	Incidence/Prevalence	Predominant Etiologies of PAH
U.S. NIH (17,18)	IPAH	Prospective, 1981–1985	32	187	NA	NA
U.S. PHC (19)	Group 1 PH, age >18 yrs	Retrospective, 1982–2004; prospective, 2004–2006	3	578	NA	IPAH, 48%; CTD-PAH, 30%; CHD-PAH, 11%
Scottish-SMR (20)	Group 1 PH (IPAH, CHD-PAH, and CTD-PAH), age 16–65 yrs	Retrospective, 1986–2001	NA	374	PAH, 7.6/26 cases/MAI; IPAH, 2.6/9 cases/MAI	IPAH, 47%; CTD-PAH, 30%; CHD-PAH, 23%
French (9,21,22)	Group 1 PH, age >18 yrs	Prospective, 2002–2003	17	674	PAH, 2.4/15 cases/MAI; IPAH, 1.0/5.9 cases/MAI	IPAH, 39%; CTD-PAH, 15% (SSc, 76%); CHD-PAH, 11%
Chinese (23)	IPAH and HPAH	Prospective, 1999–2004	1	72	NA	NA
U.S. REVEAL (8,24–33)	Group 1 PH	Prospective, 2006–2009	55	3,515 (age >3 months)	PAH, 2.0/10.6 cases/MAI IPAH, 0.9 cases/MAI	IPAH, 46%; CTD-PAH, 25% (SSc, 62%); CHD-PAH, 10%
Spanish (34)	Group 1 PH and CTEPH, age >14 yrs	Retrospective, 1998–2006; prospective, 2007–2008	31	PAH, 866; CTEPH, 162	PAH, 3.2/16 cases/MAI; IPAH, 1.2/4.6 cases/MAI	IPAH, 30%; CTD-PAH, 15% (SSc 61%); CHD-PAH, 16%
UK (6,35)	IPAH, HPAH, and anorexigen-associated PAH	Prospective, 2001–2009	8	482	1.1/6.6 cases/MI	NA
New Chinese Registry (36,37)	Group 1 PH, age >18 yrs	Prospective, 2008–2011	9	956	NA	CHD-PAH, 43%; IPAH, 35%; CTD-PAH, 19% (SLE, 51%; SSc, 9%)
Mayo (38)	Group 1 PH	Prospective, 1995–2004	1	484	NA	IPAH, HPAH 56%; CTD-PAH, 24%, other, 20%
Compera (39)	IPAH, age >18 yrs	Prospective, 2007–2011	28	587	NA	IPAH, 100%

CHEST

Pulmonary Hypertension Surveillance

United States, 2001 to 2010

Mary G. George, MD; Linda J. Schieb, MSPH; Carma Ayala, PhD; Anjali Talwalkar, MD; and Shaleah Levant, MPH

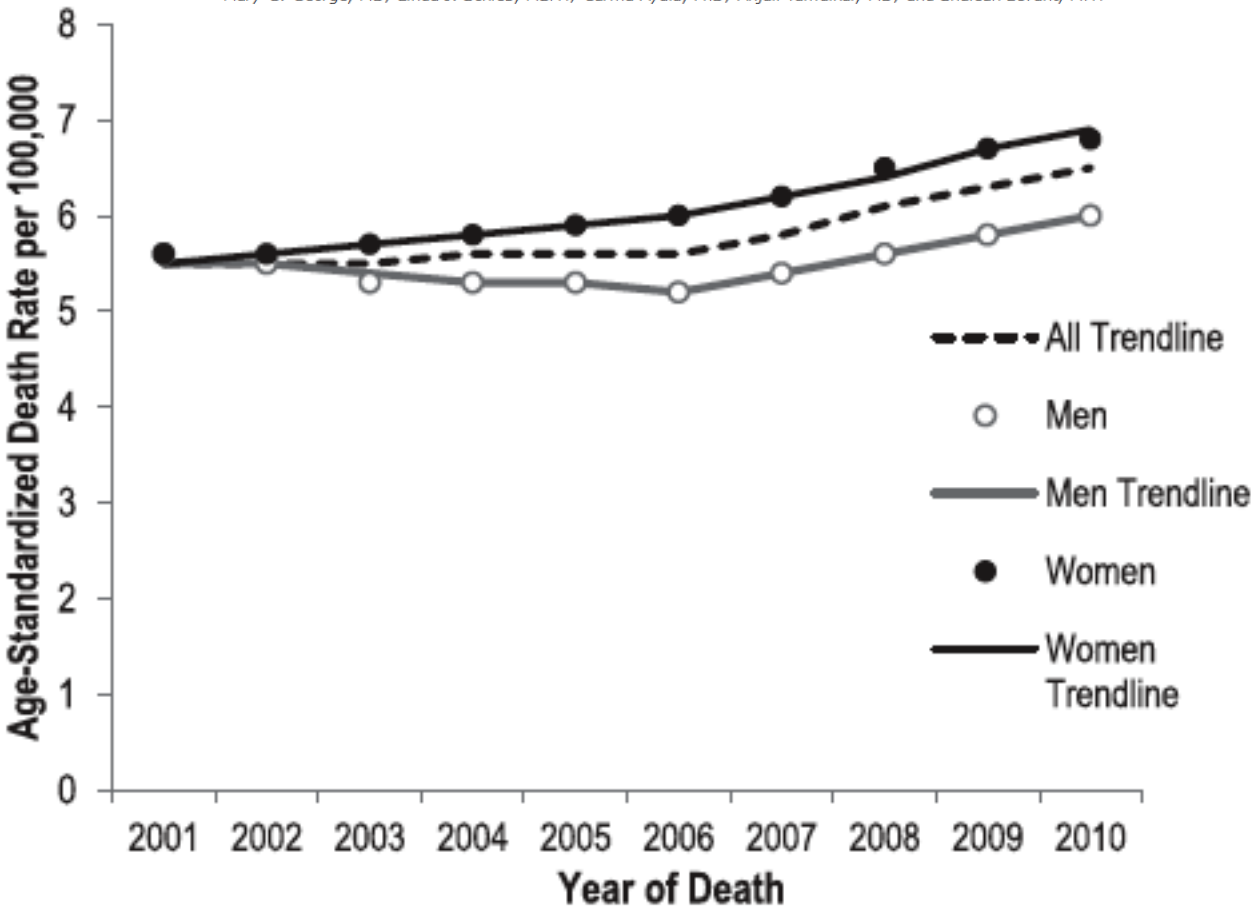
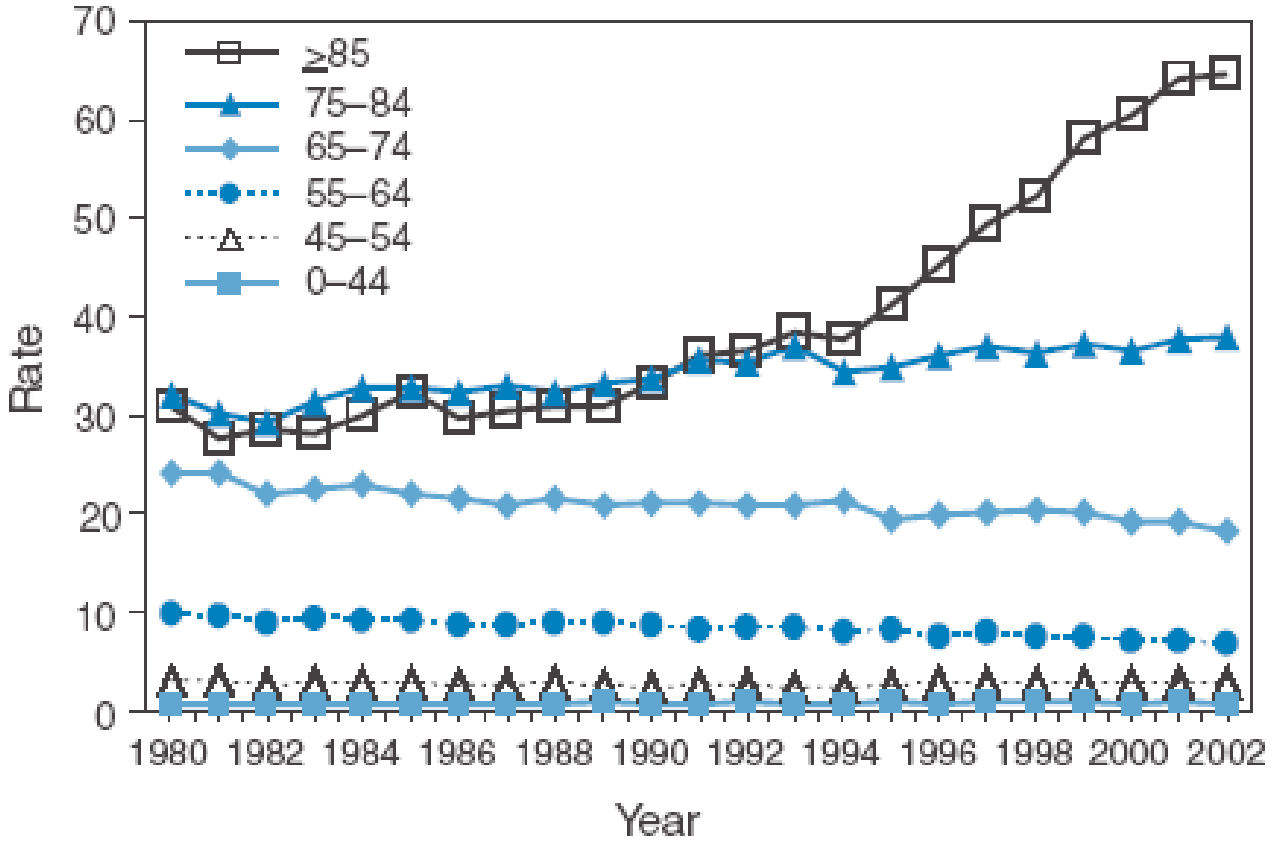


Figure 2 – *Age-standardized death rates for pulmonary hypertension as a contributing cause of death and trend lines among individuals of all ages, by sex: United States, 2001-2010. The National Vital Statistics System was used to ascertain deaths due to pulmonary hypertension*

Pulmonary Hypertension Surveillance --- United States, 1980--2002

FIGURE 3. Age-specific death rate* among decedents with pulmonary hypertension as any contributing cause of death, by age group and year — United States, 1980–2002



* Per 100,000 population.

Pulmonary Hypertension Surveillance --- United States, 1980--2002

TABLE 14. Percentage of selected diseases reported as the principal (i.e., first-listed) diagnosis on hospital records with pulmonary hypertension reported as any-listed diagnosis, by period — United States, 1980–2002

Principal diagnosis reported on hospital record (ICD-9-CM codes*)	1980–1984 (N = 500,000)	1985–1989 (N = 561,000)	1990–1994 (N = 725,000)	1995–1999 (N = 1,083,000)	2000–2002 (N = 807,000)
Heart failure (428)	5.9%	11.4%	14.6%	17.7%	18.7%
All other cardiovascular diseases (390–405, 415, 416.1,420–423,425–427,429.0, 429.1,429.3–429.9,430–434, 436–448)	6.8%	9.6%	11.8%	14.9%	16.3%
Chronic lower respiratory diseases (490–494, 496)	42.0%	23.1%	16.4%	13.4%	12.9%
Coronary heart disease (410–414, 429.2)	3.2%	5.0%	7.9%	9.2%	8.6%
Influenza and pneumonia (480–487)	4.5%	8.0%	7.7%	6.5%	8.4%
All other respiratory diseases (460–478, 495, 500–519)	6.7%	13.3%	11.2%	9.2%	6.5%
Pulmonary hypertension (416.0, 416.8, 416.9)	12.8%	10.7%	6.9%	5.3%	4.2%
Chronic valvular heart disease (424)	1.0%	1.3%	1.9%	2.3%	1.9%
Congenital malformations, deformations, and chromosomal abnormalities (740–759)	3.0%	2.6%	2.9%	1.4%	0.7%
Chronic liver disease and cirrhosis (571)	0.2%	0.1%	0.2%	0.5%	0.5%
Complications of pregnancy, childbirth, and the puerperium (640–676), or conditions originating in the perinatal period (760–771.2, 771.4–779)	0.7%	1.8%	1.3%	0.2%	0.3%
Malignant neoplasms of trachea, bronchus, and lung (162)	0.7%	0.4%	0.4%	0.6%	0.2%
Systemic lupus erythematosus (710.0), systemic sclerosis (710.1), dermatomyositis (710.3–710.4), sicca syndrome (710.2), rheumatoid arthritis (714.0–714.2), and juvenile arthritis (714.3)	0.7%	0.2%	0.7%	0.3%	0.1%
Human immunodeficiency virus infection (042–044)	0	0	0	0.1%	0
All other causes	11.8%	12.6%	16.2%	18.7%	20.7%

**International Classification of Diseases, Ninth Revision, Clinical Modification* codes 416.0, 416.8, or 416.9 for hospital diagnoses during 1980–2002.