Pathologic Correlation with Autopsy-Defined Sudden Arrhythmic Death in the San Francisco POstmortem Systematic invesTigation of Sudden Cardiac Death Study

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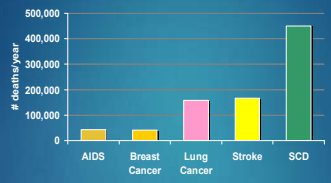
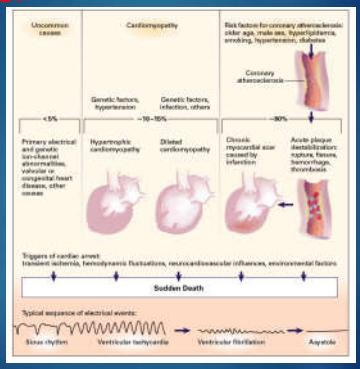
U.S. Mortality by Death Certificates



[1] U.S. Census Bureau, *Statistical Abstract of the United States*: 2001.
[2] American Cancer Society, Inc., *Surveillance Research, Cancer Facts and Figures* 2001.
[3] 2002 *Heart and Stroke Statistical Update*, American Heart Association.
[4] *Circulation*. 2001;104:2158-2163.

Etiology of Sudden Cardiac Death



Huikuri et al. *N Engl J Med*, Vol. 345 2001

RCTs, Registries: Sudden Cardiac Death

- VALIANT trial: Valsartan after acute MI and HF
  - "The cause of death was considered as SCD if death occurred suddenly and unexpectedly in a patient in otherwise stable condition, with no premonitory HF, MI, or another clear cause of death. These could have been witnessed deaths (with or without documentation of arrhythmias) or unwitnessed deaths if the patient had been seen within 24 h before death."
- MERIT-HF trial: Metoprolol for Heart Failure
  - "Witnessed instantaneous death in the absence of progressive circulatory failure lasting for 60 min or more, unwitnessed death in the absence of pre-existence progressive circulatory failure or other causes of death"
- Hinkle-Thaler, 1982:
  - "No evidence of circulatory impairment until they collapsed and the pulse disappeared"
- SCD-HeFT and MADIT2
  - No definition of SCD

ACC/AHA/HRS: Sudden Cardiac Death

ACC/AHA/HRS, 2006:

"SCA is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden cardiac death."

EMS: Out of Hospital Cardiac Arrest

2004: CDC established Cardiac Arrest Registry to Enhance Survival (CARES) to precisely define OHCA outcomes in the continuum of emergency cardiac care: 911 dispatch centers, EMS providers, and receiving hospitals

"OHCA is a cardiac arrest that occurred in the pre-hospital setting, had a presumed cardiac etiology, and involved a person who received resuscitative efforts, including CPR or defibrillation."

Sudden Cardiac Death: Definition

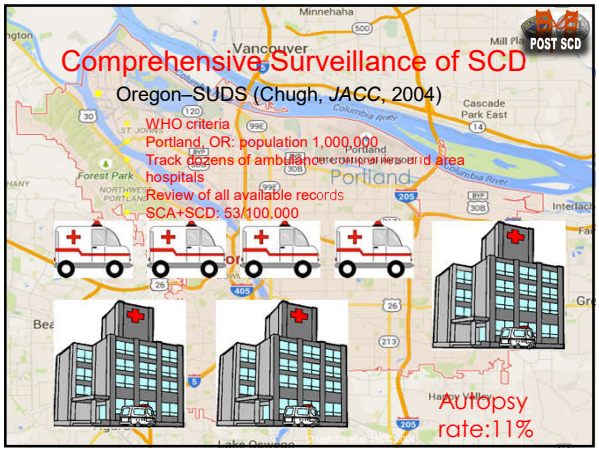
World Health Organization (WHO), 1969:

- Unexpected death within 1 h of symptom onset if witnessed
- Unexpected death within 24 h of having been observed alive and symptom-free if unwitnessed

- Out-of-hospital
- Absence of obvious noncardiac condition
- Presumed sudden pulseless condition

Methodological Issues in Population Studies of SCD

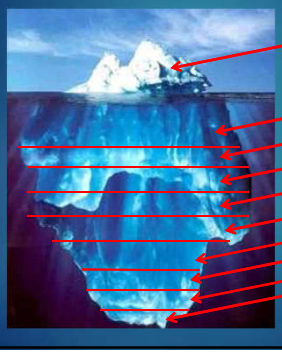
- US incidence estimates: 184,000 - 450,000 annually (2.5-fold range)
- Where does the data come from?
  - Death certificate review of listed COD
  - Retrospective review of paramedic/ER narratives
  - Incomplete medical records
- Which definition should we use for SCD?
  - WHO (Hinkle-Thaler) criteria?
  - Documented VF?
  - CARES?
  - Witnessed cases only?



Comprehensive Surveillance of SCD

- Oregon–SUDS (Chugh, *JACC*, 2004)
  - WHO criteria
  - Portland, OR: population 1,000,000
  - Track dozens of ambulance services and area hospitals
  - Review of all available records
  - SCA+SCD: 53/100,000

Sudden Arrhythmic Death



SCA

CAD
Tamponade
Valvular
Neurologic

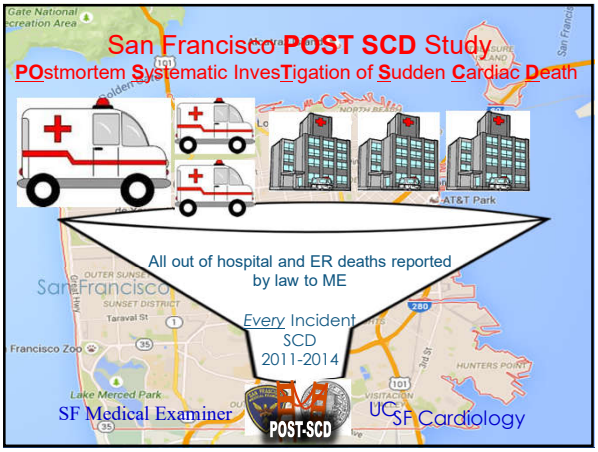
DCM

HCM
Hemorrhage
Ao Dissection

1° electrical disease

San Francisco **POST SCD** Study

POstmortem **S**ystematic Inves**T**igation of **S**udden **C**ardiac **D**eath



San Francisco County

- Single ME Office serving 49 mi², pop 864,000 (~1.5M business hrs)
- Racially/Ethnically diverse: 34% Asian, 6.1% Black, 15% Hispanic, 48% White
- 8 Hospitals, 3 ambulance companies (SFFD responds to ~65% of 911 calls)
- By CA state law, all OOH or ER deaths are reported to the ME

Methods

- Daily AM review of all OOH deaths reported to ME for 37 consecutive months to determine WHO SCDs ages 18-90 y for full autopsy, histology, tox
- All county death certificates retrieved and reviewed quarterly from DPH to cross-check for missed SCDs
- IRBs with all county hospitals and ambulance companies
- Outside medical records obtained by IRB

Case Adjudication

Data reviewed at adjudication

- PMH (active problems, prescriptions, recent visits)
- Medications (Rx, QT-prolonging, methadone)
- EMS runsheets and rhythms
- Witness/family interviews
- Autopsy, tox, histology findings

Adjudication panel


Dr. Phil Ursell
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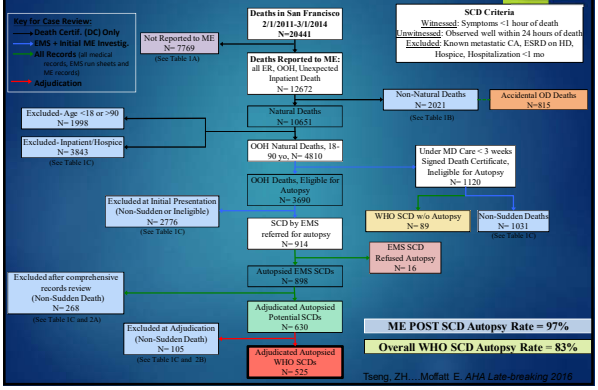
Director of UCSF Stroke Center

POstmortem **S**ystematic Inves**T**igation of **S**udden **C**ardiac **D**eath
February 1, 2011 – March 1, 2014



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POST SCD Demographics

	SCD with Autopsy	SCD without Autopsy	p* SCD with Autopsy vs. without Autopsy	SF Adult Population 2011	US Adult Population 2011
N	525	105	-	690,689	232,556,019
Age: mean ± SD†	62.8 ± 14.5	73.1 ± 11.6	**0**	-	-
	18-90	37-89	-	-	-
Male, n (%)	362 (69%)	74 (70%)	0.82	350,179 (51%)	112,848,136 (49%)
Race (%)					
White	279 (53%)	44 (42%)		290,089 (42%)	149,300,964 (64%)
Black	81 (15%)	8 (8%)		40,751 (6%)	28,371,834 (12%)
Hispanic	40 (8%)	8 (8%)	**0.001**	102,913 (15%)	37,441,519 (16%)
Asian	110 (21%)	37 (35%)		232762 (34%)	11,395,245 (5%)
Other	15 (3%)	8 (8%)		24,174 (3%)	6,046,457 (3%)
Median Income					
Tertile 1	248 (50%)	43 (45%)		266,642 (39%)	184,288,905 (79%)
Tertile 2	82 (16%)	14 (13%)	0.3446	230,900 (33%)	16,631,720 (7%)
Tertile 3	171 (34%)	43 (42%)		193,147 (28%)	31,635,394 (14%)

- for age, t-test assuming unequal variance; for categorical, Fisher's exact test
- Population data from American Community Survey 2011

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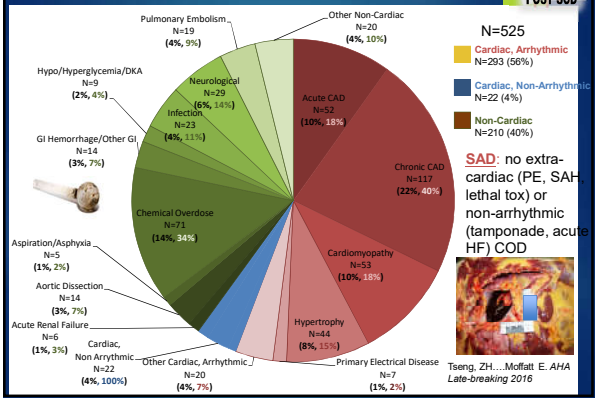
Adjudicated Etiologies of SCD



SAD: no extra-cardiac (PE, SAH, lethal tox) or non-arrhythmic (tamponade, acute HF) COD

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Sudden Cardiac Arrhythmic Death

- Is a subset of sudden cardiac arrest
- Requires autopsy with toxicology
- Can only be determined by ruling out all other causes of sudden cardiac death
  - Drugs
  - Neoplasms
  - Sudden Neurologic Death

Pre-Mortem Conditions

POST SCD

	SCD	SAD	Non-SAD	P value SAD vs. non-SAD
N	525	293	232	-
Medical Records Unobtainable	33 (6%)	15 (5%)	18 (8%)	
Confirmed No Medical History	24 (5%)	15 (5%)	9 (4%)	
History of:				
HTN	290 (55%)	175 (60%)	116 (50%)	0.0260
DM	117 (22%)	72 (24%)	46 (20%)	0.20
Dyslipidemia	157 (30%)	108 (37%)	50 (22%)	0.0001
Any cardiac history	224 (43%)	131 (45%)	93 (40%)	0.29
CHF	68 (13%)	47 (16%)	21 (9%)	0.0179
AF/AFL	54 (10%)	27 (9%)	24 (10%)	0.66
Aortic stenosis (mod or severe)	6 (1%)	2 (1%)	3 (1%)	0.47
Mitral valve prolapse	8 (2%)	5 (2%)	3 (1%)	0.70
CKD (non ESRD)	58 (11%)	33 (11%)	25 (10%)	0.86
Seizures	39 (7%)	14 (5%)	25 (11%)	**0.0093**
CVA	33 (6%)	18 (6%)	16 (7%)	0.73
Depression	93 (18%)	37 (13%)	56 (24%)	**0.0006**
COPD	64 (12%)	32 (11%)	32 (14%)	0.32
Non-Metastatic Cancer	63 (12%)	40 (14%)	23 (10%)	0.18
Tobacco Use	211 (40%)	115 (39%)	96 (42%)	0.62
Alcohol Abuse	122 (23%)	57 (19%)	65 (28%)	**0.0210**
Illicit Drug Use	79 (15%)	27 (9%)	52 (22%)	**<0.0001**

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	WHO-Defined SCD (N = 525) Autopsy-Defined SAD N = 293	Non-SAD N = 232	Trauma Death N = 104	Odds Ratio (95% Confidence Interval; p*) Autopsy-Defined SAD vs. Non-SAD	Autopsy-Defined SAD vs. Trauma Death
Coronary Disease					
Any Infarct	176 (60%)	74 (32%)	16 (15%)	2.90 (1.98-4.26); P<0.0005	6.84 (3.72-12.57); P<0.0005
Acute MI*	52 (18%)	19 (8%)	1 (1%)	1.87 (1.11-3.50); P=0.02	P<0.001
w/ Coronary Thrombus	36 (12%)	7 (3%)	0 (0%)	3.81 (1.64-8.82); P=0.002	P<0.001
Healed MI*	159 (54%)	61 (26%)	16 (15%)	3.13 (2.12-4.62); P<0.0005	5.17 (2.82-9.46); P<0.005
w/ Acute MI	35 (12%)	6 (3%)	1 (1%)	4.31 (1.76-10.56); P=0.001	P=0.0002
Total CAD	175 (60%)	58 (25%)	15 (14%)	4.37 (2.93-6.50); P<0.0005	7.15 (3.82-13.40); P<0.0005
w/o MI	33 (11.26)	13 (6%)	4 (4%)		
1 Vessel CAD	84 (29%)	30 (13%)	7 (7%)	2.70 (1.68-4.34); P<0.0005	4.24 (1.85-9.70); P=0.001
2 Vessel CAD	51 (17%)	22 (9%)	2 (2%)	1.91 (1.10-3.30); P=0.021	P<0.001
3+ Vessel CAD	40 (14%)	6 (3%)	6 (6%)	4.98 (2.04-12.14); P<0.0005	1.79 (0.72-4.49); P=0.21
LAD CAD	31 (14%)	105 (36%)	9 (9%)	3.23 (2.03-5.14); P<0.0005	4.64 (2.20-9.80); P<0.0005
LCx CAD	57 (20%)	20 (9%)	5 (5%)	2.21 (1.26-3.86); P=0.005	P=0.0002
LM CAD	17 (6%)	4 (2%)	2 (2%)	1.72 (0.99-3.00); P=0.06	P=0.1773
RCA CAD	85 (30%)	23 (10%)	4 (4%)	3.60 (2.15-6.03); P<0.0005	P<0.0001
MINOCA	8 (3%)	2 (1%)	0 (0%)	P=0.20	P=0.12
Valve Disease					
Aortic Valve Calcification (severe)	32 (11%)	16 (7%)	1 (1%)	1.46 (0.75-2.84); P=0.27	P=0.0007
Aortic Valve Bicuspid	2 (1%)	0 (0%)	0 (0%)	P=0.51	-
Mitral Annular Calcification (severe)	4 (1%)	0 (0%)	0 (0%)	P=0.13	P=0.58
Mitral Valve Prolapse	0 (0%)	1 (0.4%)	0 (0%)	P=0.25	-
LV Measurements					
Short Axis Diameter (cm)	2.8 ± 1.3	2.3 ± 1.3	1.9 ± 1.1	1.30 (1.11-1.51); P<0.001	1.81 (1.42-2.3); P<0.0005
Septal (Compact) Thickness (cm)	1.7 ± 0.4	1.6 ± 0.5	1.6 ± 0.4	1.38 (0.90-2.09); P=0.14	1.55 (0.85-2.82); P=0.16
LVH (any wall thickness > 1.5 cm)	191 (65%)	124 (53%)	50 (48%)	1.83 (1.26-2.66); P<0.001	2.21 (1.36-3.61); P<0.001
LVMI	86 ± 46	67.4 ± 46	52 ± 34.8	1.01 (1.00-1.01); P<0.0005	1.03 (1.02-1.04); P<0.0005
Other Heart Findings					
Aorta Plaques ≥ 75% ISA	71 (27%)	41 (20%)	8 (8%)	1.32 (0.82-2.11); P=.025	3.20 (1.39-7.37); P=0.006
LV Non-compaction	1 (0.3%)	0 (0%)	0 (0%)	-	-
Pericarditis	1 (0.3%)	2 (1%)	0 (0%)	P=0.58	-
Histologic Findings					
Myocarditis	5 (2%)	0 (0%)	0 (0%)	P=0.16	P=0.33
Histologically Confirmed HCM	4 (1%)	0 (0%)	0 (0%)	-	-

Coronary Artery Disease is Associated with Sudden Arrhythmic Death

POST SCD

- One vessel coronary disease is more prevalent than multivessel disease
  - In one vessel disease and SAD, the right coronary artery involvement is most common
- Multi vessel disease seems to less associated

COA: Resuscitated SCA vs. SCD

POST SCD

Table 1	Died OOH/ED (POST-SCD)	All UCSF/SFGH SCA Admissions	UCSF/SFGH Inpatient Death	UCSF/SFGH Survival to Hospital Discharge
Age (mean)	62.8	63.8	68.5	60.4
Sex (% male)	69%	59%	62%	57%
Race				
Asian	279 (53%)	7 (26%)	3 (23%)	4 (29%)
black	81 (15%)	6 (22%)	4 (31%)	2 (14%)
Hispanic	40 (8%)	2 (7%)	1 (8%)	1 (7%)
white	110 (21%)	9 (33%)	3 (23%)	6 (43%)
other/unknown	15 (3%)	3 (12%)	2 (15%)	1 (7%)
Cause of Arrest				
Cardiac-arrhythmic	293 (56%)	23 (82%)	11 (85%)	12 (86%)
Acute CAD	32	14	8	6
Chronic CAD	117	2	2	0
Cardiomyopathy	53	2	0	2
Hypertrophy	44	0	0	0
Primary Electrical Disease	7	0	0	0
Other Cardiac, arrhythmic	20	5	1	4
Cardiac-nonarrhythmic	22 (4%)	2 (7%)	0 (0%)	1 (7%)
Non-cardiac	210 (40%)	3 (11%)	2 (15%)	1 (7%)
Acute Renal Failure	6	0	0	0
Aortic Dissection	14	0	0	0
Aspiration/Asphyxia	5	0	0	0
Chemical Overdose	71	0	0	0
GI Hemorrhage/Other GI	14	0	0	0
Hypo/Hyperglycemia/DKA	9	0	0	0
Infection	23	0	0	0
Neurological	29	2	2	0
Pulmonary Embolism	19	1	0	1
Other Non-Cardiac	20	0	0	0

COD by Initial Rhythm

Witnessed SCDs

POST SCD

Initial Rhythm	Arrhythmic COD N=78	Non-Arrhythmic COD N=42	P value Fisher's Exact	Total
Agonal/Idioventricular	3 (60%)	2 (40%)	1.0	5
Asystole	26 (63%)	15 (37%)	0.84	41
NSR	3 (60%)	2 (40%)	1.0	5
PEA	2 (13%)	13 (87%)	<0.0001	15
Sinus Brady	2 (40%)	3 (60%)	0.34	5
VT/VF	39 (91%)	4 (9%)	<0.0001	43
Other	2 (67%)	1 (33%)	1.0	3
Unknown	1 (33%)	2 (67%)	0.61	3

COD by Presenting Symptom

Witnessed SCDs

POST SCD

Symptom	Arrhythmic COD N=78	Non-Arrhythmic COD N=42	P value Fisher's Exact	Total
None Known	40 (69%)	18 (31%)	0.38	58
Multiple	18 (62%)	11 (38%)	0.70	29
Other	10 (83%)	2 (17%)	0.16	12
Shortness of Breath	3 (37%)	5 (63%)	0.09	8
Chest Pain	2 (33%)	4 (67%)	0.10	6
Syncope	2 (50%)	2 (50%)	0.52	4
Vomiting / Nausea	2 (100%)	0 (0%)	0.30	2
GI	1 (100%)	0 (0%)	0.46	1
Fatigue	0 (0%)	0 (0%)	-	0
Cough	0 (0%)	0 (0%)	-	0
Total	78 (65%)	42 (35%)		120

Implications

- Reliance on EMS records and/or death certificates is insufficient for accurate determination of SCD incidence, and by implication, SAD
- Further investigation in minority groups and women
- To reduce overall public health burden of SCD/SAD, in addition to CAD, efforts also should be directed towards screening, treating and preventing OD, neurologic diseases, hypertrophy, cardiomyopathy
- SCD cohorts for genetic and molecular association studies will need refinement of phenotype

Next Steps

- Precise phenotypes for future molecular association studies
  - SAD "Transcriptome"
  - Hypertrophy as variant of HCM?
- Prediction modeling for true SAD in existing SCD cohorts
- Evaluation of myocardial fibrosis, cardiac mass, CAD, MVP as risk factors
- Precision EMS protocols
- SND: SUDEP, hemorrhage risk with anticoagulants, anti-platelets
- Determine the burden and cardiac pathologic substrate of HIV+ SCDs
- Determine the role of immunopathology in HIV+ SCD
- HIV tissue reservoirs for cure?
- FDA postmortem postmarket surveillance: all deaths, perimortem remote transmissions in VANCDSP

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