Prevention of Sudden Cardiac Death

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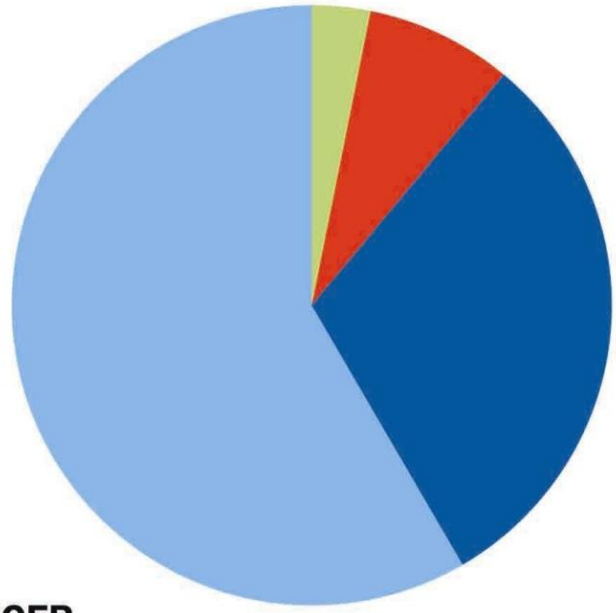
Presenter Disclosure Information

Gerhard Hindricks has received honoraria for lectures from Biosense, St. Jude Medical, Biotronik, Medtronic, Boehringer Ingelheim

Gerhard Hindricks has received research grants from St. Jude Medical, Biotronik, Biosense

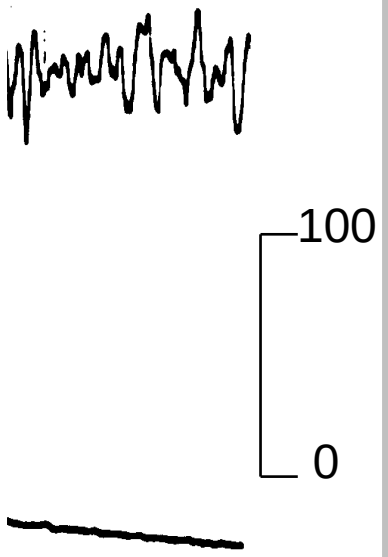
Gerhard Hindricks is a member of the Advisory Board / consultant for Biosense, St. Jude Medical, Biotronik, Stereotaxis

More people die from SCD than AIDS, breast cancer and lung cancer combined



- **SCD** (300,000)
- **AIDS** (16,000)
- **BREAST CANCER** (40,600)
- **LUNG CANCER** (157,400)

Sources:
NASPE 2001, CDC 2001,
American Cancer Society 2001



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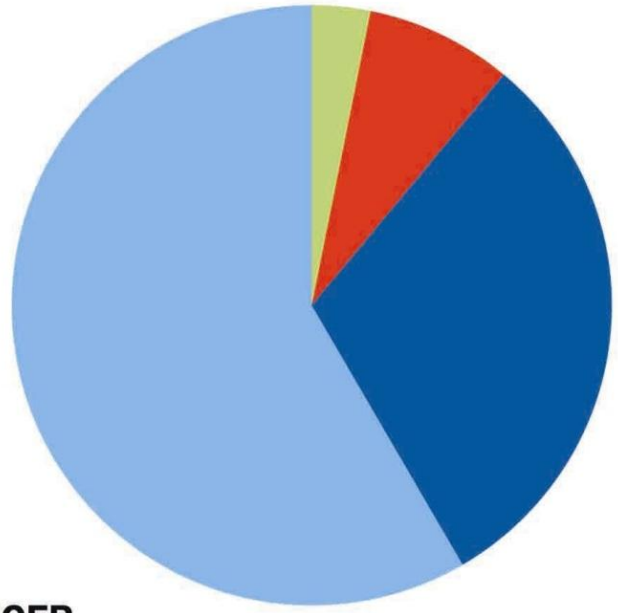

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Prevention of SCD: Agenda

- **brief overview: epidemiology of SCD**

- risk stratification for SCD
  - noninvasive markers
  - invasive markers
  - genetic markers

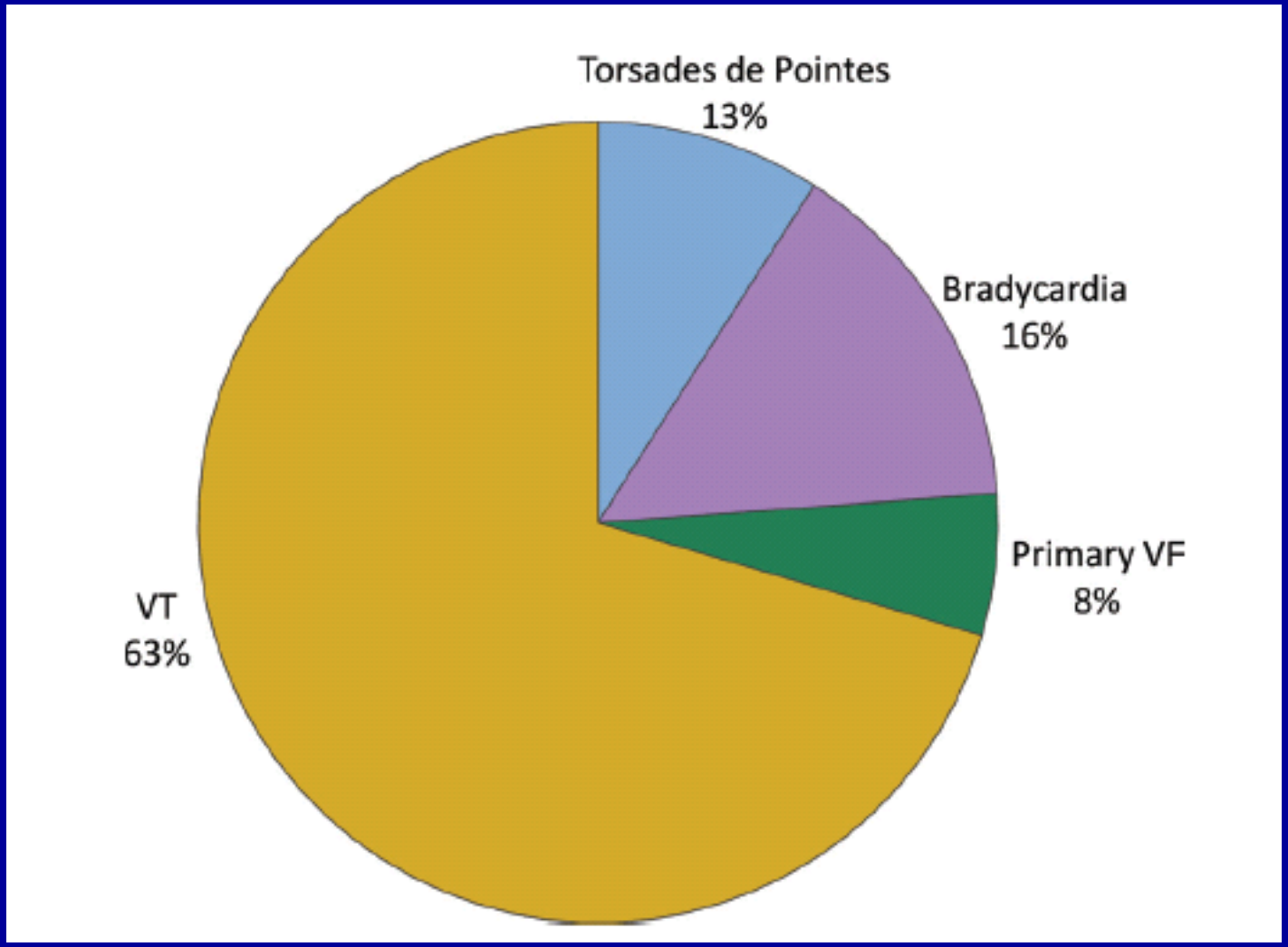
- preventive strategies
  - role of CAD / HF prevention
  - role of the ICD
  - ….beyond the ICD?

Epidemiology of SCD: USA 2012

- **annual rate 184.000 – 462.000** [1]
- **about 50% - 70% arrhythmic deaths** [2]
- vast majority of victims have organic heart disease [1,2]
  - clinically diagnosed
  - unknown / subclinical diseases
    [195.000 silent MI / yr in US]
- significant impact of age, race, and gender [1]

(1) AHA Heart disease and stroke statistics - 2012 update; Circulation 2012
(2) Goldberger JJ et al.; Circulation 2011

First rhythm documented at time of arrhythmic SCD



adopted from Bayes de Luna et al; Am Heart J 1989

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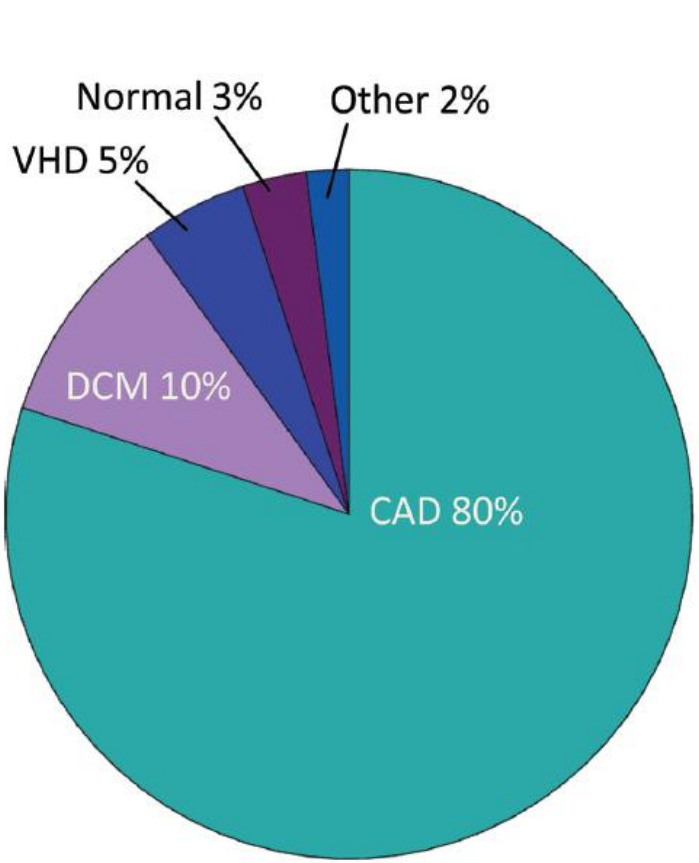
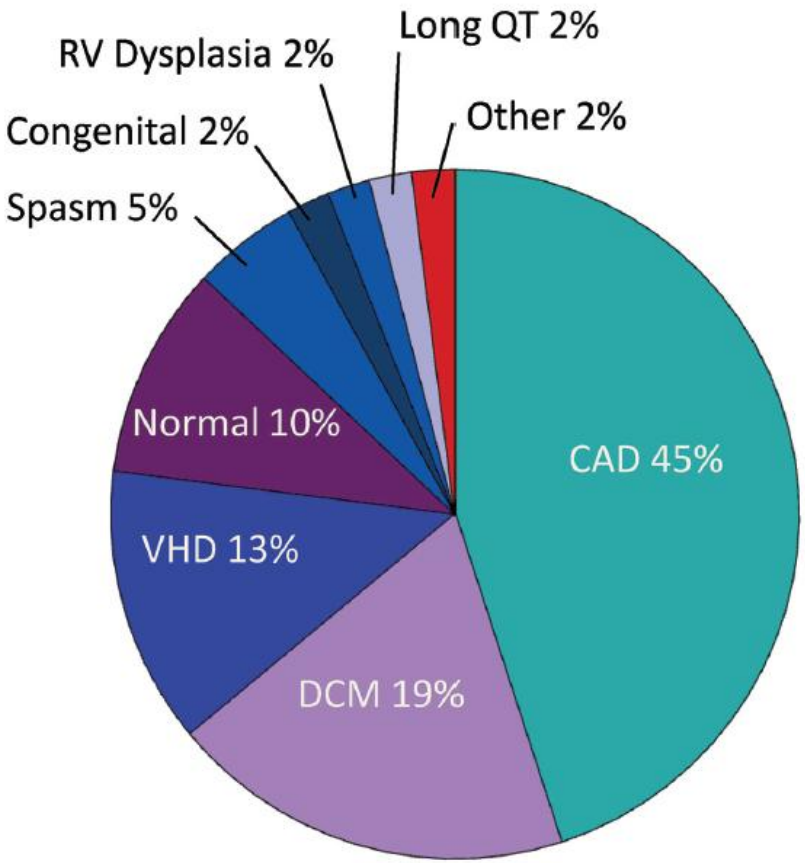
Structural heart disease in SCD survivors





Deo R, Albert CM; Circulation 2012

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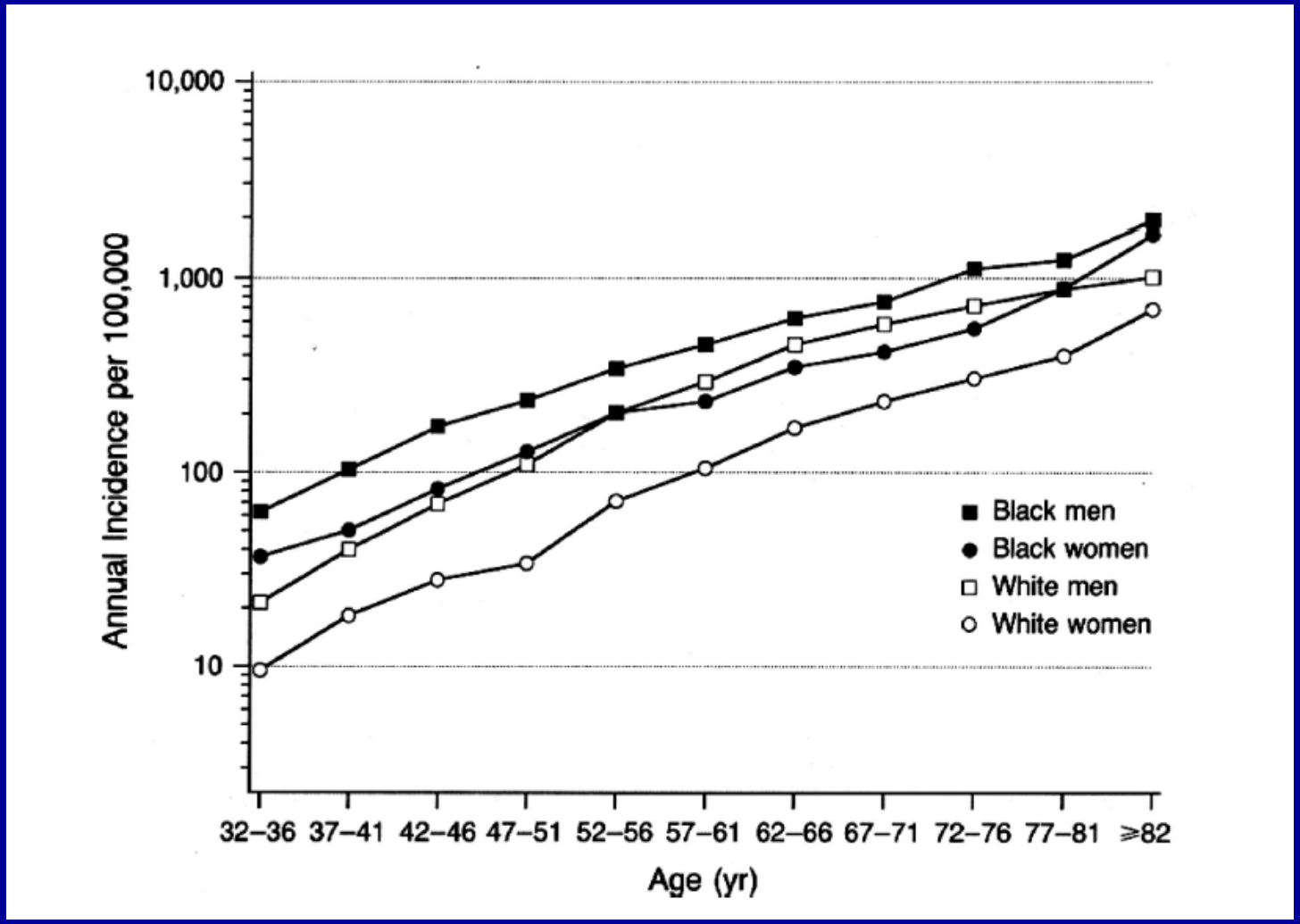
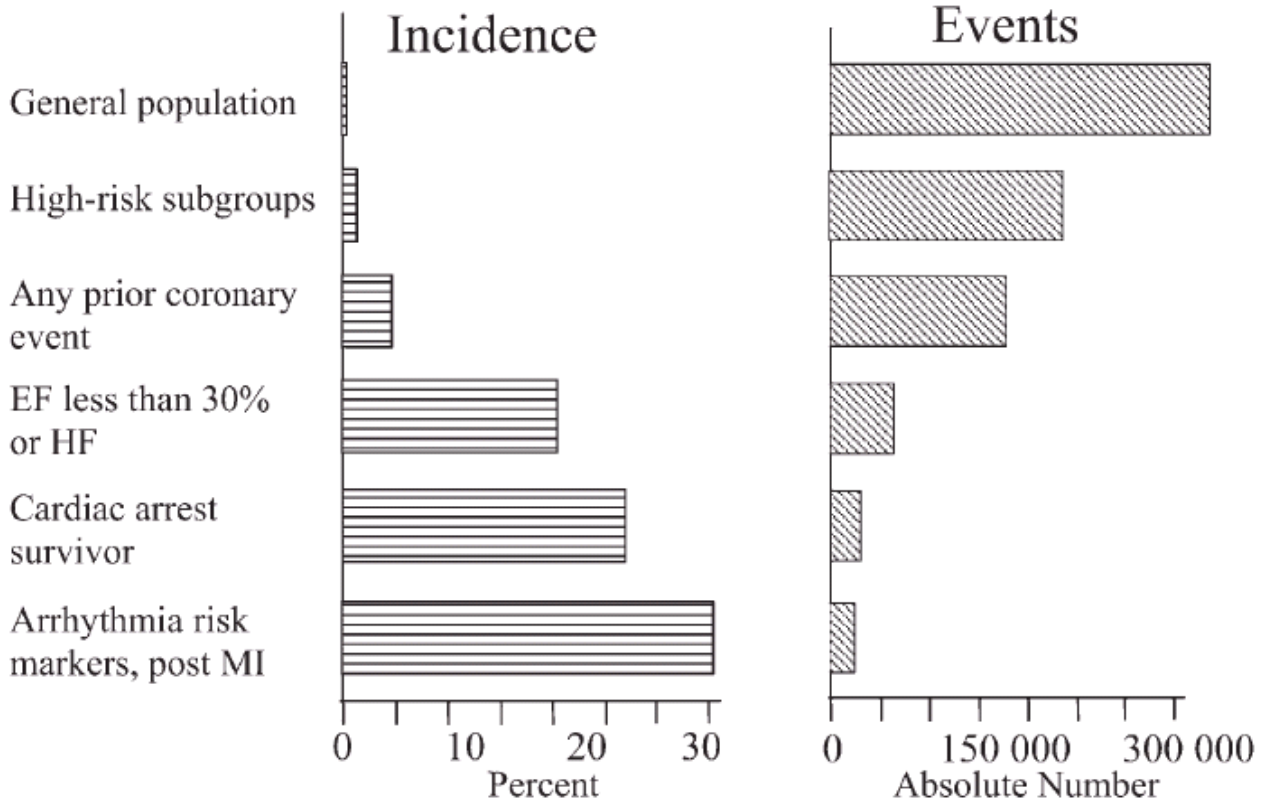
Incidence of SCD according to age, race, and gender



Deo R, Albert CM; Circulation 2012

Absolute number of events and event rates of SCD



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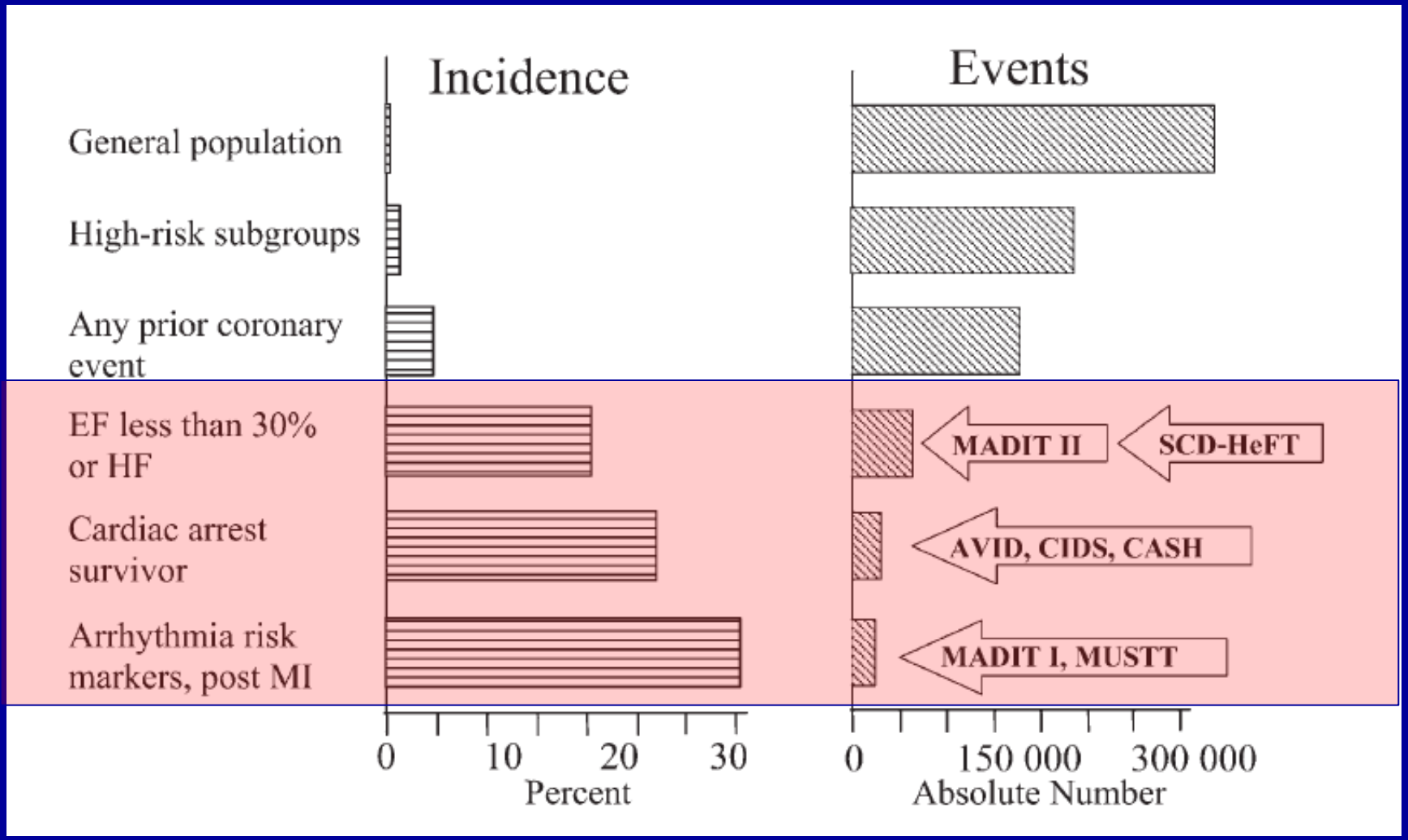

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SCD risk stratification: an ongoing dilemma

- LVEF (< 35%)

- QRS-duration
- micro T wave alternans
- venticular ectopy
- ventricular late potentials

- heart rate turbulance
- heart rate variability
- baroreflex sensitivity

- programmed ventricular stimulation

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no strategy proved effective predicting SCD to achieve guideline relevance

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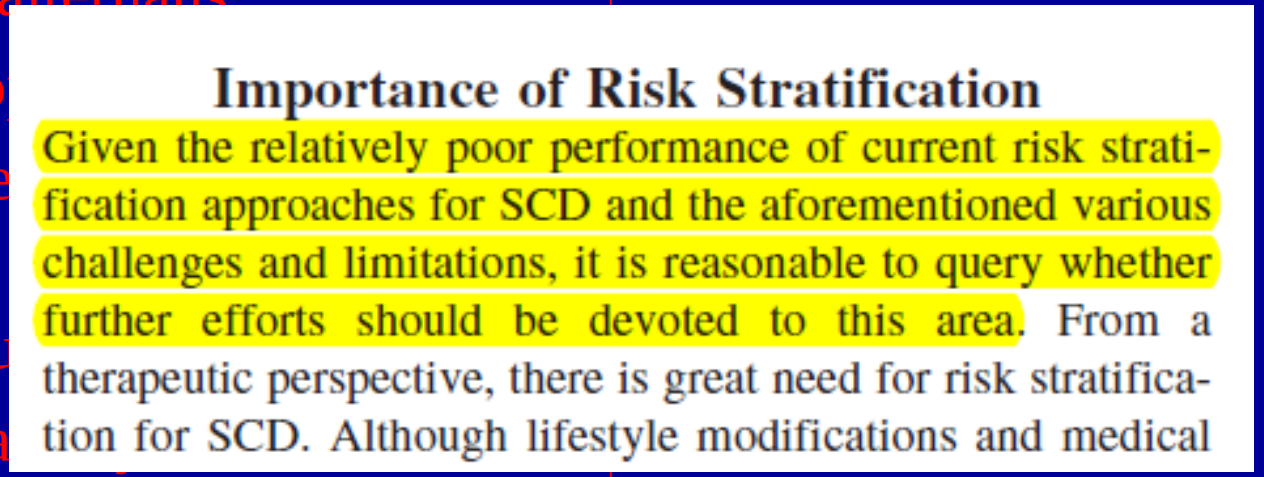


Importance of Risk Stratification

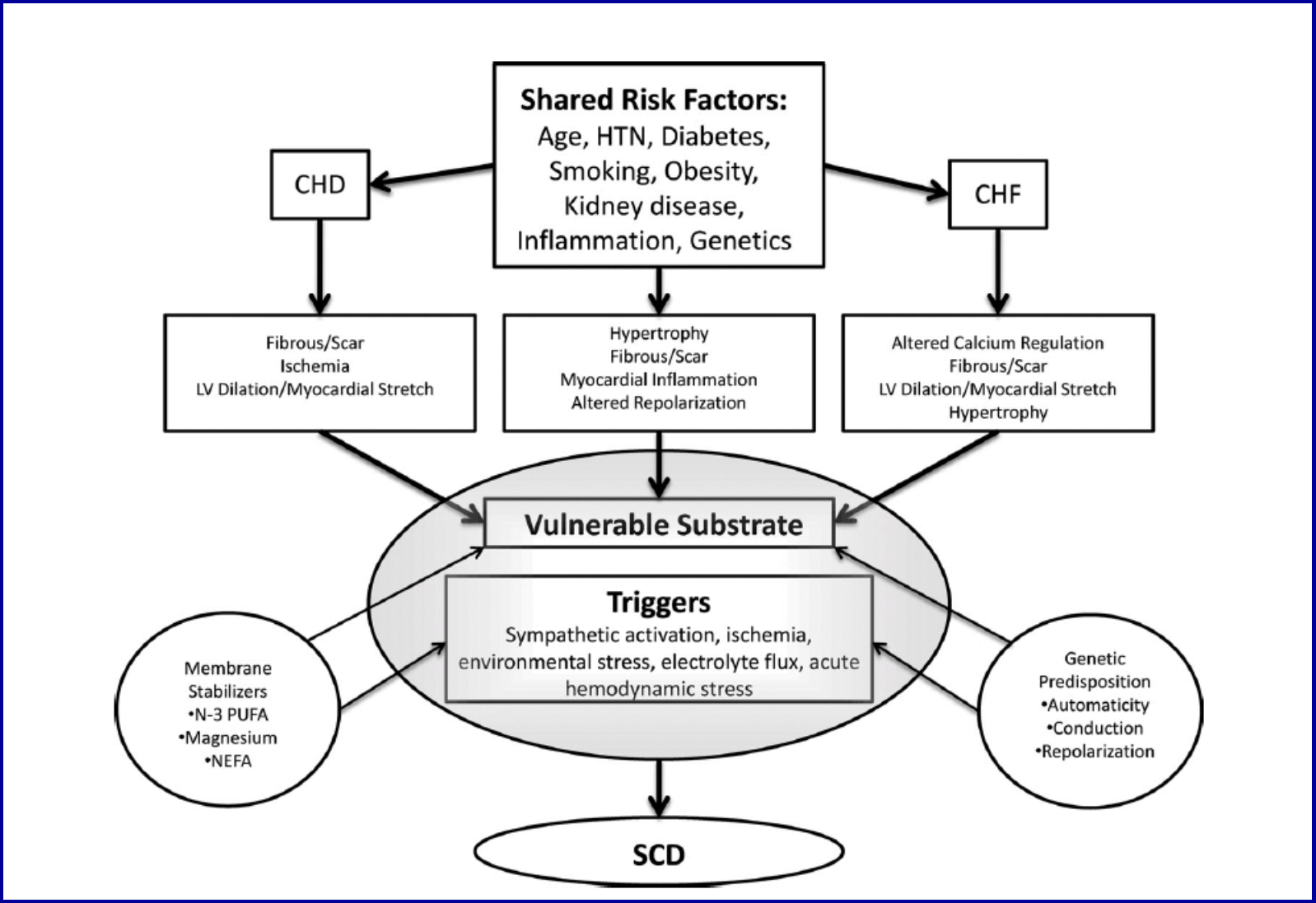
Given the relatively poor performance of current risk stratification approaches for SCD and the aforementioned various challenges and limitations, it is reasonable to query whether further efforts should be devoted to this area. From a therapeutic perspective, there is great need for risk stratification for SCD. Although lifestyle modifications and medical

Goldberger et al.; Circulation 2011

SCD risk stratification: an ongoing dilemma

- risk factors are not static but dynamic
- quantitative and qualitative durability of risk markers not defined
- temporal variation of risk factors occur as a function of
  - time of the day
  - day of the week
  - season of the year
- role of rest/exertion for risk marker assessment unclear
- frequency of risk marker assessment

Critical pathways leading to electrical instability and SCD



Deo R, Albert CM; Circulation 2012

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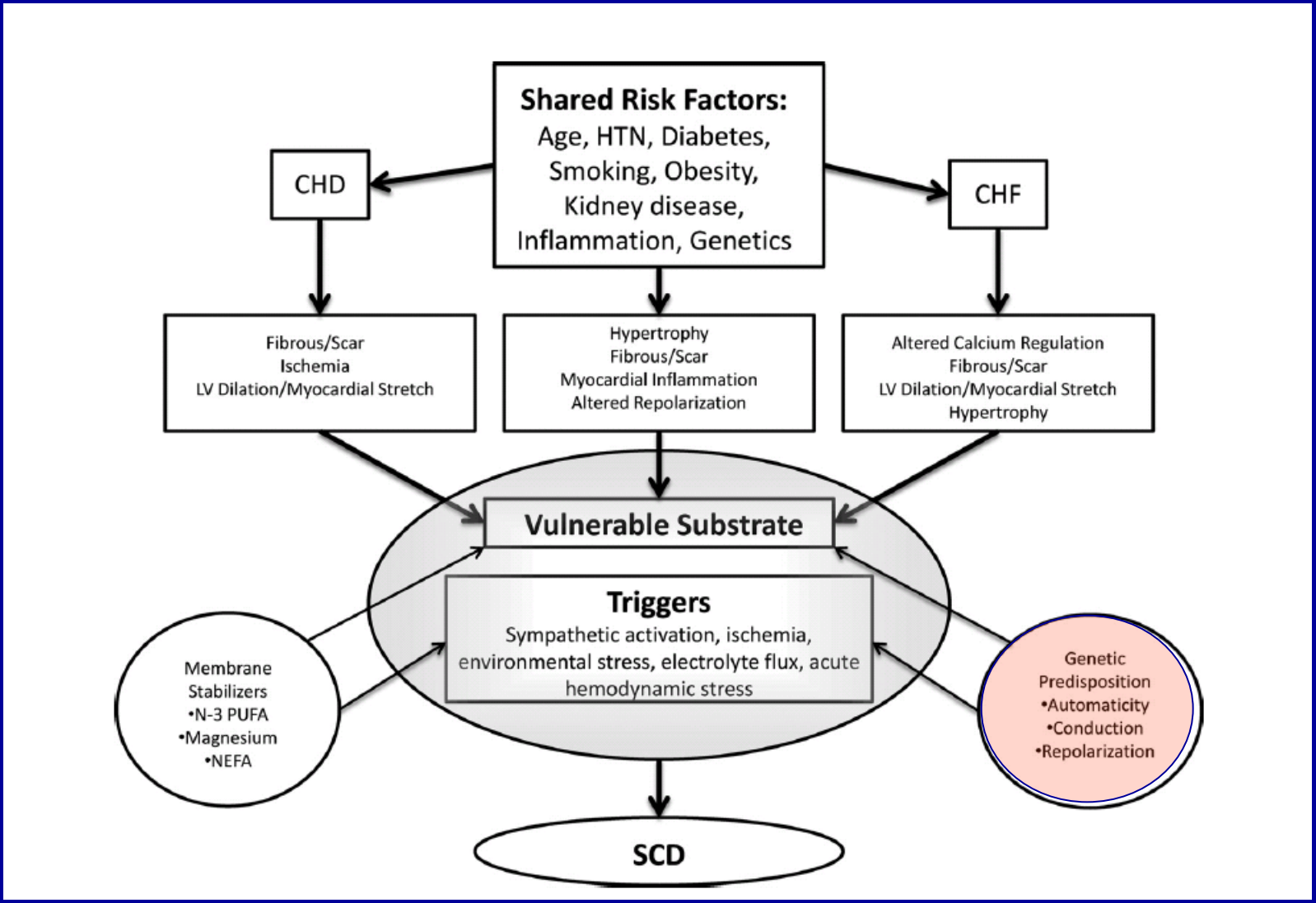

Deo R, Albert CM; Circulation 2012

SCD risk stratification: role of genetic risk assessment

- Genetic testing has proved effective for risk stratification in some patients with suspected channelopathies such as LQT-syndrome, Brugada syndrome, or CPVT.

- However, these patients represent only a small minority of SCD victims.

- Identification of genes affecting cardiac electrophysiology and modulating SCD risk has raised the possibility that common genetic variants or polymorphisms in the same region may account for SCD risk in non-channelopathy patients as well.

SCD risk stratification: role of genetic risk assessment

Table 3. Candidate Genes for SCD in the General Population

Study	Gene	Frequency of Variant Allele	Population	N (SCD Cases/ Controls)	Findings/Notes
Ion channels					
Westaway et al 2011[178]	*CASQ2 GPD1L*	10–45%	Americans of European ancestry, general population	670/299	Polymorphisms in these genes are associated with SCD
Albert et al 2010[187]	*KCNQ1 KCNH2 SCN5A KCNE1 KCNE2*	60–70%	Americans of European ancestry, general population	516/1522	2 intronic variants (1 in *KCNQ1* and 1 in *SCN5A*) were associated with SCD
Stecker et al 2006[188]	*SCN5A*	1–4%	Americans of European ancestry with coronary disease	67/91	No association was observed between *SCN5A* polymorphisms or mutations with SCD
Burke et al 2005[189]	*SCN5A* (Y1102A)	9%	Blacks, general population	182/107	Y1102A was associated with unexplained arrhythmic death and SCA
Splawski et al 2002[190]	*SCN5A* (Y1102A)	13%	Blacks, general population	23/100	Variant is associated with an increased risk of SCD or medication induced QTc prolongation
Autonomic nervous system					
Gavin et al 2011[191]	β2AR (Gln27Glu)	45%	Americans of European ancestry, general population	492/1388	When combined with the 2 analyses below, the β2AR polymorphism is associated with SCD
Tseng et al 2008[192]	β2AR and β1AR	30–40% (*β2AR*) 10–30% (*β1AR*)	Aborted SCD and history of MI/CAD, 75% Americans of European ancestry	107/388	No association was observed between any of the βAR polymorphisms and SCD
Sotoodehnia et al 2006[193]	β2AR (Gln27Glu)	43% whites, 19% blacks	American cohort (4441 European ancestry, 808 Blacks)	195/5249	The β2AR variant is associated with SCD in whites but not blacks
Snapir et al 2003[194]	*Alpha$_{2B}$-AR*	48%	Finnish, population based	278/405	The deletion/deletion genotype of the α_{2B}-adrenoceptor gene increased the risk for SCD in middle-aged men

Deo R, Albert CM; Circulation 2012

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- Genetic testing has proved effective for risk stratification in patients with suspected channelopathies such as LQT-syndrome, Brugada syndrome, or CPVT.

- However, these patients represent only a small minority of SCD victims.

- Identification of genes affecting cardiac electrophysiology and modulating SCD risk has raised the possibility that common genetic variants or polymophisms in the same region may account for SCD risk in non-channelopathy patients as well.

- **Although a rapidly increasing set of knowledge in this field has been reported, no genetic strategies for SCD risk assessment in non-channelopathy patients are currently available.**

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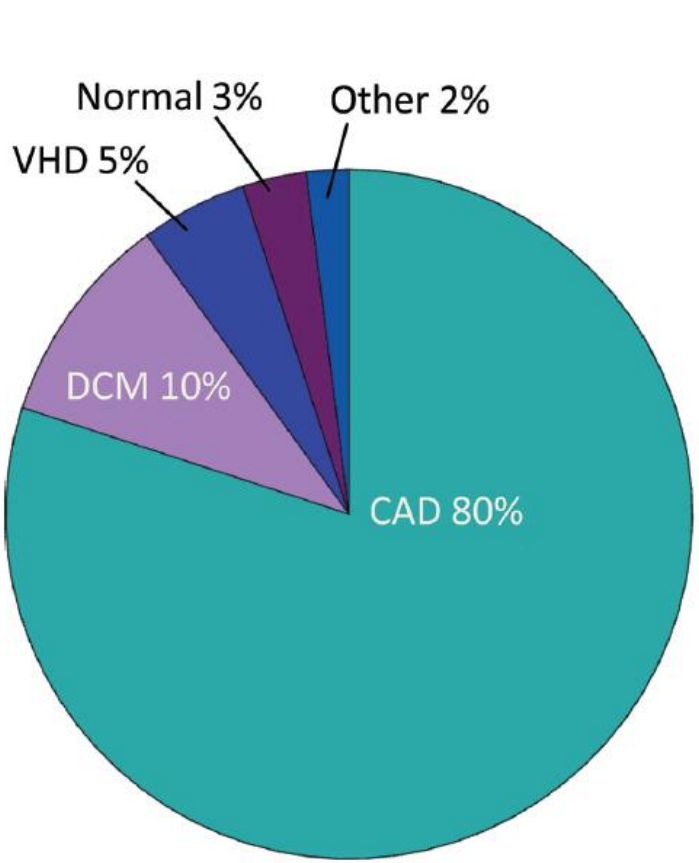
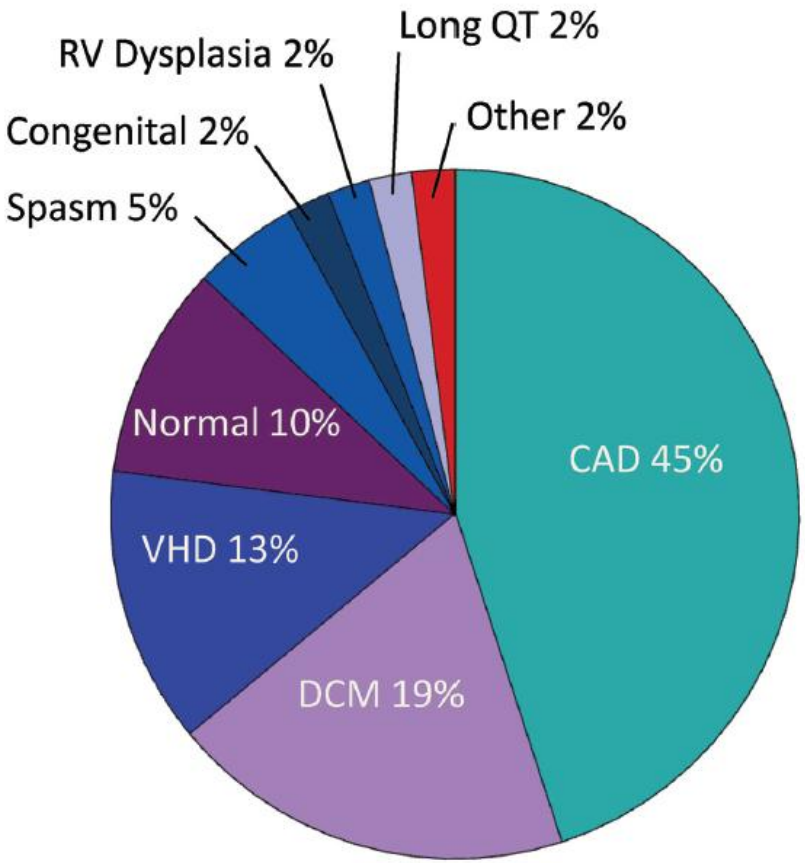
- **preventive strategies**
  - **role of CAD / HF prevention**
  - **role of the ICD**
  - **….beyond the ICD?**

Structural heart disease in SCD survivors





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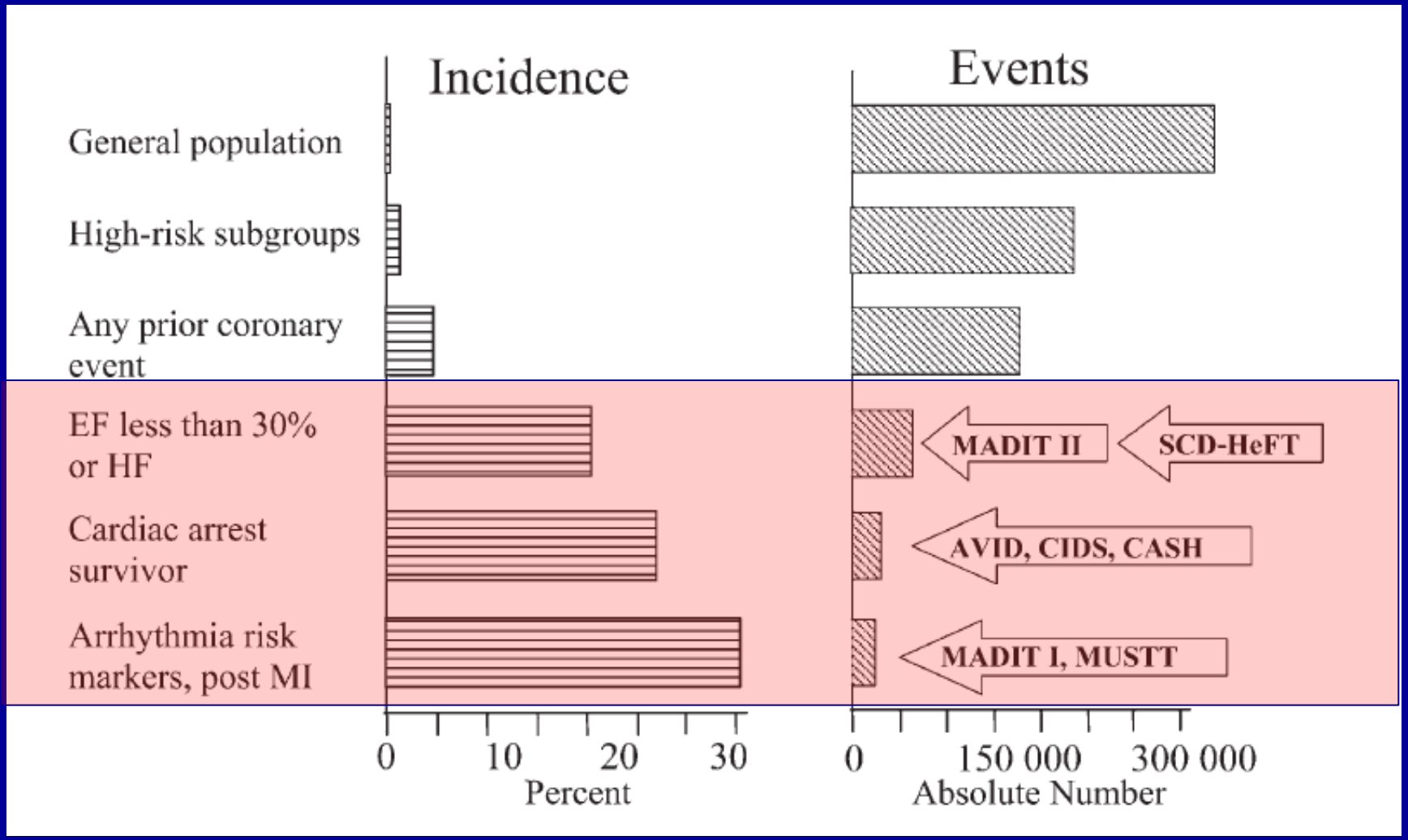

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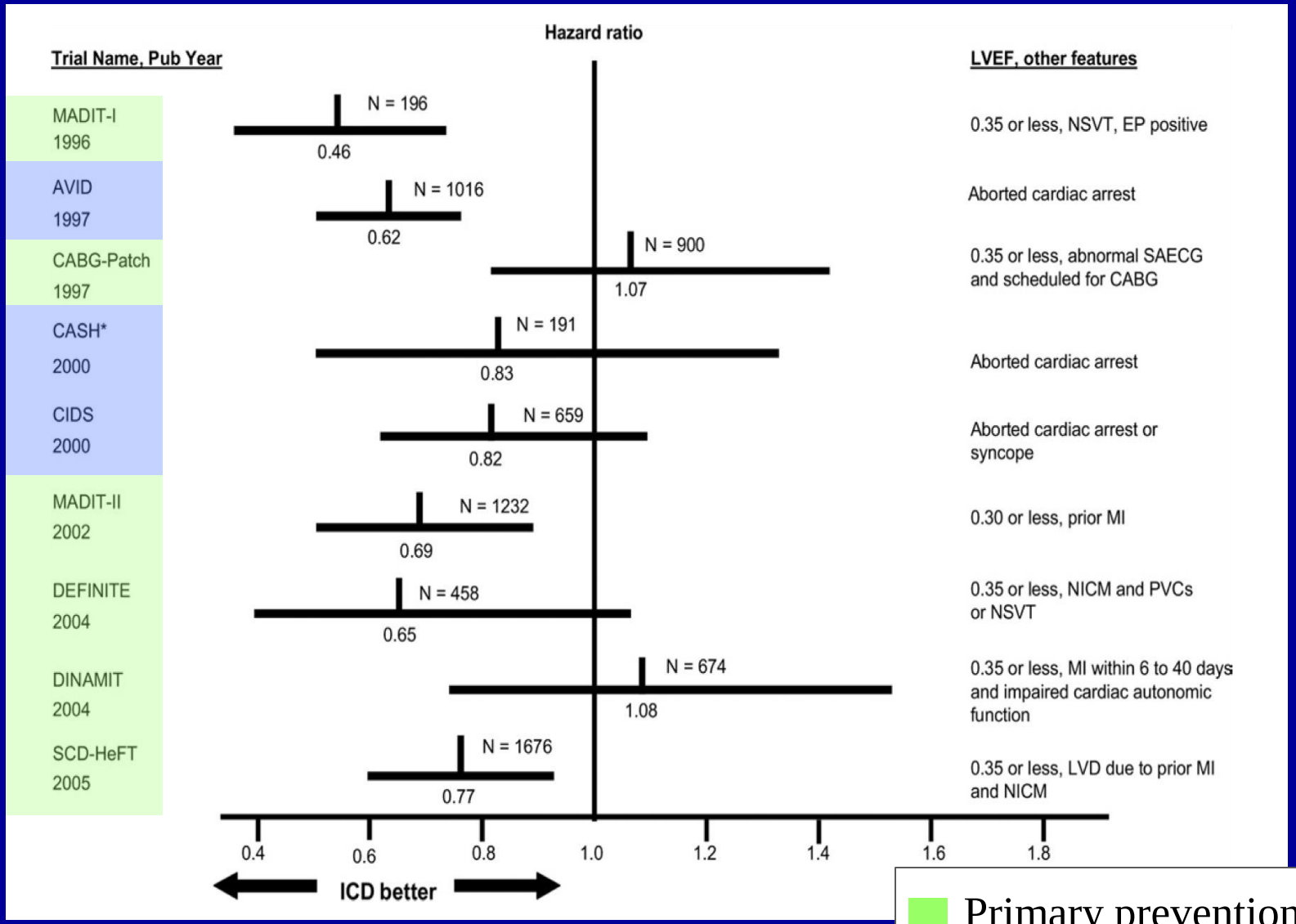
Sudden Cardiac Death

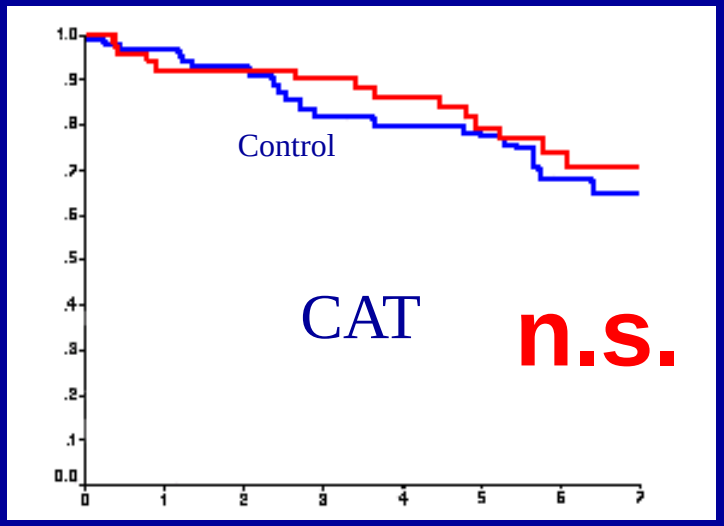


Epstein et al. JACC 2008, 52: 1122-1127

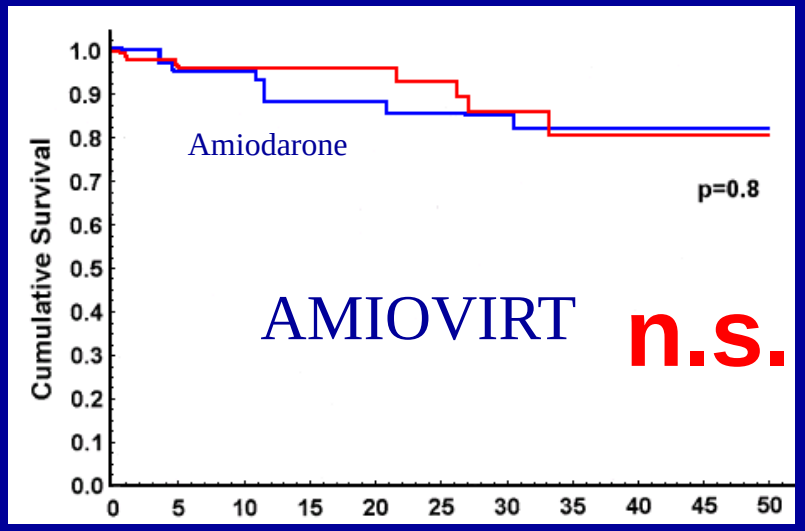
ICD therapy to prevent SCD

Study	Amiodarone		BB		ACEI/AT1		Statin		Total mortality
	ICD	Control	ICD	Control	ICD	Control	ICD	Control	(arrhythmic Death)
	%	%	%	%	%	%	%	%	p
CABG-Patch	6	3	16	10	64	68	23	23	0.64
MADIT	7	45	27	5	57	51	?	?	0.009
MUSTT	?	?	33	23	76	67	?	?	- (<0.001)
MADIT II	13	10	70	70	68	72	67	64	0.016 (<0.0001)
DINAMIT	8	14	87	87	95	94	77	80	ns
AVID	9	82	39	16	68	63	23	20	<0.02
CIDS	0	85	30	22	?	?	?	?	0.142
CASH	0	48	0	51	45	42	?	?	0.081
CAT			4	4	94	98	?	?	ns
AMIOVIRT	0	66	53	50	90	81	?	?	0.8
DEFINITE	4	7	86	84	84	87	?	?	0.08 (0.006)
SCD-HeFT	0	100/0	69	69/69	94	97/98	38	40/38	0.007

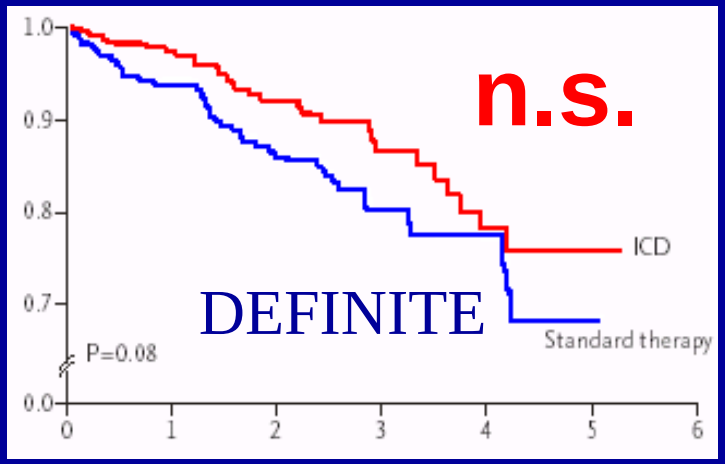
ICD therapy to prevent SCD in non-ischemic CM



Bänsch D. Circulation. 2002; 105; 1453-1458

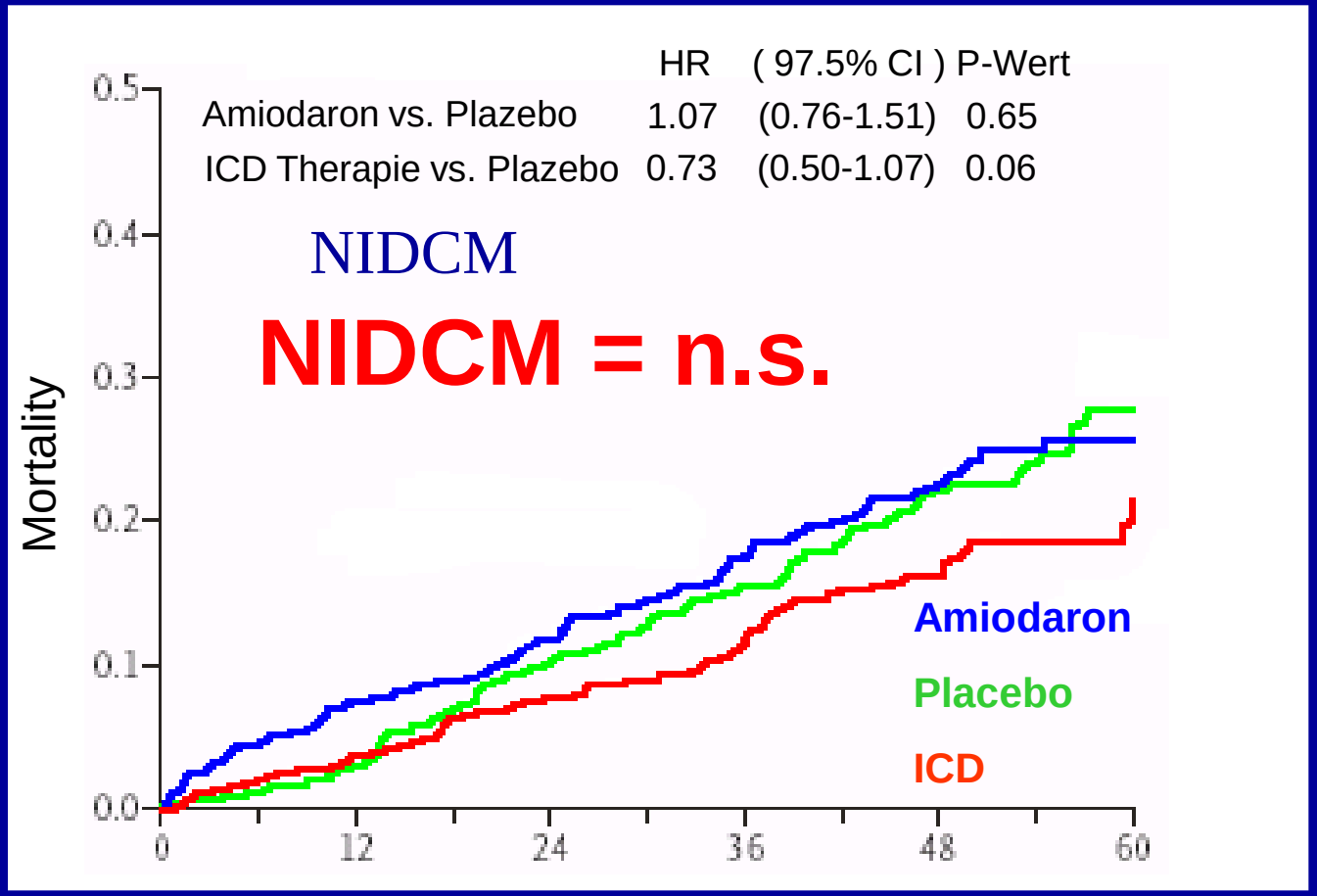


Strickberger SA. J Am Coll Cardiol. 2003; 41: 1707-12

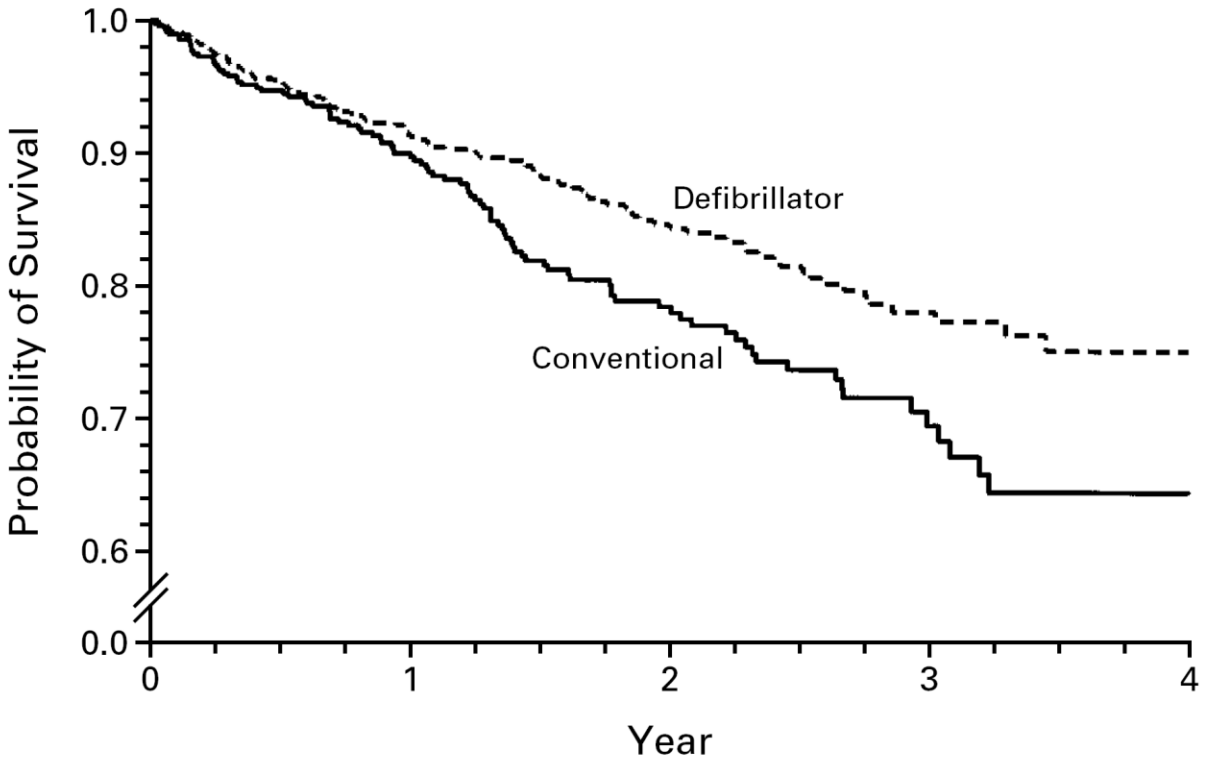


Kadish A. N Engl J Med . 2004; 350: 2151-8

ICD therapy to prevent SCD in non-ischemic CM



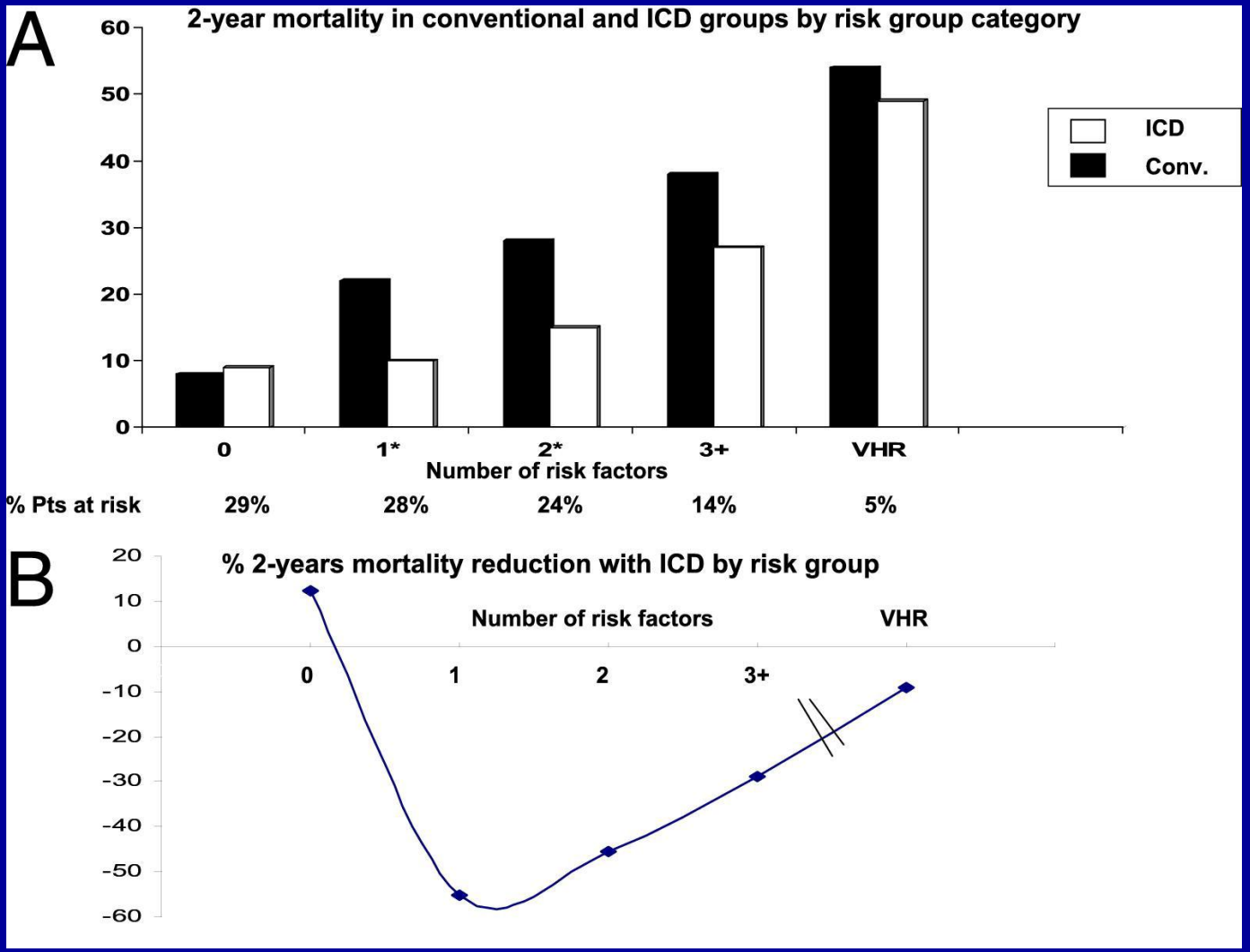
ICD therapy to prevent SCD post MI



No. at Risk					
Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

Moss AJ, et al. N Engl J Med 2002;346:877-83

ICD therapy to prevent SCD: role of competing RF

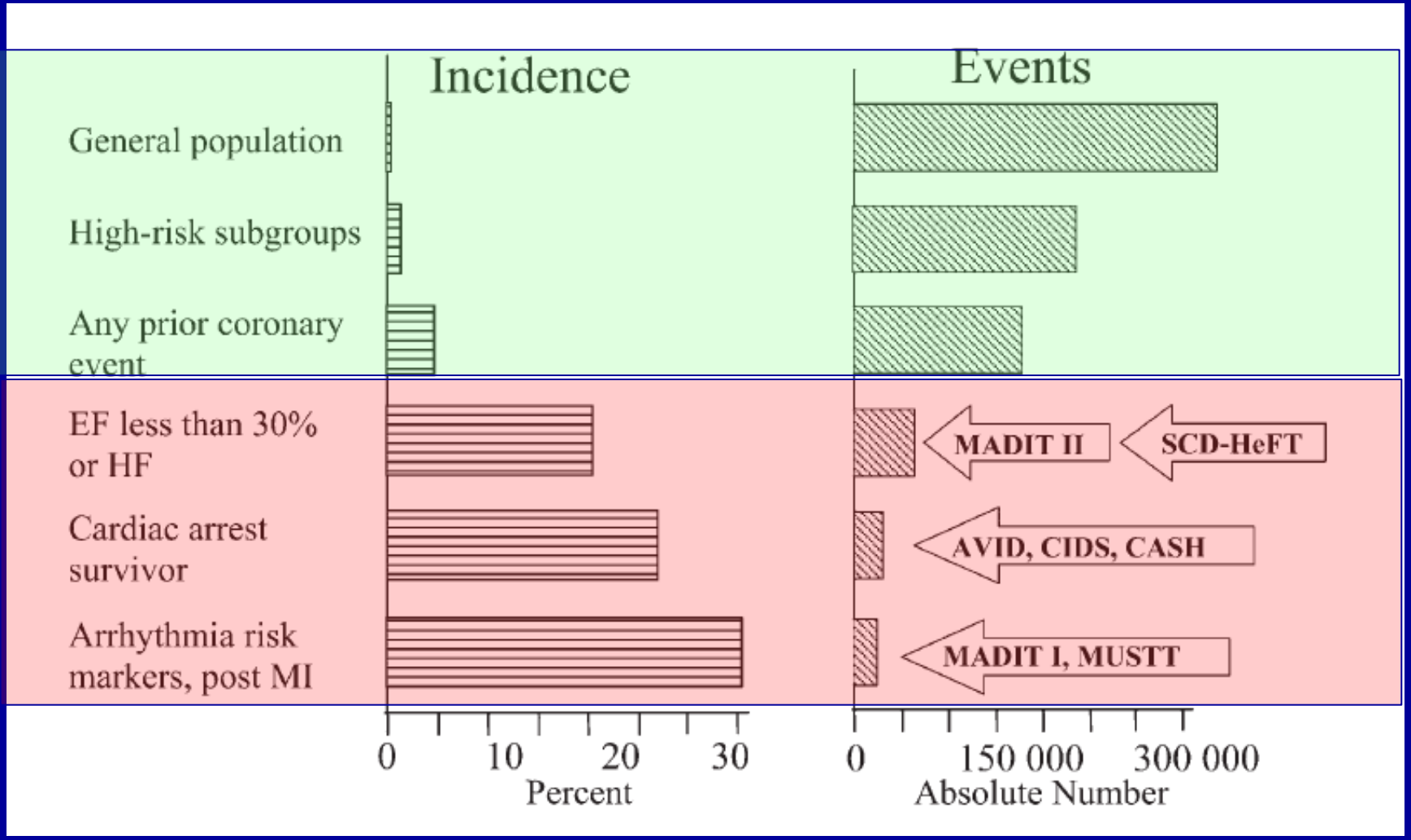


Goldenberg I, et al. J Am Coll Cardiol 2008;51:288-96

Prevention of SCD beyond the ICD: options

- Primary prevention of CAD / heart failure
  - life style modifications
  - prevention / treatment of metabolic syndrome
- Genetic risk stratification
- Appropriate / intense treatment of CAD / HF
- Electrical treatment of HF (CRT-P)
- EP interventions:
  - catheter ablation / substrate modification
  - modulation of autonomic tone

Absolute number of events and event rates of SCD

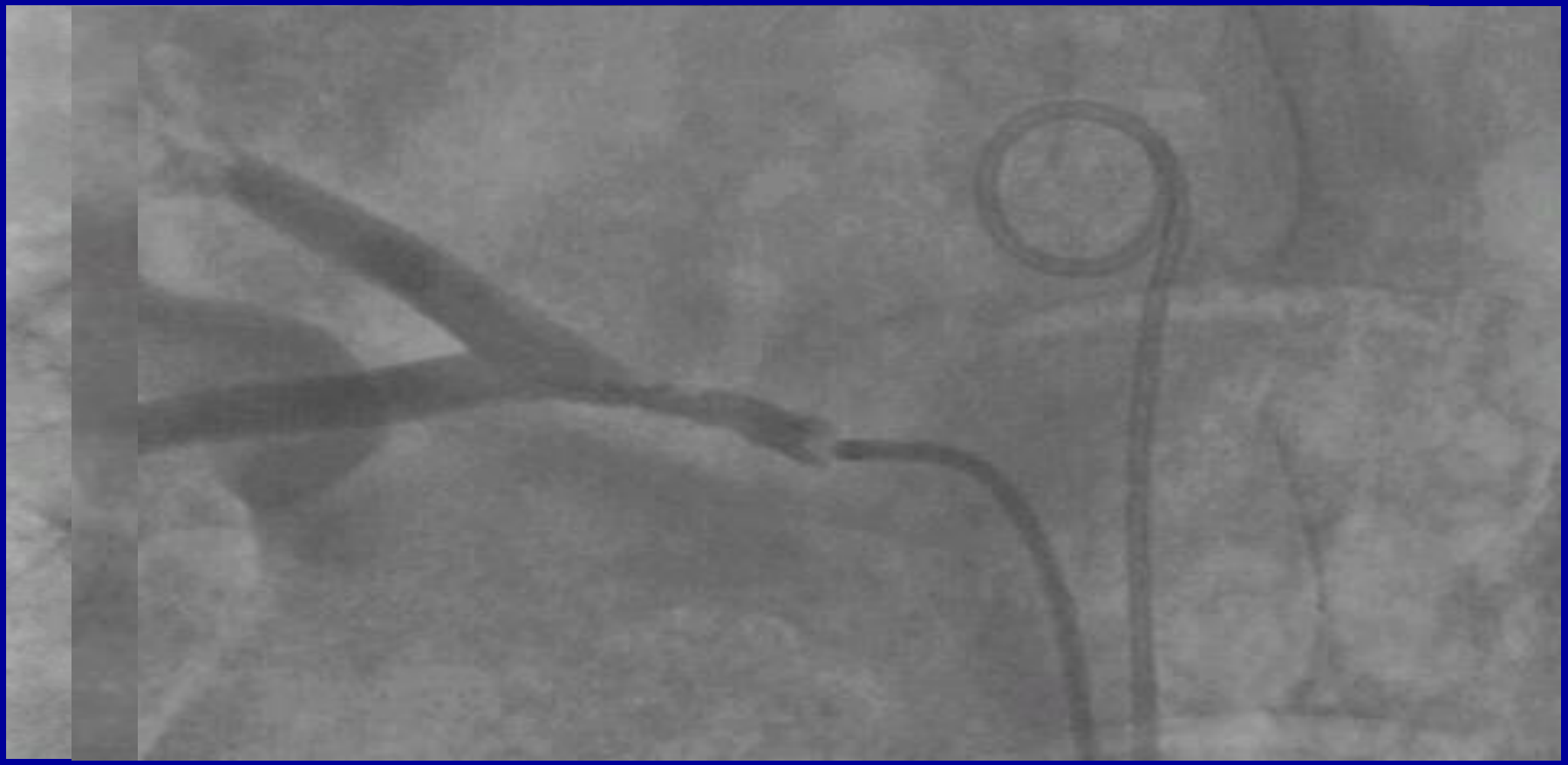


adopted from: Meyerburg RJ; Circulation 1992

Prevention of SCD beyond the ICD: “green group”

- Primary prevention of CAD / heart failure
  - life style modifications
  - prevention / treatment of metabolic syndrome
- Genetic risk stratification (?)
- Appropriate treatment of CAD / HF incl. CRT-P
- EP interventions:
  - ~~catheter ablation / substrate modification~~
  - modulation of autonomic tone (?)

Prevention of SCD: role of renal denervation?



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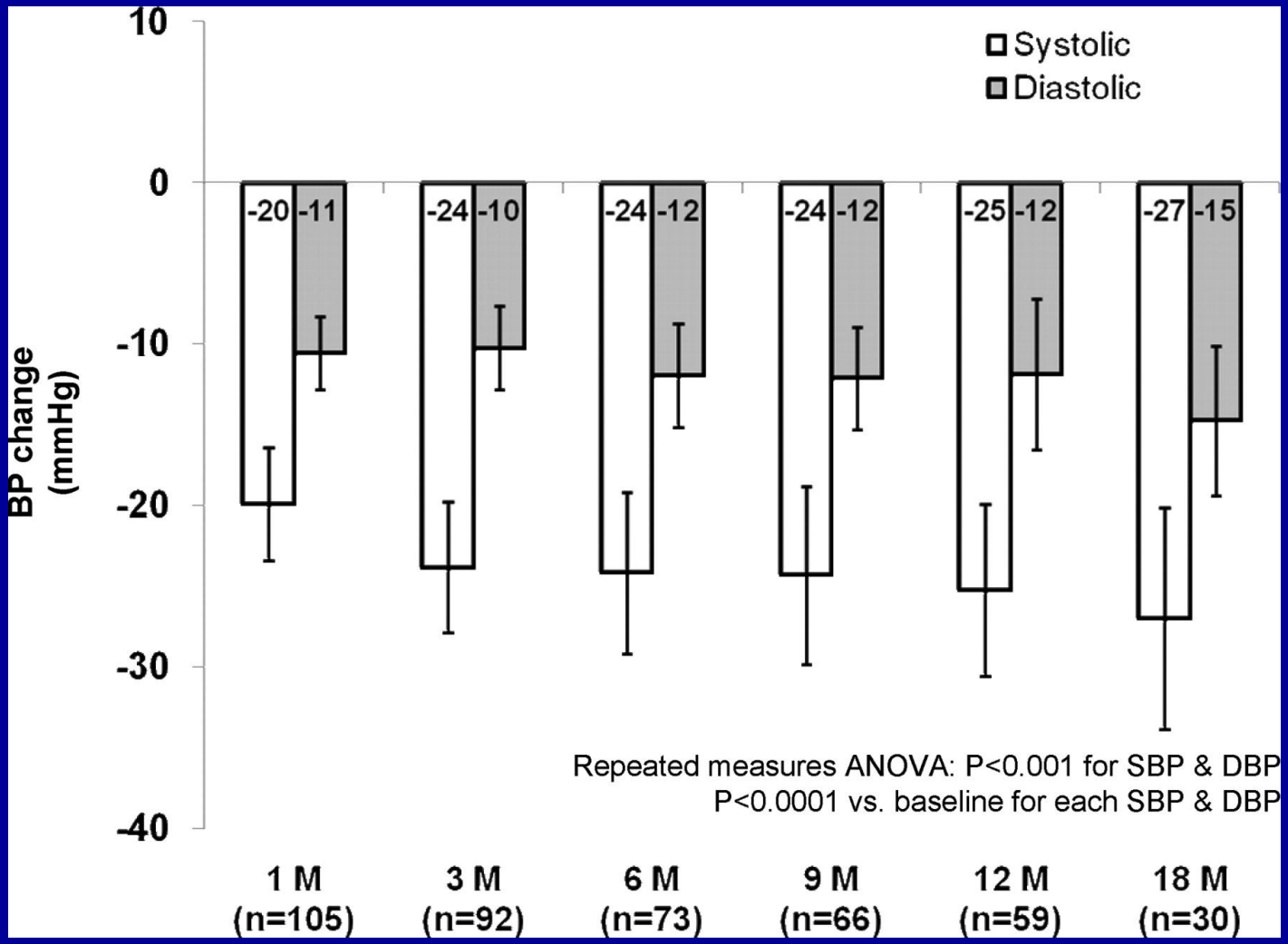

Krum H et al. Circulation 2011;123:209-215

Prevention of SCD beyond the ICD: “red group”

- Genetic risk stratification (?)
- Appropriate treatment of CAD / HF incl. CRT-P / D
- Evidence based ICD / CRT therapy
  - updated set of prospective studies
- EP interventions:
  - catheter ablation / substrate modification (?)
  - modulation of autonomic tone (?)