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SPECTRUM HEALTH

Brief Heart Failure Update: Two New Kids on the Block

David Fermin, MD FACC
Advanced Heart Failure Cardiologist
Spectrum Health, Grand Rapids, MI

No disclosures

[Master: Sequential Agenda]
Example of Sequential Agenda

SPECTRUM HEALTH

Objectives

Introduce two new pharmacologic classes/agents for systolic heart failure:

- Ivabradine (Corlanor)
- Valsartan-sacubitril (Entresto)

Review indications and guidelines for these new medications

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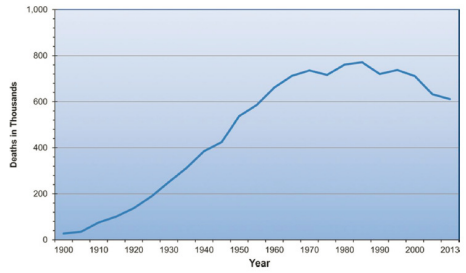
SPECTRUM HEALTH

Deaths attributable to diseases of the heart (United States: 1900–2013).



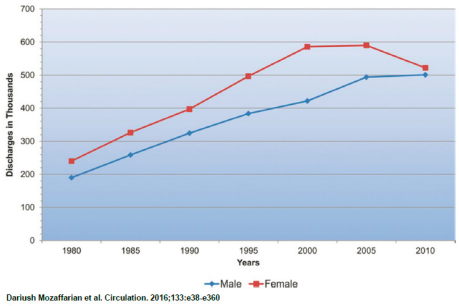
Dariush Mozaffarian et al. Circulation. 2016;133:e38-e360

American Heart Association.

3

SPECTRUM HEALTH

Hospital discharges for heart failure by sex (United States: 1980–2010).



Dariush Mozaffarian et al. Circulation. 2016;133:e38-e360

American Heart Association.

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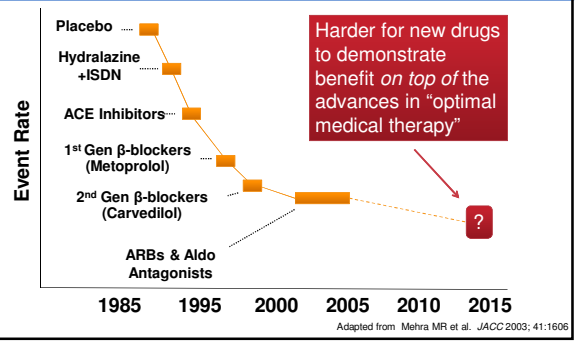
Limits to New Medical Therapy?



Adapted from Mehra MR et al. *JACC* 2003; 41:1606

SPECTRUM HEALTH

New medical therapies

- Exciting year for heart failure with reduced ejection fraction (HFrEF)
- In addition to ACEi/ARB, beta blocker, mineraolcorticoid receptor antagonists (MRA) we gained two novel classes:
  - Sinus node inhibitor
  - **ARNI** (angiotensin receptor blocker-neprilysin inhibitor)

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Heart Rate hypothesis?

- Higher heart rate is independently associated with poorer outcomes in heart failure.
- In heart failure, beta blocker dose is often limited by hypotension or fatigue side effects
- Could reducing the heart rate beyond maximally tolerated beta blocker dose improve outcomes?
- Ivabradine (Corlanor): Reduces HR at SA node
  - Blocks the "funny" current (I_f) at the sinus node.
  - Reduces *sinus* rate.

Association of Heart Rate and Outcomes in a Broad Spectrum of Patients With Chronic Heart Failure
Results From the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) Program

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SHIFT Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

RANDOMIZATION

Corlanor® 5 mg 2x/day (n = 3,241) — 2.5 mg, 5 mg, or 7.5 mg 2x/day according to heart rate and symptoms of bradycardia

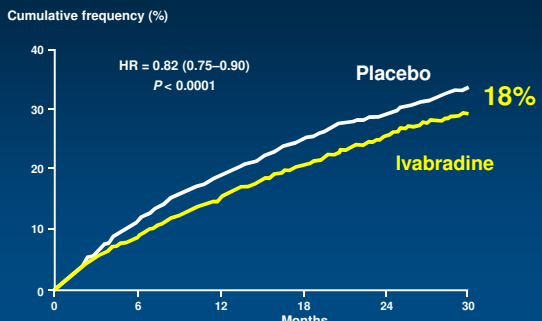
Day 0 · Day 14 · Day 28 · Month 4 · Every 4 Months

Placebo 2x/day (n = 3,264)

Median follow-up: 22.9 months

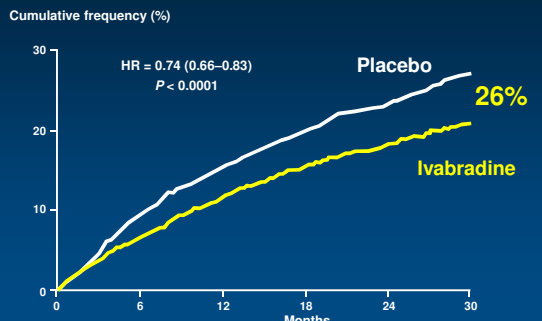
Swedberg K, et al. *Lancet.* 2010;376(9744):875-885 www.shift-study.com

SHIFT Primary composite endpoint (CV death or hospital admission for worsening HF)



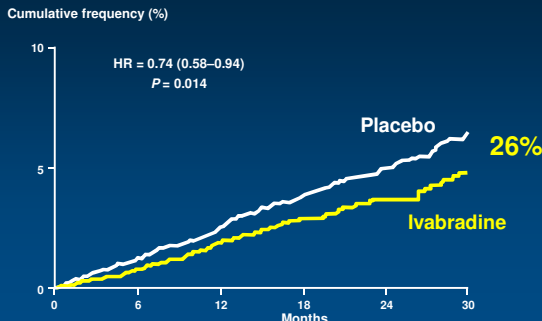
Swedberg K, et al. *Lancet.* 2010;376(9744):875-885 www.shift-study.com

SHIFT Hospitalization for HF



Swedberg K, et al. *Lancet.* 2010;376(9744):875-885 www.shift-study.com

SHIFT Death from heart failure



Swedberg K, et al. *Lancet.* 2010;376(9744):875-885 www.shift-study.com

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Answer (SHIFT Trial): It worked!

- Composite endpoint (CV death or hospitalization): Reduced 18%
- Hospitalization for HF: Reduced 26%
- Death from HF: Reduced 26%

Reducing the HR,
in addition to maximally tolerated BB,
reduced hospitalization (and HF death)

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Indications for Corlanor

Indication: Reduce hospitalization for worsening heart failure

Which patients?

- LVEF ≤ 35%
- Sinus rhythm
- Resting HR ≥ 70
- On maximally tolerated doses of beta-blockers (or unable to take beta-blockers)

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Corlanor: Important Points

- NOT for diastolic dysfunction patients.
- NOT for control of atrial fibrillation (in fact in the SHIFT trial there was a small increase in AF in patients on ivabradine)
- Does NOT cause hypotension (in fact there is a small increase in blood pressure)
- The higher the HR, the higher the HR reduction and the more likely the apparent benefit. HR ≥ 70 on maximal beta blocker

SPECTRUM HEALTH

"LCZ696" – Now Known as Entresto

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

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Paradigm HF Trial Design: At screening

- On ACEI or ARB ≥ 4 weeks (enalapril 10 mg daily or equivalent)
- On maximal tolerated doses of beta blockers
- BP ≥ 100 mmHg at screening
- CrCl ≥30
- K ≤ 5.2

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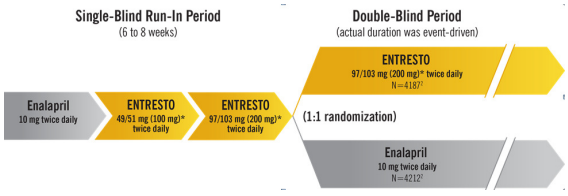
PARADIGM-HF Study Design



- This was the largest HFrEF mortality – hospitalization trial ever (>8,000 patients)
- Run-in period for tolerance due to previous trials of neprilysin inhibitors with higher incidence of angioedema

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McMurray et al. Eur J Heart Fail 2013

SPECTRUM HEALTH

It worked. All endpoints positive

Reductions:

- 20% CV death / HF hosp
- 16% all cause death
- 20% CV death
- 21% HF hosp

Adverse events:

- More hypotension and nonserious angioedema than enalapril group
- Note: prior neprilysin inhibitor trial (omapatrilat) had higher incidence of angioedema than

SPECTRUM HEALTH

Entresto: Important Points

- It works. We must consider switching to it in chronic, symptomatic (NYHA II+) HFrEF patients.
- Select patients: Not if hypotensive, hyperkalemic, CKD 4-5 or any prior angioedema.
- It replaces the ACEI/ARB (make sure that your patients know to stop the ACEI / ARB).
- Be careful! If questionable use the low dose initiation (24/26 mg BID).

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How to start Entresto

1. Prescribe 49/51 mg tablet bid. (Consider low dose initiation).
2. Instruct patient to stop ACEI 36 hours before the 1st dose (~2 days).
3. Order BMP 1 week after starting
4. Reassess at weeks and if BP and labs allow, increase to next dose (up to maximum 97/103 mg bid).

LOW DOSE INITIATION: 24/26 mg bid

- If not currently on ACEI or ARB (but no prior angioedema)
- On doses less than 10 mg enalapril, 10 mg lisinopril or 80 mg valsartan
- eGFR < 30, may start with caution
- Moderate hepatic impairment

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New ACC/AHA Guidelines 2016

Guideline update created specifically based on the significant positive results from these two trials:

Drug	Category of Recc.	Guideline	Benefit
Ivabradine (Corlanor)	IIa	Beneficial in: ▪ HFrEF EF ≤ 35% ▪ Sinus rhythm ▪ Max beta blocker ▪ HR ≥ 70 bpm	▼ hospitalization
ACEI/ARB/ARNI	I	Beneficial in HFrEF ▪ ARNI now on first line standing with ACE/ARB	▼ morbidity/ mortality
Valsartan-sacubitril (Entresto)	I	In pts with chronic sx HFrEF (NYHA II+) to replace ACEI/ARB for further benefit	▼ morbidity/ mortality

SPECTRUM HEALTH

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Go to "View… Master… Slide Master…" to access and change out images.

SPECTRUM HEALTH

Screening for Sudden Cardiac Death Risk in the Young

David Fermin, MD FACC
Program Director, Hypertrophic Cardiomyopathy
Spectrum Health, Grand Rapids, MI

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[Master: Sequential Agenda]
Example of Sequential Agenda

SPECTRUM HEALTH

Objectives

- Describe the epidemiology of sudden cardiac death/arrest (SCD/SCA) in the young
- Review guidelines and controversies in screening young athletes for cardiovascular conditions that raise SCD risk
- Demonstrate role and effectiveness of AEDs in SCD situations

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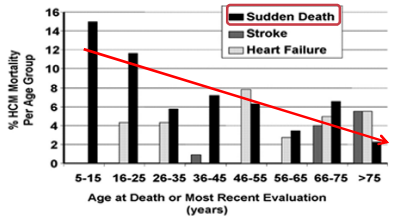
SPECTRUM HEALTH

HCM - Sudden death and age

SCD is most common before ≈25 years of age, whereas heart failure and stroke generally occur later in life



Maron B. Circulation 2010;121:445-456

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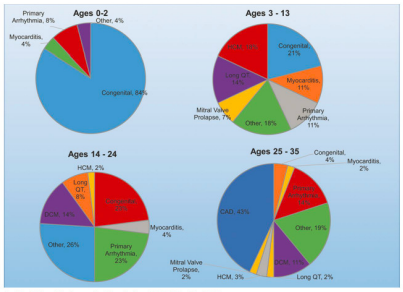
Detailed causes of arrest by age group.



Dariush Mozaffarian et al. Circulation. 2016;133:e38-e360

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American Heart Association.

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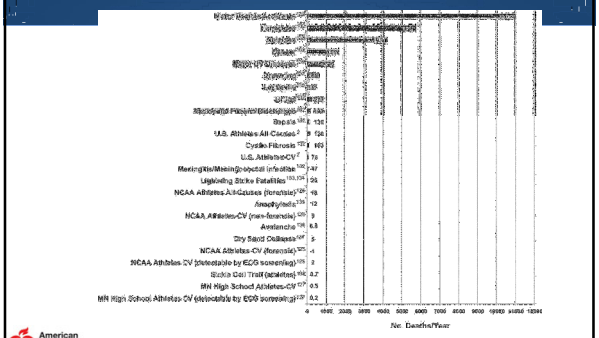
Frequencies of death attributable to all causes in young individuals aged <25 years.



American Heart Association.

SPECTRUM HEALTH

Athletic Preparticipation Screening

The role of screening tests is controversial

A single Italian study supported the recommendation of ECG screening for *all* high school athletes in Italy

Contrast: a large US study based on retrospective data from Minnesota State High School League records:

- Almost 4 million "athlete-seasons"
- Incidence of SCD was 0.24 per 100,000 athlete-years

SPECTRUM HEALTH

Assessment of the 12-Lead ECG as a Screening Test for Detection of Ca

COUNCIL PERSPECTIVES

Interassociation Consensus Statement on Cardiovascular Care of College Student-Athletes

Brian Hainline, MD,[a] Jonathan A. Drezner, MD,[b] Aaron Baggish, MD,[c] Kimberly G. Harmon, MD,[b] Michael S. Emery, MD,[d] Robert J. Myerburg, MD,[e] Eduardo Sanchez, MD, MPH,[f] Silvana Molossi, MD, PhD,[g] John T. Parsons, PhD, ATC,[a] Paul D. Thompson, MD[h]

ABSTRACT

Cardiovascular evaluation and care of college student-athletes is gaining increasing attention from both the public and medical communities. Emerging strategies include screening of the general athlete population, recommendations of permissible levels of participation by athletes with identified cardiovascular conditions, and preparation for responding to unanticipated cardiac events in athletic venues. The primary focus has been sudden cardiac death and the utility of screening with or without advanced cardiac screening. The National Collegiate Athletic Association convened a multi-disciplinary task force to address cardiovascular concerns in collegiate student-athletes and to develop consensus for an interassociation statement. This document summarizes the task force deliberations and follow-up discussions, and includes available evidence on cardiovascular risk, pre-participation evaluation, and the recognition of and response to cardiac arrest. Future recommendations for cardiac research initiatives, education, and collaboration are also provided. (J Am Coll Cardiol 2016;■■■) © 2016 by the American College of Cardiology Foundation.

Circulation, 130(15):1303-1334 October 7, 2014

JACC Journals

From: Incidence of Sudden Cardiac Death in Minnesota High School Athletes 1993–2012 Screened With a Standardized Pre-Participation Evaluation

	AY	No. of Cardiac Deaths	Incidence (/100,000 AY)
MSHSL 2003-2012	917,069	1	0.11
MSHSL 1993-2012	1,666,509	4	0.24
Italian 2001-2004 (2)	NA	2	0.43
Italian 1979-2004 (2)	2,938,730 (estimated)	55	1.90
Division 3 NCAA (3)	760,258	8	1.05
Division 2 NCAA (3)	424,572	10	2.38
Division 1 NCAA (3)	788,023	27	3.45

Table Title:

Incidence of SCD in MSHSL Athletes Compared With Italian and NCAA Rates

J Am Coll Cardiol. 2013;62(14):1298-1301. doi:10.1016/j.jacc.2013.05.080

JACC Journals

Routine ECG Screening of Young Athletes: Can This Strategy Ever Be Cost Effective?•

J Am Coll Cardiol. 2016;68(7):712-714. doi:10.1016/j.jacc.2016.06.017

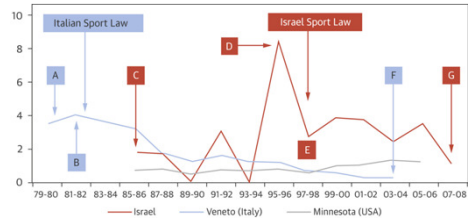
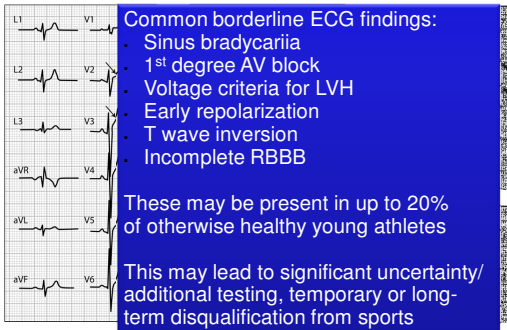


Figure Legend:

Sudden Cardiac Death in Athletes

An Italian study (blue)(6) concluded that electrocardiography (ECG) screening (started in 1982) significantly reduced the incidence of sudden cardiac death by comparing the sudden death in the 2-year pre-screening period (A to B) with the post-screening period (B to F). The study by Steinvil et al. (7) is depicted by the red graph, which compared the 12 years before screening (C to E) with the 12 years after the onset of mandatory ECG screening (E to G). Had they limited comparison of the post-screening period to the 2-year period preceding the enforcement of screening in Israel (D to E vs. E to G, as performed in the Italian study), they would have concluded erroneously that screening saved the lives of athletes in Israel. The study from Minnesota (gray)(5) shows a low mortality rate in a population of athletes not undergoing systematic ECG screening.

The Problem: ECG Abnormalities/Variants are Common in Young Athletes



Common borderline ECG findings:
- Sinus bradycariia
- 1st degree AV block
- Voltage criteria for LVH
- Early repolarization
- T wave inversion
- Incomplete RBBB

These may be present in up to 20% of otherwise healthy young athletes

This may lead to significant uncertainty/ additional testing, temporary or long-term disqualification from sports

Domenico Corrado et al. Eur Heart J 2010;31:243-259

European Heart Journal

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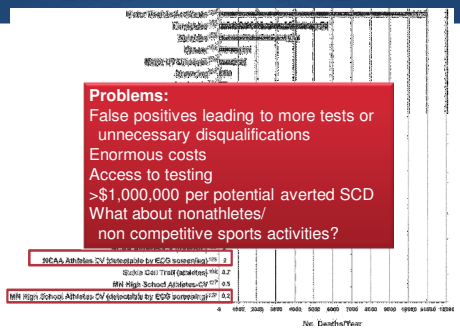
Frequencies of death attributable to all causes in young individuals aged <25 years.



Problems:
False positives leading to more tests or unnecessary disqualifications
Enormous costs
Access to testing
>$1,000,000 per potential averted SCD
What about nonathletes/ non competitive sports activities?

American Heart Association.

Barry J. Maron et al. Circulation. 2014;130:1303-1334

SPECTRUM HEALTH

"Free Student Athlete Heart Screening" Programs

Potential problems:
- **At best, well intentioned and altruistic**
- **Limited in scope and capacity**
- **Messaging unclear, not c/w guidelines**
- **At worst, misguided and may encourage secondary gain (PR, unnecessary followup testing)**
- **Resources better spent on comprehensive H&P for all, and AEDs**

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Sudden Cardiac Death in the Athlete

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Preparticipation Screening

- AHA/ACC/HRS has recommended screening young athletes every 2 to 4 years
- Aspects of cardiovascular screening:
  - History should include:
    - 1. Prior exertional CP, syncope, excessive SOB.
    - 2. PMH of heart murmur or HTN.
    - 3. FMH of early death, or HCM, LQTS, Marfans, IDCM.
  - Examination should include:
    - 1. Cardiac auscultation.
    - 2. Assessment of femoral arteries.
    - 3. Recognition of stigmata of Marfan's syndrome.
    - 4. Blood pressure.
    - *No recommendation for universal EKG*

Maron BJ et al. Circulation; Estes et al. JCE 2001

2015-2016 SPORTS QUALIFYING PHYSICAL HISTORY FORM

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Minnesota State High School League

HEART HEALTH QUESTIONS ABOUT YOU

7. Have you ever passed out or nearly passed out DURING exercise?
8. Have you ever passed out or nearly passed out AFTER exercise?
9. Have you ever had discomfort, pain, tightness, or pressure in your chest during exercise?
10. Does your heart race or skip beats (irregular beats) during exercise?
11. Has a doctor ever told you that you have? (circle):
    High blood pressure A heart murmur High cholesterol A heart infection
    Rheumatic fever Kawasaki's Disease
12. Has a doctor ever ordered a test for your heart? (for example, ECG/EKG, echocardiogram, stress test)
13. Do you get lightheaded or feel more short of breath than expected during exercise?
14. Have you ever had an unexplained seizure?
15. Do you get more tired or short of breath more quickly than your friends during exercise?

HEART HEALTH QUESTIONS ABOUT YOUR FAMILY

16. Has any family member or relative died of heart problems or had an unexpected or unexplained sudden death before age 50 (including unexplained drowning, unexplained car accident, or sudden infant death syndrome)?
17. Does anyone in your family have hypertrophic cardiomyopathy, Marfan syndrome, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, short QT syndrome, Brugada syndrome, or catecholaminergic polymorphic ventricular tachycardia?
18. Does anyone in your family have a heart problem, pacemaker, or implanted defibrillator?.
19. Has anyone in your family had unexplained fainting, unexplained seizures, or near drowning?

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I think it would be best to:
- Apply athletic preparticipation questions to all adolescents in pediatrician/FP office well visit setting (or as part of school program for all students)
- Order testing (ECG, echocardiogram) and subspecialty referral as needed

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ACC/AHA Scientific Statement:

"…we wish to underscore that SDs attributable to unsuspected genetic/congenital cardiovascular diseases are not…confined to trained athletes. Rather, it is likely that the absolute number of these SD events is higher in the larger population of young people who have not elected to engage in organized sports…it is very likely that the majority of those who die suddenly of HCM or other cardiovascular diseases do so unassociated with competitive athletic lifestyles.

SDs in nonathletes do not receive the same intense media exposure and scrutiny as athletes, which probably accounts for the misperception that such events are less common among them. Indeed, a large…study from France showed SDs in young noncompetitive or recreational athletes were >15-fold more frequent than in competitive athletes; only 6% of sports-related cardiac arrests occurred in competitive situations (10 SDs per million per year), whereas >90% took place in recreational settings.

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Maron JACC 2014; Natl Fed of St. HS Assoc (http://www.nfhs.org/participation/); Marijon Circ 2014

SPECTRUM HEALTH

Syncope and SCD:

What to think and what to do if they occur despite screening

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Syncope in the Athlete

- Syncope and presyncope in the athlete present a unique clinical challenge
- While syncope can result from benign, it can recur, cause serious trauma, place others at risk, and portent risk for SCD
- The cause is frequently difficult to define despite comprehensive evaluation
- If no cause for syncope is determined, restriction form athletic may be required
- Risk varies by age, gender, nature of the sport, underlying structural heart disease, and etiology of the syncope
- Current guidelines for restriction are based on expert opinion rather than prospective studies or data

Estes, NAM et al Report of the NASPE Policy Conference on arrhythmias in the athlete JCE, 2001:12:1208-1219.
Goldschlager, N et al Etiologic Considerations in the patient with syncope and an apparently normal heart Arch Int Med 2003:163:151-162

SPECTRUM HEALTH

AEDs in Sports

Provide a means of early defibrillation and the potential for effective secondary prevention of SCD

- Athletes
- Students
- Staff
- Spectators
- Coaches
- Officials
- Visitors

Inter-Association Task Force Recommendations on Emergency Preparedness and Management of Sudden Cardiac Arrest in High School and College Athletic Programs: A Consensus Statement

Jonathan A. Drezner, MD, Ron W. Courson, ATC, PT,† William O. Roberts, MD,‡ Vincent N. Mosesso, Jr MD,§ Mark S. Link, MD,¶ and Barry J. Maron, MH#*

Drezner JA Clin J Sport Med. 2007

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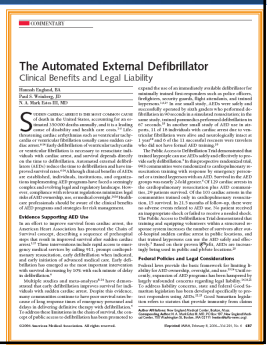
AED-Public Policy, Legislation and Legal Liability

State and Federal Polices

Legal Protection for Owners, Users, Medical Directors

Court Opinions

As evidence-based medicine has defined the clinical benefits of AED use, public policy, laws, funding programs, and court decisions have served the societal interest of promoting use of AEDs by minimizing legal liability.


COMMENTARY

The Automated External Defibrillator
Clinical Benefits and Legal Liability

Hiroshi England, BA
Paul S. Weinberg, JD
N. A. Mark Estes III, MD

England, H Weinberg P, Estes N JAMA 2006

SPECTRUM HEALTH

Scope of the problem

- SCD is rare, but serious
- When it does happen, outcomes have been poor (avg survival 11% pre-2006)
- This could change with more widespread AED use – is there evidence?

Drezner Heart Rhythm 2008

Outcomes from sudden cardiac arrest in US high schools: a 2-year prospective study from the National Registry for AED Use in Sports

Jonathan A Drezner,[1] Brett G Toresdahl,[1] Ashwin L Rao,[1] Ella Huszti,[2] Kimberly G Harmon[1]

2-year prospective observational study

2,149 high schools

Primary outcome measure:

Survival to hospital discharge

BJSM 2013

SPECTRUM HEALTH

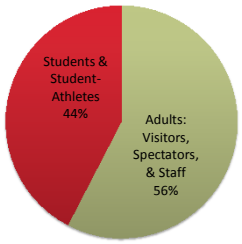
Cases of SCA

2,149 high schools

87% with AED program

95% 2-year follow-up

59 cases of SCA on campus



79% male

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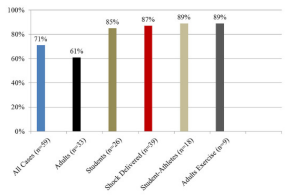

Figure 1 Survival to hospital discharge in students and adults with sudden cardiac arrest on a high school campus.

Table 5. Number of Survivors of Out-of-Hospital Cardiac Arrest.

Characteristic	CPR Only	CPR plus AED	P Value	
			Unadjusted	Adjusted
Definite cardiac arrests — no.	107	128	0.09*	
Residential units	37	33		
Public units	70	95		
Survivors of definite arrest — no.	15	30	0.03†	0.03*‡

Survival doubled with onsite AED (in both studies)

The Public Access Defibrillation Trial Investigators. N Engl J Med 2004;351:637-646.

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Significance

School-based AED programs demonstrate a high survival rate for victims of SCA occurring on school campus

SCA in students and student-athletes is largely a survivable event through prompt treatment and access to an AED

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ACC/AHA Guidelines

- Schools and other organizations hosting athletic events or providing
- management, should be available at sites to which patients are taken by EMS *(Class I; Level of Evidence A).*

AHA/ACC Scientific Statement

Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 12: Emergency Action Plans, Resuscitation, Cardiopulmonary Resuscitation, and Automated External Defibrillators

A Scientific Statement From the American Heart Association and American College of Cardiology

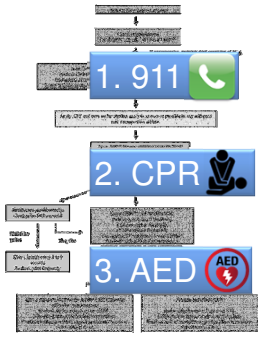
Mark S. Link, MD, FACC, Chair; Robert J. Myerburg, MD, FACC; N.A. Mark Estes III, MD, FACC; on behalf of the American Heart Association Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and the American College of Cardiology

Management of SCA in The Collapsed/Unresponsive Athlete

SPECTRUM HEALTH

Suspect SCA in any collapsed and unresponsive athlete

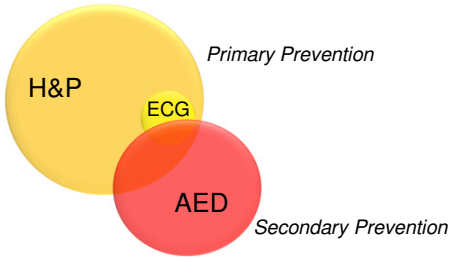
An AED should be applied as soon as possible for rhythm analysis and defibrillation if indicated



Drezner; *Heart Rhythm* 2007

SPECTRUM HEALTH

Strategies for Prevention of SCD



Complementary Strategies

SPECTRUM HEALTH

Sudden Cardiac Death: Conclusions

- Young athletes may have SCD due to underlying heart disease (HCM, ARVC, long QT, Marfan, etc.) but incidence is rare
- Current screening techniques lack sensitivity and specificity for detecting athletes at risk for SCD. ECG has not been shown to be clinically/financially effective as a screening tool.
- If you do find an abnormality, refer to pediatric cardiology – further evaluation depends on the condition.
- Unexplained syncope indicates a high risk for SCD. Comprehensive cardiac evaluation is warranted.

SPECTRUM HEALTH

Sudden Cardiac Death (SCD): Conclusions

- AEDs are effective for SCD. Further studies are needed to assess the efficacy and cost of making AEDs available at all athletic events (but note the benefit of AEDs for all people attending public events)
- Remember that SCD does not just occur in athletes or in children doing athletic activities – more universal screening by history/physical in primary care/school setting may be best
- Sudden syncope and unresponsiveness is SCD until proven otherwise: **911—CPR—AED**

SPECTRUM HEALTH

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