Risk Stratification for Arrhythmic Sudden Cardiac Death

Identifying the Roadblocks

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Introduction

- the range for the number of sudden cardiac deaths (SCDs) per year in the United States alone has been reported from 184,000 to 462,000
- 50% to 70% are due to tachyarrhythmic mechanisms
  - Previously unrecognized cardiac disease
  - Unstable plaques
  - Acute or healed MI

Dichotomization of Risk and Risk Stratification

- Risk is a challenging concept for physicians and patients
- Implantable cardioverter-defibrillator (ICD)
  - Indication?
  - Risk?
  - Gene? (Variable expression, environmental interactions, modifier genes)
  - Ex: LVEF: 35%
- A continuous risk function

Competing Risks

- Competing risks for nonsudden death can modify the relationship between arrhythmia risk and mortality
- Multicenter Unsustained Tachycardia Trial (MUSTT) in which a scoring system was generated for total mortality and arrhythmic death:
  - ejection fraction
  - history of heart failure
  - Intraventricular conduction defect
  - inducible ventricular tachycardia

Dynamic Risk Profiling

- Many risk functions are likely dynamic
- Valsartan in Acute Myocardial Infarction (VALIANT): the monthly risk of SCD declined from 1.4% the first month to 0.14% after 2 years
- Risk Estimation Following Infarction—Noninvasive Evaluation (REFINE) : risk stratification testing 2 to 4 weeks after MI did not predict risk of 10 to 14 weeks did
- Risk of sudden death is also known to be dramatically increased during exertion

Statistical Issues

- Odds ratio or relative risk of sudden death
- The identification of such risk factors can be helpful in:
  - understanding mechanisms
  - identifying new targets for therapy
  - Initiating therapies to prevent the outcome of interest
- Odds ratio > 15 to 20
- Receiver operating characteristic (ROC)
- REFINE (combined AUC 0.74)
  - ejection fraction (AUC 0.62)
  - repolarization alternans(AUC 0.62)
  - heart rate turbulence (AUC 0.66)

What Information Do Implantable Cardioverter-Defibrillator Clinical Trials Provide Regarding Risk Stratification?

- The single most widely used criterion or risk stratification tool for implantation of an ICD is a depressed left ventricular ejection fraction, typically 30% to 35%.
- ICD, LVEF, unknown risk, SCD
  - penicillin, pharyngitis, positive culuture, acute rheumatic fever
- a noninferiority or equivalence trial would be required

Stakeholders' Varying Views on Risk Stratification

- *Individual investigators* often develop a strong interest in a particular technique and design their research efforts around the specific technique
- *Payors* are focused on data-driven use of devices, but not necessarily the research questions

Financial Issues

- ICD: the invasive nature, significant expense and risk
- Identify those patients who currently meet criteria for an ICD but derive no benefit from its use
- A post-hoc from MADIT II

Table. Projected Sample Size for a Noninferiority Trial Postulating That Survival With Medical Therapy Alone Is No Worse Than Survival With an Implantable Cardioverter-Defibrillator

	2-Year Mortality (ICD Patients), %	Margin of Noninferiority, %	Sample Size
Low-risk group	8	1	17 717
	8	1.6	7375
Very-high-risk group	50	2	13 128
	50	5	2248
	50	8	856

Importance of Risk Stratification

- From the perspective of the patient, a clearer delineation of risk may lead to a more informed decision about therapeutic options.

Conclusion

- General importance of SCD, the history of risk stratification research, and our current state of knowledge
- Forming a solid foundation for risk stratification with the currently available clinical information and statistical approaches
- An era of new imaging techniques, proteomics, and genomic approaches is likely to emerge.

Sensitivity of the Aortic Dissection Detection Risk Score, a Novel Guideline-Based Tool for Identification of Acute Aortic Dissection at Initial Presentation

Result From the International Registry of Acute Aortic Dissection

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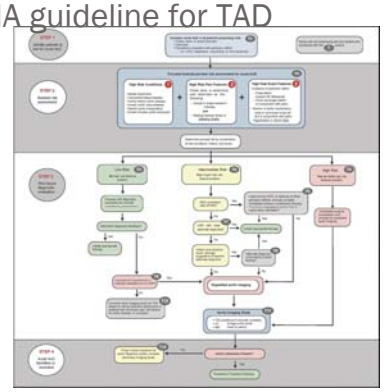
Background

- Acute aortic dissection (AD), among the most lethal of cardiovascular catastrophes, is suspected at initial evaluation in fewer than half of patients ultimately diagnosed with the disease.
- A single case of acute AD would be expected in only 1 in 10,000 emergency department presentations.
- Signal-to-noise theory

Background

- Symptoms:
  - Chest pain, back pain, abdominal pain
- Related signs of perfusion deficit:
  - Stroke, MI, limb ischemia, mesenteric ischemia
- Accurate identification or exclusion of the disease requires an advanced imaging study.
- The cost and radiation exposure would be prohibitive.

AHA guideline for TAD



Method

- Patients with acute AD enrolled in IRAD(International Registry of Acute Aortic Dissection) centers between January 1, 1996 and December 31, 2009(24 centers).
- Acute AD was defined as any nontraumatic dissection with in 14 days of symptoms onset

High-risk clinical markers

- High-risk predisposing conditions
- High-risk pain features
- High-risk examination features

High-risk predisposing conditions

- thoracic aortic aneurysm (14.7%)
- known aortic valve disease (11.9%),

High-risk pain features

- Abrupt onset of pain (79.3%)
- Severe intensity of pain (72.7%)
- Pain described as ripping or tearing (21.7%)

High-risk examination features

- A new murmur of aortic insufficiency in conjunction with pain (23.6%) and a pulse deficit or systolic blood
- Pressure differential between extremities (20.3%)

ADD Score

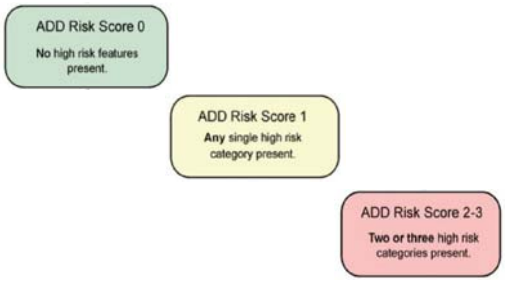


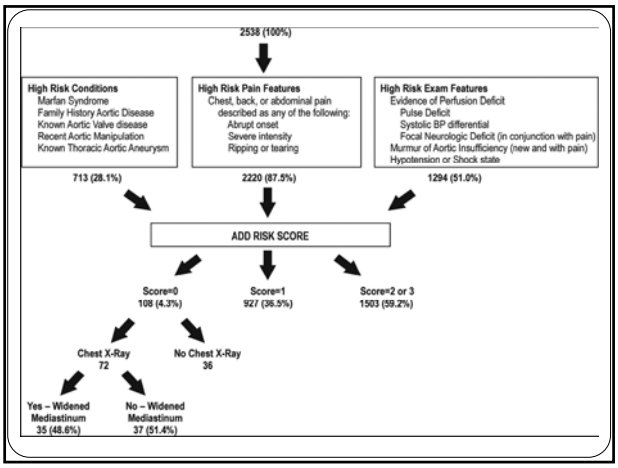
Table 1. Number of Patients With Acute Aortic Dissection Presenting With 1 or More Clinical Risk Markers (n=2538)

No. of Risk Markers	No. of Patients	Percentage of Patients
0	108	4.3
1	307	12.1
2	666	26.2
3	750	29.6
4	426	16.8
5	187	7.4
6	79	3.1
7	15	0.6
Total	2538	100.0

Table 2. Number of Patients With Acute Aortic Dissection Identified by Each Clinical Risk Marker (n=2538)

	No. of Patients	Percentage of Patients
01: Marfan syndrome	110	4.3
02: Family history of aortic disease	48	1.9
03: Known aortic valve disease	303	11.9
04: Recent aortic manipulation	70	2.8
05: Known thoracic aortic aneurysm	374	14.7
06: Abrupt onset of pain	2012	79.3
07: Severe pain intensity	1845	72.7
08: Ripping or tearing pain	551	21.7
09: Pulse deficit or SBP differential	515	20.3
10: Focal neurological deficit (in conjunction with pain)	273	10.8
11: Murmur of aortic insufficiency (new in conjunction with pain)	599	23.6
12: Hypotension or shock state	407	16.0

SBP indicates systolic blood pressure.

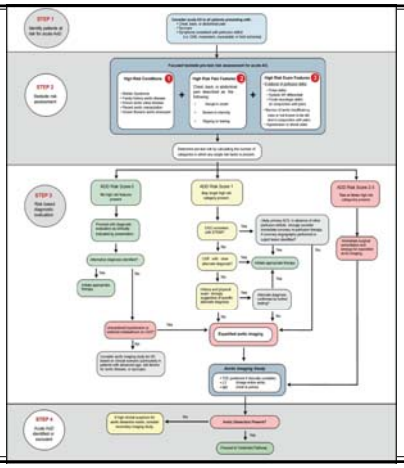


Specificity and Potential Overtesting

- The present study does not allow for any estimation of the specificity of the ADD risk score.

Specificity and Potential Overtesting

- A significant percentage of patients presenting with chest, abdominal, or back pain of a nonaortic pathogenesis would be classified as intermediate or high risk
  - sharp or stabbing was not included as a stand-alone marker of risk
  - Connective tissue disease was also excluded whereas patients with Marfan syndrome continue to meet criteria
- D-dimer or other biomarkers



Conclusion

- The clinical risk markers proposed in the 2010 TAD guidelines and their application as part of the ADD risk score comprise a highly sensitive clinical tool for the detection of acute AD.