EBM – Biostatistics Review

Why Clinical Trial Design Matters

Anthony J. Busti, MD, PharmD, MSc, FNLA, FAHA

HIGH-YIELD
MED REVIEWS

Introduction

Anthony Busti, MD, PharmD, MSc, FNLA, FAHA

Agenda

- Does clinical trial design matter?
  - Show me the evidence!
- Key areas the trial design influences:
  - The type of question needing answered
  - The validity of trial results
  - The type of statistical analysis used
  - The final conclusions of a meta-analysis
  - The context + degree of confusion by guidelines
- A special coupon code & feedback opportunity
- Live Q&A

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Does Clinical Trial Design Matter?

- An Example from the Cardiology Literature -

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Example Literature

JAMA
THE JOURNAL of the
American Medical Association
Aug 1, 1980 Vol 244, No. 5

Standards and Guidelines for
Cardiopulmonary Resuscitation (CPR)
and Emergency Cardiac Care (ECC)

JAMA 1980;244:453-509.

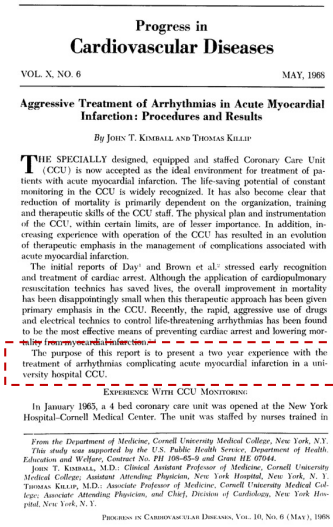
Example Literature

2. Acute Myocardial Infarction With Dysrhythmias.—Dysrhythmias may or may not occur in the course of acute myocardial infarction. When they occur, appropriate treatment may have an important effect on outcome.

a. Premature Ventricular Complexes (PVCs).—This form of dysrhythmia is particularly common in patients with acute myocardial infarction and may precipitate ventricular tachycardia or ventricular fibrillation. Suppressive therapy with lidocaine or procainamide is indicated.[53]

JAMA 1980;244:453-509.

Reference: 53



Progress in
Cardiovascular Diseases

VOL. X, NO. 6 MAY, 1968

Aggressive Treatment of Arrhythmias in Acute Myocardial Infarction: Procedures and Results

By JOHN T. KIMBALL AND THOMAS KILLIP

THE SPECIALLY designed, equipped and staffed Coronary Care Unit (CCU) is now accepted as the ideal environment for treatment of patients with acute myocardial infarction. The life-saving potential of constant monitoring in the CCU is widely recognized. It has also become clear that reduction of mortality is primarily dependent on the organization, training and therapeutic skills of the CCU staff. The physical plan and instrumentation of the CCU, within certain limits, are of lesser importance. In addition, increasing experience with operation of the CCU has resulted in an evolution of therapeutic emphasis in the management of complications associated with acute myocardial infarction.

The initial reports of Day[1] and Brown et al.[2] stressed early recognition and treatment of cardiac arrest. Although the application of cardiopulmonary resuscitation technics has saved lives, the overall improvement in mortality has been disappointingly small when this therapeutic approach has been given primary emphasis in the CCU. Recently, the rapid, aggressive use of drugs and electrical technics to control life-threatening arrhythmias has been found to be the most effective means of preventing cardiac arrest and lowering mortality from myocardial infarction.

The purpose of this report is to present a two year experience with the treatment of arrhythmias complicating acute myocardial infarction in a university hospital CCU.

EXPERIENCE WITH CCU MONITORING

In January 1965, a 4 bed coronary care unit was opened at the New York Hospital-Cornell Medical Center. The unit was staffed by nurses trained in

From the Department of Medicine, Cornell University Medical College, New York, N.Y. This study was supported by the U.S. Public Health Service, Department of Health, Education and Welfare, Contract No. PH 108-65-9 and Grant HE 07044.
JOHN T. KIMBALL, M.D.: *Clinical Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, New York Hospital, New York, N. Y.* THOMAS KILLIP, M.D.: *Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, and Chief, Division of Cardiology, New York Hospital, New York, N. Y.*

PROGRESS IN CARDIOVASCULAR DISEASES, VOL. 10, NO. 6 (MAY), 1968

483

Prog Cardiovasc Dis 1968;10:483-504.

Example Literature

- Prehospital administration of prophylactic lidocaine in stable patients coming to the ER with chest pain.
- Prospective, RCT in Milwaukee, Wisconsin; 1 year long
- Treatment Groups:
  - Prophylactic lidocaine (n=222)
  - No lidocaine (n=224)
- Results:
  - Overall hospital mortality 8.1% vs. 6.7% (p = 0.35)
  - The development of cardiac dysrhythmias 14.7% vs. 13.1% (P=0.45)

Risk of a type 2 error?
What is the trend in results?

Ann Emerg Med 1986;15(8):881-885.

Example Literature

- Prehospital administration of prophylactic lidocaine in stable patients coming to the ER with chest pain.
- Prospective, RCT in Milwaukee, Wisconsin; 10 ERs; 1 year long
- Discussion:
  - "By studying only patients at low risk for arrhythmias, the number of cases needed to achieve an acceptable beta error in support of the hypothesis is greatly increased. *Based on the incidence of sudden death seen in our population, 1,500 to 2,000 patients would be needed to achieve a beta error of 0.2*."

Ann Emerg Med 1986;15(8):881-885.

Example Literature

- Power = 1 - β
  - Indicates the probability that a statistical test can detect a significant difference when in fact, it truly exists.
  - Since Beta (β) indicates the probability of making a type II error, the power calculation tells you the probability that you will NOT make a type II error.

		Reality	
		Null Hypothesis True	**Null Hypothesis False**
Decision	**Accept Null Hypothesis**	Correct Decision	Type II Error (β)
	Reject Null Hypothesis	Type I Error (α)	Correct Decision

Example Literature

- _____ Trial was a P, R, PC trial in (n=1,498) patients with asymptomatic or minimally symptomatic PVCs within 2 yrs post-MI.
- Class Ic Antiarrhythmics (Encainide or Flecainide) vs. Placebo
- Results:
  - Stopped early due to higher mortality in antiarrhythmic group (except moricizine)
  - At 10 months f/u 59 died of arrhythmia (43 in antiarrhythmic group vs. 16 in placebo); p = 0.0004
  - 22 died of non-arrhythmia causes (17 in antiarrhythmic group vs 5 in placebo); p=0.01
  - Cardiac deaths not due to arrhythmia were from AMI (11 in antiarrhythmic group vs. 3 in placebo)

NEJM 1991;324:781-8.

Areas Influenced by Trial Design

- Type of Question Needing Answered -

"Potential" for Bias

Lower

Higher

Study Design	Best Use for Design	Ability
Experimental		
Clinical Trial	• Evaluating a treatment or intervention	• Causality
Observational		
Cohort Study	• Determine the incidence or natural history of a disease	• Associations
Case-Control	• Ideal for rare diseases	
Cross-Sectional	• Determining the prevalence • Useful at assessing need	
Case-Reports or Case-Series	• Generating awareness and/or hypotheses	• Hypothesis Generating
Qualitative Study	• When concerned about understanding human behavior & their experience	• Human reasoning

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Areas Influenced by Trial Design

- The Impact on Validity -

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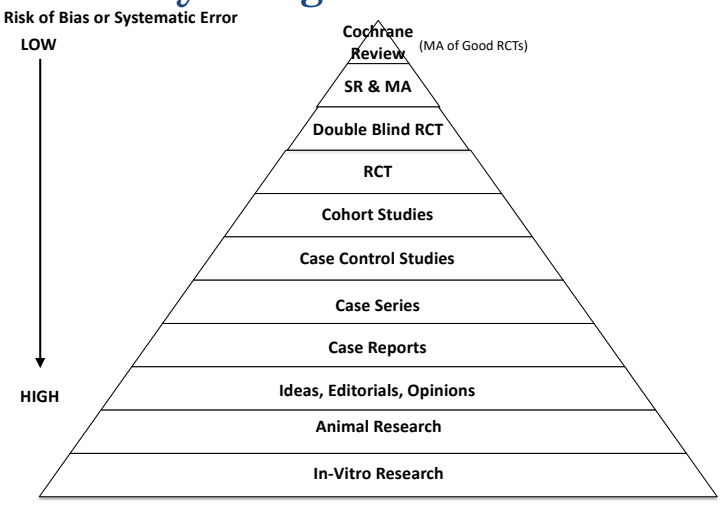
Validity

Valid Results = Truth + Bias + Random Error

- Truth: Use of Good Study Design; Use Critical Appraisal
- Bias: Researcher; Reader
- Random Error: Use Large Sample Size; Confidence Intervals & P-values

Study Design & Risk of Bias



Internal vs. External Validity

Type of Validity	Description
Internal Validity	• Being able to conclude that the independent variable was in fact responsible for the change seen in the dependent variable.
External Validity	• Concerned with the "generalizability" of the results to and across populations of subjects or settings.

HIGH-YIELD MED REVIEWS

Is there evidence that bias matters?

- The Impact on Validity -

HIGH-YIELD MED REVIEWS

Empirical Evidence of Bias

Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials

Kenneth F. Schulz, PhD, MBA; Iain Chalmers, MBBS, MSc; Richard J. Hayes, MSc; Douglas G. Altman

Objective.—To determine if inadequate approaches to randomized controlled trial design and execution are associated with evidence of bias in estimating treatment effects.

Design.—An observational study in which we assessed the methodological quality of 250 controlled trials from 33 meta-analyses and then analyzed, using multiple logistic regression models, the associations between those assessments and estimated treatment effects.

Data Sources.—Meta-analyses from the Cochrane Pregnancy and Childbirth Database.

Main Outcome Measures.—The associations between estimates of treatment effects and inadequate allocation concealment, exclusions after randomization, and lack of double-blinding.

Results.—Compared with trials in which authors reported adequately concealed treatment allocation, trials in which concealment was either inadequate or unclear (did not report or incompletely reported a concealment approach) yielded larger estimates of treatment effects ($P<.001$). Odds ratios were exaggerated by 41% for inadequately concealed trials and by 30% for unclearly concealed trials (adjusted for other aspects of quality). Trials in which participants had been excluded after randomization did not yield larger estimates of effects, but that lack of association may be due to incomplete reporting. Trials that were not double-blind also yielded larger estimates of effects ($P=.01$), with odds ratios being exaggerated by 17%.

Conclusions.—This study provides empirical evidence that inadequate methodological approaches in controlled trials, particularly those representing poor allocation concealment, are associated with bias. Readers of trial reports should be wary of these pitfalls, and investigators must improve their design, execution, and reporting of trials.

(JAMA. 1995;273:408-412)

ditionally, they suspected that methodologically inferior trials might produce bias in both directions, thereby causing greater variability in estimates of treatment effects. In neither analysis, however, did they detect a relationship.

Using a database of systematic reviews of controlled trials in pregnancy and childbirth,[12] we sought evidence of bias related to use of inadequate methodological approaches to trial design and execution. Rather than using quality scores, we investigated specific aspects that we believed might be influential.[13] We hypothesized that estimates of treatment effects would be larger in trials in which (1) adequate measures had not been taken to conceal treatment allocation; (2) adequate measures had not been taken to generate the allocation schedule; (3) some allocated participants had been excluded from the analysis; and (4) measures had not been taken to implement double-blinding. Furthermore, we examined whether treatment effects varied more in trials in which allocation schedules had not been adequately concealed.

MATERIALS AND METHODS

Areas Influenced by Trial Design

- The Type of Statistical Analysis Used -

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Type of Data	Two Independent Samples	Related or Paired Samples	3 or more Independent Samples	3 or more Related Samples	Measures of Correlation
Nominal	1.Chi-square 2.Fisher's Exact	McNemar Test	Chi-square for k independent samples	Cochran Q	Contingency coefficient
Ordinal	1.Mann-Whitney U 2.Wilcoxon Rank Sum	1.Sign test 2.Wilcoxon Signed Rank	Kruskal-Wallis one way ANOVA	Freidman 2 way ANOVA	1.Spearman 2.Kendal rank 3.Kendal Coe
Continuous	1.Student's t-test 2.Mann-Whitney U	Paired t-test	1-way ANOVA	2-way ANOVA	Pearson's Correlation

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Continuous	1.Student's t-test 2.Mann-Whitney U	Pai		2-way ANOVA	Pearson's Correlation

Nonparametric

Parametric

Areas Influenced by Trial Design

- The Final Conclusion of a Meta-Analysis -

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Are all "Heparins" the same?

That is like saying all antibiotics are the same

HIGH-YIELD
MED REVIEWS

The Heparin Disaster

Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes (Review)

Magee K, Sevcik WW, Moher D, Rowe BH

Trials from 1966 – 2000

Published in **2003**

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2003, Issue 1

http://www.thecochranelibrary.com

The Heparin Disaster

Trials from 1966 – 2000

Published in **2003**

of the following: a previous history of known coronary artery disease, ECG changes, or cardiac enzyme elevation.

Interventions: The studies included 11,092 patients and involved four different LMWH. In total, 7045 patients (63%) were eligible to receive enoxaparin, 2535 patients (23%) nadroparin, 1482 patients (13%) dalteparin and 40 patients (<1%) tinzaparin. Most patients received the intervention within 24 hours of the onset of

The Heparin Disaster

Trials from 1966 – 2000

Published in **2003**

Main results

We identified 27 potentially relevant studies, 7 studies (11,092 participants) were included in this review.

We found no evidence for difference in overall mortality between the groups treated with LMWH and UFH (RR = 1.0; 95% CI: 0.69, 1.44).

Some pooled outcomes showed some evidence of heterogeneity, few of the pooled outcomes were statistically heterogeneous most were homogeneous.

LMWH reduced the occurrence of MI (RR = 0.83; 95% CI: 0.70, 0.99) and the need for revascularization procedures (RR = 0.88; 95% CI: 0.82, 0.95). We found no evidence for difference in occurrence of recurrent angina (RR = 0.83; 95% CI: 0.68, 1.02), major bleeds (RR = 1.00; 95% CI: 0.80, 1.24) or minor bleeds (RR = 1.40; 95% CI: 0.66, 2.90). A decrease in the incidence of thrombocytopenia (RR = 0.64; 95% CI: 0.44, 0.94) was observed for patients given LMWH. From these results, 125 patients need to be treated with LMWH to prevent 1 additional MI and 50 patients need to be treated to prevent 1 revascularization procedure. Insufficient data exist to compare different types of LMWH.

Authors' conclusions

LMWH and UFH had similar risk of mortality, recurrent angina, and major or minor bleeding but LMWH had decreased risk of MI, revascularization and thrombocytopenia. New trials with longer follow up are required.

The Heparin Disaster

- 2003 Cochrane Review: LMWH vs UFH in "ACS"
  - LMWH & UFH appear equal on overall mortality & bleeding
  - LMWH *beat* UFH in reducing risk of MI, revascularization
  - The primary LMWH was *enoxaparin* pulling the benefit over UFH

The "Heparin" Disaster

Heparin versus placebo for acute coronary syndromes (Review)

Trials from 1966 – 2002

Published in **2008**

Magee K, Campbell SG, Moher D, Rowe BH

THE COCHRANE COLLABORATION®

The "Heparin" Disaster

Trials from 1966 – 2002

Published in **2008**

Interventions

The studies were conducted over an 11-year time period from 1985 until 1996 and included 3110 patients treated with either UFH or LMWH. In total, 1602 patients (52%) were eligible to receive LMWH and 1508 patients (48%) were eligible to receive UFH. Two different LMWHs were used: dalteparin (1498 eligible subjects) and nadroparin (104 eligible subjects). Of the patients receiving UFH, 19% were switched to warfarin when the UFH

The "Heparin" Disaster

Trials from 1966 – 2002

Published in **2008**

Authors' conclusions

Compared to placebo, patients treated with heparins had similar risk of mortality, revascularization, recurrent angina, major bleeding and thrombocytopenia. However, those treated with heparins had decreased risk of MI and a higher incidence of minor bleeding.

The "Heparin" Disaster

Trials from 1966 – 2002

Published in **2008**

Which LMWH?

What about the "abstract" conclusions?

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review of randomized controlled trials supports the use of heparins in the early treatment of acute coronary syndromes. Given in addition to aspirin to patients with a history of typical angina accompanied by either a past medical history of coronary artery disease or ECG/cardiac enzyme changes, heparins reduced the incidence of myocardial infarction yet not mortality. In this review, heparins were given within 24 to 72 hours of the onset of symptoms as a weight-adjusted dose for a 2 to 8 day period, with most studies administering it for 2 to 7 days. The small number of studies makes it impossible to recommend a particular dosing regimen. As a subgroup, LMWH and not UFH was the only group to show a statistically significant improvement in any of the outcomes. LMWH reduced the incidence of myocardial infarction, recurrent angina and the need for revascularization procedures. Given the advantages of LMWH over UFH demonstrated in a previous review (Magee 2003) and the evidence reported here, LMWH should be the agent of choice in the early treatment of unstable angina and NSTEMI. In those institutions which have active primary angioplasty suites, there is limited data to recommend LMWH over UFH. Available evidence suggests that both therapies are safe and efficacious although the two treatments have

The Heparin Disaster

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- 2008 Cochrane Review: "Heparin" vs Placebo in NSTEMI-UA
  - *Excluded enoxaparin* (one with the most supporting data)
  - Combined 2 of the LMWHs with UFH and called them "heparin" as if they were all the same

The "Heparin" Disaster

Trials from 1966 – 2014

Published in **2014**

Heparin versus placebo for non-ST elevation acute coronary syndromes (Review)

Andrade-Castellanos CA, Colunga-Lozano LE, Delgado-Figueroa N, Magee K

THE COCHRANE COLLABORATION®

GRADE

- GRADE
  - Grading of Recommendations Assessment, Development and Evaluation (GRADE)
  - Began in 2000
  - Goal:
    - Reduce the confusion among variations in grading the evidence and recommendations
    - International working group to define standardized criteria
      - GRADE Centers
      - GRADE Networks (U.S., Dutch, UK)
      - GRADE Groups & Projects
    - Rates the "quality" of evidence

The "Heparin" Disaster

Trials from 1966 – 2014

Published in **2014**

Main results

There were no new included studies for this update. Eight studies (3118 participants) were included in this review. We found no evidence for difference in overall mortality between the groups treated with heparin and placebo (risk ratio (RR) = 0.84, 95% confidence interval (CI) 0.36 to 1.98). Heparins compared with placebo, reduced the occurrence of myocardial infarction in patients with unstable angina and NSTEMI (RR = 0.40, 95% CI 0.25 to 0.63, number needed to benefit (NNTB) = 33). There was a trend towards more major bleeds in the heparin studies compared to control studies (RR = 2.05, 95% CI 0.91 to 4.60). From a limited data set, there appeared to be no difference between patients treated with heparins compared to control in the occurrence of thrombocytopenia (RR = 0.20, 95% CI 0.01 to 4.24). Assessment of overall risk of bias in these studies was limited as most of the studies did not give sufficient detail to allow assessment of potential risk of bias.

Authors' conclusions

Compared with placebo, patients treated with heparins had a similar risk of mortality, revascularization, recurrent angina, and thrombocytopenia. However, those treated with heparins had a decreased risk of myocardial infarction and a higher incidence of minor bleeding. Overall, the evidence assessed in this review was classified as low quality according to the GRADE approach. The results presented in this review must therefore be interpreted with caution.

The "Heparin" Disaster

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The Heparin Disaster

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- 2008 Cochrane Review: "Heparin" vs Placebo in NSTEMI-UA
  - *Excluded enoxaparin* (one with the most supporting data)
  - Combined 2 of the LMWHs with UFH and called them "heparin" as if they were all the same
- 2014 Cochrane Review (repeated using GRADE)
  - No new studies but *now they recommend caution to the results* (and interpretation in 2008).

Areas Influenced by Trial Design

- The Context + Degree of Confusion by Guidelines -

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Areas Influenced by Trial Design

- The Context + Degree of Confusion by Guidelines -

- NTG SL Tabs for NSTEMI -

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Example of Disconnect

4.1.2. Anti-Ischemic and Analgesic Medications

4.1.2.1. Nitrates: Recommendations

Class I

1. **Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 mg to 0.4 mg) every 5 minutes for up to 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin if not contraindicated (216-218). *(Level of Evidence: C)***
2. **Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, HF, or hypertension (219-224). *(Level of Evidence: B)***

216. Goldstein RE, Rosing DR, Redwood DR, et al. Clinical and circulatory effects of isosorbide dinitrate. Comparison with nitroglycerin. Circulation. 1971;43:629-40.
217. Bassan MM. The daylong pattern of the antianginal effect of long-term three times daily administered isosorbide dinitrate. J Am Coll Cardiol. 1990;16:936-40.
218. Kohli RS, Rodrigues EA, Kardash MM, et al. Acute and sustained effects of isosorbide 5-mononitrate in stable angina pectoris. Am J Cardiol. 1986;58:727-31.

2014 ACC/AHA NSTEMI Guidelines

Areas Influenced by Trial Design

- The Context + Degree of Confusion by Guidelines -

- Epinephrine in ACLS -

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1st CPR Guidelines - 1966

Cardiopulmonary Resuscitation

Statement by the Ad Hoc Committee on Cardiopulmonary Resuscitation of the Division of Medical Sciences, National Academy of Sciences–National Research Council

JAMA 1966;198(4):138-145.

1st CPR Guidelines - 1966

ABCD Steps

Emergency cardiopulmonary resuscitation involves the following steps:

A—*A*irway opened
B—*B*reathing restored
C—*C*irculation restored
D—*D*efinitive therapy

These should always be started as quickly as possible and always in the order shown. The recommended basic steps for performing the ABCs are shown in the Figure. Definitive therapy involves diagnosis, drugs, defibrillation (when indicated), and disposition. These definitive procedures are restricted to physicians or to members of allied health professions and paramedical personnel under medical direction. They are beyond the scope of

JAMA 1966;198(4):138-145.

JAMA
THE JOURNAL of the American Medical Association
Aug 1, 1980 Vol 244, No. 5

Standards and Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiac Care (ECC)

JAMA 1980;244:453-509.

A. Epinephrine hydrochloride produces beneficial effects in the treatment of cardiac arrest, probably through both its α- and β-adrenergic receptor stimulating properties.[36] Clinically, the drug elevates perfusion pressure generated during chest compression, enhances the contractile state of the heart, stimulates spontaneous contractions, and increases the vigor and intensity of ventricular fibrillation, usually described as a conversion of "fine" ventricular fibrillation to "coarse" ventricular fibrillation that may be more amenable to termination by electrical shock. The primary beneficial effect of epinephrine in cardiac arrest may in fact be secondary to its vasoconstrictor action, resulting in improved perfusion pressure during resuscitation.[37] Elevated perfusion pressure may improve coronary blood flow during external chest compression in cardiac arrest, and this may explain some of the beneficial effects of epinephrine in the cardiac arrest setting.

The recommended dose of epinephrine hydrochloride is 0.5 to 1.0 mg (5 to 10 mL of a 1:10,000 solution) given IV during the resuscitation effort. It is necessary to repeat this dose at approximately five-minute intervals when given IV because of the short duration of action of epinephrine.

JAMA 1980;244:453-509.

treating ventricular fibrillation:

1. Initiate BCLS and summon defibrillation equipment and assistance. Give precordial thump if the patient is monitored.
2. Continue BCLS while the cardiac rhythm is evaluated. If adequate help is available, an IV lifeline should be started at this time and supplemental oxygen administered.
3. The following steps should be accomplished interrupting BCLS for as brief a time as possible:

a. Apply conductive, low-resistance paste or gel to the paddles.

b. Select appropriate energy level and charge the capacitor. The initial attempt at defibrillation should be made using 200 to 300 joules of delivered energy.

c. If this is unsuccessful, a second defibrillation should be immediately attempted using 200 to 300 joules of delivered energy.[71,72]

d. If a second defibrillation attempt is unsuccessful, it is then recommended that BCLS be continued with supplemental oxygen. Epinephrine should be administered. Sodium bicarbonate should be given at this time if metabolic acidosis is documented by arterial pH and P_{CO_2} measurements. If these determinations are not immediately available, the decision to administer bicarbonate should be based on clinical judgment of the duration of cardiac arrest. A third defibrillation attempt should then

JAMA 1980;244:453-509.

b. Management of Ventricular Asystole.—When cardiac arrest has resulted from ventricular asystole (or when this has occurred as the end result of ventricular fibrillation or electromechanical dissociation), the presence of a severe metabolic deficit, extensive myocardial damage, or both should be suspected. It is possible also that high levels of parasympathetic tone can result in cessation of both supraventricular and ventricular pacemaker activity.[33] In the presence of ventricular asystole, the prognosis for resuscitation is poor. In addition to beginning CPR, inserting an endotracheal tube or esophageal airway for optimal ventilation and starting an IV infusion, the following steps should be taken:

1. Administer epinephrine and sodium bicarbonate IV.
2. If ineffective, administer calcium chloride IV.
3. If a rhythm is not restored, atropine may be administered.[33]
4. The administration of additional sodium bicarbonate should be based on arterial pH and P_{CO_2} determination. If this is not available, additional bicarbonate may be administered at ten-minute intervals.
5. If ventricular asystole persists, an IV infusion of isoproterenol may be started, or epinephrine may be administered by the intracardiac route.
6. In persistent asystole, a temporary pacemaker (transvenous or transthoracic) may in rare instances result in the restoration of an effective paced ventricular rhythm.

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35. Richman S: Adverse effect of atropine during myocardial infarction: Enhancement of ischemia following intravenously administered atropine. *JAMA* 228:1414-1416, 1974.

36. Redding JS, Pearson JW: Resuscitation from ventricular fibrillation. *JAMA* 203:255-260, 1968.

37. Livesay JJ, Follette DM, Fey KH, et al: Optimizing myocardial pressure during resuscitation.

JAMA 1980;244:453-509.

Resuscitation From Ventricular Fibrillation

Drug Therapy

Joseph S. Redding, MD, and John W. Pearson, MD

JAMA 1968;203(4):93-98.

Methods

One hundred and five mongrel dogs weighing between 6.8 and 13.2 kg (14.9 to 29 lb) were divided into seven groups of 15 dogs each. They were lightly anesthetized with methohexital sodium, 10 mg/kg, given intravenously, and the trachea of each was intubated with a cuffed endotracheal tube. A catheter was inserted through a femoral artery into the aorta for monitoring aortic pressure, and lead II of the electrocardiogram was recorded continuously. Another catheter was inserted 1 cm into a femoral vein for administration of drugs.

With each animal secured in the supine position and breathing air spontaneously, ventricular fibrillation was induced by a 110-volt alternating current shock applied to the chest wall for three seconds. A period of ten minutes was allowed to elapse between circulatory arrest and the start of resuscitation. Intermittent positive-pressure ventilation with air was then begun at a rate of 20 breaths per minute and tidal volumes of 25 ml/kg. External cardiac massage was started at the same time. The sternum was compressed five times during each exhalation with sufficient force to create an artificial systolic pressure of 50 to 100 mm Hg. The rate of cardiac compression was 100 per minute.

All drugs were injected into the femoral vein just before resuscitation was started. The following drugs were given: group A, no drug; group B, sodium bicarbonate (20 ml of 7.5% solution);

JAMA 1968;203(4):93-98.

Table 1.—Effect of Drug Therapy on Ventricular Defibrillation

Group*	Drug, Dose	Number Defibrillated	Countershocks Required 1	2	3	4	Number With Return of Circulation
A	None	3		2		1	1
B	Sodium bicarbonate, 1.5 gm	6		2		4	0
C	Epinephrine, 1 mg	7	5	2			7
D	Epinephrine, 1 mg; lidocaine, 40 mg	13	11	2			7
E	Phenylephrine hydrochloride, 10 mg	12	11	2	1	1	10
F	Methoxamine hydrochloride, 20 mg	14	12	2			13
G	Epinephrine, 1 mg; sodium bicarbonate, 1.5 gm	13	7	6			13

*Each group contained 15 dogs.

JAMA 1968;203(4):93-98.

Table 2.—Relation Between Drug Therapy and Survival

Group*	Drug, Dose	Circulation Restored	Condition in 24 hr: Awake	Unconscious	Dead	
A	None	1			1	
B	Sodium bicarbonate, 1.5 gm	0				
C	Epinephrine, 1 mg	7	3	2	2	57%
D	Epinephrine, 1 mg; lidocaine, 40 mg	7	1	1	5	85%
E	Phenylephrine hydrochloride, 10 mg	10		3	7	
F	Methoxamine hydrochloride, 20 mg	13	2	1	10	
G	Epinephrine, 1 mg; sodium bicarbonate, 1.5 gm	13	10	1	2	

*Each group contained 15 dogs.

JAMA 1968;203(4):93-98.

Epinephrine vs No-Epi in Cardiac Arrest

WORSE Survival	NO DIFFERENCE in Survival	IMPROVED Survival
JACC 2014;64(22):2360-7. ▪ Cohort study (n=1556) ▪ Jan 2000 – Aug 2012 ▪ Showed a dose effect	**Resuscitation 2011;82(9):1138-43.** ▪ P, DB, RCT n = 601 ▪ ROSC greater with adrenaline	**BMJ 2013;347:f6829.** ▪ Only in sub-group of non-shockable heart rhythm
Resuscitation 2012;83:327-32. ▪ Analysis of an RCT (n=848) ▪ Improved short-term survival ▪ Lower survival to d/c & increase risk of severe brain damage	**J Cardiol 2012;60(6):503-7.** ▪ Retrospective Study (n=644) ▪ Also no diff in brain damage	
JAMA 2012;307(11):1161-1168. ▪ P, Non-Randomized, Obs Propensity Analysis (n=417,188) ▪ Greater chance of ROSC, BUT decreased survival & good functional outcomes at 1 month	**Ann Emerg Med 2007;50:635-42.** ▪ Observation, Before-After Study (n = 1296) ▪ No diff in survival to d/c after adjustment for rhythm, ROSC, survival to admission	
Circ J 2012;76:1639-45. ▪ P, Pop-Based, Obs study (n=3161) ▪ Only benefit at 1 month was in VF with epi given within 10 min	**Resuscitation 1995;30:243-9.** ▪ P, RCT (n = 194) ▪ Also no diff in high-dose vs placebo	
Resuscitation 2002;54(1):37-45.		
Resuscitation 1995;29(3):195-201.		

Beta-Blocker Use in Cardiac Arrest

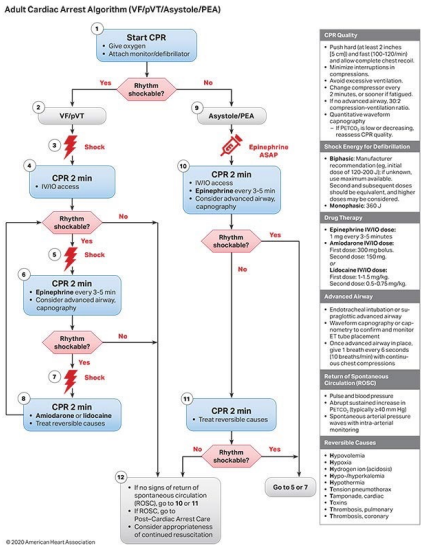
- Retrospective study
- Urban academic ED from (Jan 2011 – Jan 2014) in n = 25 patients
- Out of hospital arrest → VF/VT initial rhythm → at least 3 defibrillation attempts + 300 mg amiodarone and 3 mg of epi.
  - Esmolol (n = 6)
  - No esmolol (n = 19)
- Results:
  - 67% vs 42% had "temporary" ROSC with esmolol
  - 67% vs 32% had "sustained" ROSC with esmolol
  - 66% vs 32% survived to ICU admission with esmolol
    - 50% vs. 16% survived to hospital discharge
    - 50% vs. 11% survived to discharge with favorable neurologic outcome

Resuscitation 2014;85(10):1337-41.

PARAMED C2
The Adrenaline Trial

- Prospective, DB, RCT in the UK
- Groups:
  - Epi (n=4,015)
  - Saline placebo (n=3,999)
  - All received standard of care
- Results (at 30 days):
  - 130 patients (3.2%) in the EPI group vs 94 (2.4%) in the placebo group were alive
    - Unadjusted OR for survival, 1.39; 95% CI, 1.06 to 1.82; P=0.02).
  - There was no evidence of a significant difference in the proportion of patients who survived until hospital discharge with a favorable neurologic outcome (2.2% vs. 1.9%)
    - Unadjusted OR, 1.18; 95% CI, 0.86 to 1.61).
  - At the time of hospital discharge, *severe neurologic impairment* had occurred in more of the survivors in the EPI group than in the placebo group (31.0% vs. 17.8%).

NEJM 2018;379:711-721.



AHA. ACLS. 2020.

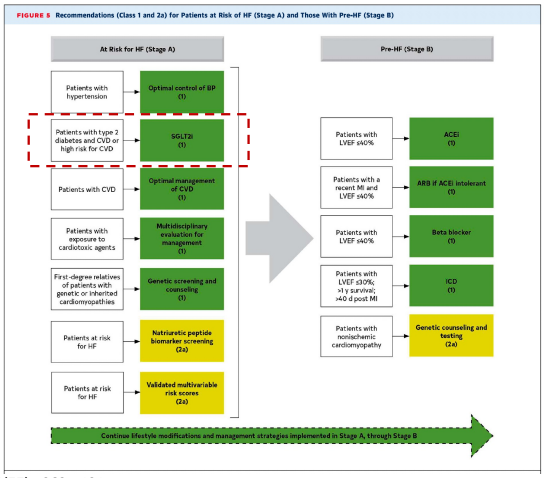
Areas Influenced by Trial Design

- The Context + Degree of Confusion by Guidelines -

- SGLT2i in Heart Failure -

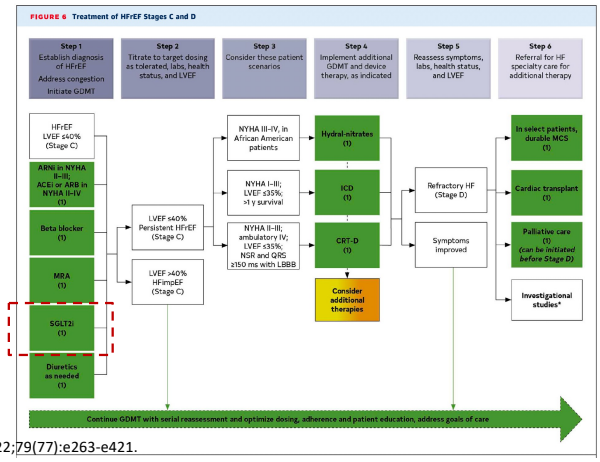
HIGH-YIELD MED REVIEWS

SGLT2i & HF Guidelines



JACC 2022;79(77):e263-e421.

SGLT2i & HF Guidelines



JACC 2022;79(77):e263-e421.

EMPEROR & DAPA-HF Trials

	EMPEROR-Reduced		DAPA-HF
	Empagliflozin (n=1863)	Placebo (n=1867)	Dapagliflozin (n=2373)
Age (yr)	67.2 ± 10.8	66.5 ± 11.2	66.2 ± 11.0
Women (%)	437 (23.5)	456 (24.4)	564 (23.8)
Diabetes mellitus (%)	927 (49.8)	929 (49.8)	993 (41.8)
Ischemic cardiomyopathy (%)	983 (52.8)	946 (50.7)	1316 (55.5%)
NYHA functional class II (%)	1399 (75.1)	1401 (75.0)	1606 (67.7%)
LV ejection fraction (%)	27.7 ± 6.0 (72% ≤30%)	27.2 ± 6.1 (75% ≤30%)	31.2±6.7
NT-proBNP (median, IQR), pg/mL	1887 (1077, 3429) (79% ≥1000)	1926 (1153, 3525) (80% ≥1000)	1428 (857-2655)
Hospitalization for heart failure within 12 months	577 (31.0)	574 (30.7)	647 (27.3)
Atrial fibrillation	664 (35.6)	705 (37.8)	916 (38.6)
Glomerular filtration rate (ml/min/1.73 m^2)	61.8 ± 21.7	62.2 ± 21.5	66.0 ± 19.6
Treatment for heart failure			
RAS inhibitor without neprilysin inhibitor	1314 (70.5)	1286 (68.9)	2007 (84.6)
RAS inhibitor with neprilysin inhibitor	340 (18.3)	387 (20.7)	250 (10.5)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)	1696 (71.5)
Beta blocker	1765 (94.7)	1768 (94.7)	2278 (96.0)
Implantable cardioverter-defibrillator	578 (31.0)	593 (31.8)	622 (26.2%)
Cardiac resynchronization therapy	220 (11.8)	222 (11.9)	190 (8.0%)

NEJM 2020;383:1413-1424.

HF Guidelines

TABLE 15 Benefits of Evidence-Based Therapies for Patients With HFrEF (3-6,8,10-14,23,31-42)

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal RCTs, %	NNT to Prevent All-Cause Mortality Over Time*	NNT for All-Cause Mortality (Standardized to 12 mo)	NNT for All- Cause Mortality (Standardized to 36 mo)
ACEi or ARB	17	22 over 42 mo	77	26
ARNI†	16	36 over 27 mo	80	27
Beta blocker	34	28 over 12 mo	28	9
Mineralocorticoid receptor antagonist	30	9 over 24 mo	18	6
SGLT2i	17	43 over 18 mo	63	22
Hydralazine or nitrate‡	43	25 over 10 mo	21	7
CRT	36	12 over 24 mo	24	8
ICD	23	14 over 60 mo	70	23

JACC 2022;79(77):e263-e421.

EBM/Biostatistics Integration

- RR = <u>incidence rate in exposed patients</u>
  incidence rate in non-exposed patients
  - RR = 1 (incidence is the same for both groups)
  - RR = >1 (incidence in exposed group is higher)
  - RR = <1 (incidence in exposed group is less)

EBM/Biostatistics Integration

- Relative Risk Reduction (RRR)
  - Remember it is = 1 – RR
- Absolute Risk Reduction (ARR)
  - It is the difference between the incidence of the exposed group and the unexposed group
  - Used to calculate NNT or NNH
    - NNT = 1/ARR
    - It must then be put into the context of the clinical trial duration/method of treatment

HF Guidelines

TABLE 15 Benefits of Evidence-Based Therapies for Patients With HFrEF (3-6,8,10-14,23,31-42)

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ICD	23	14 over 60 mo	70	23

Dapagliflozin ~ $550/month
Empagliflozin ~ $580/month

X 12 months = ~ $6,750 per yr X 63 NNT = ~ $425,000

That means we have to spend $425,000 over the course of 1 year by treating 63 people to prevent 1 death. This is in addition to the cost of ACEi/ARNI + BB + MRA +/- ICD +/- clinic or ER visits for UTIs or yeast infections etc.

JACC 2022;79(77):e263-e421.

Closing

- Clinical trial design has a major impact on not only the:
  - Type of question being answered
  - Statistical analysis utilized
  - Validity
  - Other studies that follow (i.e., meta-analyses)
  - Guidelines
  - But most importantly ….
    - Clinician perception and medical decision making

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