SIH: Trials and Research Endeavors

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Disclosures

- No relevant disclosures
- RSNA Research Scholar Grant
- ASNR Comparative Effectiveness Award
- NIH R01

Objectives

- Getting from here to there
- Types of research
- What is good research?
- Where are we now?
- Where are we going?

Getting From Here to There

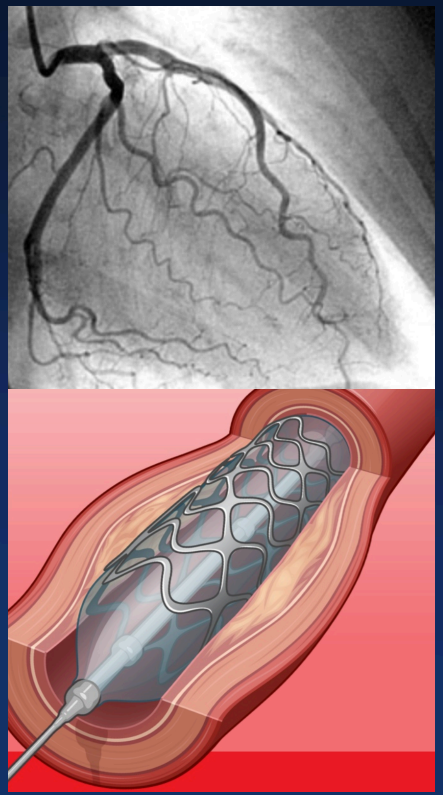
Getting From Here to There

- Myocardial Infarction
  - 1912 (JAMA): “wound of heart”
    - physical and emotional rest
    - quiet isolation in bed 6 wks

Herrick JB. JAMA 1912; 59: 2015–20

Getting From Here to There

- Myocardial Infarction
  - 1912 (JAMA): “wound of heart”
    - physical and emotional rest
    - quiet isolation in bed 6 wks
  - 2018 (JAMA): myocardial reperfusion
    - ECG, blood markers, echo, medications (thrombolytics), cath lab, stenting, ICU



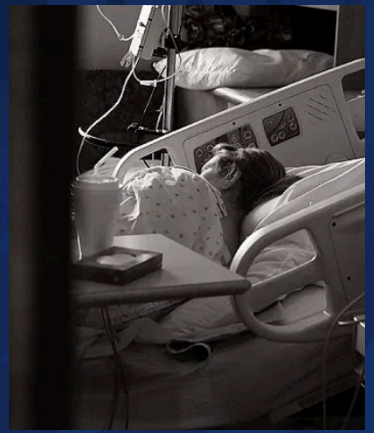
Ibanez et al Eur Heart Journal; 39(2):119-177

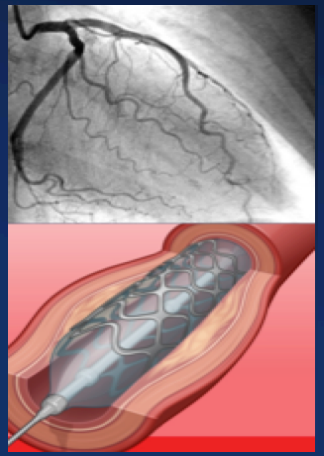
Myocardial Infarction

1912

2018

RESEARCH!!!





General Research Goals

- Create *generalizable* knowledge
- Determine: best treatments, causation, prevalence of disease

Types of Research

Expert Opinion

- Statements of opinion from thought leader
  - Can say whatever they want
- Claim's validity based on *person* making claim rather than *evidence*
- Conflicts of interest
  - industry / financial, personal
- Bias: based on single person's experience
  - limited in scope

Expert Opinion

- Miasma theory of disease
  - cholera, chlamydia, plague
  - caused by “bad air” or pollution
- 1880: germ theory

A resident physician of long experience recommends, *as a protection against the prevailing pestilence*, called Asiatic cholera, that every person be provided with small silk bags (about the size of small square flat pin-cushions filled with pounded myrrh and camphor. These bags to be constantly worn in the waistcoat and coat pockets, so that the bodies of those who wear them may be surrounded by an aromatic atmosphere. The protecting property of aromatic effluvia has been acknowledged by many of the best writers on pestilential epidemics. It is not asserted that these aromatic effluvia *destroy contagion*; but, being in part inhaled into the lungs and in part absorbed by the skin, they exert a beneficial influence on the whole frame—keeping it in proper tone and under gentle excitement; *and thereby enabling persons to resist contagion*. The powder in the aforesaid bags should consist of four parts of myrrh and one part of camphor—this last ingredient being rendered pulverizable by moistening it with a few drops of rectified spirit. Each bag should contain three tea spoonsful (or by weight two drachms) of the powder; and the contents should be renewed every fortnight or three weeks. The cost of two of these aromatic bags (supposing each of them to contain myrrh and camphor in the quantity above-mentioned) will be about threepence halfpenny; but if frankincense (i. e. *Olibanum*) which is also a fine aromatic, be substituted in place of myrrh, the cost of each bag will then not exceed three halfpence.

Nottingham Journal Aug 4th 1832

Case Series

- Report one or multiple patients with same disease or treatment

PROS

- Describes characteristics
- Easy, Low cost, Less time
- Generate hypothesis

CONS

- No control or comparison group
- Information bias
- Selection bias

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- Useful for:
  - Reporting sentinel events: toxicity of therapy, recognition of epidemics, initial identification of new disease

Case Control

- Retrospective
- Two groups:
  - Case: group of subjects with disease
  - Control: similar group of subjects without disease
- Look for differences in predictors of disease
  - (e.g. smoking in lung cancer)
- Odds Ratio: relative risk of developing disease

Case Control

PROS

- Efficiency for rare diseases

Example: SIH in Ehlers-Danlos

(made up numbers)

- 0.16% incidence SIH in non-EDS
- assume relative risk 50
- 80% power
- 6000 patients cohort or RCT
  - multiple years follow
- 16 each group for case-control

Case Control

PROS

- Efficiency for rare diseases
- Relatively easy and low cost
- Generate hypothesis

CONS

- Only one outcome studied
- Cannot estimate prevalence

Case Control

PROS

- Efficiency for rare diseases
- Relatively easy and low cost
- Generate hypothesis

CONS

- Only one outcome studied
- Cannot estimate prevalence
- Sampling bias
- Retrospective measurement bias

Cohort Studies

- Longitudinal studies:
  - patient group assembled at beginning
  - repeated data acquired over time in same patients
- Only observing, no active intervention
- Retrospective or prospective
- Two purposes: descriptive and analytic
- Can suffer from confounding

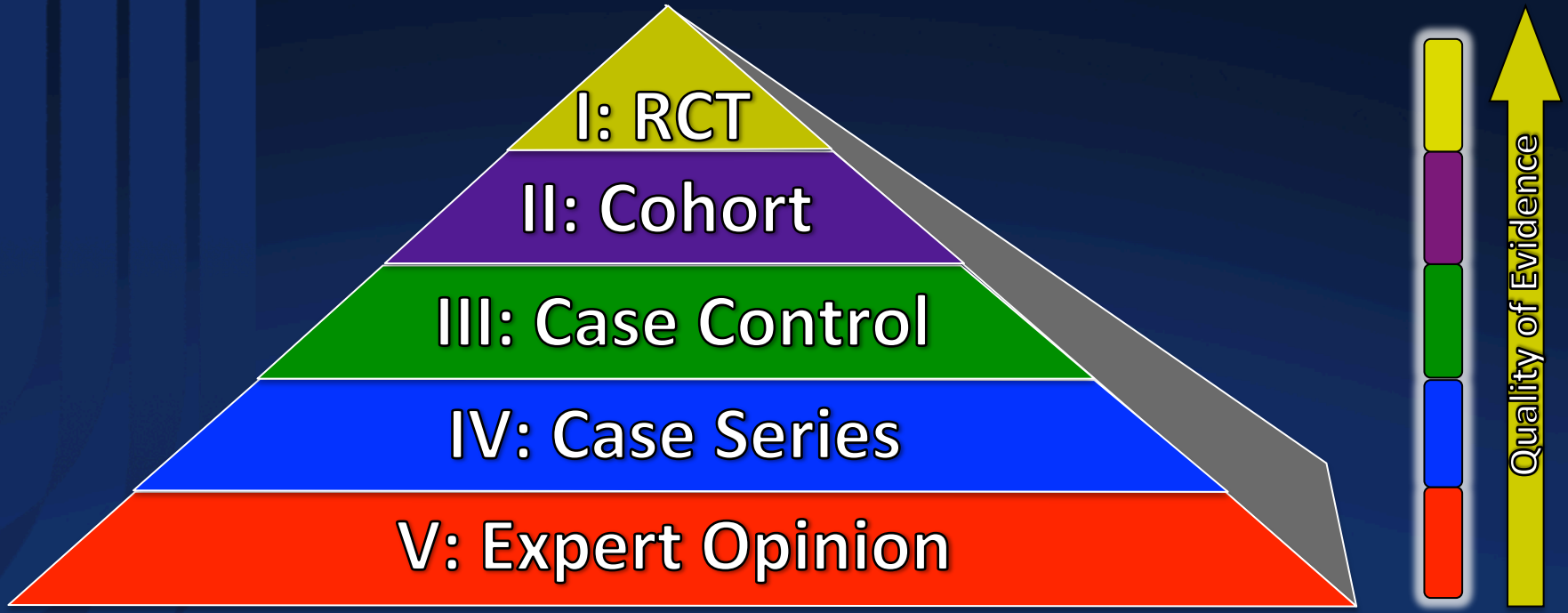
Randomized Controlled Trials (RCT)

- Prospective
- “Experimental”: active intervention
- Patients are randomly assigned to arms of study
- Eliminates confounding and reduces bias
- Gold standard
- Difficult, time consuming, expensive

What is “good” research?

How to avoid “fake news”

Levels of Evidence

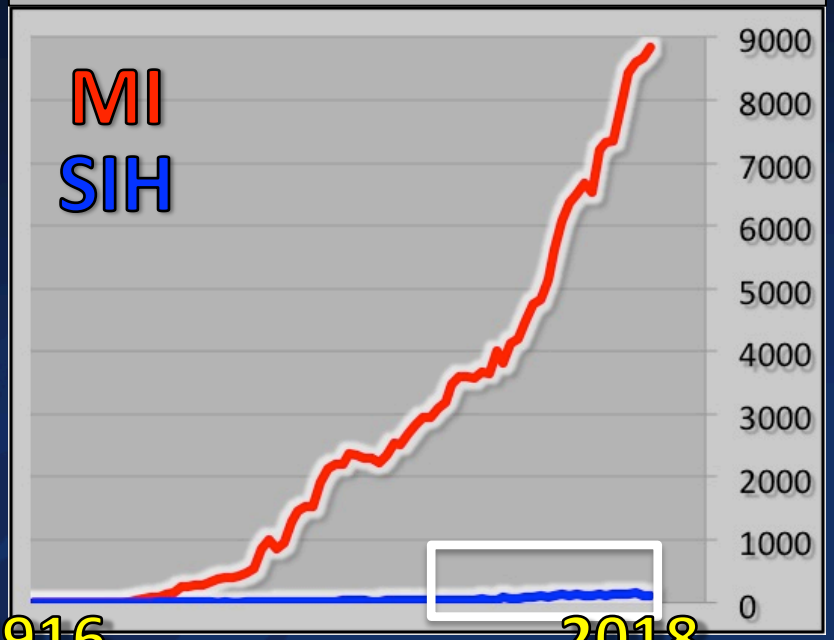


Sacket DL et al How to Practice and Teach EBM

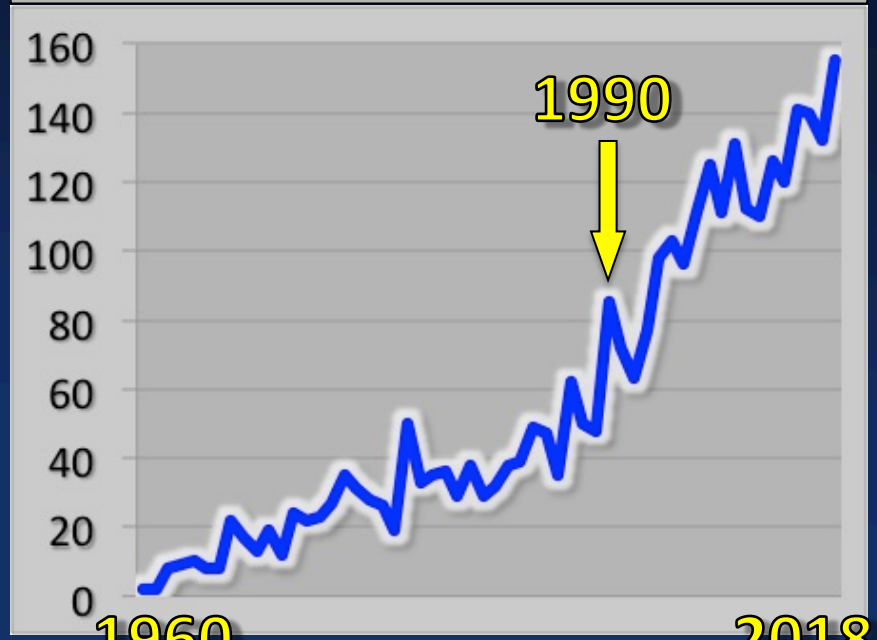
Where are we now?

Past Research

Publications

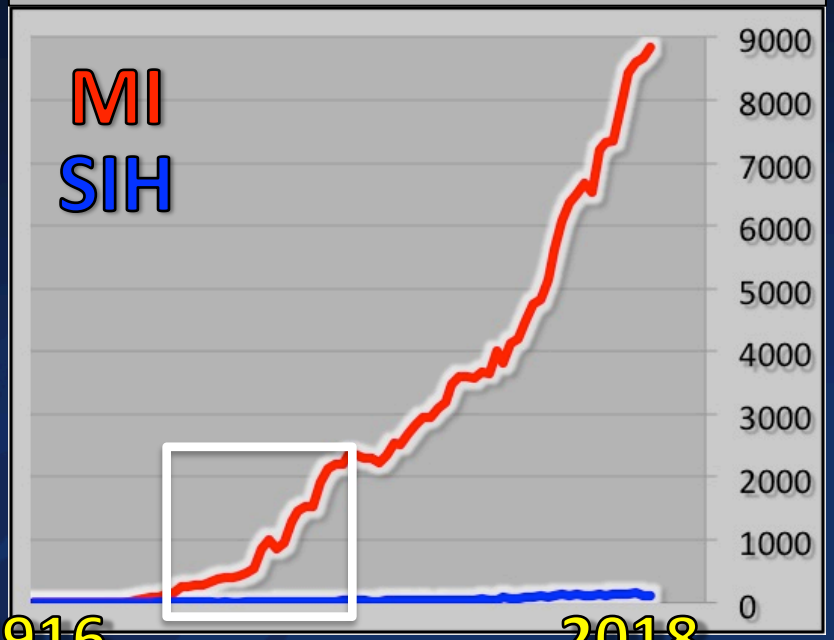


SIH



Past Research

Publications



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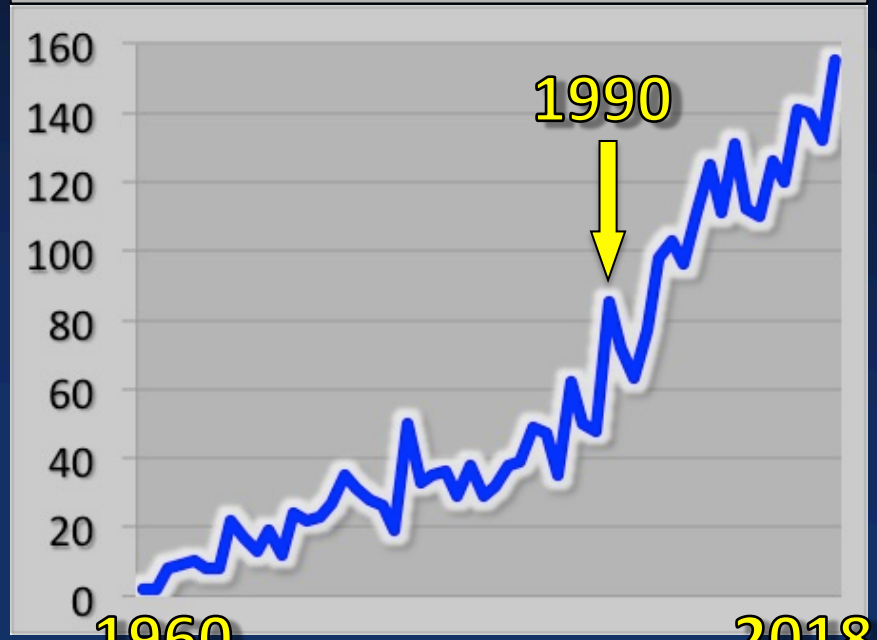
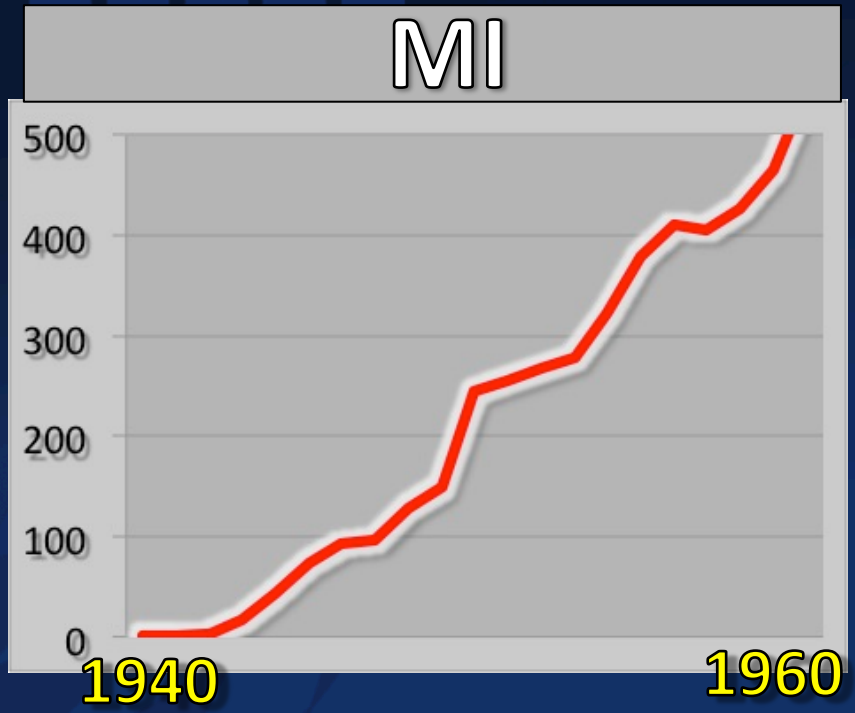


Past Research



Expert Opinion

EDITORIAL AJNR Am J Neuroradiol 29:1–4 | Jan 2008

Intrathecal Gadolinium: Its Time Has Come?

W.P. Dillon, MD

- Off label use of Gd in CSF space
- May be helpful to find slow leaks and CVFs
- Unsure of risks
- Advocates for its use in selected cases

Expert Opinion

Intrathecal Gadolinium for Magnetic Resonance Myelography in Spontaneous Intracranial Hypotension: Valuable But May Be Risky

Dimitrios Parissis, PhD
Panos Ioannidis, PhD
Dimitrios Karacostas, PhD

JAMA Neurology June 2014 Volume 71, Number 6

- Opinion against MR myelography
- States that lumbar puncture in patients with CSF leaks could be risky
- Cites no evidence

Case Series

- First
- Pros:
  - describe
  - basis for
- Cons:
  - selection bias: doesn't tell us much about patients with CVFs
  - no comparator group

Case Series

AJNR Am J Neuroradiol 26:2663–2666, November/December 2005

Case Report

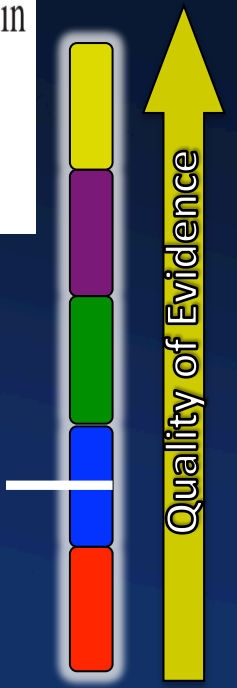
Epidural Blood Patch at C2: Diagnosis and Treatment of Spontaneous Intracranial Hypotension

- Single patient
- CSF leak at C2
- Successful treatment via targeted cervical patch
- Concludes targeted patching needed

False localizing sign of C1–2 cerebrospinal fluid leak in spontaneous intracranial hypotension

WOUTER I. SCHIEVINK, M.D., M. MARCEL MAYA, M.D., AND JAMES TOURJE, M.D.

- 25 patients
- 3 with C2 contrast
- All had surgically proven CSF leak elsewhere
- Contrast spills out at C1/2 → false localizing



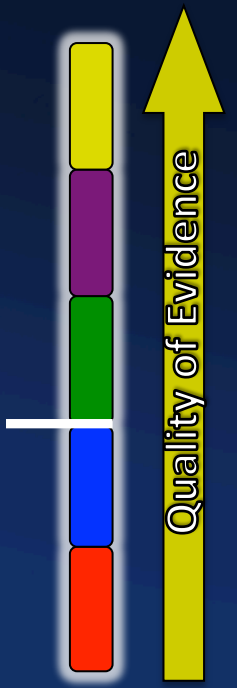
Cross-Sectional Study

Wouter I. Schievink, MD
M. Marcel Maya, MD
Stacey Jean-Pierre, PA-C
Miriam Nuño, PhD
Ravi S. Prasad, MD
Franklin G. Moser, MD,

A classification system of spontaneous spinal CSF leaks

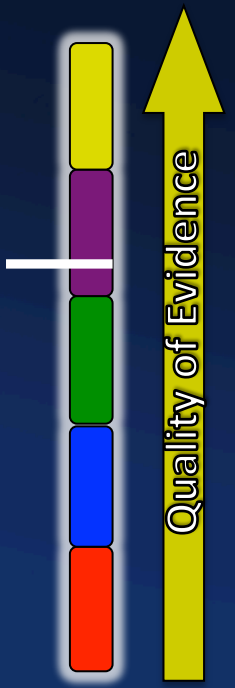
- 568 patients
- Three types:
  - Type 1: dural tear (27%)
  - Type 2: diverticula (42%)
  - Type 3: CSF – venous fistula (2.5%)
  - Indeterminate (29%)
- Snapshot in time
  - prevalence of disease
  - describes characteristics of subtypes

- Limitations:
  - referral / selection bias
  - difficult to confirm causal relationships between predictors and SIH subtypes
- Study type does not answer questions about comparative efficacy of different treatments

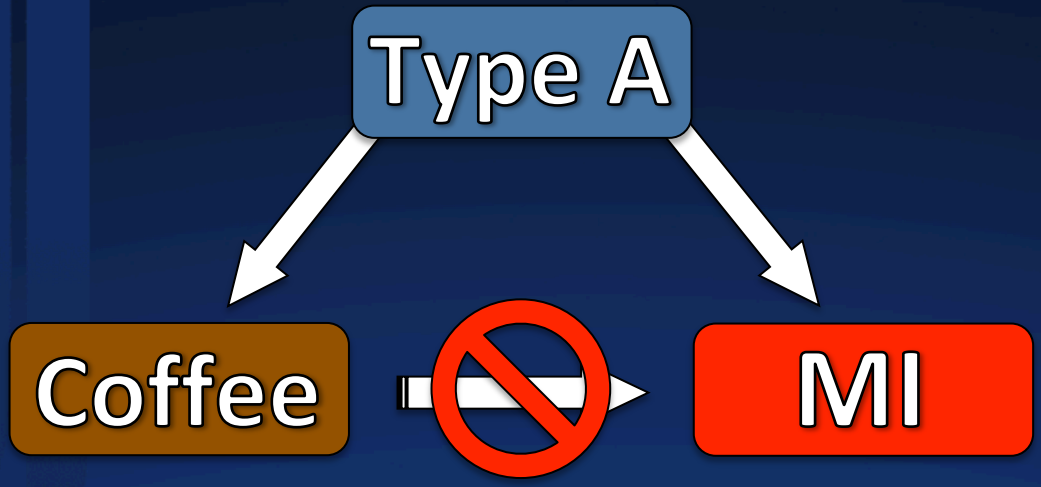


Cohort Studies

- Several *retrospective* observational studies
- No *prospective* studies
- Strengths:
  - less costly and time-consuming than prospective and RCTs
  - allows for inference of causality
- Weaknesses:
  - limited control over quality and nature of data
    - may not have outcomes measured correctly or systematically
  - confounding



Cohort Studies



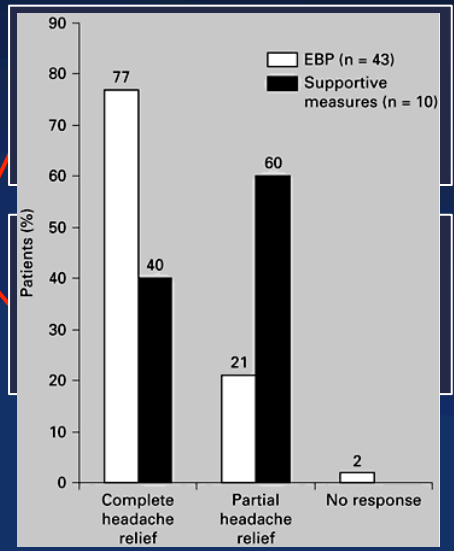
- confounding

Evidence for EBP in Treatment of SIH

Author	Year	# Patients	# BP	Targeted or Blind	Pro/Retro	Outcome metric	Follow up	Estimate of efficacy
He	2018	165	1-4	T	Retro	Subjective	1-7 years	88% with first patch, 7% second, 4% third, 0.6% fourth.
Wu	2017	150	1-3	T	Retro	Subjective	48 hr	59% with first patch, 33% second, 6% third. 2 pts (1.3%) not cured
Cho	2011	56	1	T + B	Retro	Subjective	6 mos-5.2 years	87% (targeted) vs 52% blind (p<0.05)
Ferrante	2010	42	1-3	B	Retro	NS	1 mo, 3mos, 6mos-5yrs	90% with first, 5% second, 5% third
Chung	2005	53	1.5 (mean)	T + B	Retro	Subjective	1 mo	77% (targeted), 77% blind, 40% conservative
Berroir	2004	27	1-2	B	Retro	VAS decrease >90%	1 month, 1-4 years	90% immediate relief, one third relapsed. Of relpases, 66% cured with second EBP. Total 'cure' 77%
Sencakova	2001	25	1-6	T + B	Retro	NS	NS	36% with 1st patch, 20% with second, then 6 went to surgery and 4 had 3-6 additional patches. Logistic regression showed trend toward improvement with targeting (p=0.07), OR not reported.

EBP vs. Conservative

77% vs. 40% (p<0.05)



Courtesy of Dr. Peter Kranz

Randomized Controlled Trials

- Prospective, blinded, and randomized
- Randomization eliminates confounding
- Blinding reduces bias
- “Gold standard”
- SIH Literature: *NONE*

Randomized Controlled Trials

- Vertebroplasty:
  - place large needles into a vertebral body fracture
  - inject “cement” to fix fracture
- Industry sponsored case and unblinded nonrandomized studies suggested efficacy
- Based on this → billion $ industry in USA
- No prior RCTs

Randomized Controlled Trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures

David F. Kallmes, M.D., Bryan A. Comstock, M.S., Patrick J. Heagerty, Ph.D., Judith A. Turner, Ph.D., David J. Wilson, F.R.C.R., Terry H. Diamond, F.R.A.C.P., Richard Edwards, F.R.C.R., Leigh A. Gray, M.S., Lydia Stout, B.S., Sara Owen, M.Sc., William Hollingworth, Ph.D., Basavaraj Ghdoke, M.D., Deborah J. Annesley-Williams, F.R.C.R., Stuart H. Ralston, F.R.C.P., and Jeffrey G. Jarvik, M.D., M.P.H.

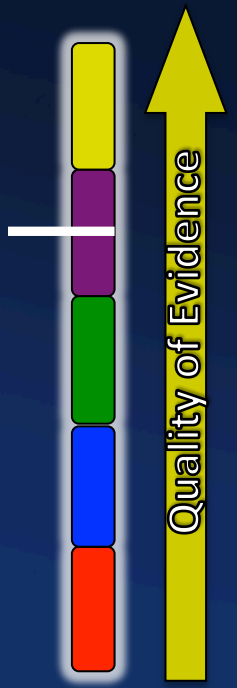
- 131 patients
- Randomized to vetebroplasty or simulated procedure
- Improvements in both groups
- No difference between the two groups!

Kallmes et al N Engl J Med 2009;361:569-79

Where are we going?

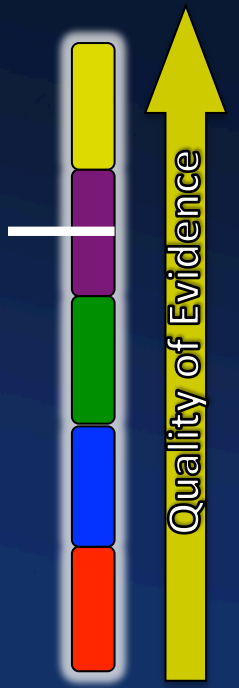
Cohort Studies

- Prospective observational studies
- Cedars-Sinai, Duke, Mayo



Unification via Registry

- Centralized registry:
  - GUIDs
  - Maximize:
    - geographic reach
    - data heterogeneity
    - data completeness
- Allows for epidemiology



RCTs: The PATCH Trial

- Sponsored by RSNA RSG
- Duke – single center
- Optimal treatment vs. Simulated procedure
- Prove patching works

The PATCH Trial

RSNA

Primary Endpoint:
HIT-6 at 1 month
(reduction from

Spontaneous Intracranial Hypotension

CT or dynamic myelogram positive for CSF leak

Eligible patients consented

Baseline: HIT-6, MIDAS, NRS, EQ-5D, WPAI, Duke Headache Questionnaire

Inclusion Criteria:
- Adult
- Meets ICHD-3 SIH criteria
- MRI Brain with contrast
- Definite CSF leak on myelography
- Baseline HIT-6 > 56

Exclusion Criteria:
- Contraindication or inability to undergo procedure
- Recent blood patch (< 2 weeks)
- Inability to provide informed consent
- Expected inability to complete follow up
- Contraindication to contrast media or fibrin glue

Randomization

CT fluoroscopy-guided targeted blood and fibrin glue patch

CT fluoroscopy-guided targeted saline injection

immediate

1 week

Assess for Adverse Events

2 weeks: Outcome measures

2 weeks: Outcome measures

1 months: Outcome measures

1 months: Outcome measures

Patient Crossover Allowed

2 months

4 months: Outcome measures

4 months: Outcome measures

Brain MRI: SIH findings

RCTs: Future Endeavors

- PATCH trial: multi-institutional
- Targeted vs. Non-targeted patching
- Blood vs. Fibrin glue

Conclusions

- Substantial progress over the past 10 – 15 years!
- But, we have a long way to go!
- Quality research needed – tough to do
  - Requires: dedication, organization leadership, funding
- The future is bright

Thank you!

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