Your Target May Be Incorrect

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Disclaimer

(Probably) Apocryphal Quotation

"Not everything that counts can be counted, and not everything that can be counted counts."

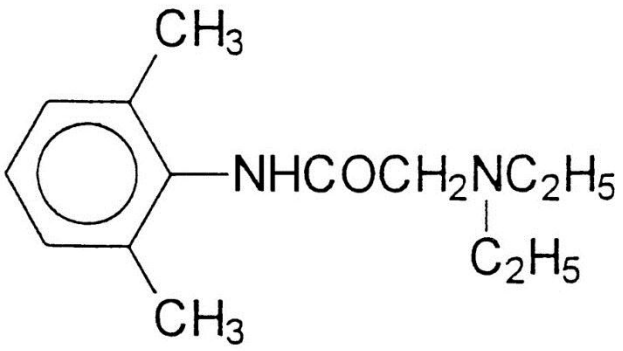
Attributed to A. Einstein but likely coined first by sociologist William Bruce Cameron, commenting on the difficulty in performing statistical analyses of problems for which data is often lacking.

Context for the Tocainide Story

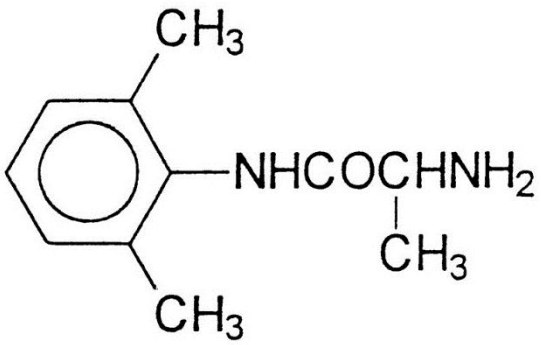
- Sudden (non-traumatic) cardiac death (SCD) is a major health problem affecting patients with and without coronary disease. According to the American Heart Association, at least 420,000 Americans die this way each year.
- SCD is a result of electrical instability in the heart at a cellular level, structural level, or both.
- Anti-arrhythmic medications for outpatients are sought to reduce the incidence of SCD in those at risk for it.
    - Those experiencing SCD during a heart attack (myocardial infarction) have a better prognosis than those who don't

Tocainide – Enticing Initial Evaluation

- Tocainide was developed as an oral analog to Lidocaine, a mainstay of IV anti-arrhythmic medications



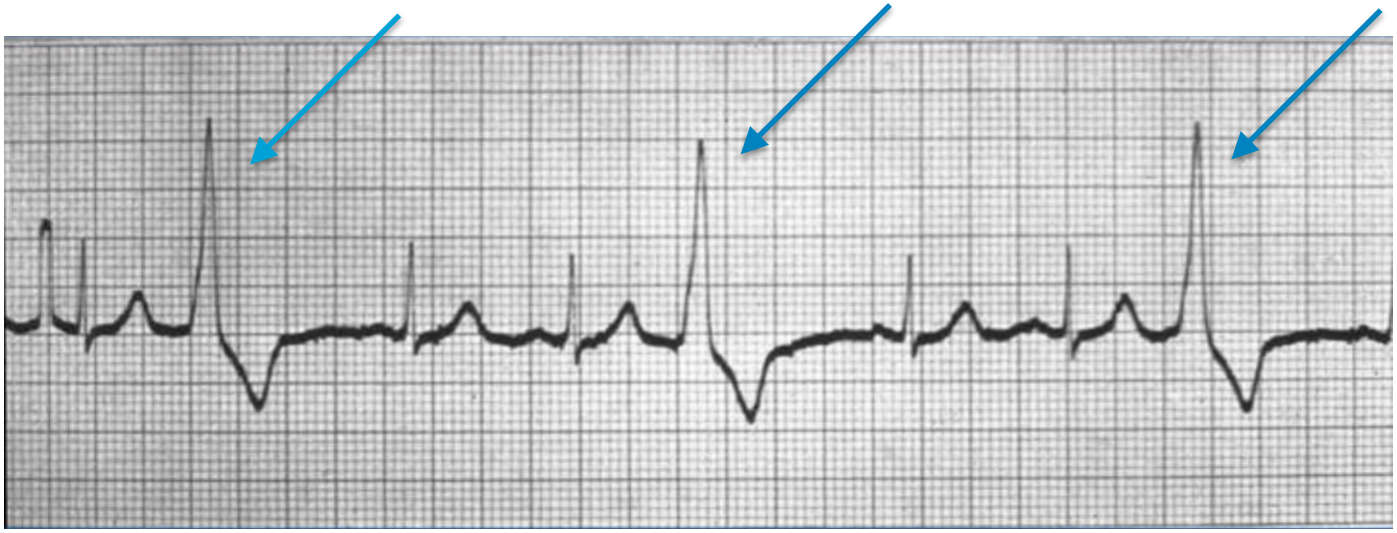
Lidocaine



Tocainide

SCD – How to Measure a Treatment?

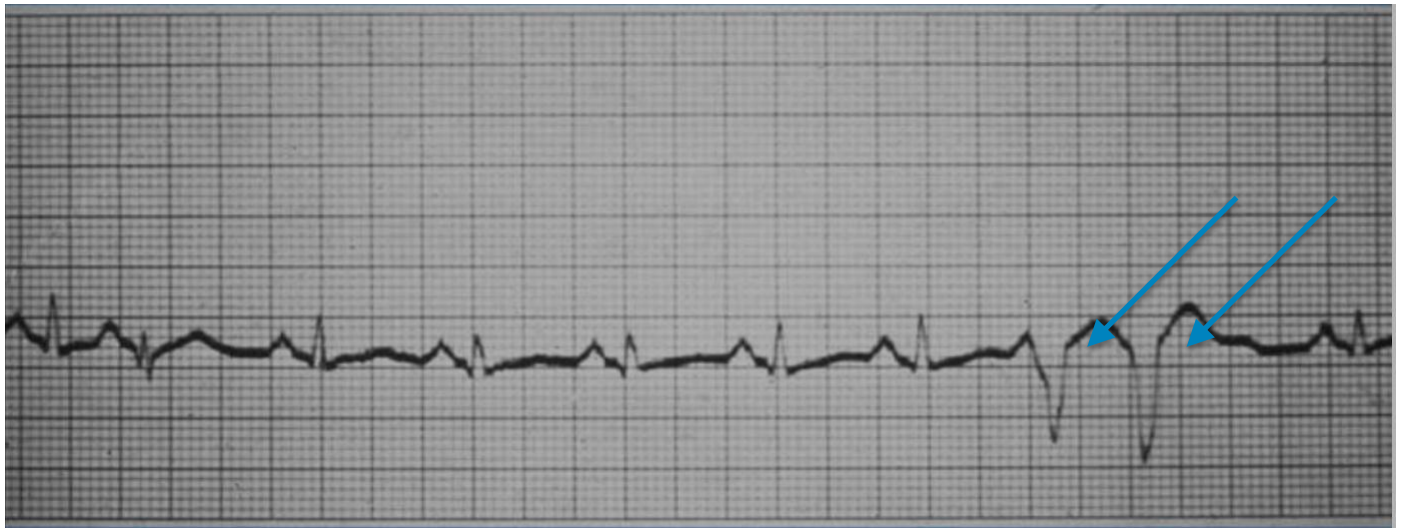
- Risk of SCD used clinical markers, the best of which was the frequency of funny beats called PVC's per unit time



blue arrows show the PVCs – other (smaller) waveforms are normal

A Little More on PVCs

- Similar to previous except **two PVCs in a row**:



Very Strong Association between PVC Frequency and SCD

- Multiple large epidemiological studies showed a strong association
  - Increasing frequency of PVCs correlated with SCD
  - Increasing number of forms of the PVCs correlated with SCD

- Tocainide (and two other drugs from the same class) dramatically reduced the frequency of PVCs
  - Common to reduce the number from thousands per day to fewer than a dozen

- Because of this strong evidence, Tocainide was widely prescribed

Then the Randomized Controled Trials

- Showed a trend towards increased mortality in the treated group
  - Many trials performed, in part because it was hard to accept the result, given such good results in reducing the frequency of PVCs
  - Repeated trials showed the entire class of medications showed this result and no combination of particular medication and particular subgroup of patients could be found to show any benefit

- Result today: these drugs are only used where patients' rhythms can be continuously monitored and treated (i.e., in a hospital)
  - They do have some benefit in this circumstance
  - Because patients on the oral versions of these medications can't be monitored and treated for complications, they have essentially been abandoned.

LDL Cholesterol–Not a Good Marker

- Statin medications
  - Used since the early 1990s
  - Big picture summary of results
    - A decreasing relationship between the dose of statin given and significant vascular events (basically – heart attack, stroke, cath lab intervention, coronary surgery, and death)

Important Consideration in Statin Evidence

- All the major studies identified a decreasing risk of the significant vascular events when increasing doses of statin were given
  - Also, when comparing statins, using equivalent doses, the more potent ones decreased significant vascular events more than the less potent ones
- Non of them investigated the relationship between *statin doses and LDL-cholesterol levels* or other lipid markers

Guidelines for Statin Use

- Original Guidelines (2002) from AHA were formulated in terms of target levels of LDL-cholesterol
- For about a decade, prevention of CAD was about “the numbers”

A new(er) drug in 2006: Ezetimibe (brand name Zetia)

- Worked by a different mechanism from statins
- Dramatically lowered LDL-cholesterol, often by 30-50% more than maximum tolerated dose of statins
- So far, there is no evidence that Ezetimibe decreases the rates of significant vascular events
- But use of the drug continues apace
  - Still increasing in Canada
  - Tapering in the USA (but still higher than Canada)

One more point–then some questions of you

- Ezetimibe use did not decrease in Canada after well publicized negative results, but behavior in the US did change a little
  - The guidelines in Canada now more strongly emphasize levels of LDL-cholesterol than those in the US

One more point–then some questions of you

- Question #1: given the evidence available:
  - Allowing yourself hindsight bias, would you have used guidelines at all?
  - What guidelines would you suggest have been used in 2002?
- Question #2: review your own projects and others' (in and out of the fellowship)
  - Do you see potential for repeating this kind of error?