The end of the wellfare state :Education and research

Clinical research – endangered species

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EUROPEAN SOCIETY OF CARDIOLOGY®

Feasting on the common resources for research

A scene from a our research units???

Clinical research endangered species

- Randomised controlled
- Surveys
- Registry studies
- Observational studies

- Trial and error
- Wishful thinking

Obervational studies/ Single site randomised studies

- **Small/inexpensive**
- **Surrogate endpoints**
- **Open or single blind**

- **Inclusion**
  - done by investigators selection bias

- **Evaluation**
  - Exaggeration of treatment effects
  - No validation of measurements , Placebo effects overlooked,

Observational or small randomised trials
AV synchronous pacing in AV block and SND

- **It took 15 yrs**
- **to show that DDD was *not* superior to VVI / AAI**
  - CTOPP; UK Pace, DanPace

- **It took 20 yrs**
- **to show that extent of RV pacing (and not benefit of AV synchronous pacing) was what mattered**
  - MOST
  - DAVID

Randomised controlled studies

- **Advantage:**
  - Inclusion criteria. TOPCAT- SYMPLICITY HTN 3 did the right pts get included?
  - Control in all senses. Early termination in case of great benefit, futility or harm,
  - Patients recognize advantages of participating also in device studies

- **Disadvantage:**
  - costs, administration at all levels not only sponsor
  - No time/resources for clinical research at hospitals

- **Takes time (years):**
  - Early studies to demonstrate some benefit
  - Functional improvement, QoL, echoparamters

  - Followed by very expensive morbidity / mortality studies

Randomised studies- generalizing too soon

- Dronedarone- reduced stroke and rhythm control in px AF
- superior rate control

- But worse survival in heart failure patients (Pallas trial) in high risk perm AFpts

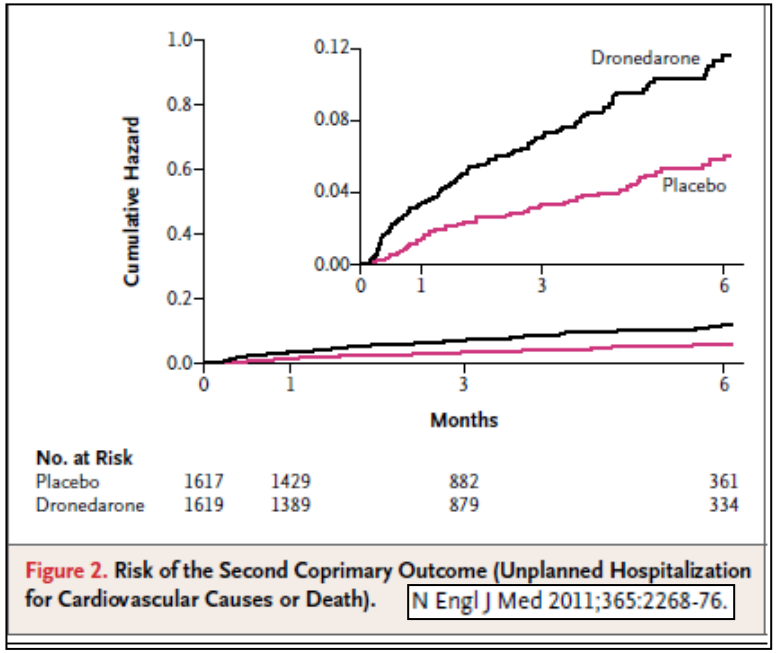


Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death). N Engl J Med 2011;365:2268-76.

Randomised studies- presuming too soon
Selection criteria for CRT

- **Does Mechanical dyssynchrony add to electrical (QRS width) in response to CRT**
  - ***No*** PROJECT study Chung et al Circulation 2008
- **Is it enough to select pts due to mechanical dyssynchrony**
  - ***No*** ECHO CRT study Ruschitzka et al New Eng J Med 2013
- **QRS width versus BBB**

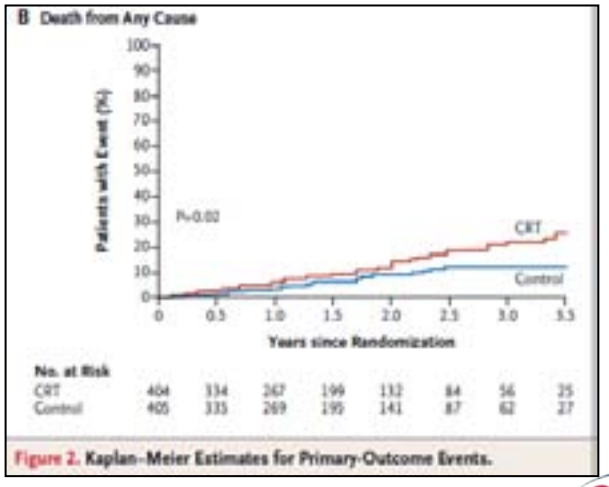


Figure 2. Kaplan–Meier Estimates for Primary-Outcome Events.

European Heart Journal Advance Access published July 29, 2013

European Heart Journal
doi:10.10

FASTTRACK CLINICAL RESEARCH

An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure

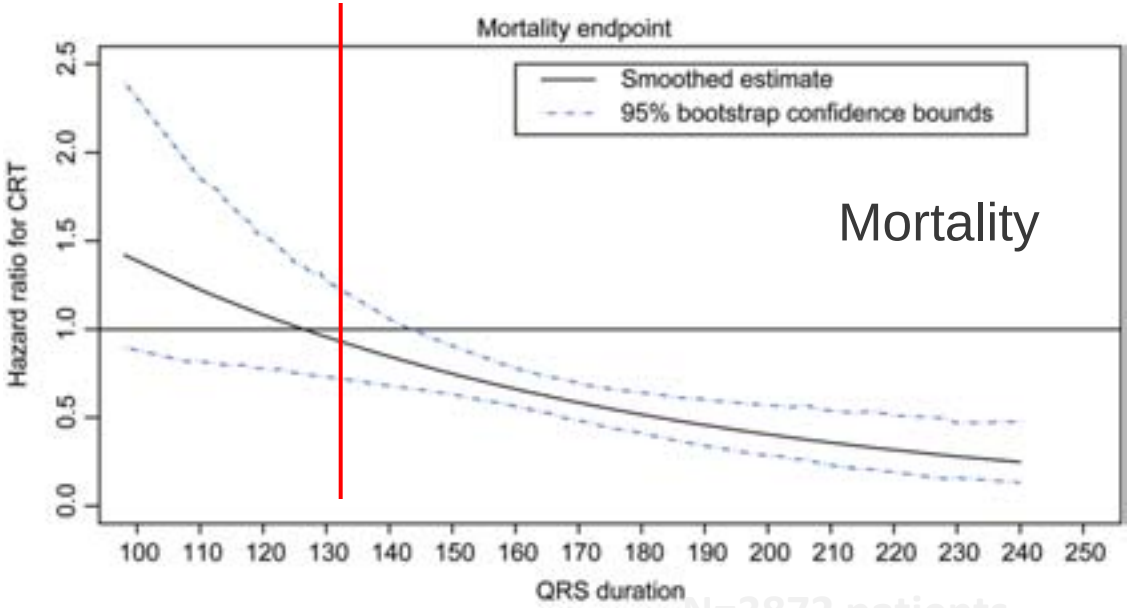
John G. Cleland[1]*, William T. Abraham[2], Cecilia Linde[3], Michael R. Gold[4], James B. Young[5], J. Claude Daubert[6], Lou Sherfesee[7], George A. Wells[8], and Anthony S.L. Tang[9]

Table I Characteristics of five studies included in the patient-level meta-analysis of cardiac resynchronization therapy

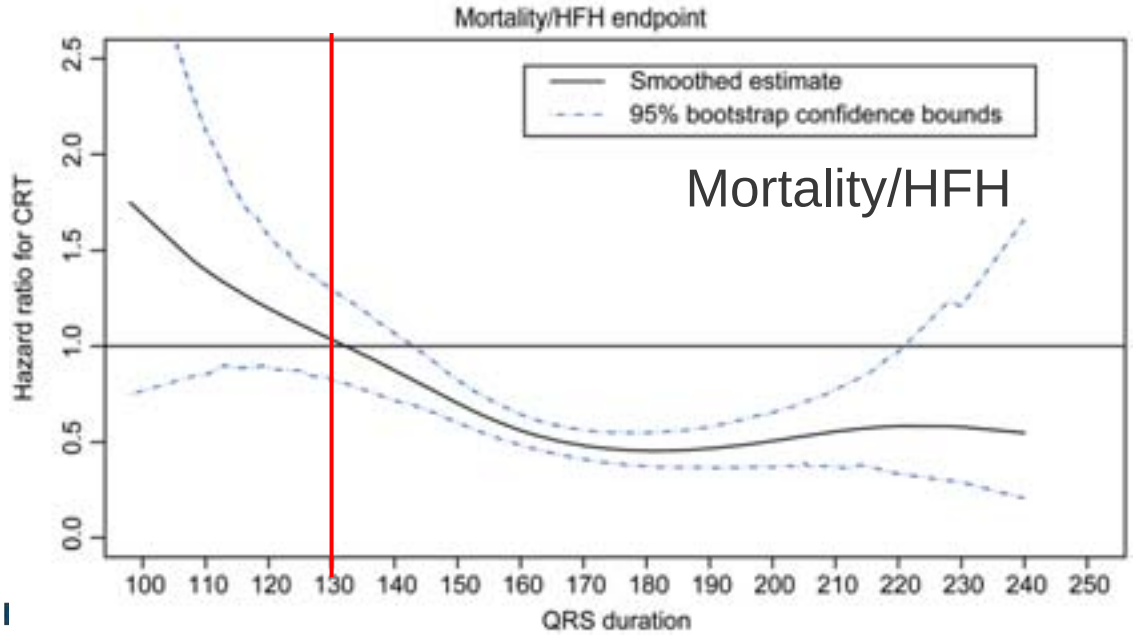
Study	Patients	Randomization	Sample	Median follow-up[a]
MIRACLE	NYHA III–IV, QRS ≥ 130 ms, EF ≤ 35%	1:1 (CRT-P vs. VDI-30)	541	6 months
MIRACLE ICD	NYHA II–IV, QRS ≥ 130 ms, EF ≤ 35%, ICD indication	1:1 (CRT-D vs. DDI-35)	555	6 months
CARE-HF	NYHA III–IV, QRS ≥ 120 ms, EF ≤ 35%	1:1 (CRT-P vs. OMT)	813	29 months (35 months for mortality)
REVERSE	NYHA I–II, QRS ≥ 120 ms, EF ≤ 40%	2:1 (CRT ± D vs. VVI-35)	610	12 months (24 months, EU cohort)
RAFT	NYHA II–III, QRS ≥ 120 ms (pQRS ≥ 200 ms), EF ≤ 30%	1:1 (CRT-D vs. ICD)	1798	40 months

[a]Follow-up is for median of the randomized period only.
CRT-P, cardiac resynchronization therapy - pacemaker only, with no defibrillator function; OMT, optimal medical therapy.

Hazard ratios and 95% CI of benefit of CRT in relation to QRS width



N=3872 patients



Cleland J et al Eur Heart J 2013; 46:3547-56.

Surveys

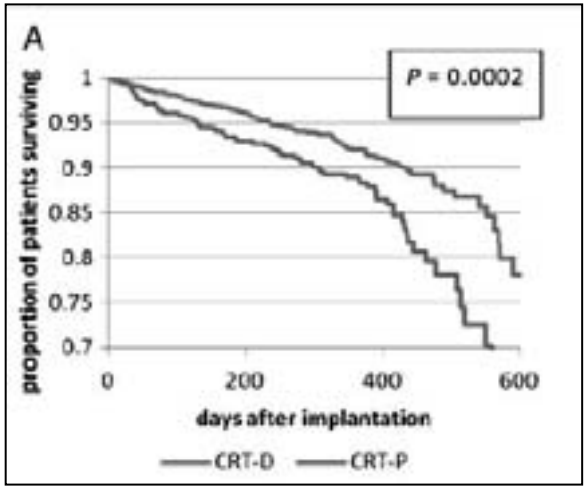
- **Advantage:**
  - Less expensive
  - Snapshot
  - Real life patients depending on participating centres
    - meaning > 5 yrs older than study patients

Disadvantage

- Better at studying guidelines implementation and
- Quality of care in different countries/cites

Useful for research in established therapies
Outside of study populations= target populations for most treatments

- CRT Survey mean age 70 yrs (CRTD vs CRT P)



European Journal of Heart Failure (2012) **14**, 61–73

Are registries the right way to randomise pts

- If large enough and age and sexmatched pt with the required profile (say duration of atrial fibrillation) can be found
- Possible to ” randomise” to compare treatments
- Depending on registry validation of data is done in a subgroup of patients- no monitoring of entered patient
- Outcome must be something already measured such as mortality
- Ethics committee application is necessary
- Statistical expertise is prerequisite

Potential advantages

- Better representation of older patients , women etc
- More point of care- i.e. both excellent and less excellent centres are involved
- Good for benchmarking
- Might be a way to test drug in phase III study but not against placebo (if drugs)
- For interventions against none or no device

- Does not work for device or intervention studies?

Can Registry studies replace RCTs

- This is the hot issue
- National ongoing registries are becoming spread
- They are not all designed for follow up outside of Mortality / morbidity
- It may be possible to include follow up parameters QoL , NYHA class etc but requires work
- Better for quality control of established therapy and implementation than for novel
- Conclusions – will not match RCT

Collaboration one potential way to reduce costs

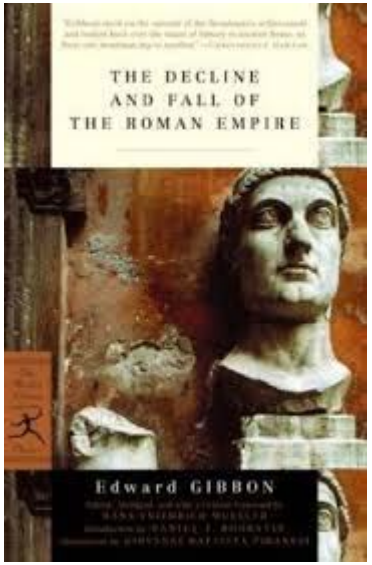
- Stratified pt record inside entire area that may serve as CRF
- Common evalutation e.g. echo and ECG interpretation and storage to avoid double work
- Bridge between private and state hospital systems for
- Long term continuous work may weaken interest
- Will probably lead to regional studies and requires broad consensus betweem collegues

Varus defeated by Arminius in Teutoburg Forest 9AD and lost his legions (30.000 men) Arminius had 10.000

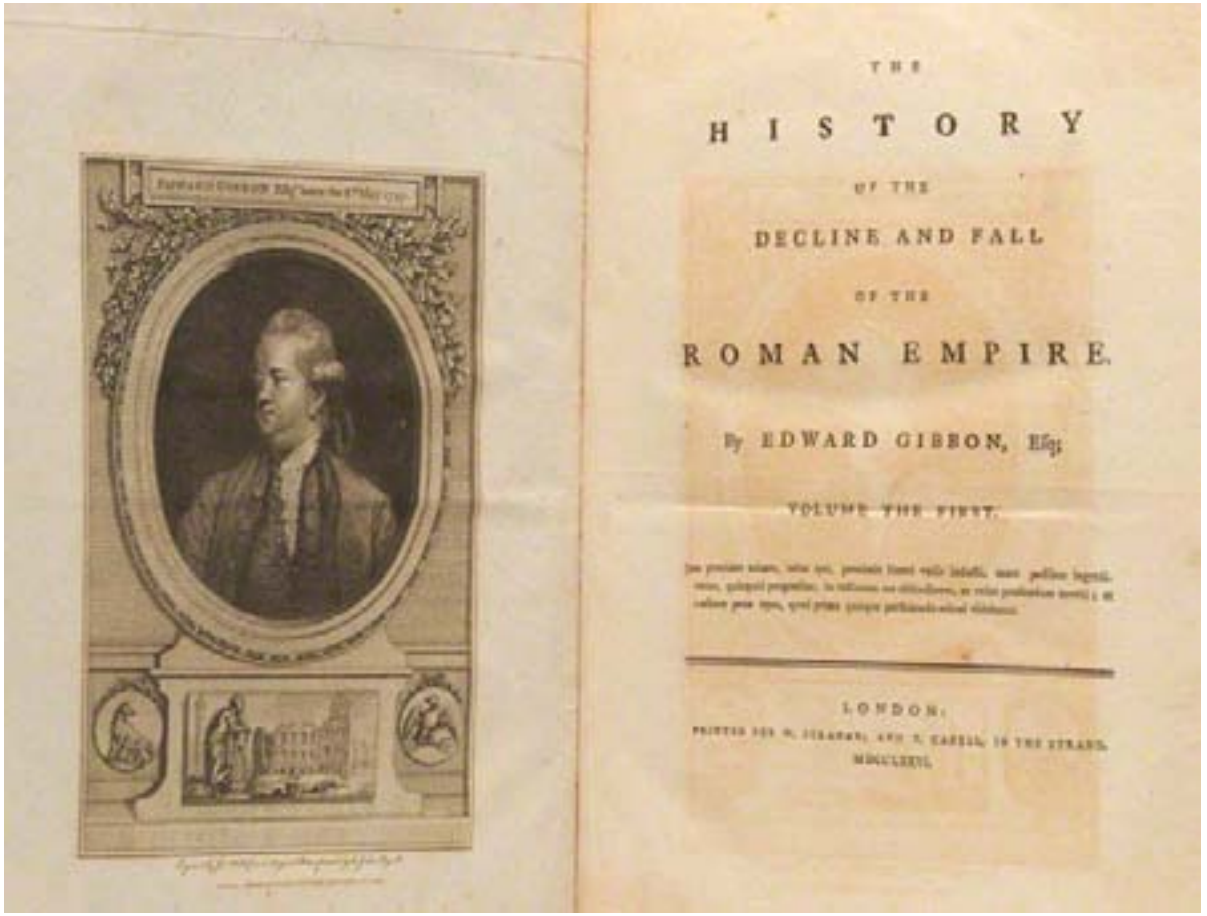
Vare-Vare
Give me back my legions

Augustus 27AD-14

Constantine`s vision of the cross the divides Rome which was the start of the decline and fall ……..



of the Roman Empire in 5 parts first volume



THE

HISTORY

OF THE

DECLINE AND FALL

OF THE

ROMAN EMPIRE.

By EDWARD GIBBON, Esq;

VOLUME THE FIRST.

LONDON.

Conclusion

- Randomised studies are still needed
- But are more justified in novel therapy and truly novel approaches, CCM, LAA occlusion devices
- But costs need to be controlled
- Most expensive are morbidity and mortality trials- may they be done in registry studies? But with interim follow up?