Endpoints in Hemorrhagic Shock Studies

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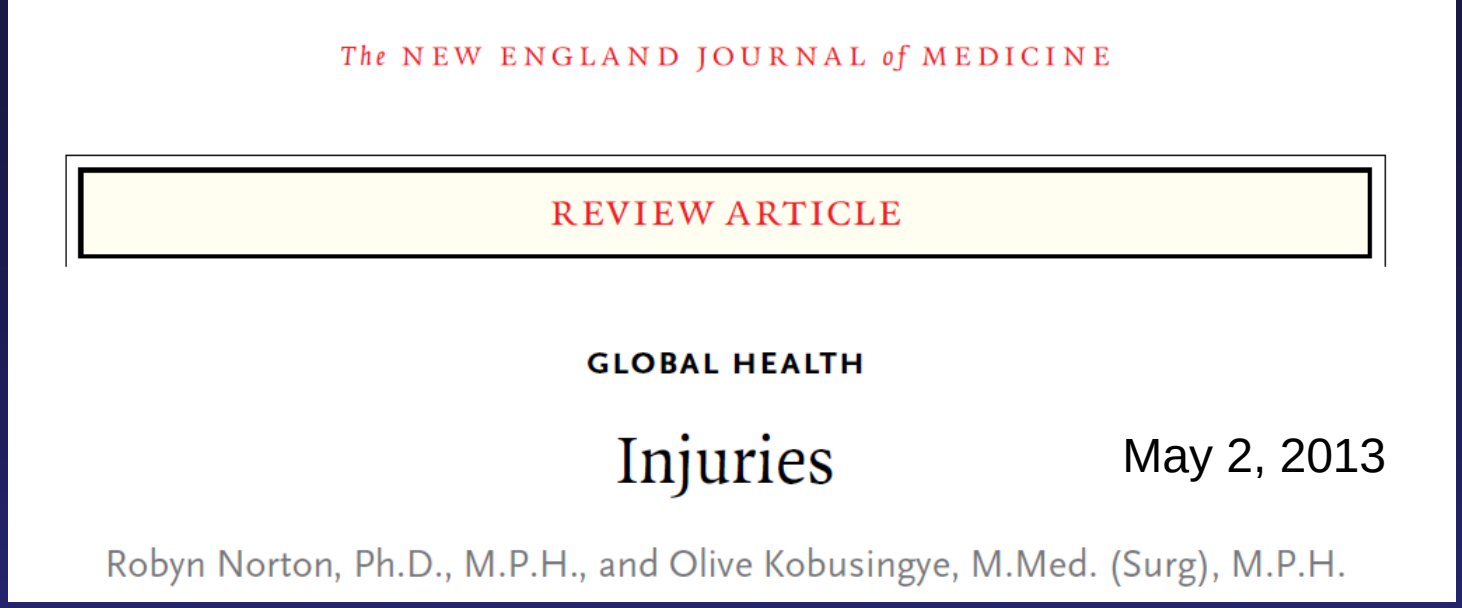

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REVIEW ARTICLE

GLOBAL HEALTH

Injuries

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- In 2010, there were 5.1 million deaths from injuries
  - Deaths from injuries was > HIV, tuberculosis and malaria combined (3.8 million).
- Overall, the number of deaths from injuries increased by 24% between 1990 and 2010.

Need for Quality Hemorrhage Control Studies

- Hemorrhagic shock is the leading potentially preventable cause of death on the battlefield and in the civilian community

TIME TO DEATH IN HEMORRHAGING TRAUMA PATIENTS- EVIDENCE FROM THE LITERATURE

Time to Death Summary

- 5 recent prospective resuscitation trauma studies (n = 4064 patients)
- 4 studies showed that the median time to hemorrhagic death was within 3 hours, despite differences in 30 day mortality

Study	N	Year	Time to hemorrhagic death (hrs)	All-cause mortality at 24 hrs	All-cause mortality at 30 days
rFVIIa	573	2010	NA	NA	11.6%
HSD shock	852	2011	2	NA	26.9%*
PolyHeme	714	2011	2	NA	11.5%
PROMMTT	1245	2013	2.6	11.9%**	20.9%**
PROPPR	680	2015	1.9	14.9%	24.1%

* all-cause mortality at 28 days
** in-hospital mortality

Trauma deaths occur in a consistent pattern

- Early deaths are largely from hemorrhage
  - Over first 2-3 hours (median)
- TBI deaths largely occur within 2-3 days of admission
- The death rate decreases over time
  - After 3 days, small numbers of deaths occur daily due to various causes (PE, MI, stroke, MOF, TBI, withdrawal of support, etc)
  - Very little MOF (< 5%)
  - But ~25% of all deaths occur after 3 days (24% in PROPPR)

POTENTIAL ENDPOINTS FOR HEMORRHAGE CONTROL TRIALS

All-cause mortality

- Pros
  - Definitive and objective
  - Widely used and understood
- Cons
  - In what time frame should mortality be analyzed?
    - Is 30 days the most appropriate for all trauma studies?
  - Competing risks may dilute the effect of interventions targeting hemorrhage

Timing of primary endpoints

- Timing should be based on the biology of the disease and the intervention in question
  - Why use arbitrary clock (24 hrs) and calendar (30 days) based endpoints?
- According to multiple previous studies, the median time to hemorrhagic death is 1-3 hours
- Some interventions may be efficacious within 1 hour (e.g. tourniquets), some within 3 hours (e.g. blood products)
  - Therefore a promising primary endpoint may be death due to hemorrhage (cause-specific mortality)

Cause-specific mortality

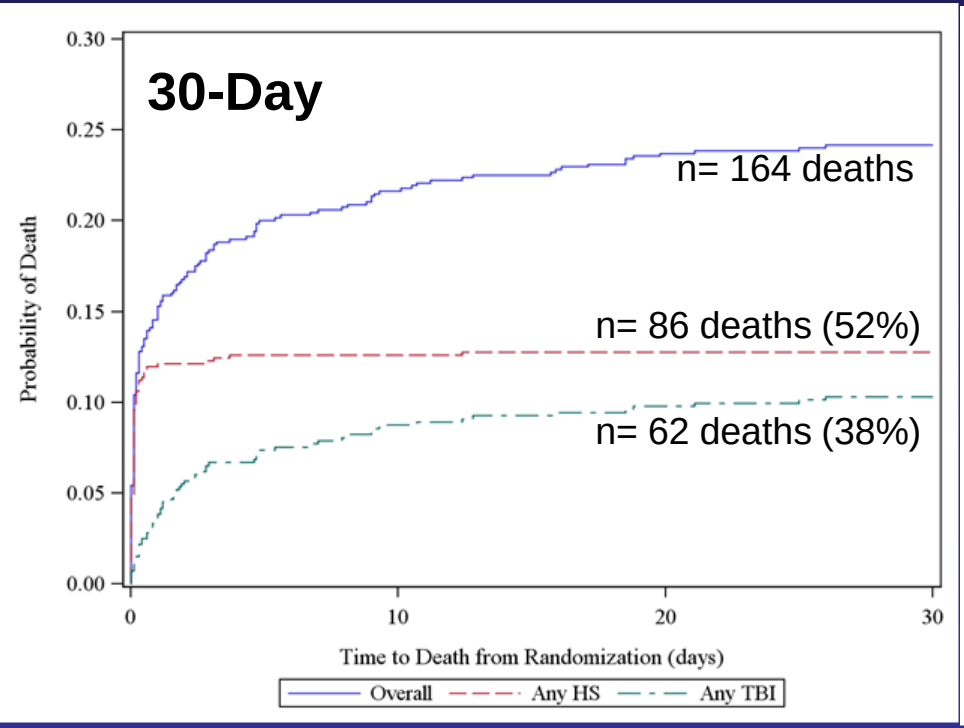
- Pros
  - If the intervention of interest is strictly for hemorrhage control, it is the most direct endpoint for efficacy in patients with hemorrhagic shock
- Cons
  - Not as objective as all-cause mortality
  - Must have standardized definitions of CODs
  - CODs must be adjudicated
  - All causes for very early deaths may be incompletely known, especially TBI

Examining the differences between all-cause and cause-specific mortality using PROPPR data

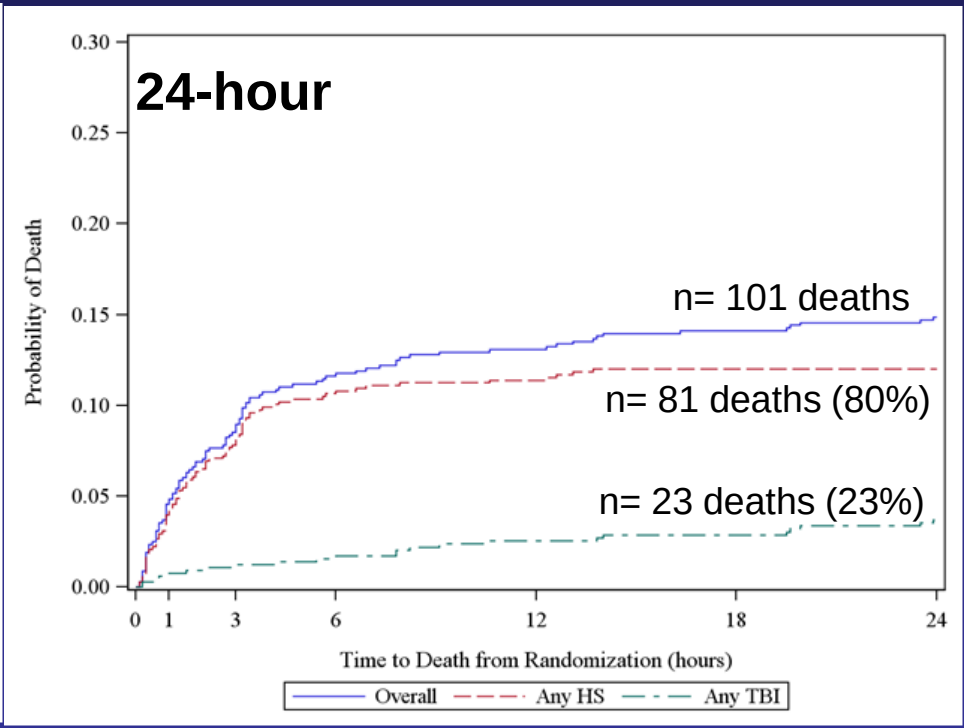
- In PROPPR, investigators reported all possible causes of death
  - A subject may have more than one cause of death (no primary cause)
  - *Any HS* – Hemorrhagic Shock (HS) was reported as a cause of death
  - *Any TBI* – Traumatic Brain Injury (TBI) was reported as a cause of death.

- All-cause failure curves were overlaid with cause-specific curves for all subjects irrespective of treatment at various times of interest (30 days, 24 hours, 6 hours, 3 hours)
  - For cause-specific curves, deaths other than the specified cause are censored

KM failure curves of cause-specific and all-cause mortality (PROPPR data)

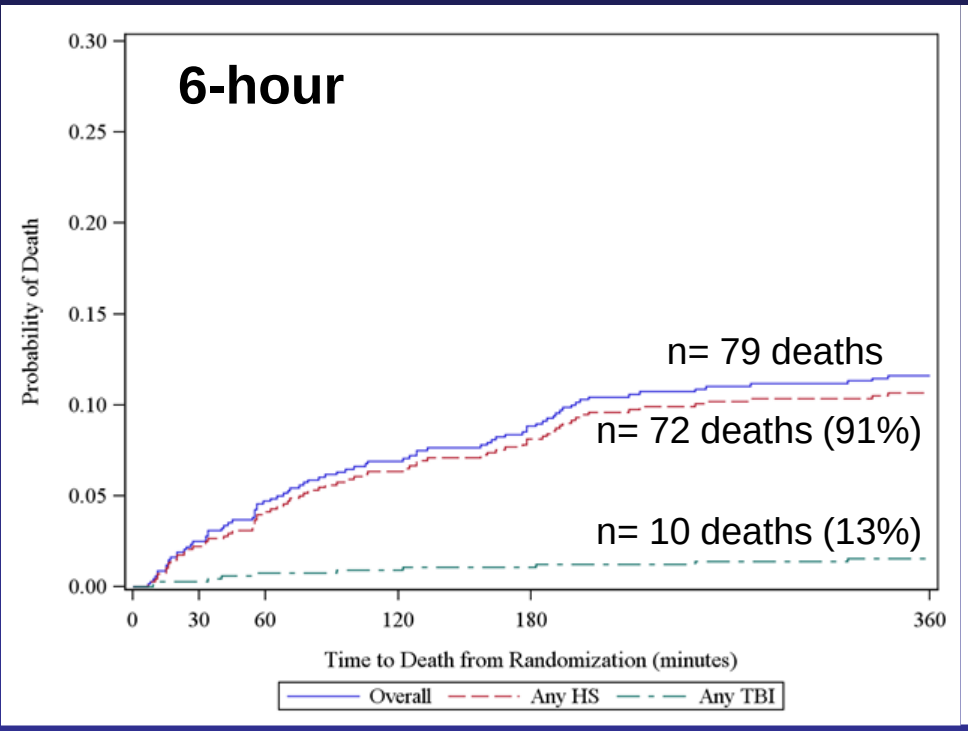


Includes 8 subjects with both HS and TBI and 24 subjects with neither.

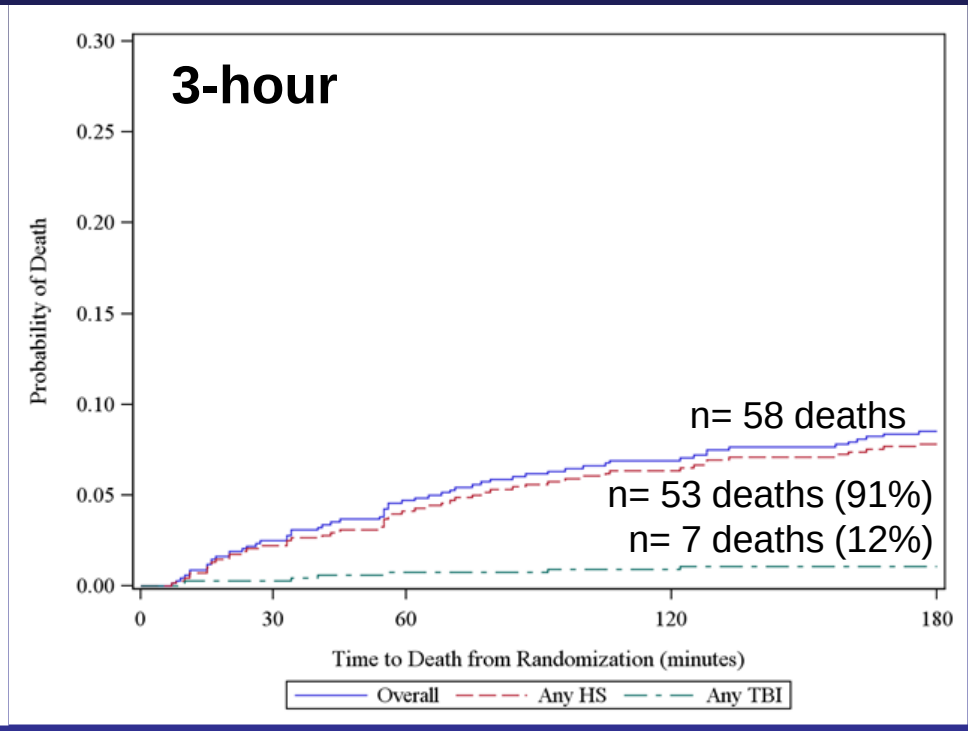


Includes 7 subjects with both HS and TBI and 4 subjects with neither.

KM failure curves of cause-specific and all-cause mortality (PROPPR data)



Includes 5 subjects with both HS and TBI and 2 subjects with neither.



Includes 4 subjects with both HS and TBI and 2 subjects with neither.

Conclusions from comparison of all-cause and cause-specific mortality

- TBI had a small, but real effect in the 3 and 6-hour time frames
  - Most TBI deaths occurred after 24 hours

- If shorter time periods are used as the endpoint for a hemorrhage-control study (e.g. 3 hours in PROPPR), the all-cause mortality is nearly equivalent to cause-specific mortality (death due to hemorrhage)
  - Earlier primary endpoints (1-3 hours) are within the median time to hemorrhagic death
  - Earlier primary endpoints (1-3 hours) enable all-cause mortality to be used
  - Later primary endpoints (e.g. 24 hours and 30 days) require cause-specific mortality and additional analysis of competing causes of death