How should studies be designed to evaluate new carotid protection devices and stents?

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A good---no, a great---question! There is no “one” answer

• The answer will depend on:
  – Goals of the new technology
    • “Me too” vs. new/improved
    • Regulatory approval?
  – Chosen comparator
    • CEA
    • Pre-existing class of CAS devices: yes or no
    • Pre-existing CAS outcomes
  – Capacity for duration, size and cost of the trial
What are the options for study designs?

- **Trial types**
  - RCT vs. CEA (or CAS)
  - Single-arm vs. a performance goal (PG)

- **Primary endpoints**
  - Clinical: death/stroke/MI (DSMI)
  - Composite Morbidity Measure (CMM)
  - Surrogate: MR-DWI or neuropsychometric testing

- **Study populations**
  - Standard or high-risk for CEA
  - Symptomatic and/or asymptomatic
Generic considerations

• The event rates of interest (death/stroke) for a new device in carotid intervention---CEA or CAS---are very low
  – This means that if the goal is to prove superiority of a new device, a large (several thousand) trial is necessary
    • Even with inclusion of only symptomatic patients, it is difficult to adequately “enrich” the population to increase events and lower trial numbers

• Experimental environment is key (willingness to change practice patterns for the study of new device)
Considerations: Trial type

• RCT vs. CEA (or CAS)
  – Highest level of evidence
  – Typically reserved for proof of superiority
  – If done on clinical outcomes basis are large, expensive, lengthy trials

• Single-arm vs. a performance goal (PG)
  – Most common
  – Non-inferiority with a PG with upper boundary of 95% CI
  – Much smaller and shorter study, even with clinical endpoints
Considerations: primary endpoints

• Clinical
  – Death/stroke for new devices most relevant (MI less so), but for US regulatory purposes it will be a composite of all 3 endpoints. If a comparison to CEA, all are important
    • FDA-driven standard for new devices
    • The composite also helps with increasing the event rate and therefore reduces the size of the trial
Considerations: primary endpoints

- Surrogate
  - MR-DWI is a very sensitive marker of embolic activity, represents cellular edema
    - A reasonable set of data exist for indirect comparison
    - Direct (randomized) comparison does not require nearly the number of patients as clinical endpoint trial, especially if “treatment effect” is substantial (e.g., device results in significant reduction of embolic activity)
  - Neuropsychometric (cognitive) testing is too “blunt” a tool to distinguish outcomes
Considerations: Secondary endpoints

• Composite Morbidity Measure (CMM)
  • cranial/peripheral nerve injury
  • vascular injury
  • non-cerebral bleeding
  • wound complications related to the neck incision/femoral puncture site
  • anesthetic complications
Considerations: study population

- High vs. standard CEA risk
  - PG event rates are higher in high-risk patients = smaller trial
- Symptomatic and/or asymptomatic
  - If randomized trial, can be any combination
  - If PG trial, can also be any combination since the PG will be adjusted for the final mix of patients
  - Practical point: there are many more potential asymptomatic patients for inclusion
Conclusion

• For new devices seeking regulatory approval:
  – a single-arm in high-surgical risk patients in a mixed symptom population using an established clinical PG

• For new devices seeking to demonstrate greater procedural effectiveness
  – Single-arm or randomized in any population of patients using surrogate endpoint of MR-DWI
  – clinical endpoints will also need to be collected/compared, but the trial does not need to be powered to show differences there
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