Is Carotid Stent Design Important?

Don’t Blame the Stent for Stroke and Death in CAS!

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Disclosures

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None

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I will not be discussing products that are investigational or not labeled for use under discussion.
“Princess of CAS”
The definitions used for stroke are unusual and will presumably affect the message. For example, most clinicians would define a neurological event lasting less than 24 h as a TIA and not include it as a major outcome measure by calling it a minor stroke. Presumably this was a tool of convenience for the authors to increase the number of outcome events they could include in the analysis. Unfortunately this could well change message of the study. If count is only made of death and major stroke, which would be the conventional way of assessing outcome using these authors definitions, the Protégé and Exponent stents become the devices with best outcome (0% stroke and death), and contrary to the message of the paper, have an open cell design with large cell size. Again, contrary to the conclusion of the paper, the NexStent has the worst outcome (stroke and death 3.3%), even though it has a closed stent design with small free cell area (2.5–5 mm²).
Clarifications

- Will not address death singularly as a stent-related outcome
  - Will refer only to stroke, which will necessarily omit neurologic death

- Stent design is at issue here and not the stent itself, which appears to actually reduce stroke and restenosis (CAVATAS)
What are the possible causes of stroke in CAS?

- **Operator error**
  - Technique (balloon sizing, wire misadventure, EPD error, etc.)
- **Patient factors**
  - Vulnerable plaque (lesion, aorta)
  - Vascular anatomy or characteristics (calcium, thrombus, etc.)
  - Genetics related to thienopyridine metabolism
- **Inadequate technology**
  - EPD, stent, procedural pharmacology
Reasoned arguments

- Stent design is not responsible for all (or even the majority) of stroke in CAS
  - Define proportion of strokes possibly related to stent design among the other viable causes

- The data, anatomy, and timing do not support stent design as a cause of stroke in the remainder
Non-stent related strokes: logic

- **Procedural**
  - EPD is in place, so any stroke that occurs is a failure of the EPD and not of stent.

- **Hemorrhagic**
  - Typically hyperperfusion syndrome related to a territory with compromised autoregulation

- **Non-ipsilateral**
How many strokes can we blame on the stent?
Eliminating the obvious

168 total strokes (4.8%)

- 31 non-ipsilateral strokes (18%)
- 12 hemorrhagic strokes (7%)
- 29 procedural strokes (17%)

96 possible stent strokes (2.7%)

What about post-procedural strokes?
Account for similar mechanisms

How many strokes can we blame on the stent? 
Re-calculating

168 total strokes (4.8%)
- 31 non-ipsilateral strokes (18%)
- 31 ipsilateral strokes (18%)
- 12 hemorrhagic strokes (7%)
- 29 procedural strokes (17%)

65 possible stent strokes (1.9%)
Which strokes can we blame on the stent?

- Clearly, the non-hemorrhagic, ipsilateral, non-procedural strokes

- But wait…can all post-procedural strokes be assigned a stent cause?
  - Since the 18% of strokes non-ipsilateral to the stent “occurred” post-procedure, there must be a similar non-stent explanation for the ipsilateral “late events”
Post-procedural control of permissive HTN uncovers procedural events and leads to a “late stroke”

Fig 2. Systolic and diastolic blood pressure (95% CI) before and after stenting in patients with and without post-procedure symptomatic hypotensive events.
How many strokes can we blame on the stent?
Re-calculating: ~1.0%-1.5%

168 total strokes (4.8%)

- 31 non-ipsilateral strokes (18%)
- 31 ipsilateral strokes (18%)
- 12 hemorrhagic strokes (7%)
- 31 procedural strokes (18%)
- 29 procedural strokes (17%)

34 possible stent strokes (1.0%)
Are the proposed mechanisms of stent stroke after EPD removal plausible?

- Open cells have larger cells than closed cells, and promote more emboli

- Cells (open or closed) are too large and allow meaningful emboli

- Thrombus formation on stent and subsequent emboli
Open and closed cell design elements

Closed cell

Open cell
All pore (MCUSA) sizes ARE created equal.
No difference between OC and CC stents.

N.B. filter pore size ~1/10th the stent pore size

<table>
<thead>
<tr>
<th>Pore Size (mm)</th>
<th>Wallstent</th>
<th>Xact</th>
<th>Protégé</th>
<th>Precise</th>
<th>Acculink</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.92</td>
<td>0.96</td>
<td>1.08</td>
<td>1.12</td>
<td>1.06</td>
<td></td>
</tr>
</tbody>
</table>

Xact, PROTÉGÉ RX and Acculink = 8-6mm tapered stents (distal portion)

Precise and Wallstent = 8mm straight stent
Are the proposed mechanisms of stent stroke after EPD removal plausible?

- Open cells are larger than closed cells, and promote more emboli
- Cells (open or closed) are too large and allow meaningful emboli
- Thrombus formation on stent and subsequent emboli
Distal minor stroke vessel: <1.0 mm
Are the proposed mechanisms of stent stroke after EPD removal plausible?

- Open cells are larger than closed cells, and promote more emboli
- Cells (open or closed) are too large and allow meaningful emboli
- Thrombus formation on stent and subsequent emboli
If stents are the cause, shouldn’t they be associated with known risks for CAS?
Clinical predictors do not correlate with stent strokes: No differences in stroke timing by age

- **Age ≥ 80 (n=63)**
  - After 24 hours: 44%
  - Within 24 hours: 56%

- **Age <80 (n=107)**
  - After 24 hours: 35%
  - Within 24 hours: 65%
Clinical predictors do not correlate with stent strokes: No differences in stroke timing by symptom status
What about the pharmacology in CAS? Is this procedure immune to such considerations?
Marked thienopyridine response variability

Variability of platelet aggregation after loading with clopidogrel 600mg

Hochholzer et al., Circulation 2005; 111: 2560
Age-related CAS outcomes and platelet reactivity on clopidigrel

J Am Coll Cardiol 2010 June; 55(22):2427-34
Intestinal absorption

Hepatic generation of active metabolite

Platelet inhibition

Clopidogrel
(oral ingestion of pro-drug)

Intestinal absorption

Hepatic generation of active metabolite

Platelet inhibition

ABC\textsubscript{7} (MDR-1)
Chromosome 7

CYP enzyme system
Two sequential steps:
One step: CYP3A4, CYP3A5, CYP2C9, CYP1A2
Both steps: CYP2B6, CYP2C19
Chromosome 10

Platelet membrane receptors
P2Y\textsubscript{12}, GP IIb/IIIa, GP Ia

Marin F & Angiolillo DJ. J Am Coll Cardiol 2009;54:1041-57
CYP2C19 Polymorphisms and Response to Clopidogrel and Prasugrel


**Clopidogrel**

(n=1477)

8.0

CV Death, MI, or Stroke (%)

Days After Randomization

HR [95%CI] = 1.53 [1.07-2.19]

P=0.01

No. at Risk:

Noncarrier

Carrier

1064 395
1009 364
999 360
980 348
870 306
755 270
542 181

**Prasugrel**

(n=1466)

9.8

CV Death, MI, or Stroke (%)

Days After Randomization

HR [95%CI] = 0.89 [0.60-1.31]

P=0.27

No. at Risk:

Noncarrier

Carrier

1048 407
991 383
982 376
951 364
849 320
750 276
541 188

*2 Carriers: 27.1% of the population
ABCB1 Polymorphisms and Response to Clopidogrel and Prasugrel

Mega JL et al. Lancet 2010:online

Homozygotes (TT): 27.4% of the population
CYPC2C19/ABCB1 Polymorphisms and Response to Clopidogrel and Prasugrel

Mega JL et al. Lancet 2010:online
Improvement in CAS outcomes is unrelated to stent type used
EXACT (CC) and CAPTURE 2 (OC)
No differences in prospective, adjudicated study

Hierarchical - Includes only the most serious event for each patient and includes only each patient first occurrence of each event.
Improvement in CAS outcomes independent of stent type used

EMPiRE OC stent usage: 51%

- Xact ® 39.8%
- Precise ® 27.0%
- NexStent ® 9.0%
- Acculink ® 19.9%
- Protégé ® 4.3%

% of Subjects (N=243)
Improvement in CAS outcomes independent of stent type used

EMBOLDEN OC stent usage: 70%

- Precise® 36%
- Xact® 25%
- Wallstent® 5%
- Protégé® 7%
- Acculink® 27%

% of Subjects (N=250)
The stent is only one of several other very plausible causes of stroke in CAS.
Conclusion

Res ipsa loquitur
“the thing speaks for itself”

The multifactorial nature of stroke and unidentified contributors make the likelihood that the stent is significant cause or is deficient in its construct