# Is Carotid Stent Design Important?

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

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# Disclosures

## William Gray, MD

For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

**Honoraria received from:**

None

**Consulted for:**

Abbott Vascular, Boston Scientific Corporation, Cordis Corporation, Covidien, Gore & Associates, Medrad Interventional/Possis, Medtronic Invatec, Pathway Medical Technologies, Inc., Terumo Medical Corporation

# Disclosures

## William Gray, MD

**Held common stock in:**

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Abbott Vascular, Atritech, Cordis Corporation, CREST, Gore & Associates, Medtronic Invatec

**I will not be discussing products that are investigational or not labeled for use under discussion.**

# “Princess of CAS”

# Peter Gaines comment "no difference observed"

INVITED COMMENTARY

## Re: Does Free Cell Area Influence the Outcome in Carotid Artery Stenting?

P.A. Gaines

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 $mm^2$).



Eur J Vasc Endovasc Surg 33.142-143 (2007)

# 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

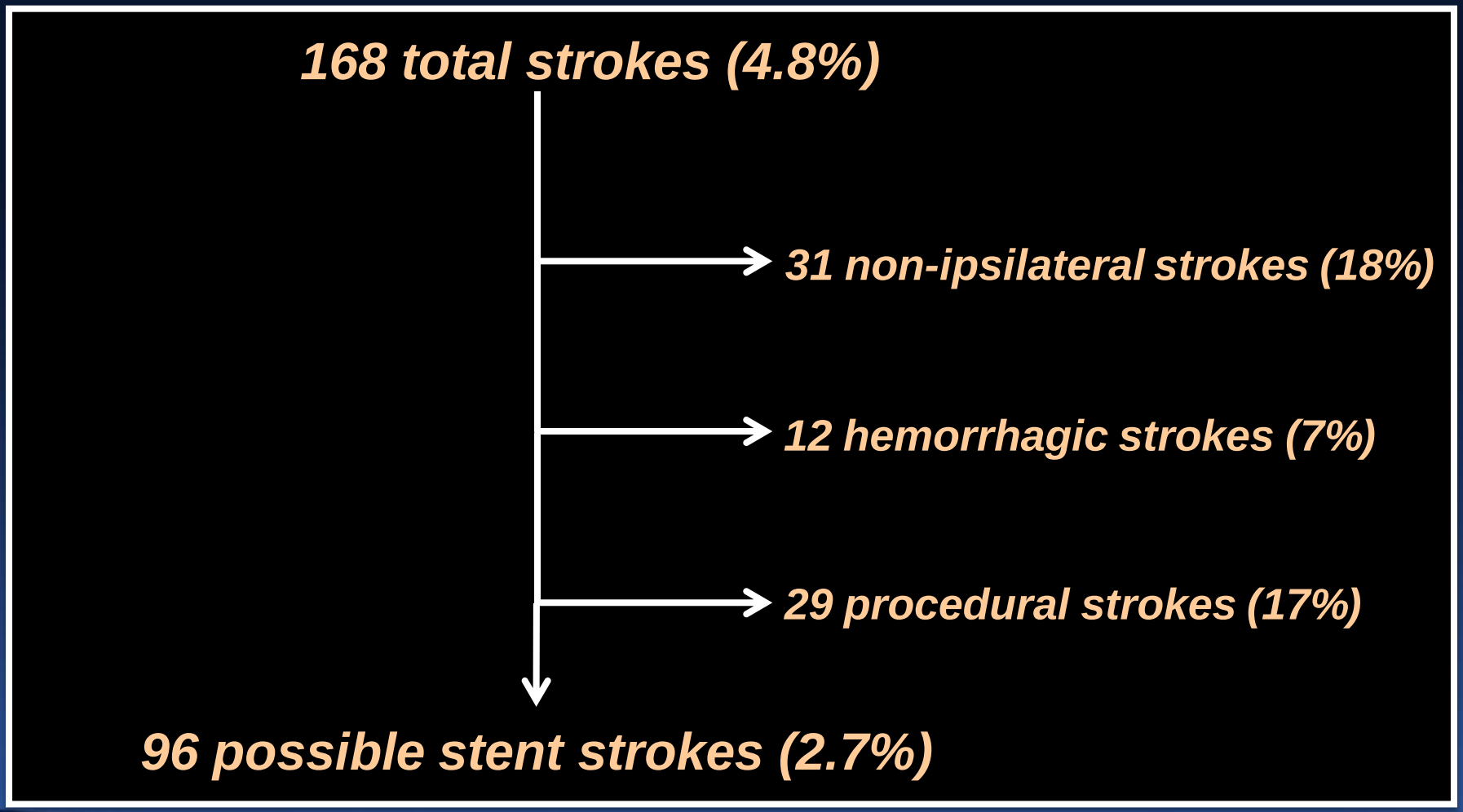
# Reasoned arguments

- 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

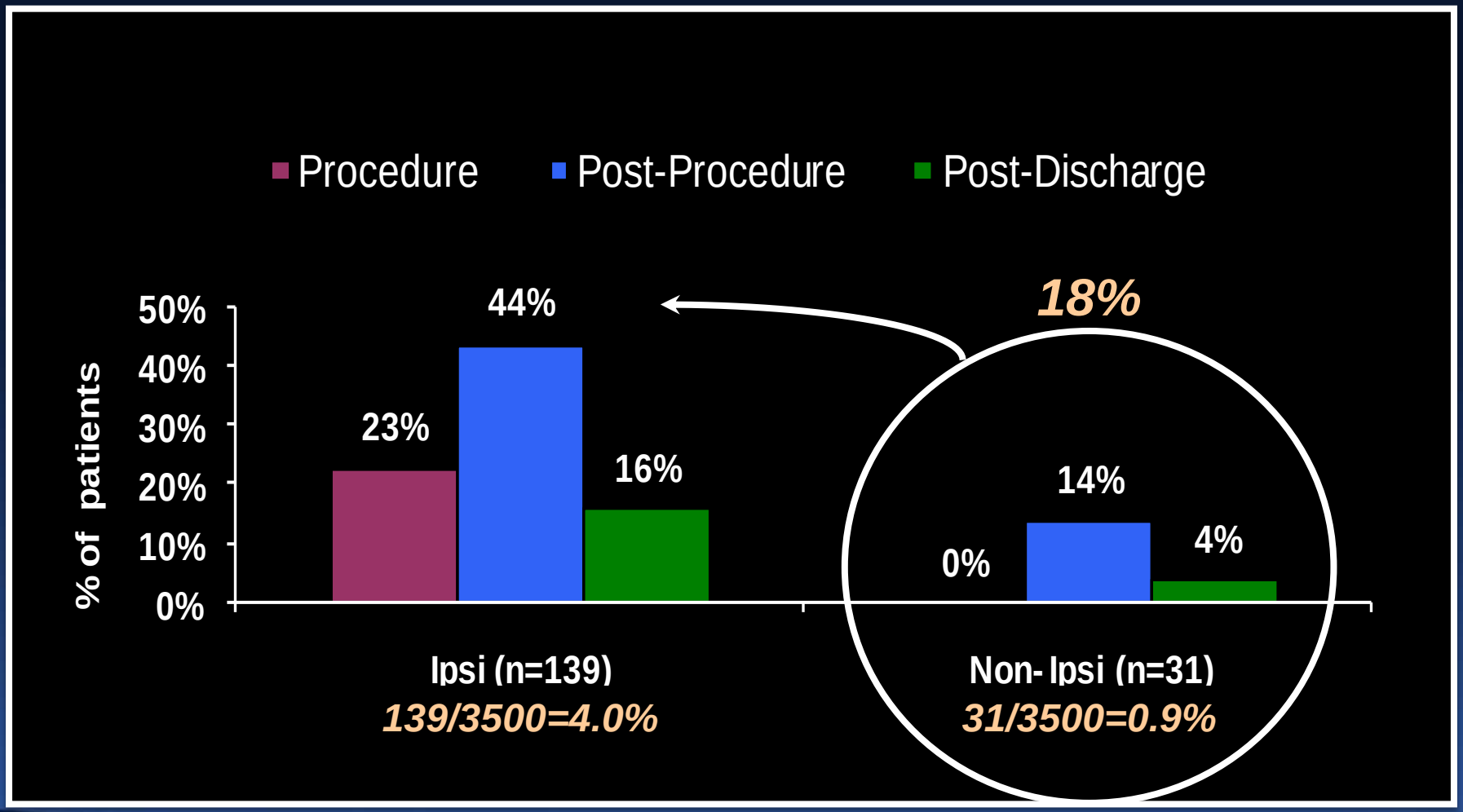
- Procedural
  - EPD is in place, so any stroke that occurs is a failure of the EPD and not of stent.
- Hemorrhagic
  - Typically hyperperfusion syndrome related to a territory with compromised autoregulation
- Non-ipsilateral

# How many strokes can we blame on the stent?
## Eliminating the obvious



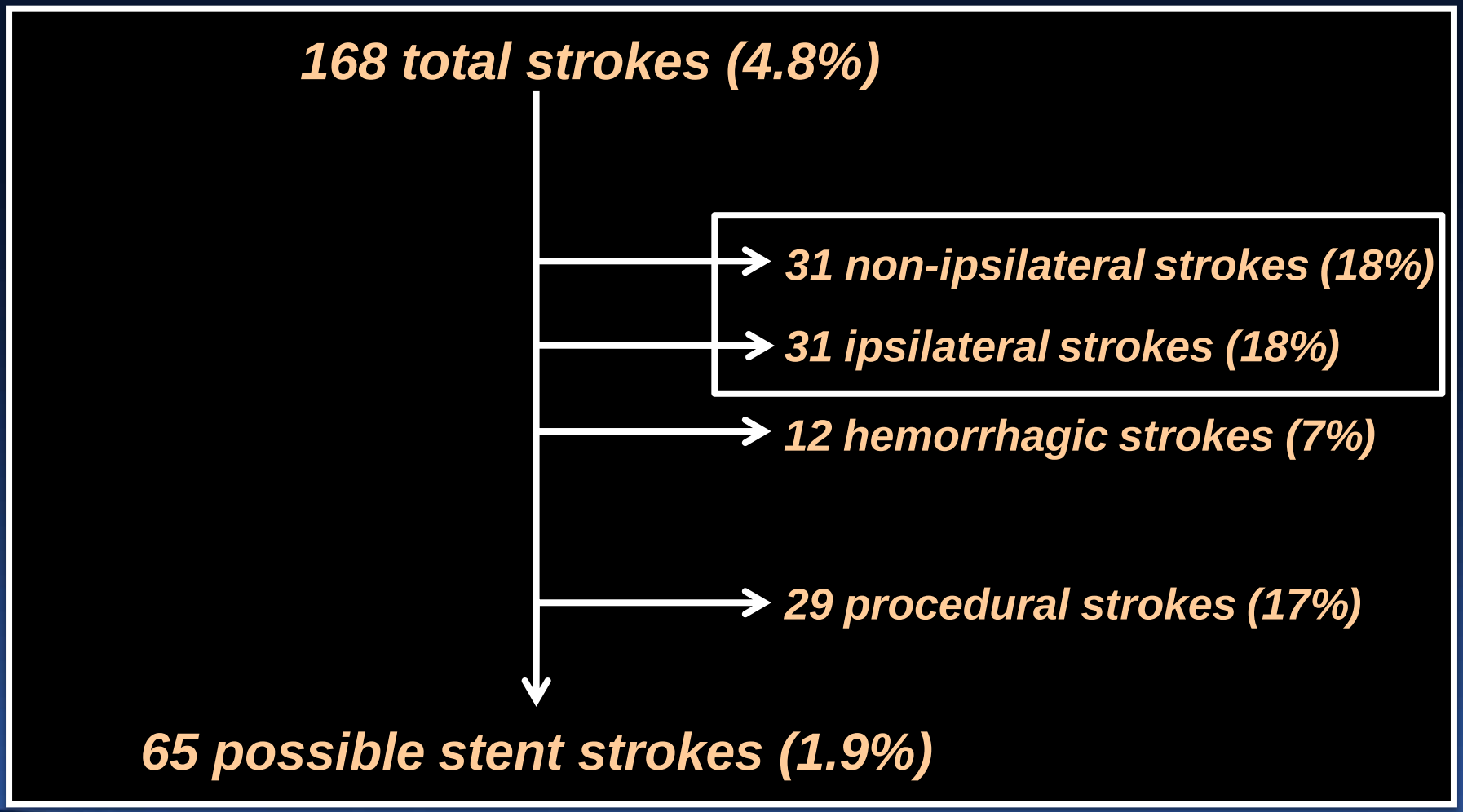

Fairman R, Gray W, Scicli A et al. Ann Surg 246 (4) Oct 2007

# What about post-procedural strokes?
## Account for similar mechanisms




Fairman R, Gray W, Scicli A et al. Ann Surg 246 (4) Oct 2007

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



# 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"

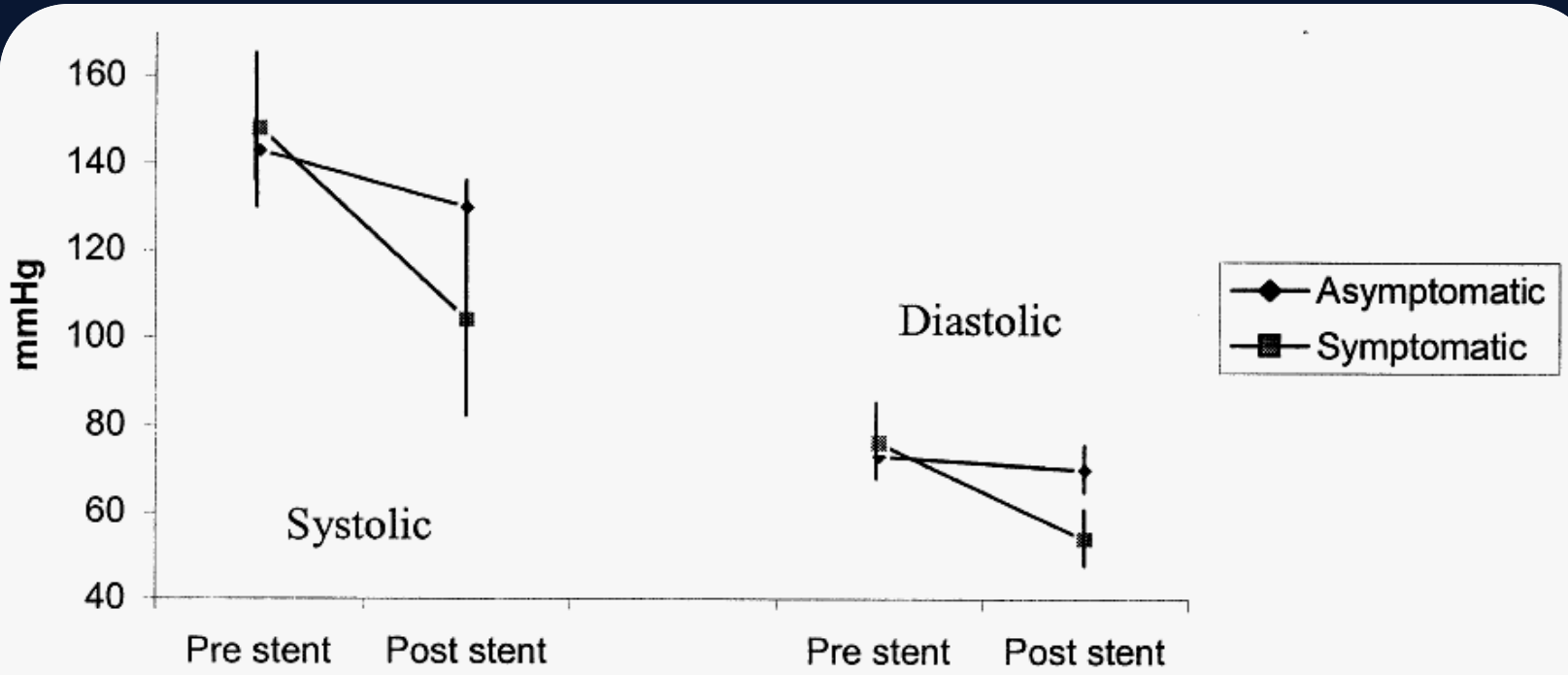
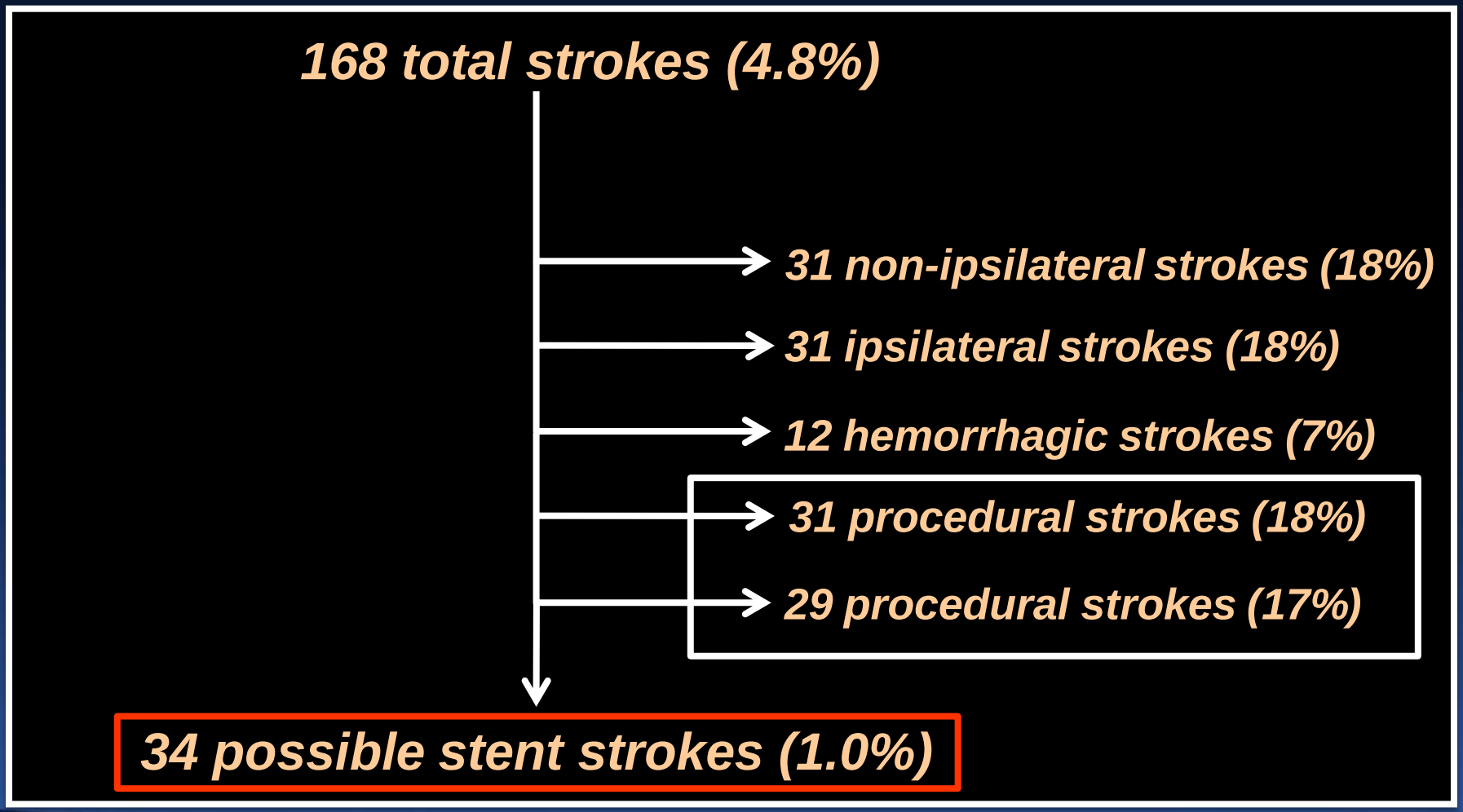



**Fig 2.** Systolic and diastolic blood pressure (95% CI) before and after stenting in patients with and without post-procedure symptomatic hypotensive events.

Tan KT, Cleveland TJ, Berczi V et al. J Vasc Surg 2003;38:236-43

# How many strokes can we blame on the stent?

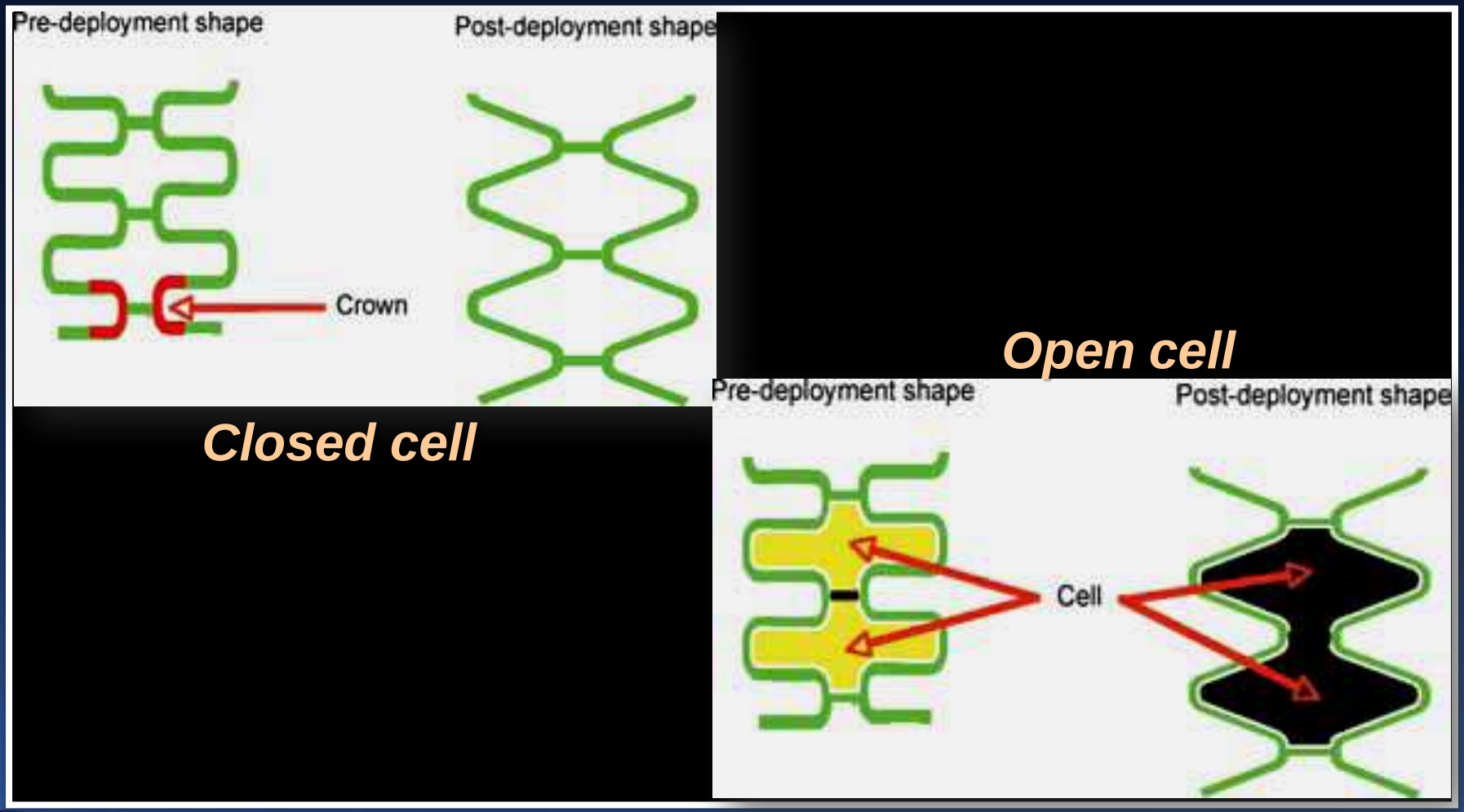
## Re-calculating: ~1.0%-1.5%



# Are the proposed mechanisms of stent stroke after EPD removal plausible?

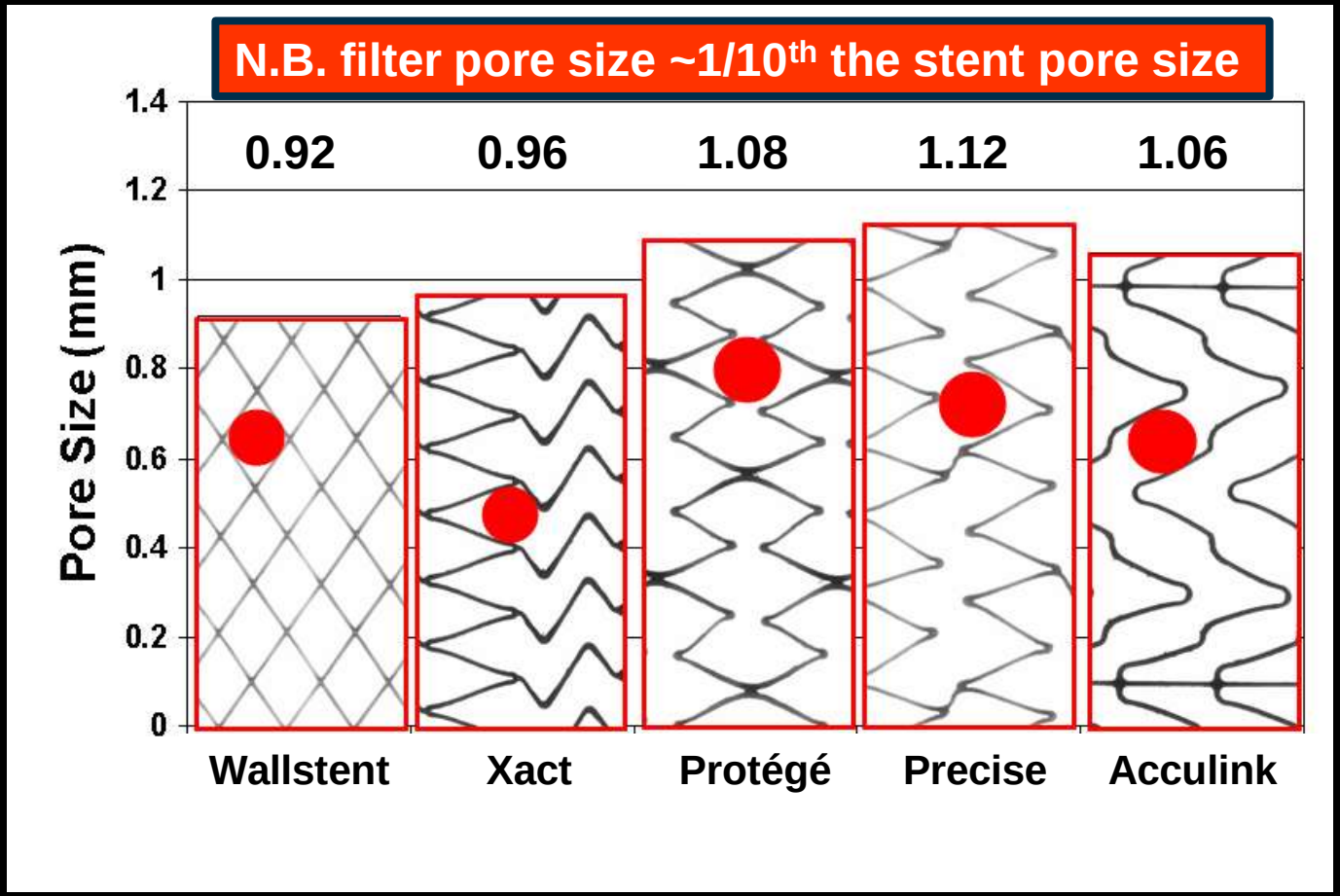
- Open cells have larger cells than closed cells, and promote more emboli
- Cells (open or closed) are too large and allow meaningful emboli
- Thrombus formation on stent and subsequent emboli

# Open and closed cell design elements



# All pore (MCUSA) sizes *ARE* created equal

## No difference between OC and CC stents



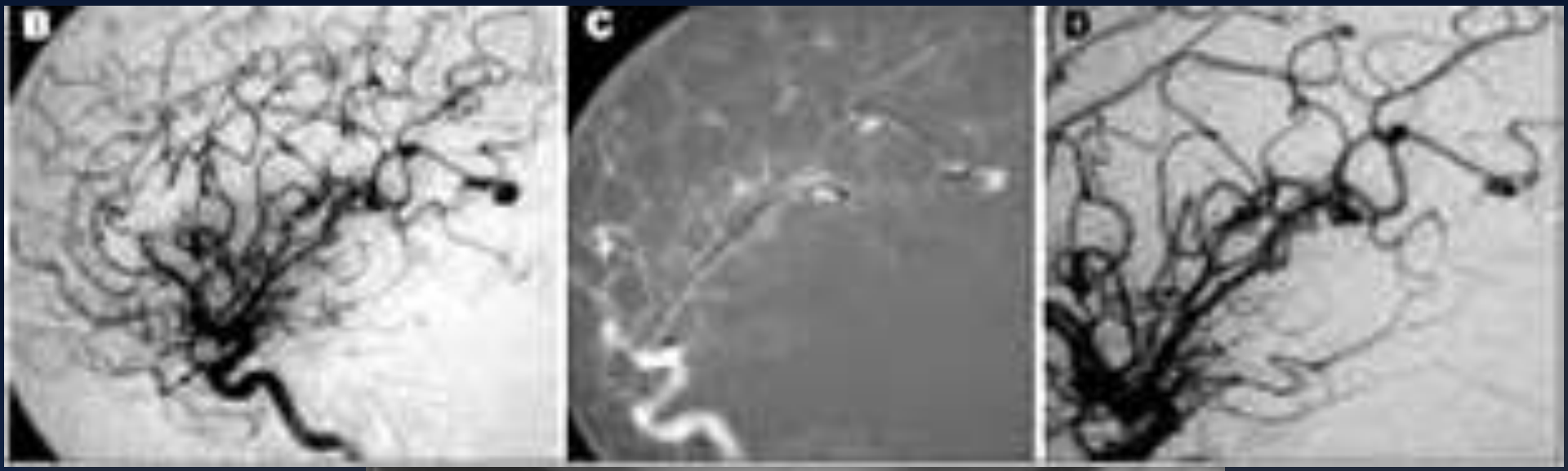

Xact, PROTÉGÉ RX and Acculink = 8-6mm tapered stents (distal portion)

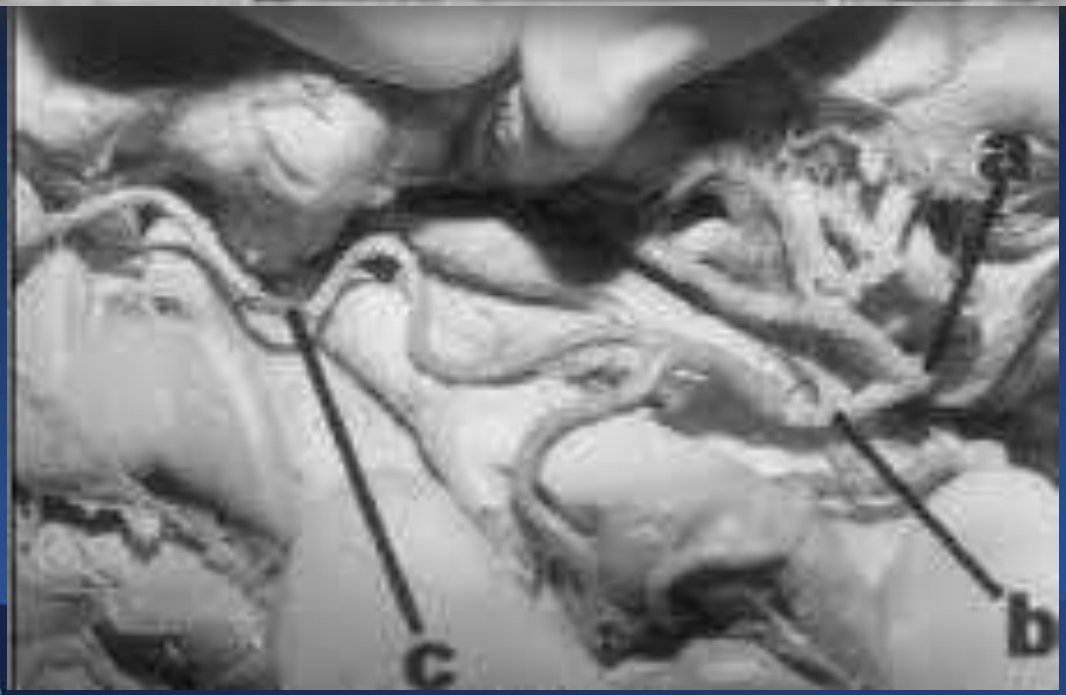
Precise and Wallstent = 8mm straight stent

# 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



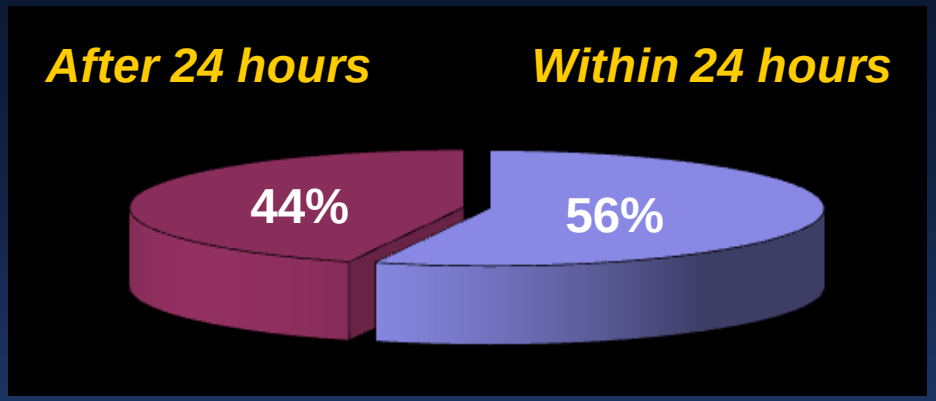



# Are the proposed mechanisms of stent stroke after EPD removal plausible?

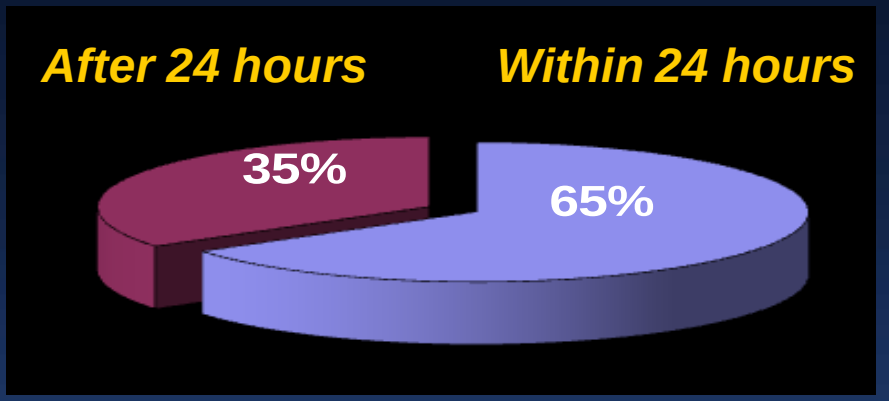
- Open cells are larger than closed cells, and promote more emboli
- Cells (open or closed) are too large and allow meaningful emboli
- Thrombus formation on stent and subsequent emboli

# 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

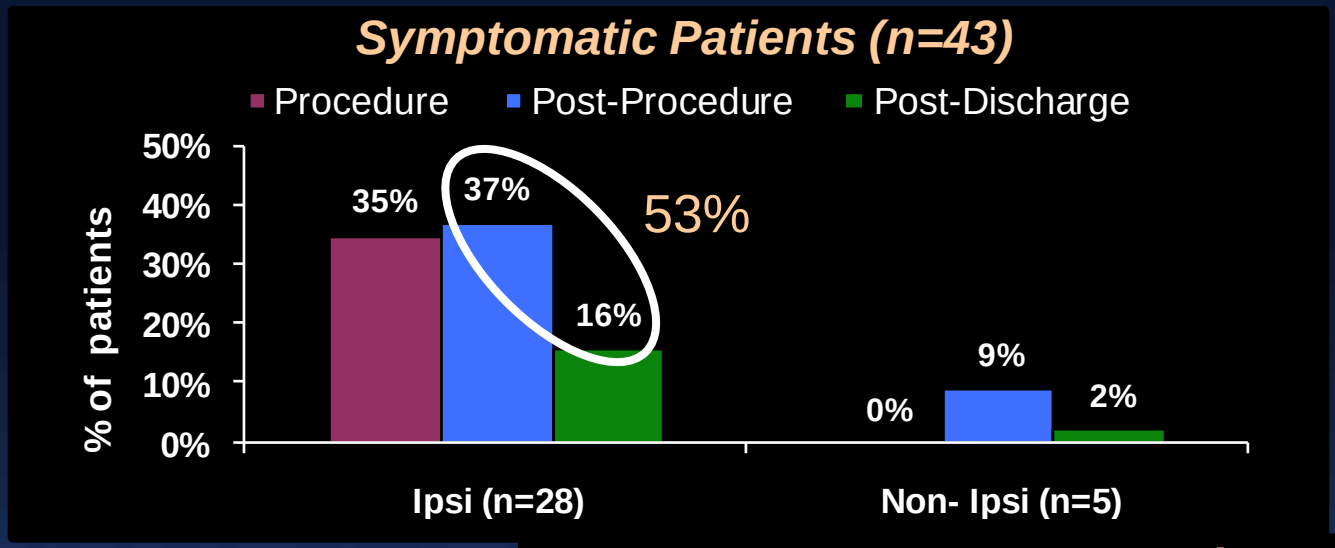


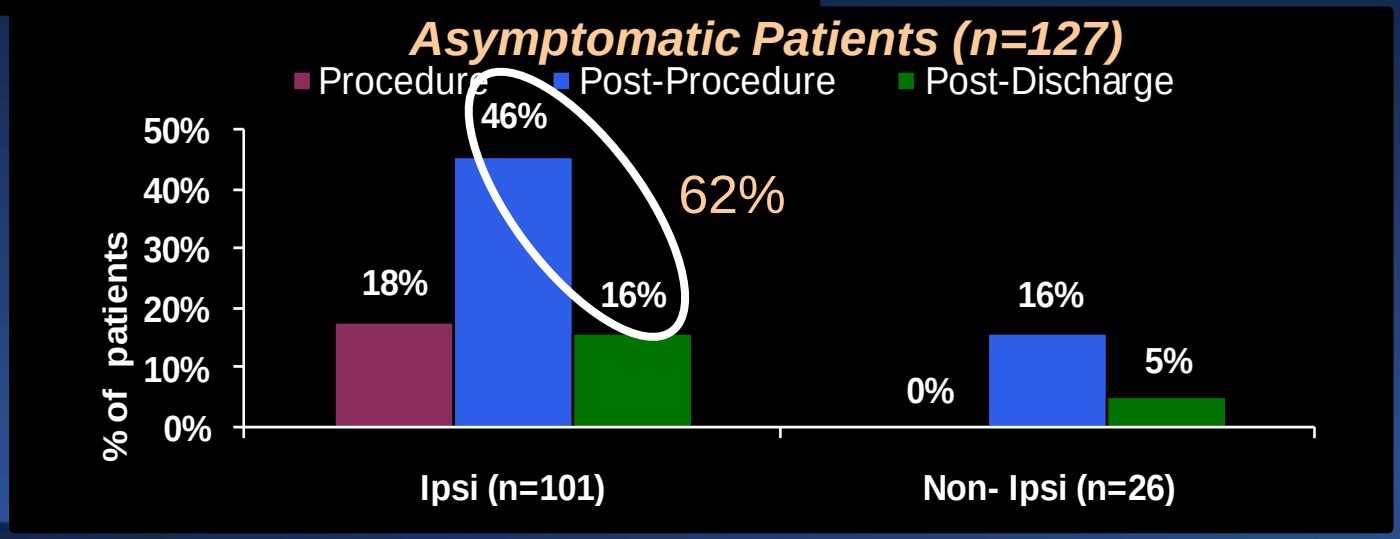

Age ≥ 80 (n=63)




Age <80 (n=107)

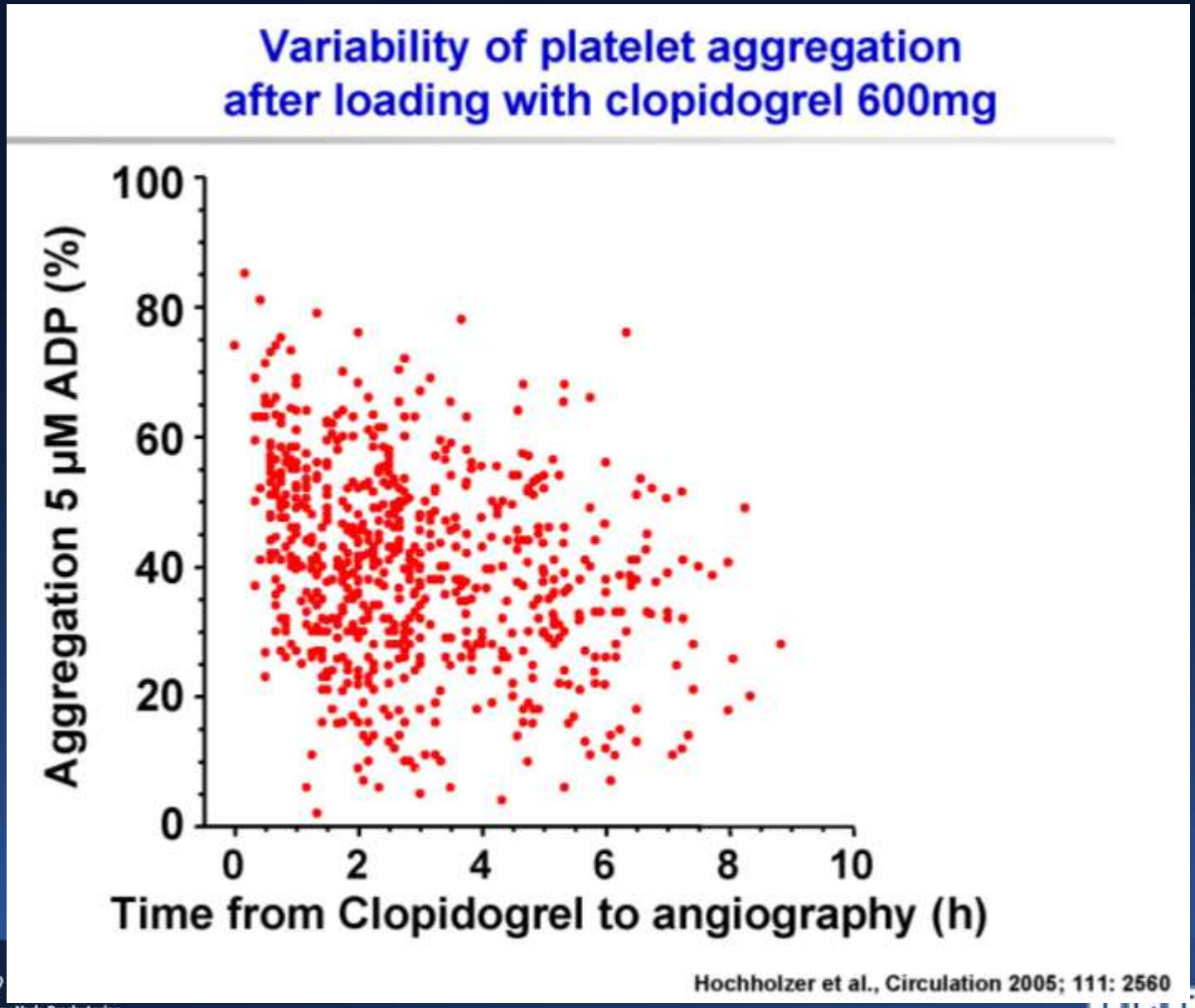
# Clinical predictors do not correlate with stent strokes: No differences in stroke timing by symptom status



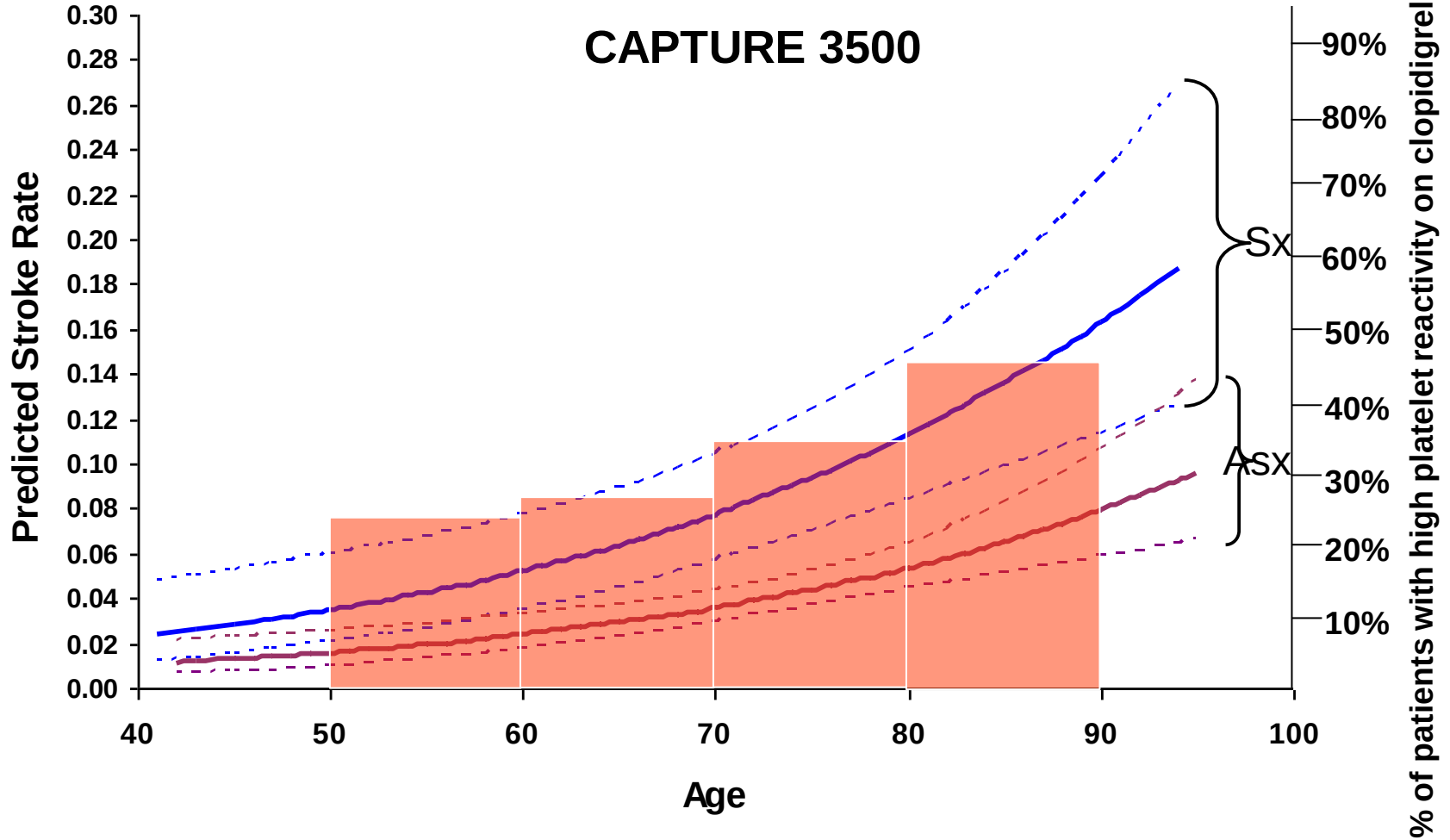



# What about the pharmacology in CAS? Is this procedure immune to such considerations?

# Marked thienopyridine response variability

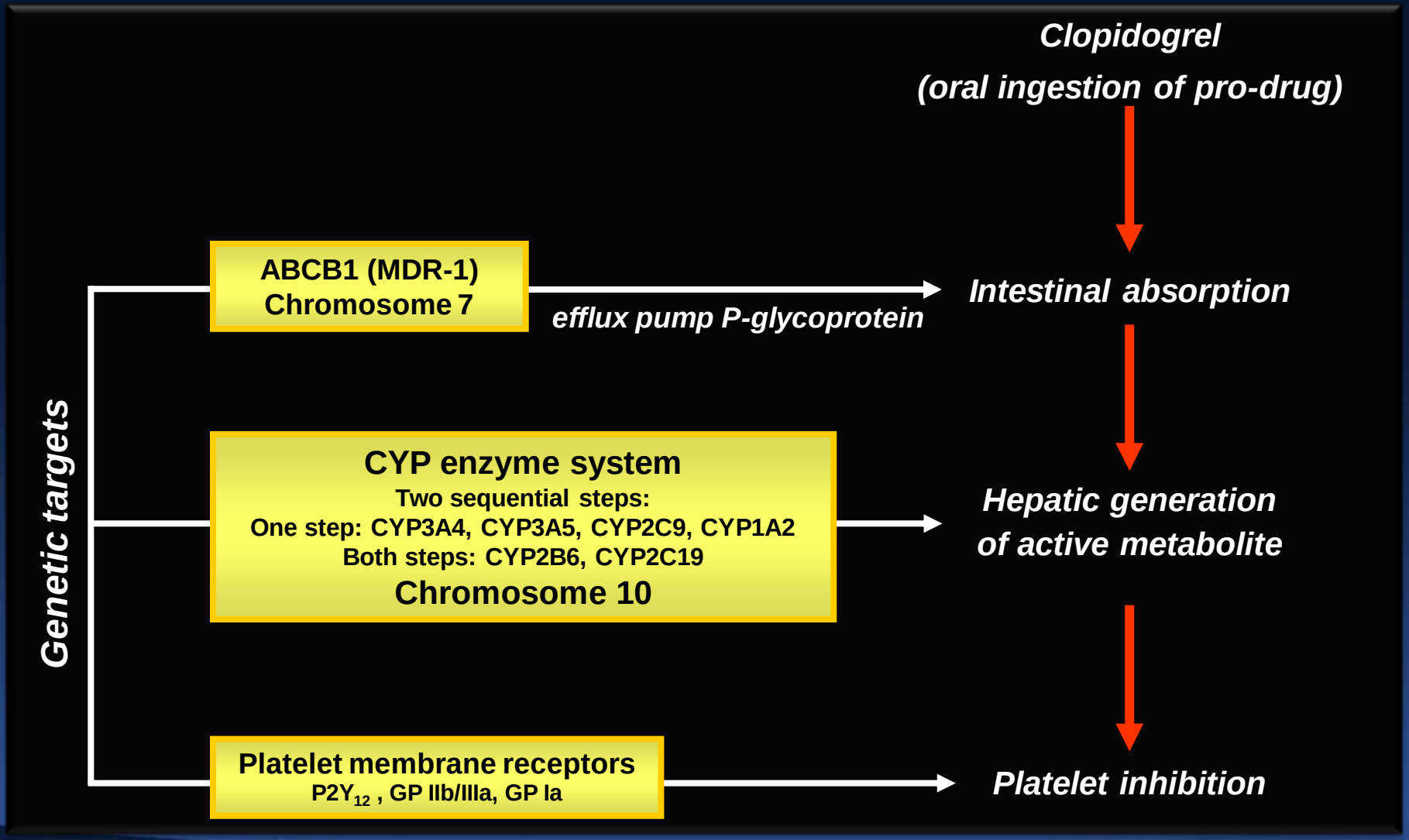


# Age-related CAS outcomes and platelet reactivity on clopidigrel



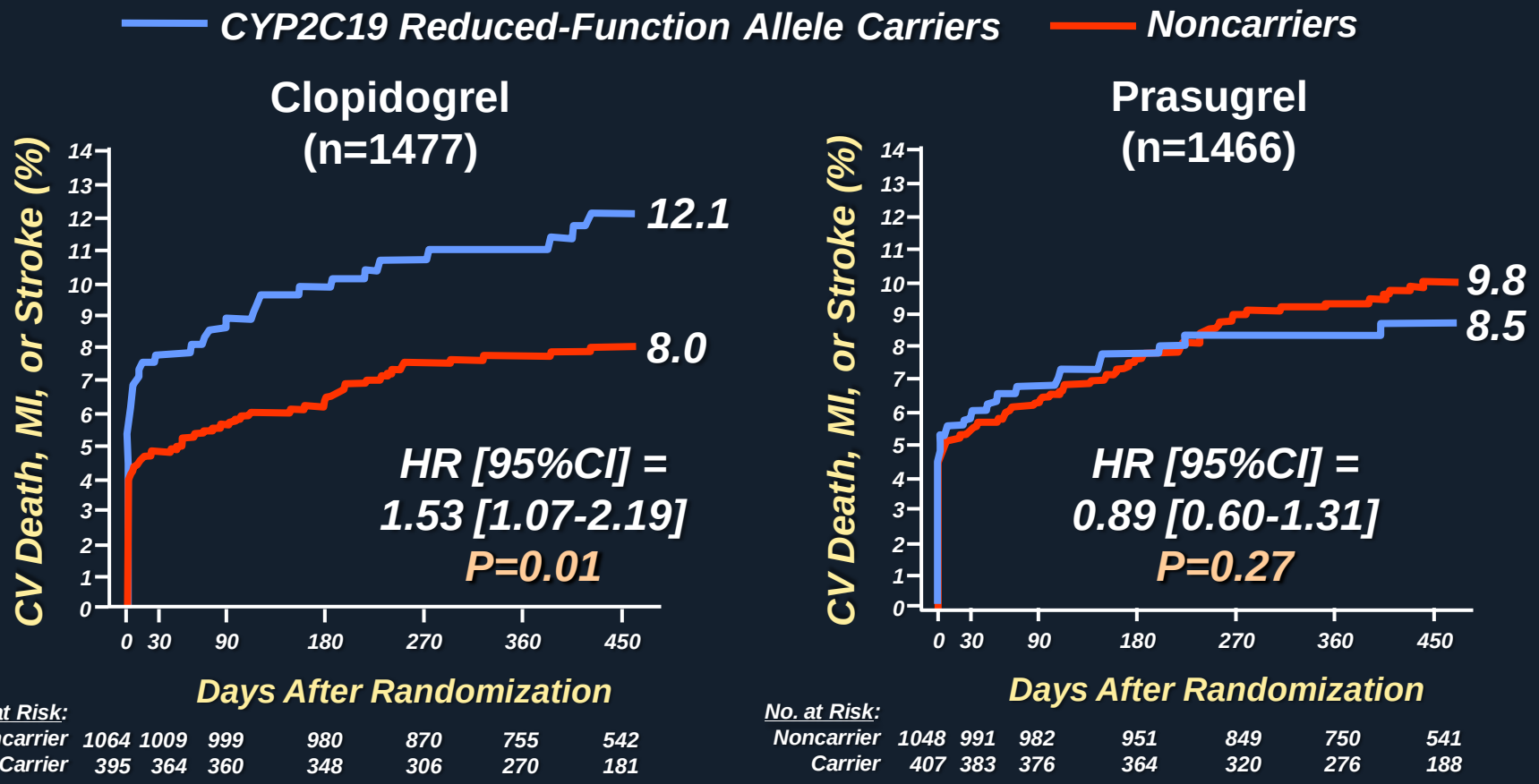

J Am Coll Cardiol 2010 June; 55(22):2427-34

# Pharmacogenetics of cardiovascular antithrombotic therapy




Marin F & Angiolillo DJ. J Am Coll Cardiol 2009;54:1041-57

# CYP2C19 Polymorphisms and Response to Clopidogrel and Prasugrel



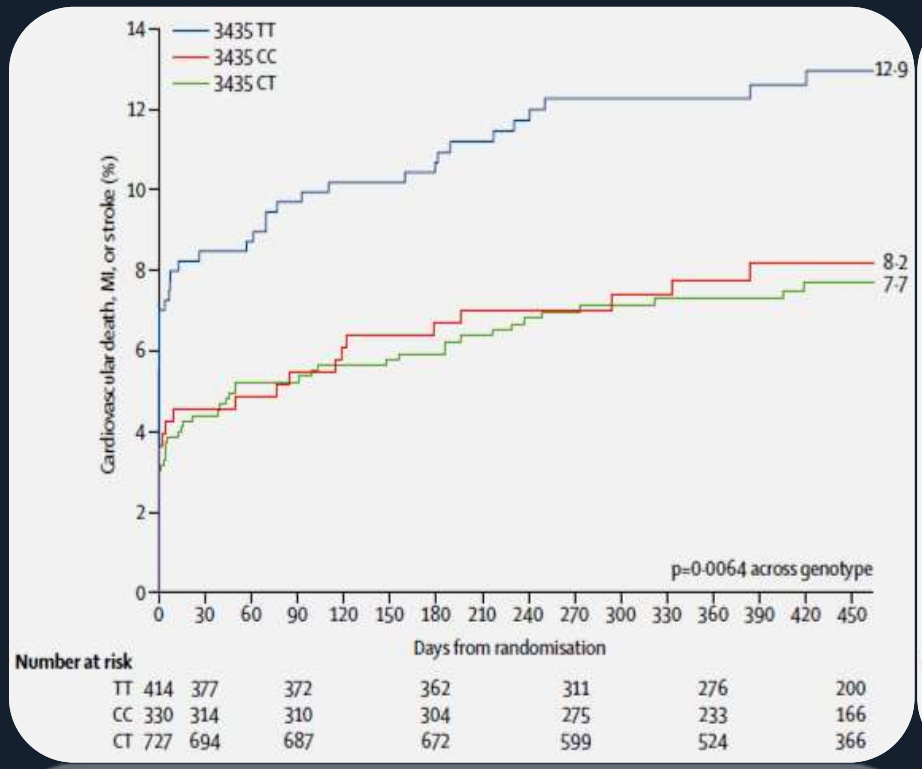

*2 Carriers: 27.1% of the population



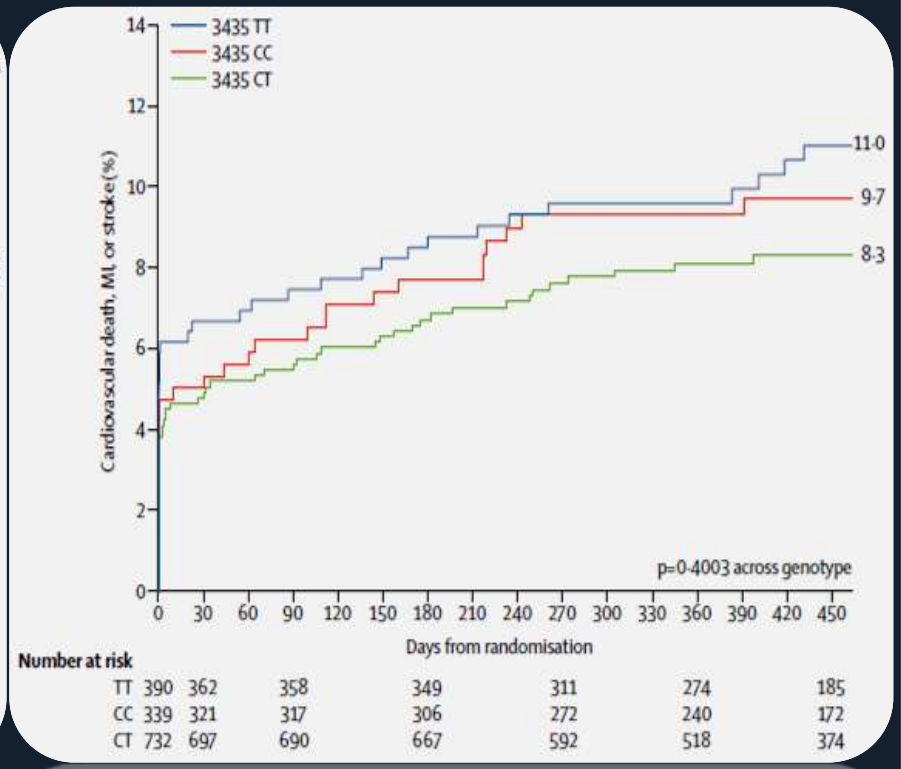

Mega JL et al. AHA 2008.
Mega JL et al. N Engl J Med. 2008;360.

# ABCB1 Polymorphisms and Response to Clopidogrel and Prasugrel

## Clopidogrel (n=1471)




## Prasugrel (n=1461)




***Homozygotes (TT): 27.4% of the population***

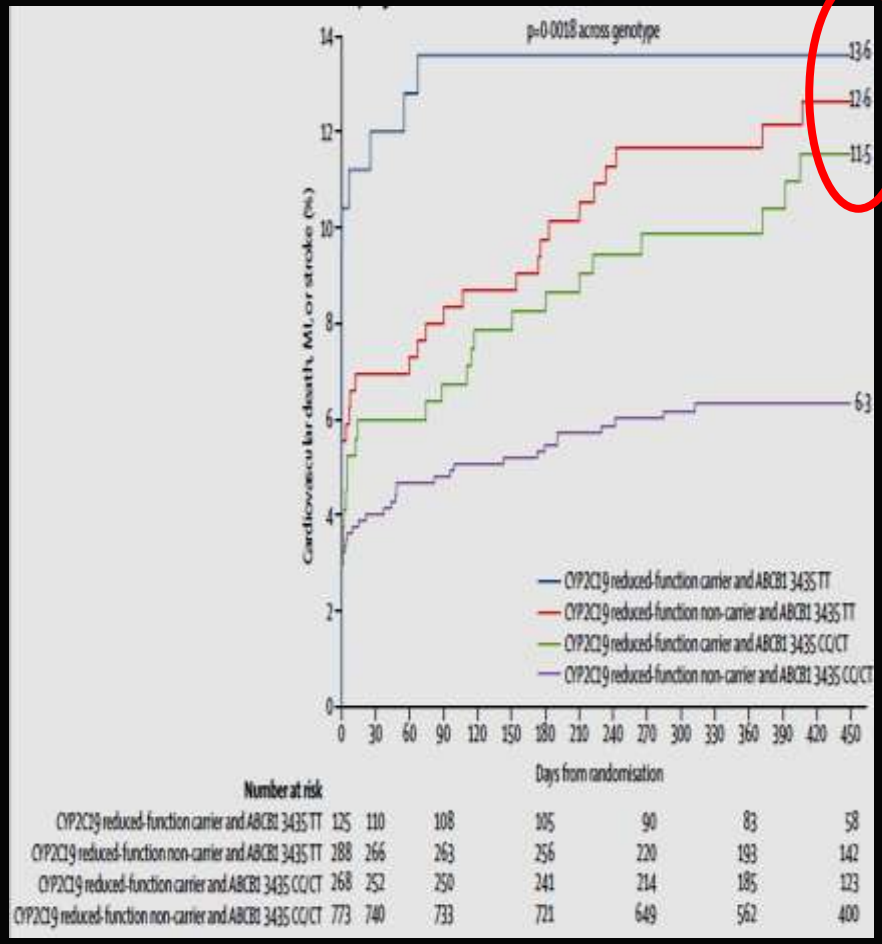
*Mega JL et al. Lancet 2010:online*

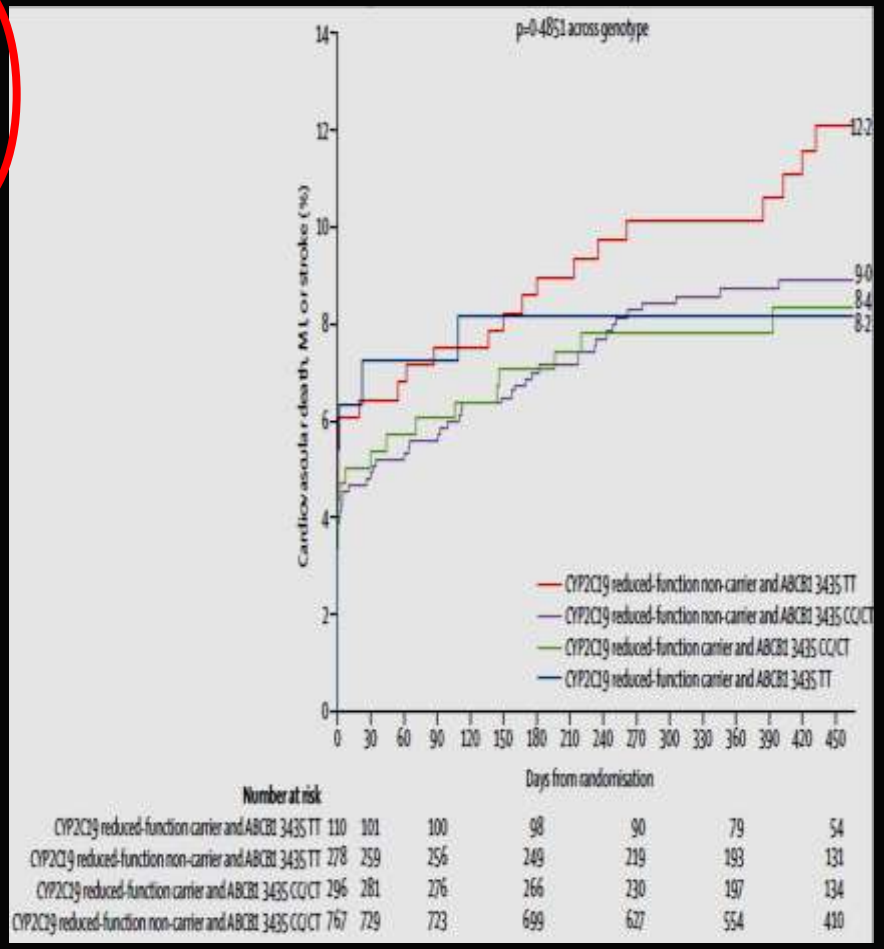
# CYPC2C19/ABCB1 Polymorphisms and Response to Clopidogrel and Prasugrel

***Clopidogrel (n=1454)***

***47%***

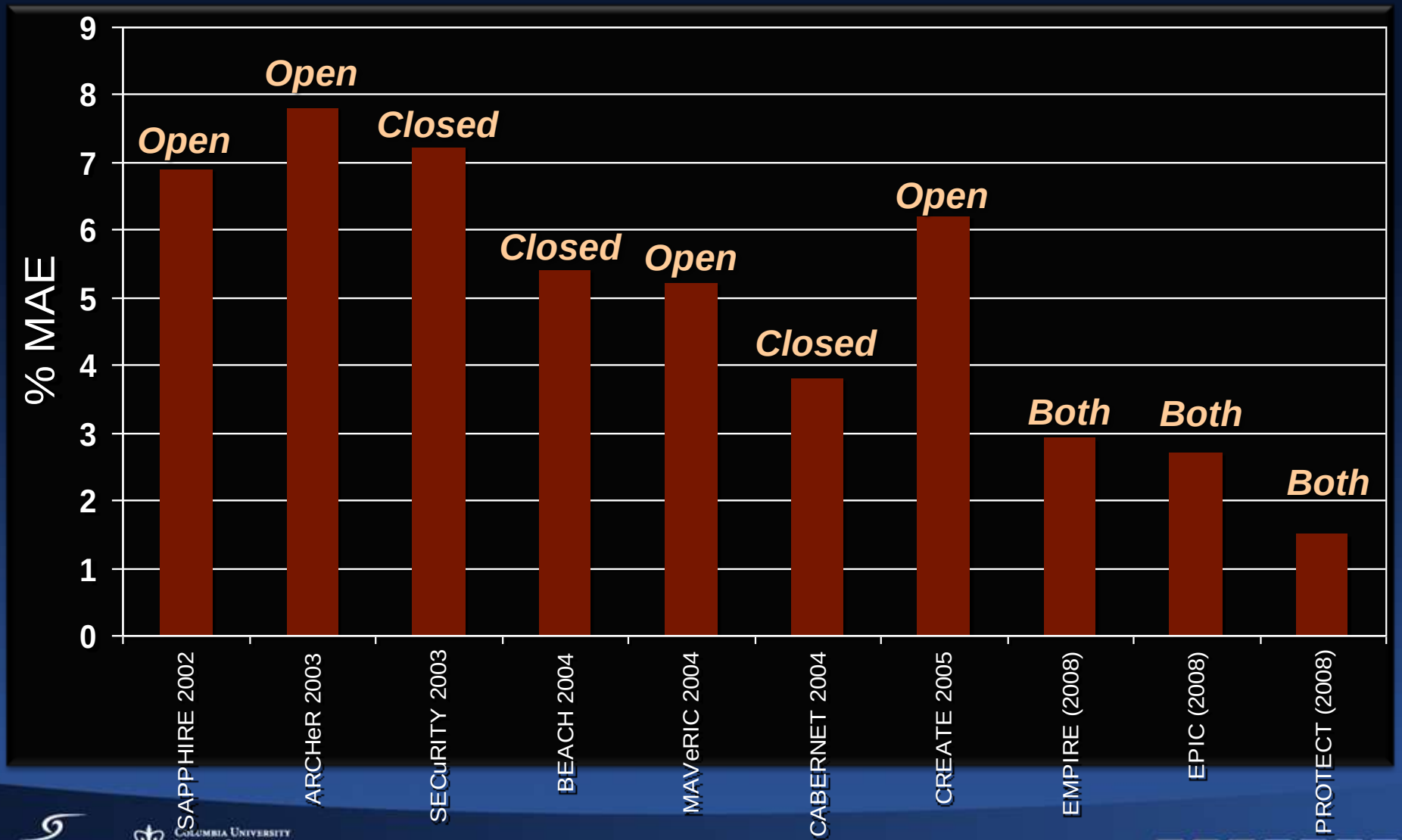
***Prasugrel (n=1461)***



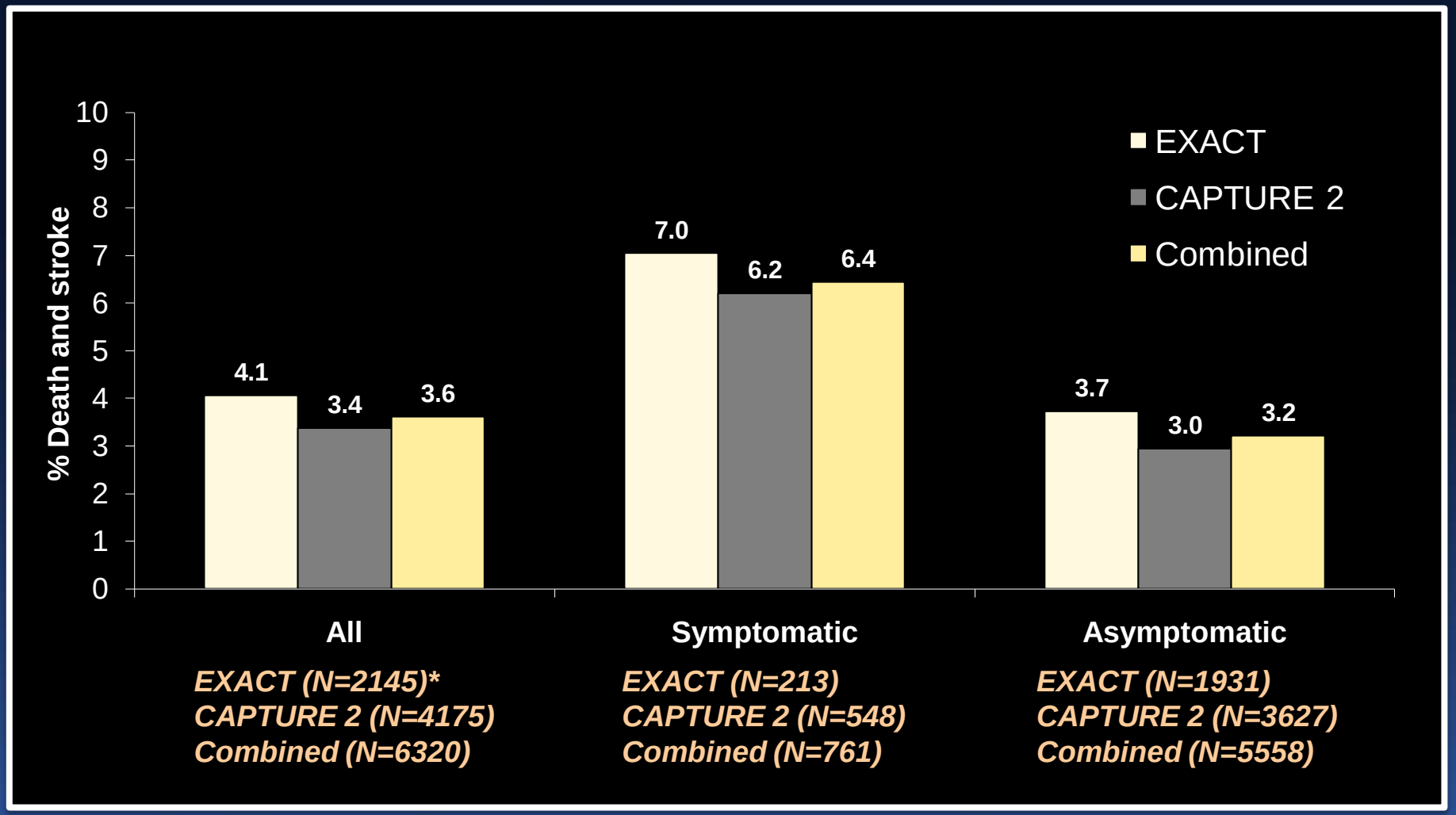




*Mega JL et al. Lancet 2010:online*

# Improvement in CAS outcomes is unrelated to stent type used



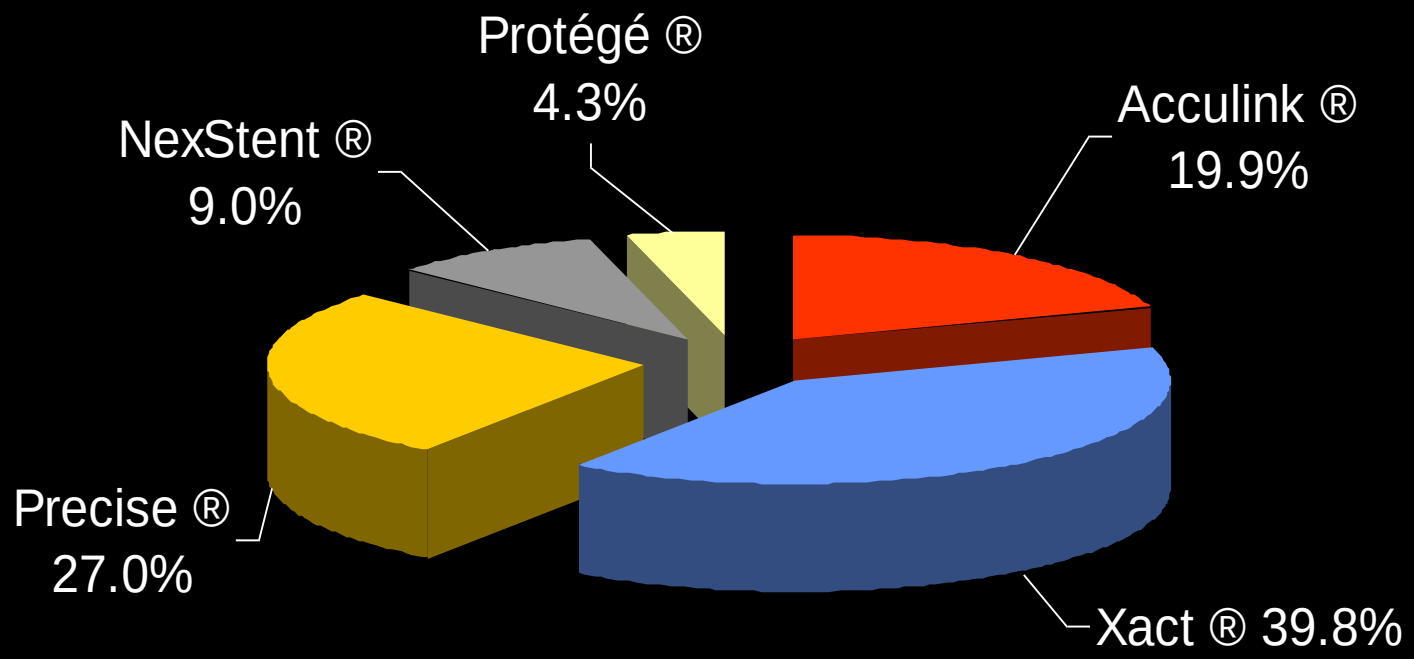
# EXACT (CC) and CAPTURE 2 (OC)
# No differences in prospective, adjudicated study




*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

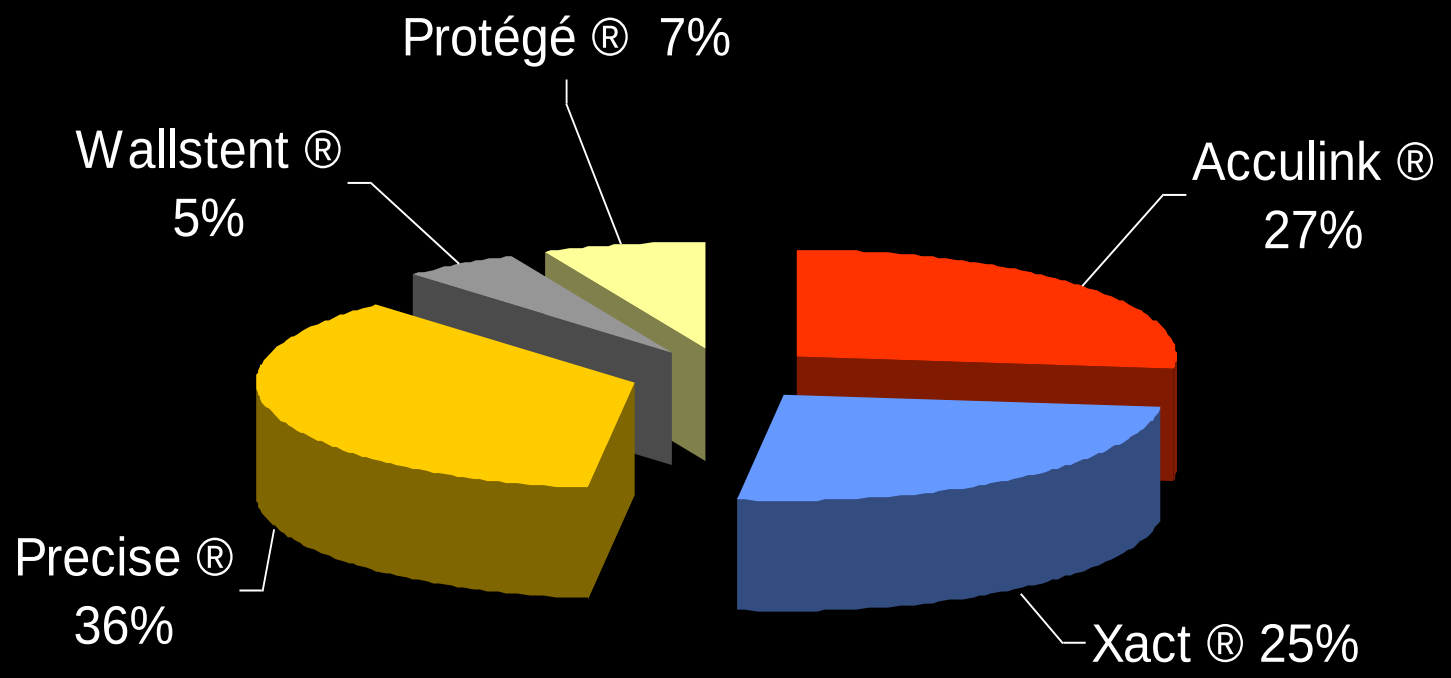
## EMPiRE OC stent usage: 51%




*% of Subjects (N=243)*

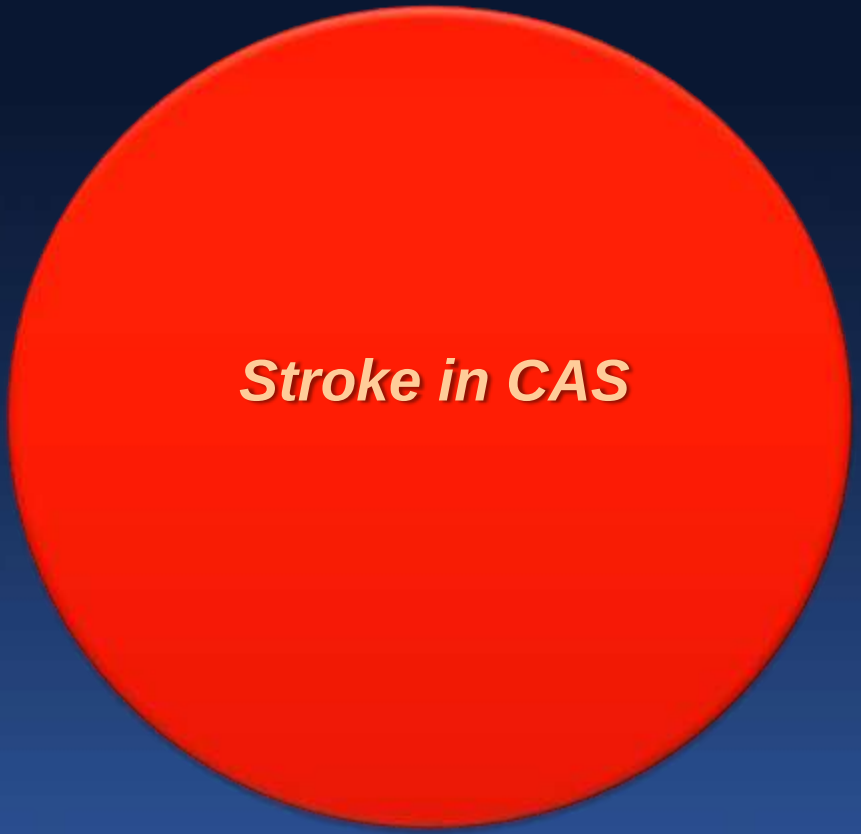
# Improvement in CAS outcomes independent of stent type used

## EMBOLDEN OC stent usage: 70%




*% 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