

Myths and facts of modern thromboprophylaxis *without routine use of potent anticoagulation.*



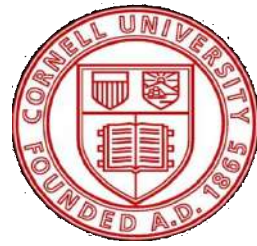
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HOSPITAL
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SURGERY





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Conflict of interest: None

 Indicates that the data was generated at Hospital for Special Surgery
 Indicates that the data was generated by investigators in the UK.

In the **unlikely** event of a mortality following elective primary total joint replacement, the surgeon has a tendency to believe that the death was probably caused by a pulmonary embolism (PE).

Why do we think that way?

Because...

- Orthopaedic surgeons have historically feared the occurrence of PE and fatal PE
- Have seen PE as a preventable complication
- PE is a “thrombotic phenomenon”, thus the medical team has been prone to recommend potent anticoagulation as the only means of thromboprophylaxis

The choice of thromboprophylaxis is also affected by external factors

- Litigious medical environment
- Restrictive ACCP guidelines widely adopted by the internal medicine community
- Intensive marketing campaign by industry

Salvati E, Sharrock N, Gonzalez Della Valle A, et al. 2007 Nicholas Andry Award

Three decades of clinical, basic, and applied research on thromboembolic disease after THA.

Clin Orthop 2007;459:246-254.



Multimodal approach with selective_use of anticoagulants for elective THR

- Perfected in HSS over the last 30 years
- Clinical and basic research
- Pre-, intra-, and post-operative measures
- SAFE and INEXPENSIVE
- Address all three pillars of Virchow's Triad
- Surgeons, anesthesiologists, internists, RN, PT

Multimodal thromboprophylaxis

- **PRE**-operative measures
- **INTRA**-operative measures
- **POST**-operative measures

Multimodal thromboprophylaxis

Pre-operative measures

1. Risk stratification to determine personal and familiar (genetic) risk of VTE

 *Beksac B, et al. Clin Orthop 2006;453:211-24.*

 *Salvati E, et al. Clin Orthop 2005;441:40-55.*

2. Discontinuation of procoagulant meds

 *Beksac B, et al. Clin Orthop 2006;453:211-24.*

3. Autologous blood donation

 *Bae H, et al. J Bone Joint Surg Br. 2001;83(5):676-9.*

Multimodal thromboprophylaxis

Intra-operative measures

1. Hypotensive epidural anesthesia

 Sharrock NE, et al. Acta Orthop Scand 1996;67(1):91-107.

2. Intraoperative iv sodium heparin (10-15U/kg)

 Sharrock NE, et al. Clin Orthop 1995;319:16-27.

3. Minimization of femoral work time and concomitant venous stasis

 Sharrock NE, et al. J Arthroplasty 2005;20(4):499-502.

4. Expedient surgery

 Sharrock NE, et al. Anesth Analg 1993;76(4):765-71.

Multimodal thromboprophylaxis

Post-operative measures

1. Pneumatic compression devices

 Westrich G, et al. Clin Orthop 2000;372:180-91.

 Ryan M, et al. J Bone Joint Surg Am 2002;84(11):1998-2004.

2. Foot + ankle exercises and prompt rehabilitation

 Markel DC, et al. Clin Orthop 1997;334:168-74.

3. Chemoprophylaxis for 4 to 6 wks

- Aspirin for the vast majority of patients who have no risk factors for VTE ($\approx 87\%$)
- Warfarin in those considered at high risk ($\approx 12\%$)
- Rarely: LMWH or VCF ($<1\%$)

What is thromboprophylaxis for?

To prevent...

Minor
complications

PPS

DVT

Major
complications

PE

Death

Complications of prophylaxis

The routine use of potent anticoagulation to prevent VTE in elective TJR surgery would be justified if ...

Hypothesis #1

PE and fatal PE
are frequent
complications of
surgery

Hypothesis #2

PE and fatal PE are preventable with routine use of potent anticoagulants

Hypothesis #3

All-cause mortality is lower with the routine use of anticoagulants

Hypothesis #4

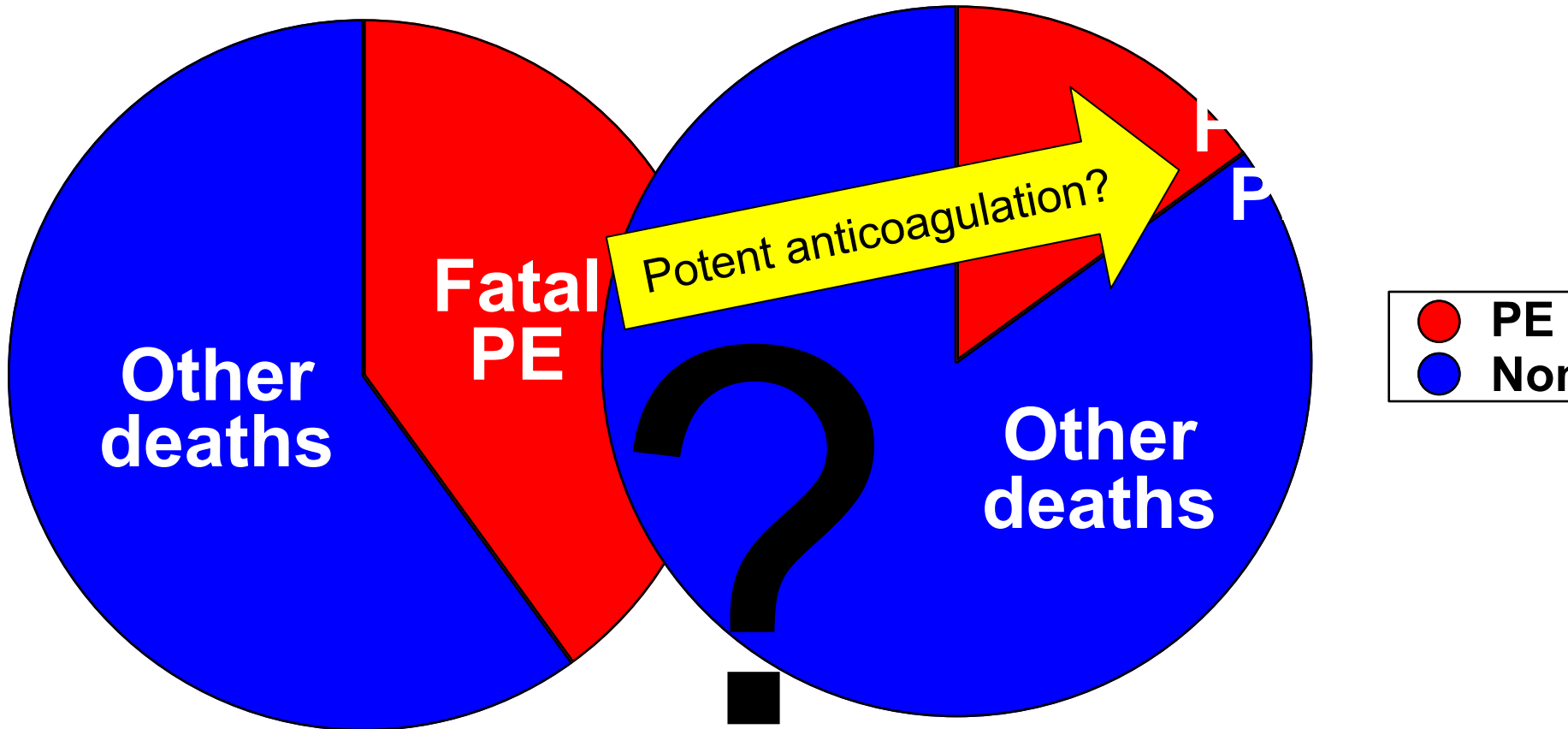
The proportion of deaths due to PE can be lowered with the routine use of anticoagulants

Without

anticoagulation

With

anticoagulation



These four hypotheses may be based on historic concepts and may not be true today in patients undergoing elective joint replacement surgery

Hypothesis #1

PE and fatal PE are
~~frequent~~ rare
complications of
elective TJR surgery

PE was the leading cause of death
in the 1960s and 1970s

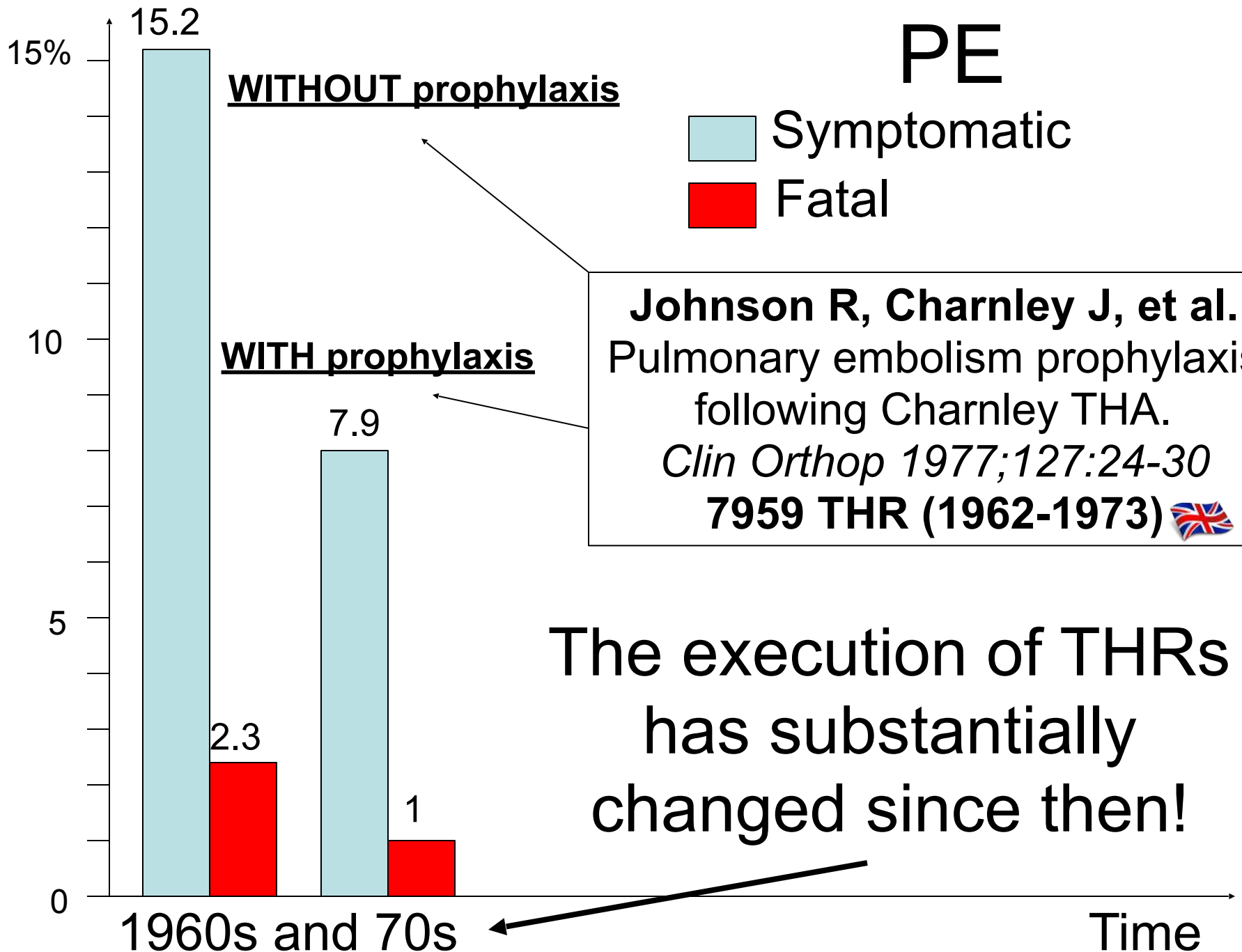
Fredin et al. Fatal pulmonary embolism after total hip replacement. *Acta Orthop Scand* 1982;53(3):407.

- 90-day mortality
- 1,324 THRs (1969 – 1978)
- Thromboprophylaxis with Dextran
- 16 deaths (14 autopsies)
- 9 FATAL PEs (56%) (8 autopsy-proven)
- Pneumonia (3); MI (2); CCI (1)

 **Johnson R, Charnley J, et al.** Pulmonary embolism prophylaxis following Charnley THA.
Clin Orthop 1977;127:123-132

- 7959 THRs
- 1962 – 1973
- Symptomatic PE and death
- With and without prophylaxis
- 88% of fatal PEs confirmed by autopsy

PE



Johnson R, Charnley J, et al.
Pulmonary embolism prophylaxis
following Charnley THA.
Clin Orthop 1977;127:24-30
7959 THR (1962-1973) 🇬🇧

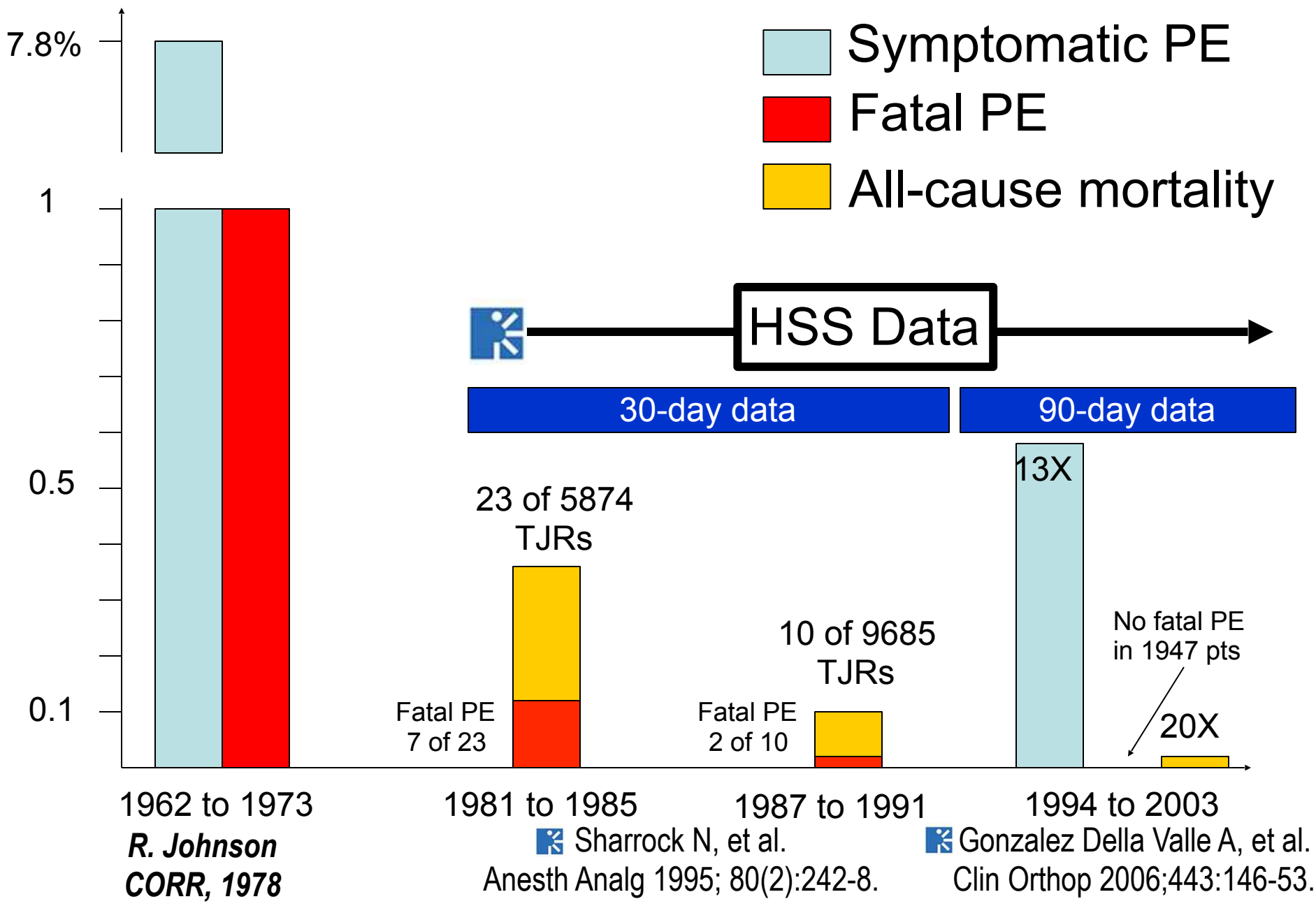
The execution of THRs
has substantially
changed since then!

THA in 1960s-1970s

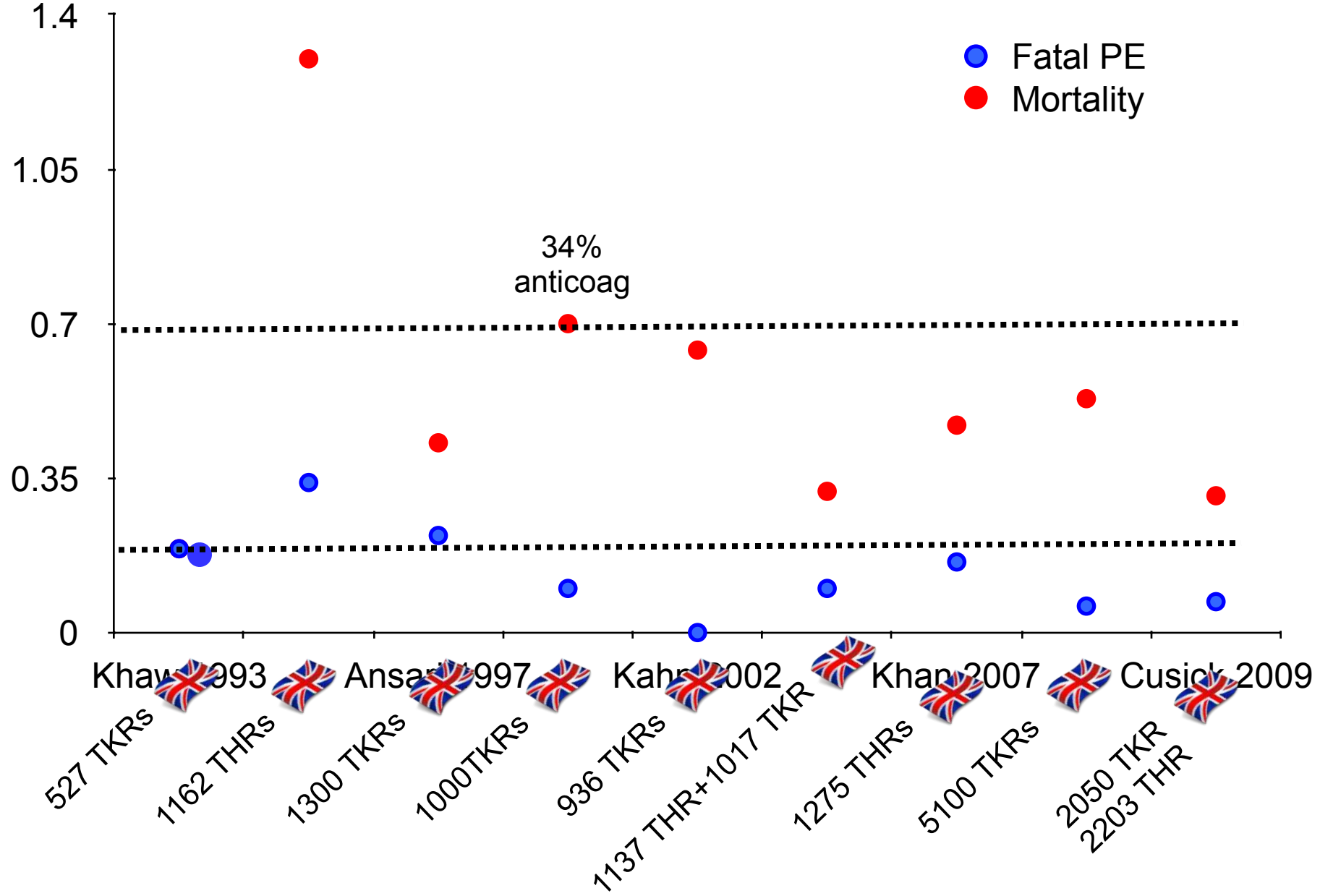
Variable	60'-70'	90'-present
Surgical technique	Rudimentary	Advanced
Anesthesia	General	Regional
Surgical time	$\geq 3h$	$< 1.5h$
Bleeding	$\geq 1l$	$< 250cc$
Bed rest	Prolonged	No
Knowledge on VTE	Minimal	Advanced

Coventry et al JBJS 1973

Johnson, Charnley CORR 1977



Fatal PE and mortality following TKA/THA (anticoagulation only used in high-risk patients)



Given today's
low prevalence of fatal PE and mortality when no routine anticoagulation is
used...

Hypothesis #2

PE and fatal PE are

not always preventable

with routine use of potent
anticoagulants

Has the frequency of postoperative VTE and PE diminished since the use of routine potent anticoagulation for prophylaxis?

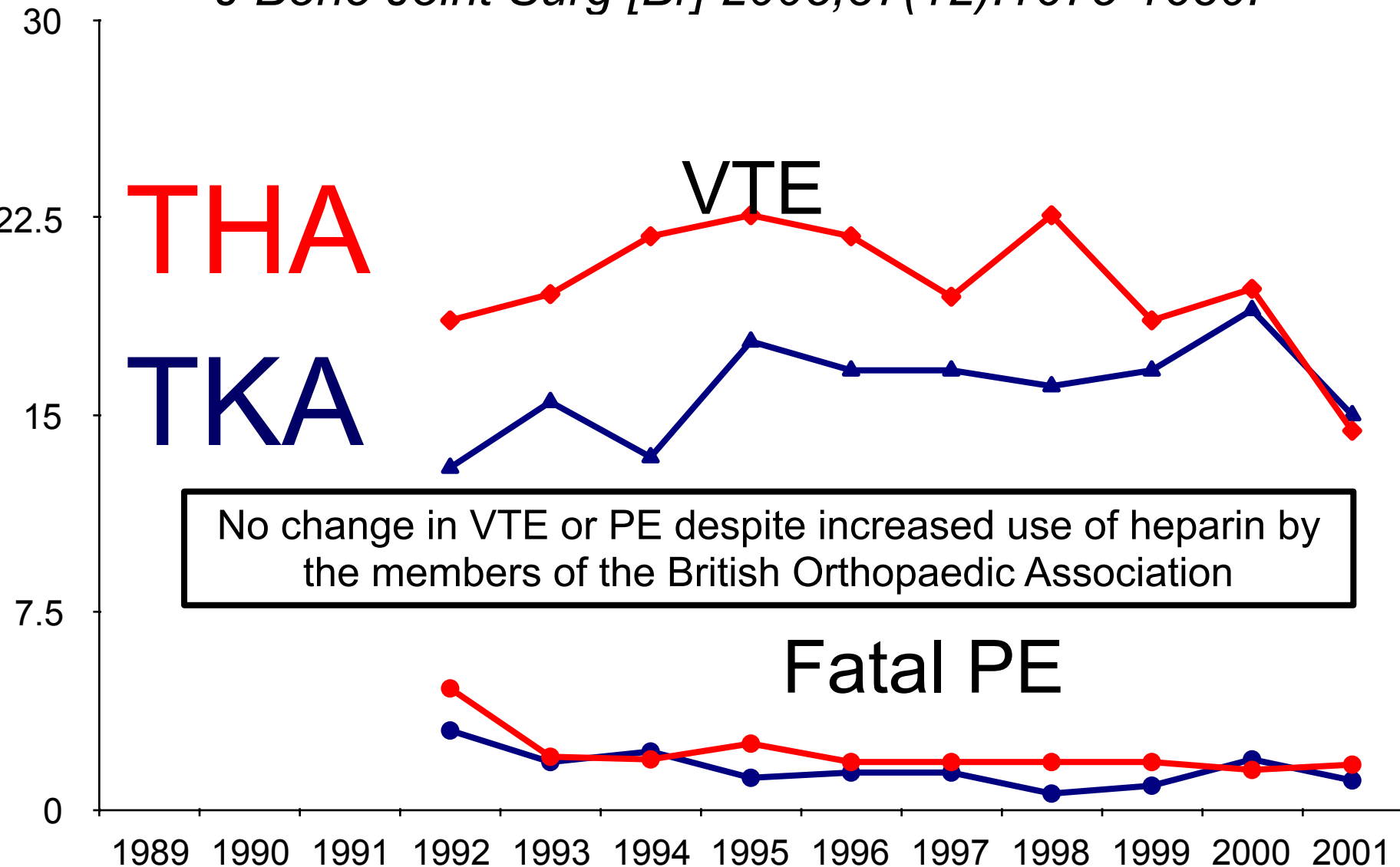
No evidence suggesting that this is the case



Howie C, et al. Venous thromboembolism associated with THR and TKR over a 10-year period.
J Bone Joint Surg [Br] 2005;87(12):1675-1680.

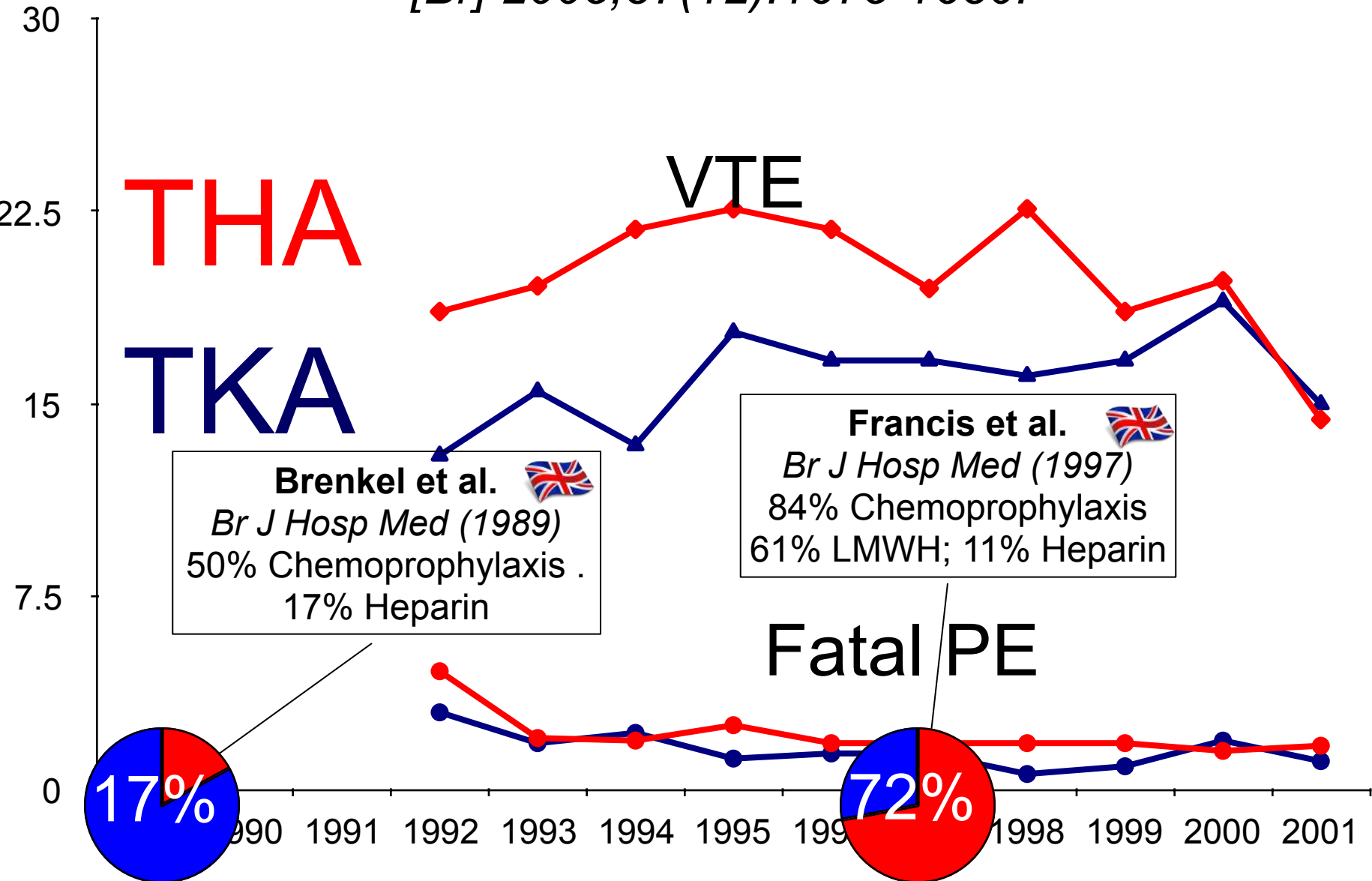
- Scottish Morbidity Record System
- Registrar General's death records
- 1992 - 2001
 - Symptomatic VTE (DVT, PE)
 - Fatal PE
 - Fatal MI
 - Fatal CVE

Howie C, et al. Venous thromboembolism associated with hip and knee replacement over a 10-year period.
J Bone Joint Surg [Br] 2005;87(12):1675-1680.



Two surveys of the membership of the British Orthopaedic Association demonstrated that the use of anticoagulants among British orthopaedic surgeons increased during the study period.

Howie C, et al. Venous thromboembolism associated with hip and knee replacement over a 10-year period. *J Bone Joint Surg [Br]* 2005;87(12):1675-1680.





Jameson S, et al. The impact of national guidelines for the prophylaxis of VTE on the complications of arthroplasty of the lower limb.
J Bone Joint Surg (Br) 2010;92(1):123-9.

- National Joint Registry
- 219,602 patients
- 12 months before and after NICE guidelines (2007)
- 90-day VTE rate → **NO CHANGE**
- Return to OR rate → **NO CHANGE**
- HITT → **INCREASED**

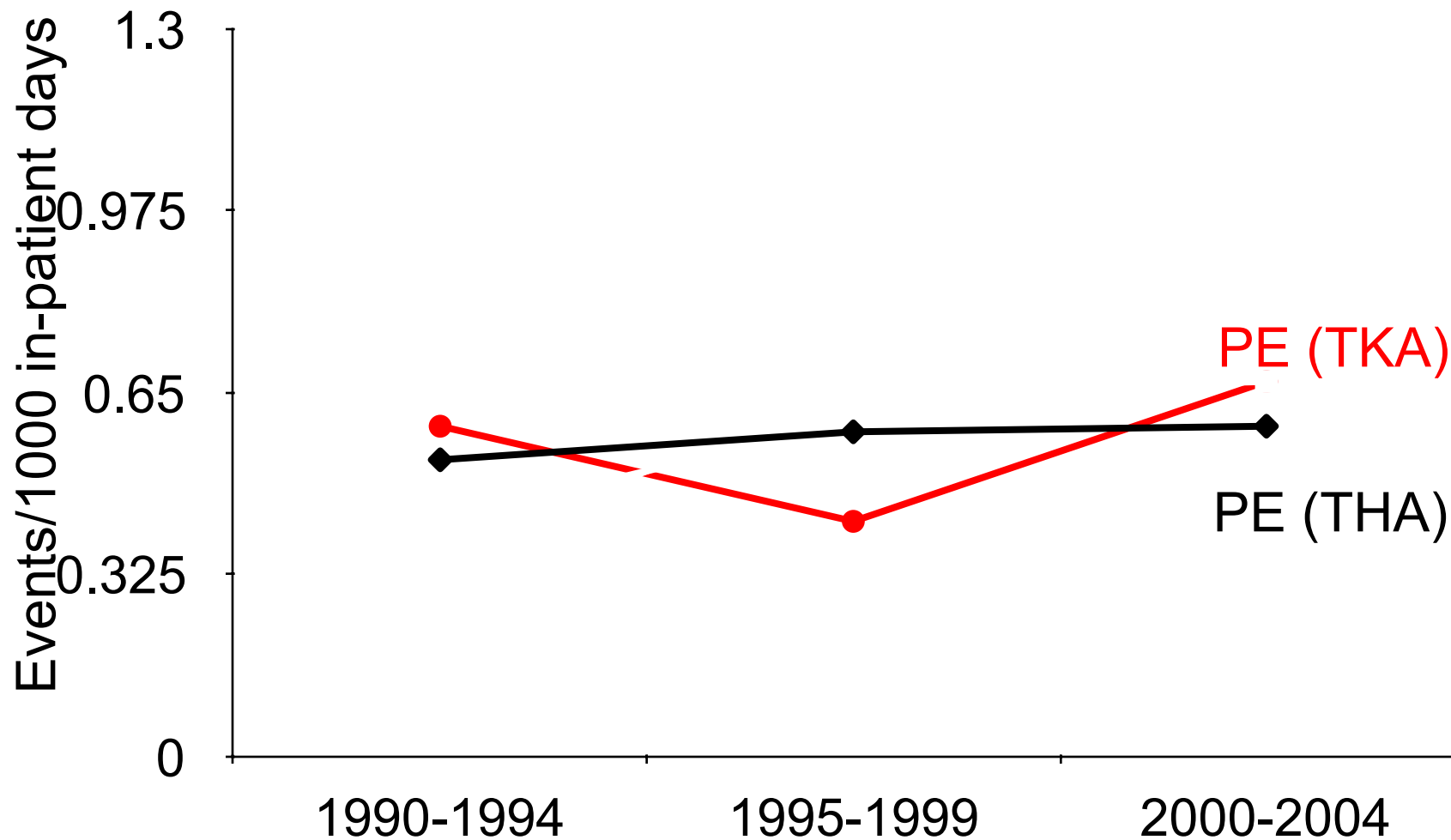
Diagnosis of in-hospital PE and mortality in the US

■ **Memtsoudis S, Gonzalez Della Valle A, et al.** Trends in demographics, complications, and mortality of TKA performed in the United States. A study of **3,830,420 patients** operated between 1990 and 2004.
J of Arthroplasty 2008;24(4):518-527.

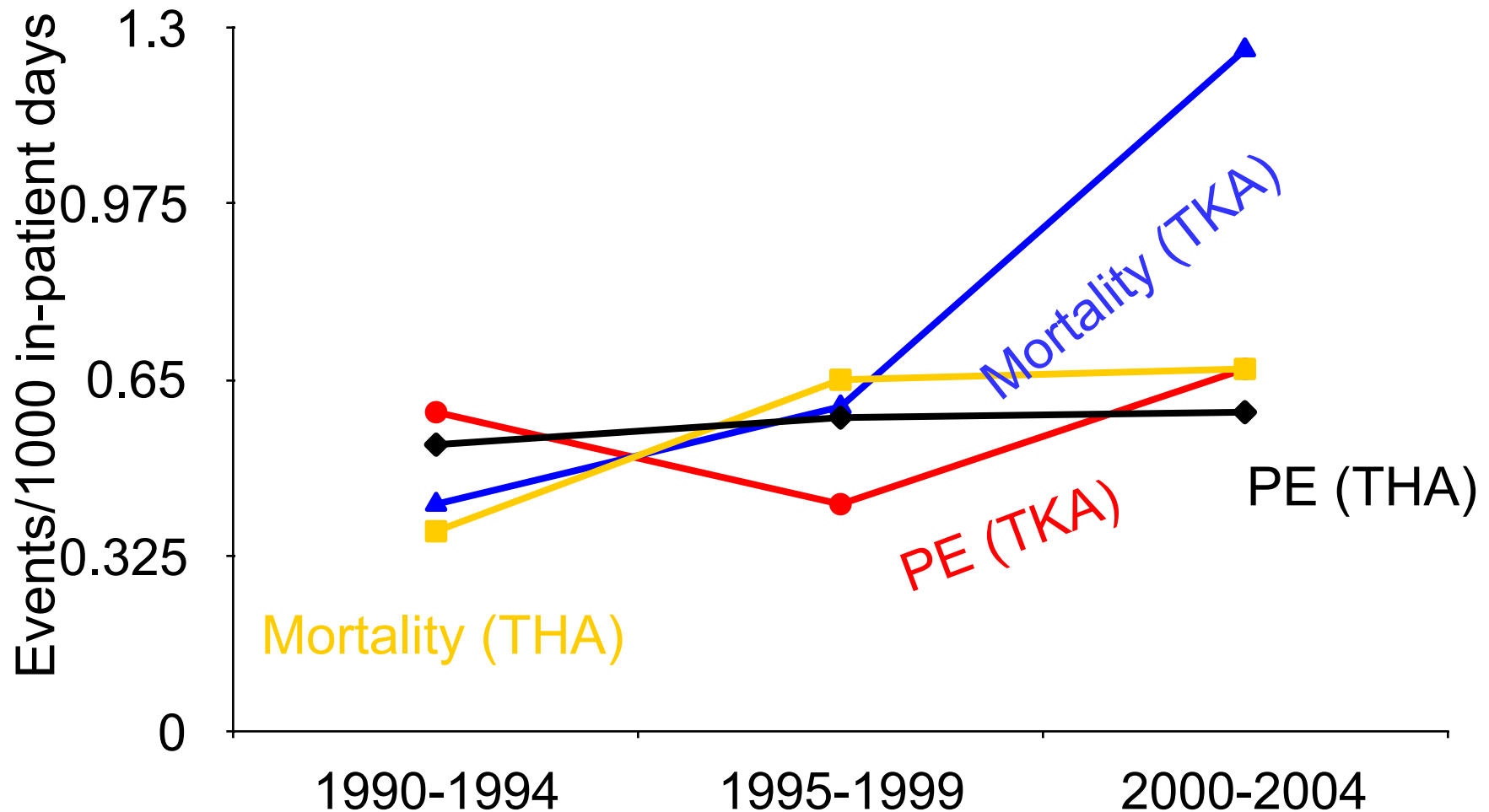
■ **González Della Valle A, Memtsoudis SG, et al.** Trends in mortality, complications, and demographics for primary THA in the United States. **2,288,579 patients** operated between 1990 and 2004.
Int Orthop 2009,33(3):643-651.

- National Hospital Discharge Survey from the Center for Disease Control.
- Three periods: ('90-'94, '95-'99, '00-'04)

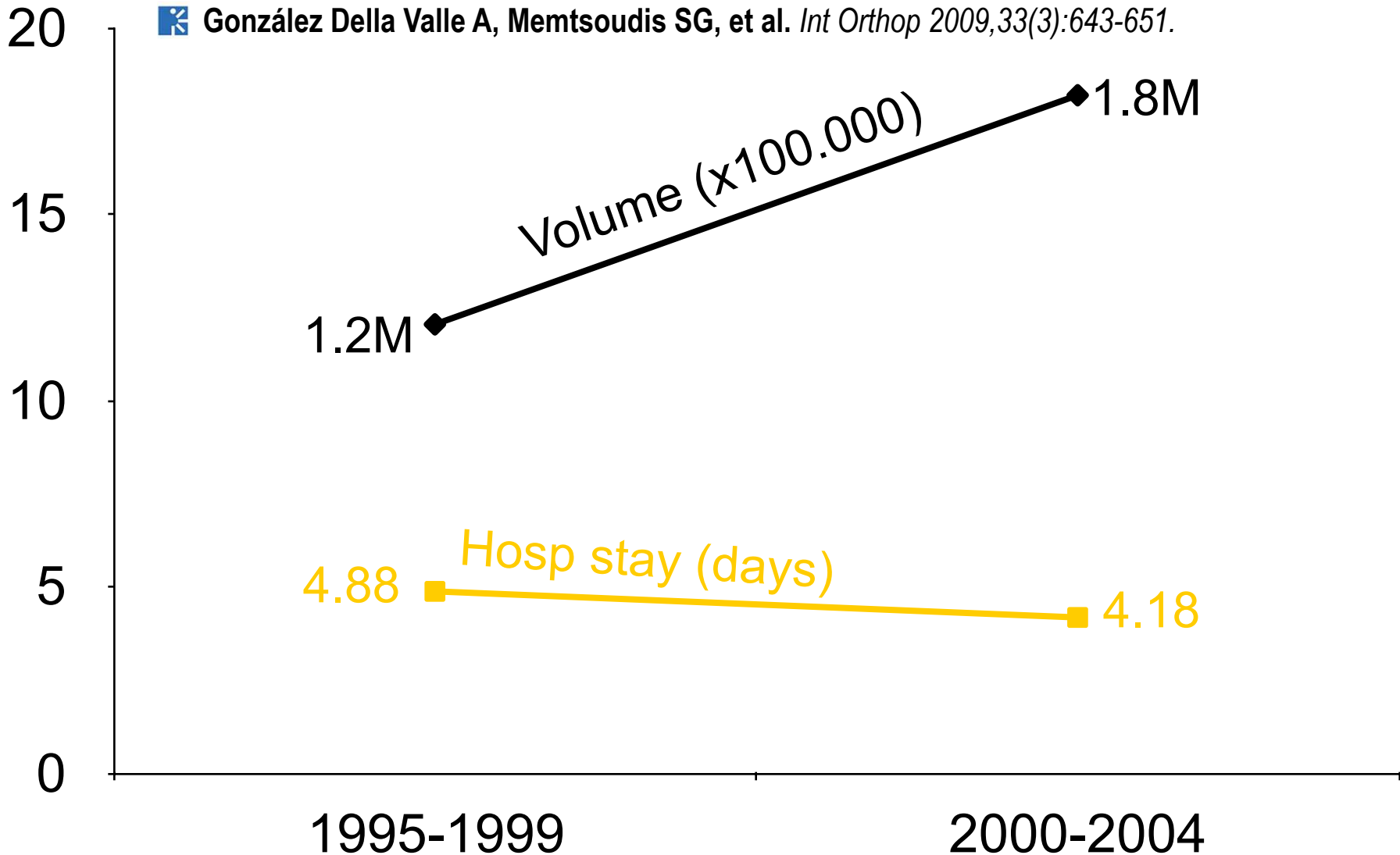
Trends in in-hospital diagnosis of death and PE following THA and TKA in US (1990-2004)



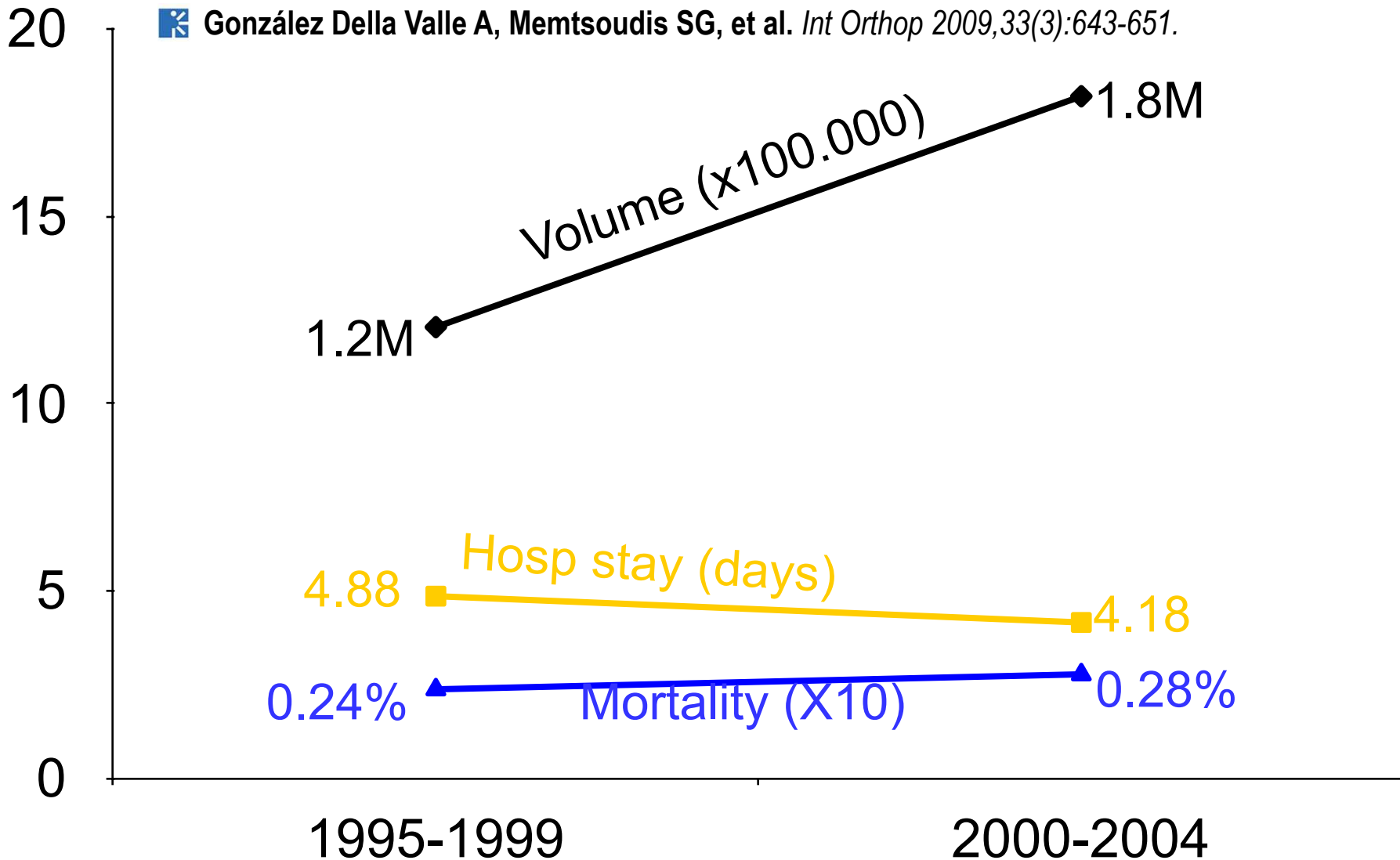
Trends in in-hospital diagnosis of death and PE following THA and TKA in US (1990-2004)



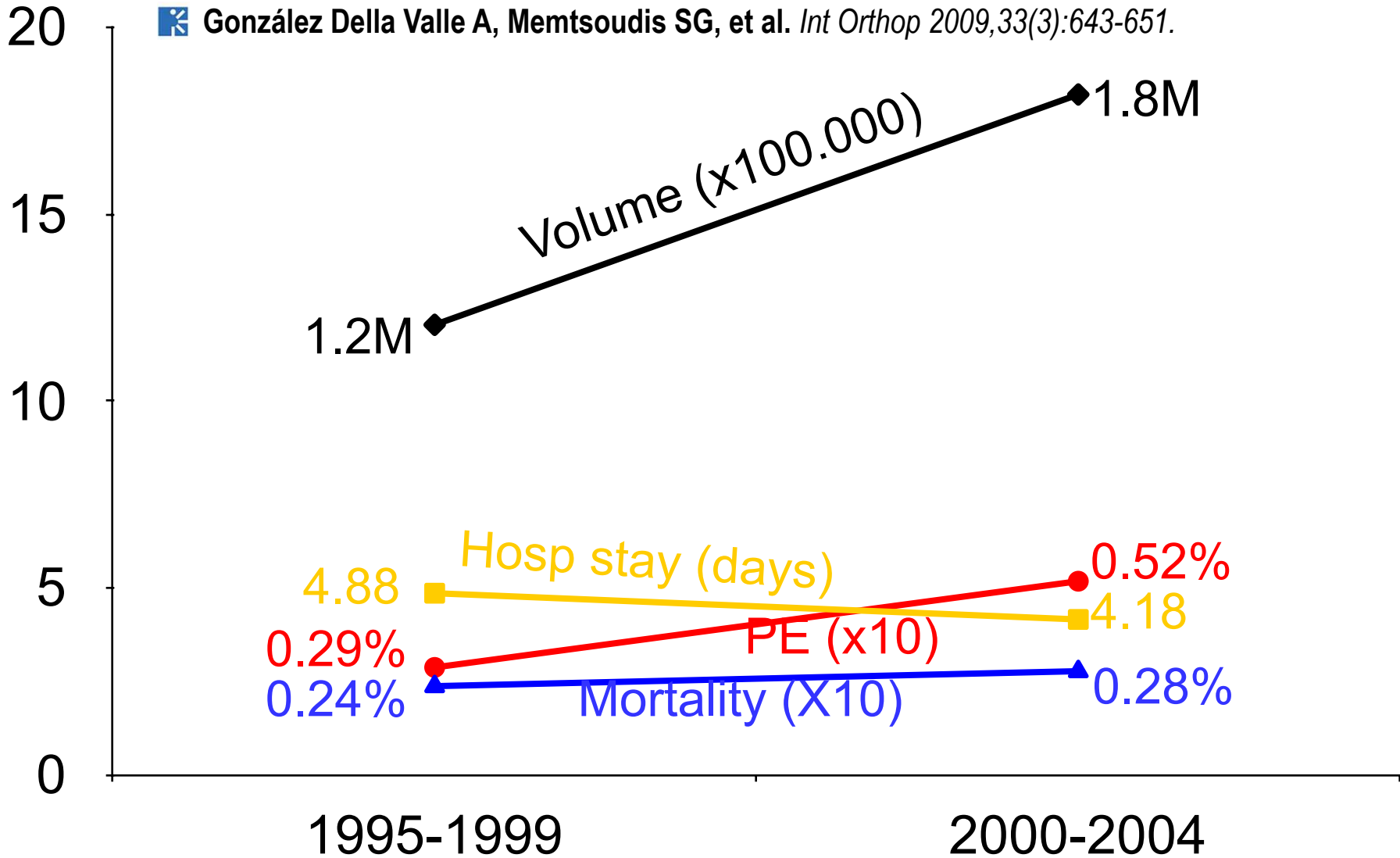
Trends in volume, hospital stay and in-hospital mortality in US (1995-2004)



Trends in volume, hospital stay and in-hospital mortality in US (1995-2004)

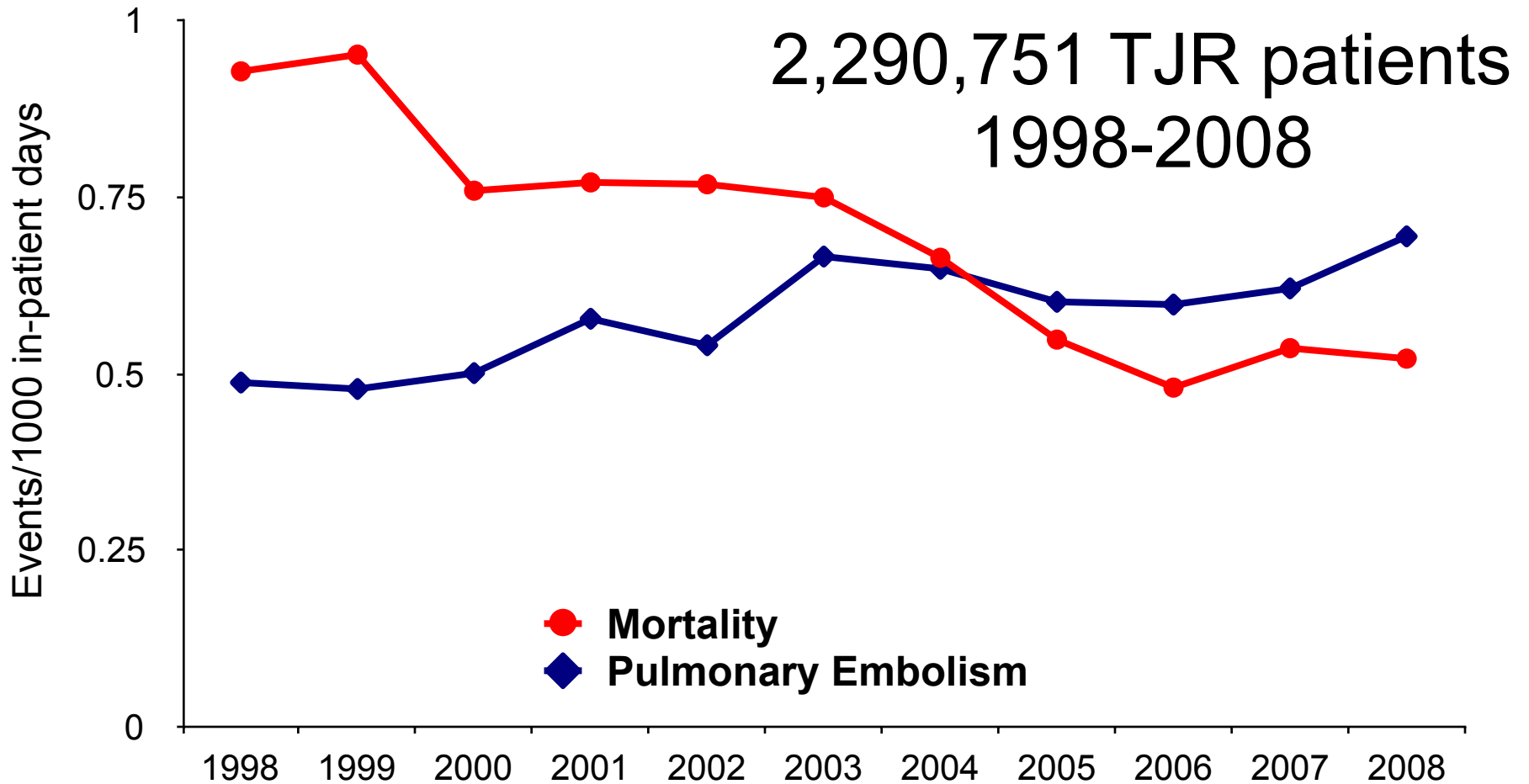


Trends in volume, hospital stay and in-hospital mortality in US (1995-2004)





Unpublished data from
National In-Patient Sample (NIS)
(20% of all admissions in the US)




Hypothesis #3

All-cause mortality is

higher?
lower with the routine

use of anticoagulants

 **Sharrock NE, González Della Valle A, Salvati EA, et al.**
Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty.
Clin Orthop 2008;466:714-72.

Systematic review of
THA and TKA studies
18 publications – **25,000 patients**

Goal: assess influence of different thromboprophylaxis regimens on the rate of:

1. Symptomatic PE
2. All- cause mortality

Why “all-cause mortality”?

- Ultimate goal of prophylaxis: reduce death for any reason
- Encompasses major benefits and risks of prophylaxis
- Cause of death is often difficult to define

Thromboprophylaxis Regimens

1. Potent anticoagulants:

- LMWH
- fondaparinux
- ximelagatran
- rivaroxaban

2. Warfarin

3. Multimodal

Multimodal included *intention to use*

- Regional anesthesia
- Pneumatic compression
- Aspirin
- Anticoagulation in selected cases

18 articles identified

	# of Articles (*)	Patients
Potent anticoagulants	10	13380
Warfarin	4	4370
Multimodal	6	7193

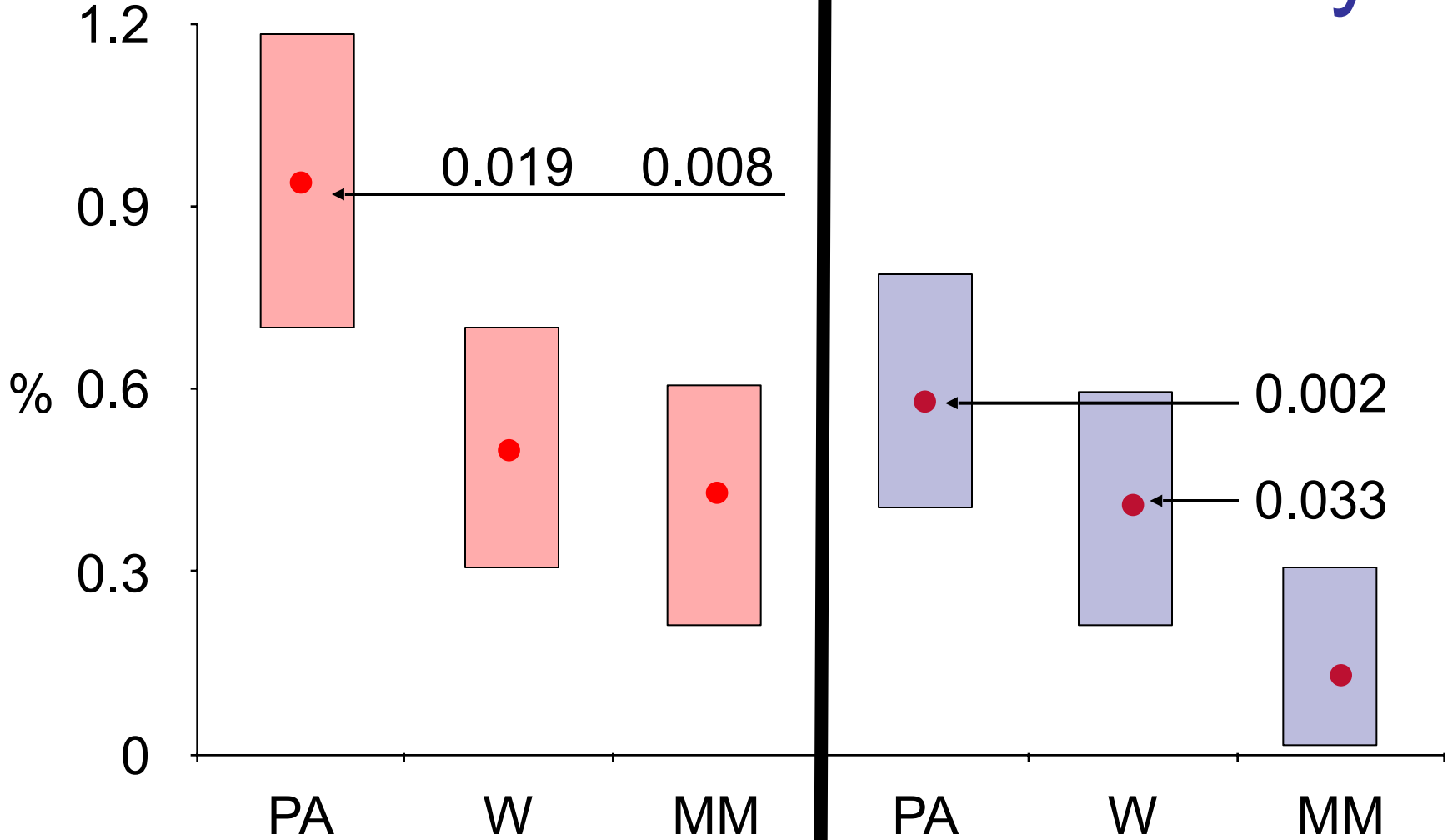
All operations performed from 1993 onwards

*2 included warfarin + potent anticoagulation

3 months after surgery

Non-fatal PE

Mortality

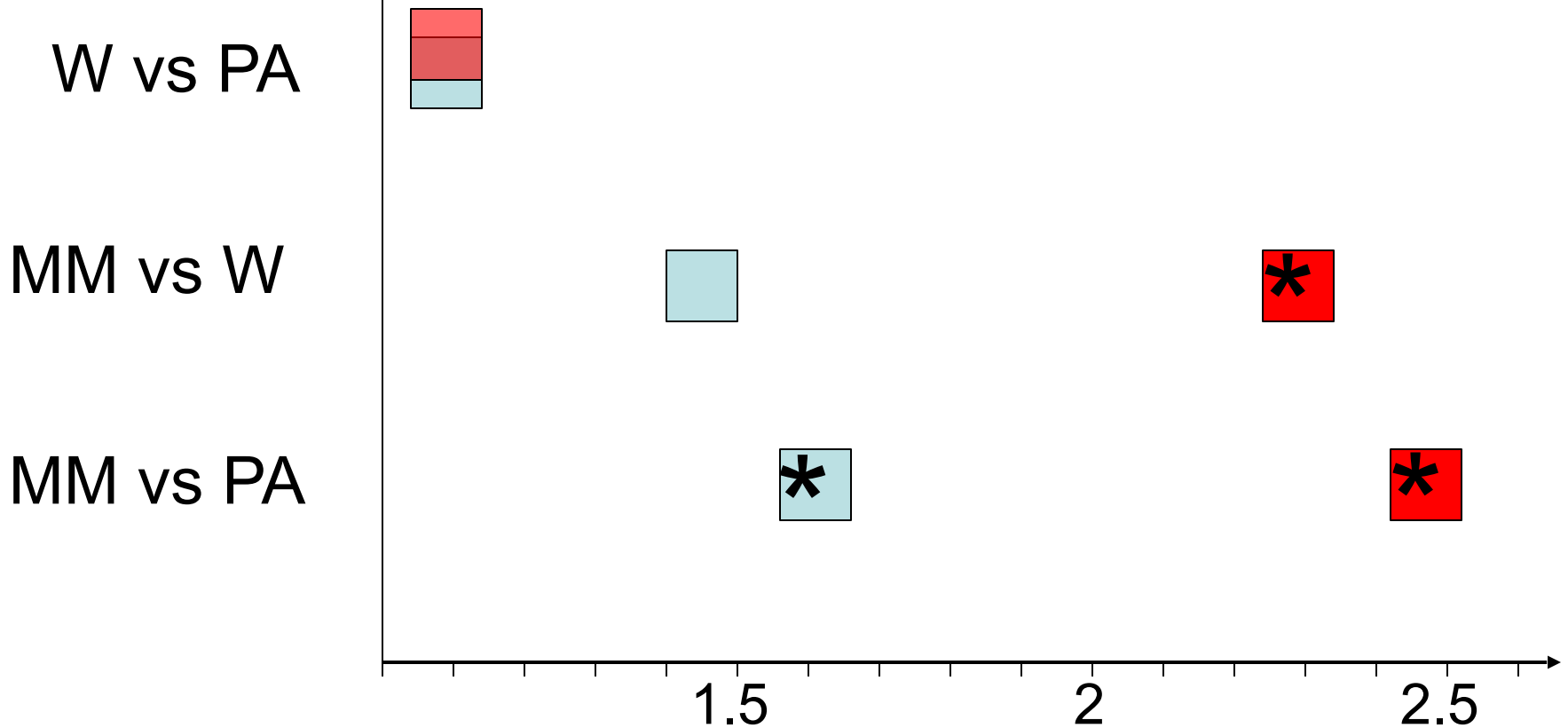


Relative risk

RR=1

■ Symptomatic, non fatal PE
■ All-cause mortality

(*) indicates statistical significance



Possible explanations

- Multimodal in high-volume centers
- Regional anesthesia may confer additional benefit
- Potent anticoagulants: life threatening side effects (major bleeding, HITT) → increase all-cause mortality


 Sharrock NE, González Della Valle A, Salvati E, et al.
Clin Orthop 2008;466:714-72.

Conclusions

- Routine use of potent anticoagulants do not prevent symptomatic PE
- Potent anticoagulants appear to result in higher all-cause mortality
- Multimodal appears to be a safer, more efficacious prophylaxis

Hypothesis #4

The proportion of deaths due to PE is low and cannot be lowered with the routine use of anticoagulants

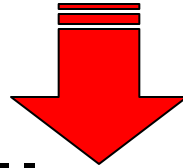
 **Memtsoudis S, Gonzalez Della Valle A, Salvati E, Sharrock N, et al.** Meta-analysis of cause of death following elective total joint replacement utilizing different thromboprophylaxis regimens
AAOS Meeting 2011.

- What are the most frequent causes of death following surgery (90 days)
TODAY?
- Is cause distribution (% of deaths due to PE) affected by **CURRENT** thromboprophylaxis protocols?

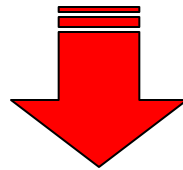
Meta-analysis of last 15 years

- Pubmed, EMBASE and Cochrane databases
- Studies published between 1995 to 2009
- Surgeries performed after 1990
- Represent modern surgical, anaesthetic techniques, and perioperative care
- Time frame coincides with the introduction of LMWH to clinical practice

437 abstracts



106 full papers



70 publications included

99,441 patients – 373 deaths

7 thromboprophylaxis regimens
compared for outcomes

Prophylaxis regimens analyzed

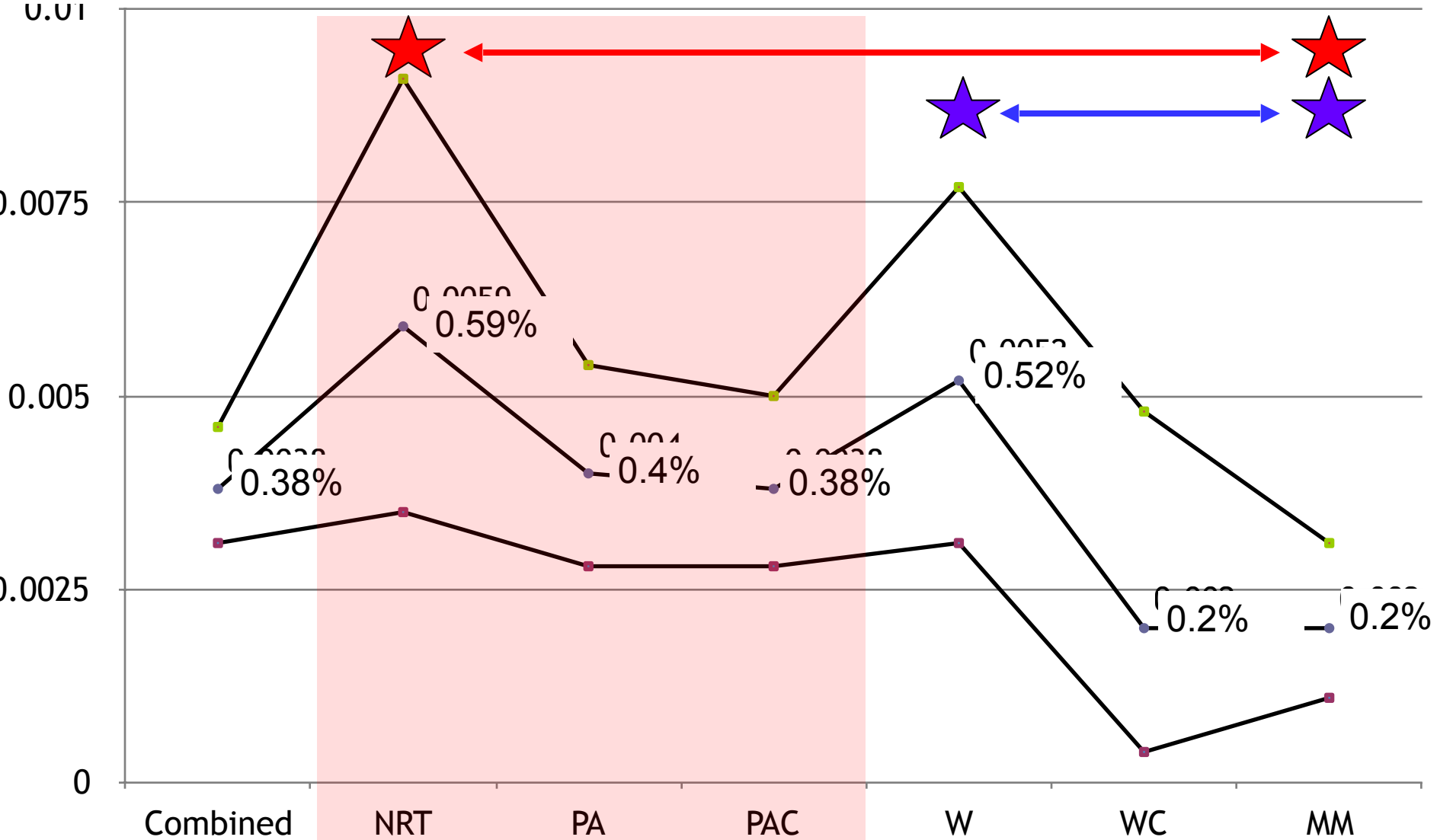
1. No routine pharmacologic prophylaxis
2. Aspirin (1 paper only → regimen was excluded)
3. Multimodal (regional + PCD + aspirin)
4. Warfarin
5. Warfarin combined (regional and/or PCD)
6. Potent anticoagulants
7. Potent anticoagulants combined (regional and/or PCD)

Cause of death

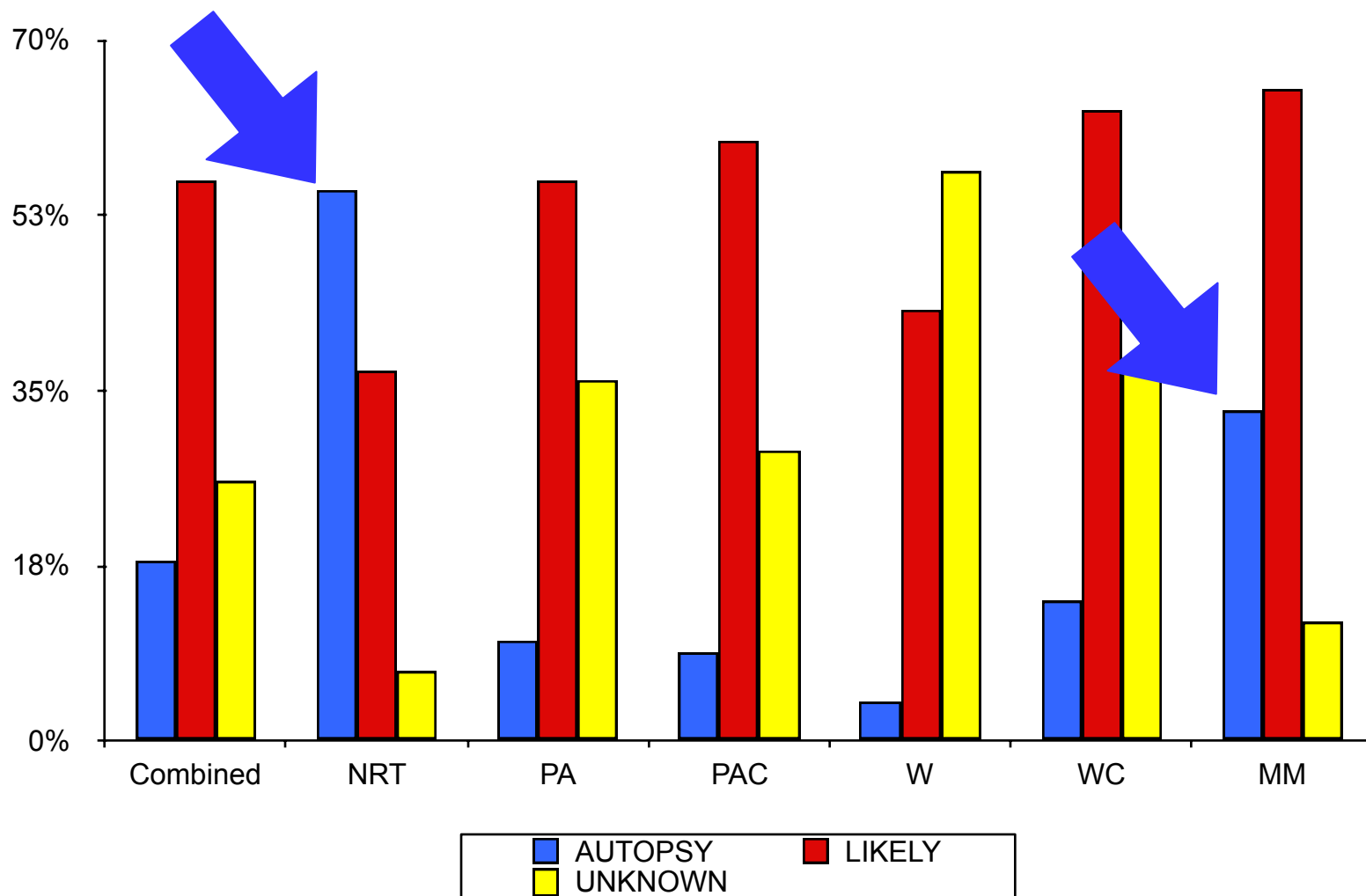
- Autopsy proven
- Likely cause
- Unknown
 - Not mentioned
 - “unrelated to PE”
 - “sudden death”

Mortality rates

(pooled proportions and 95%CI - ☆SS)

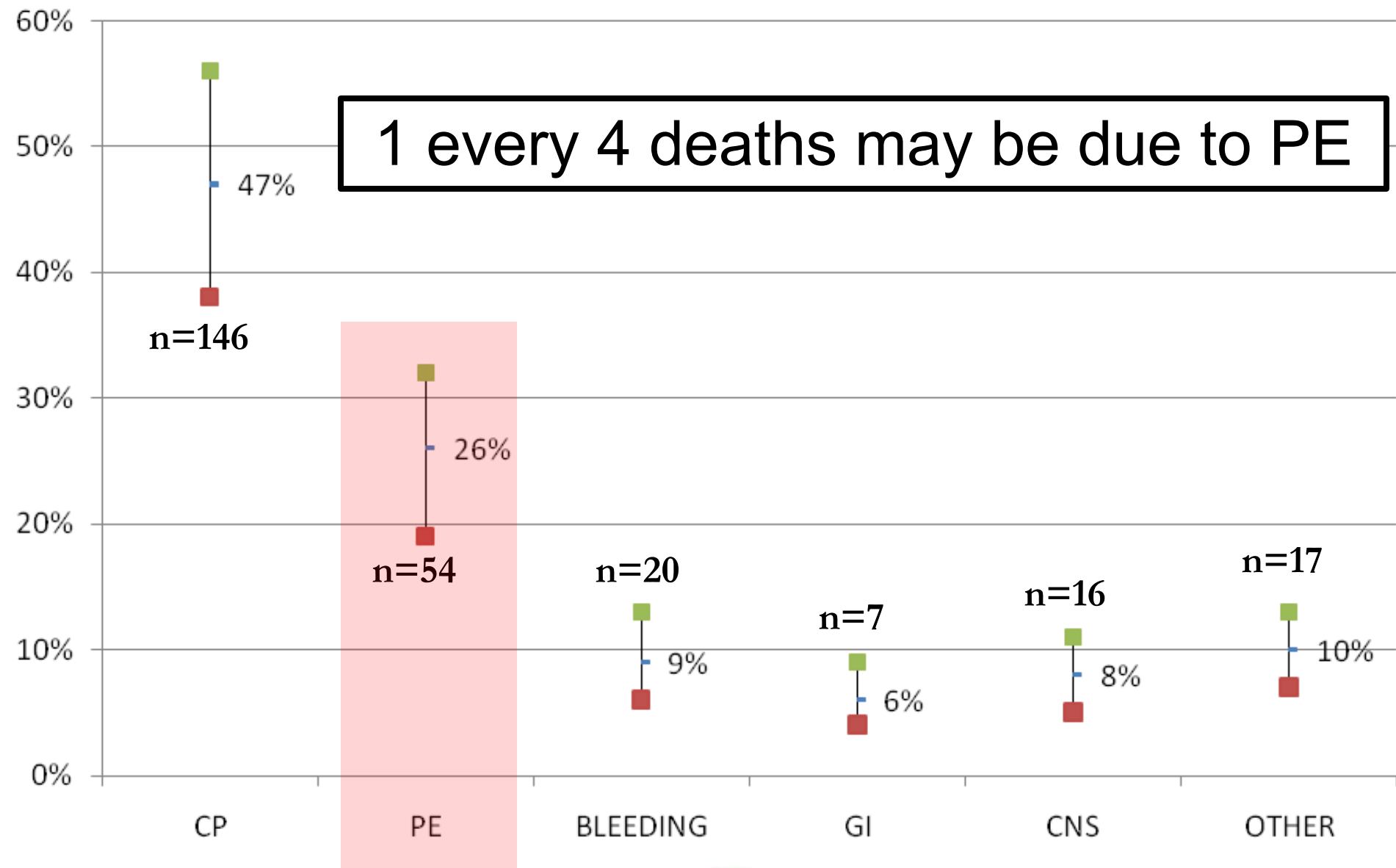


Highest proportion of autopsy proven deaths in the NRT and MM groups!

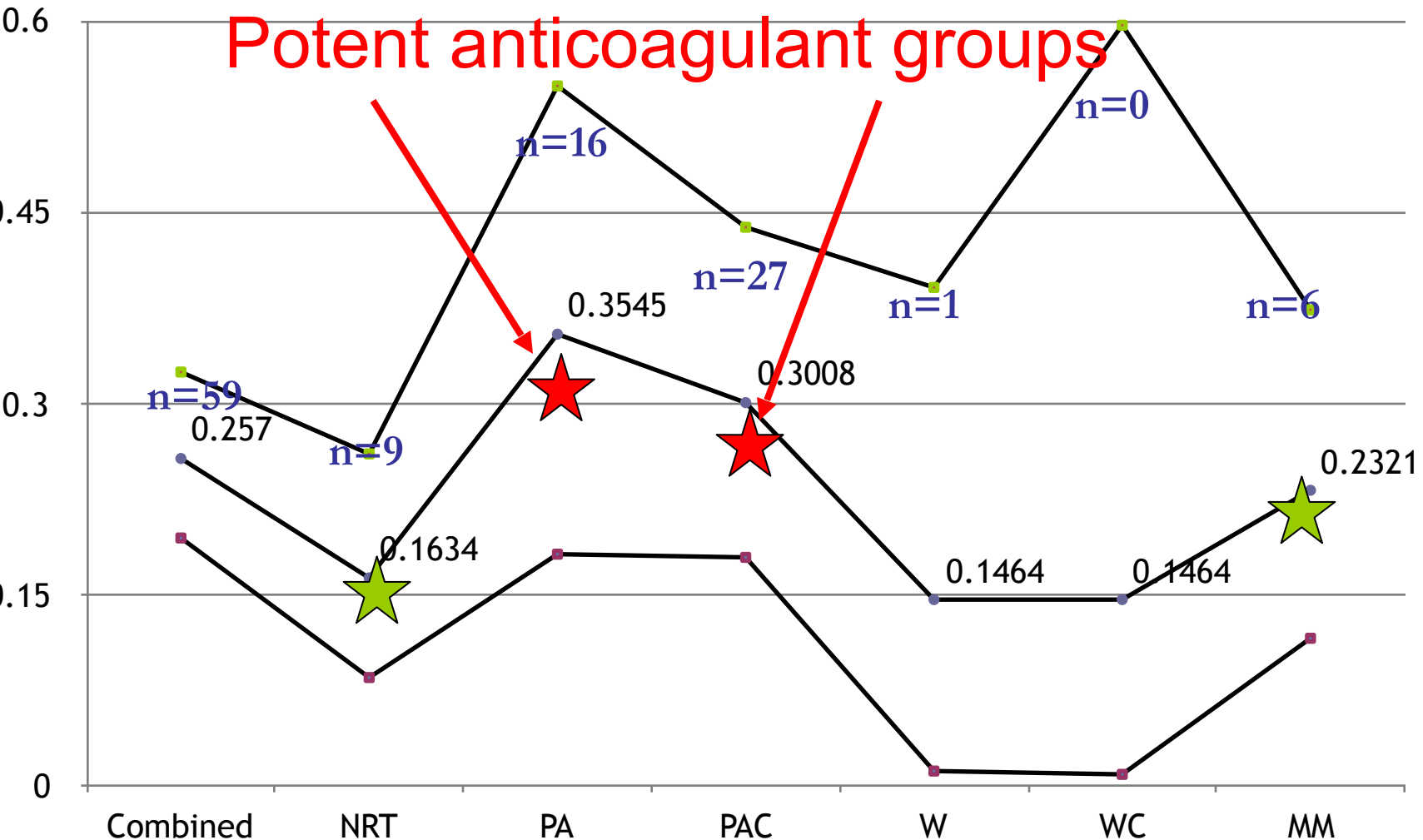


Cause of death (pooled proportions) NOT AFFECTED BY PROPHYLAXIS

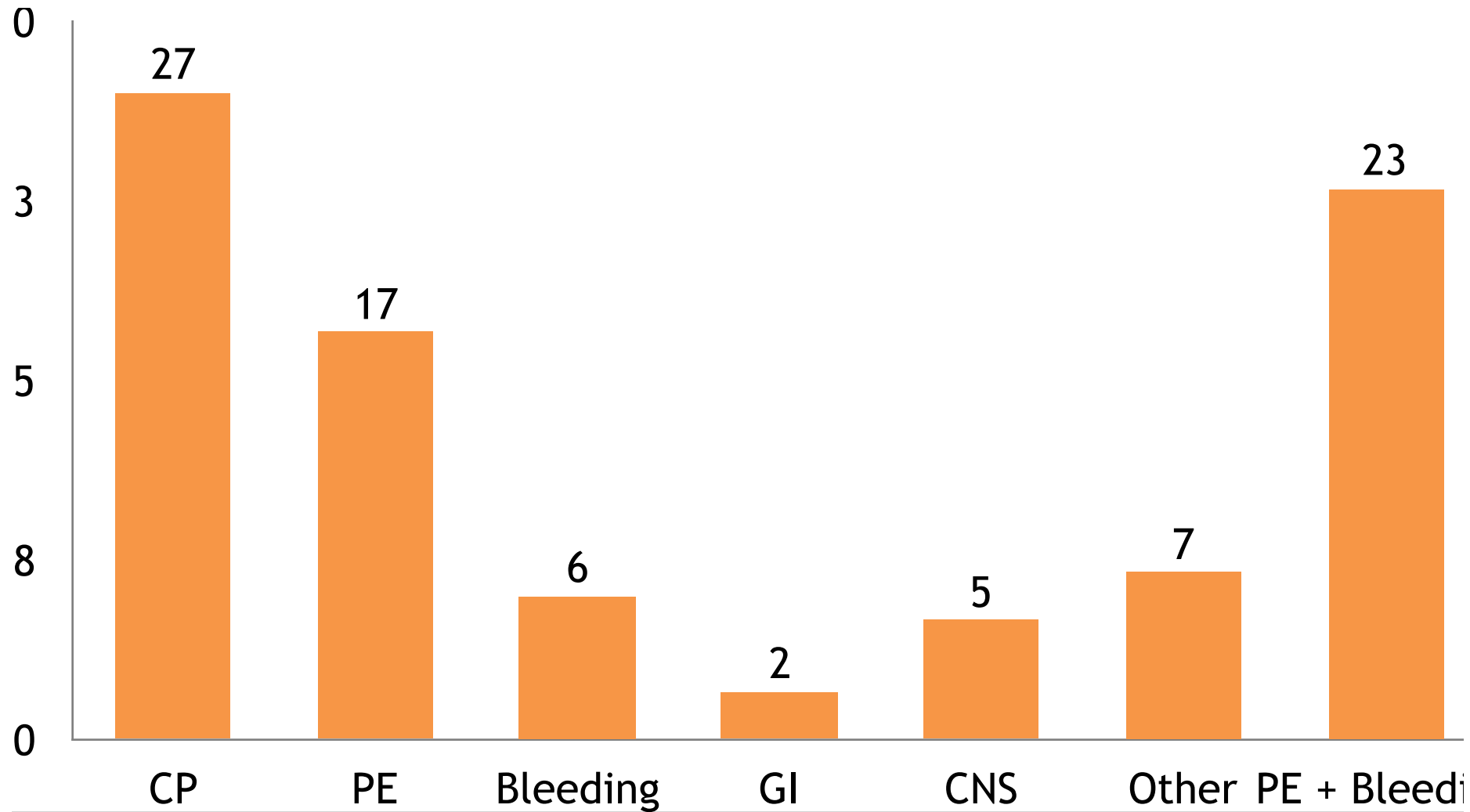
1 every 4 deaths may be due to PE



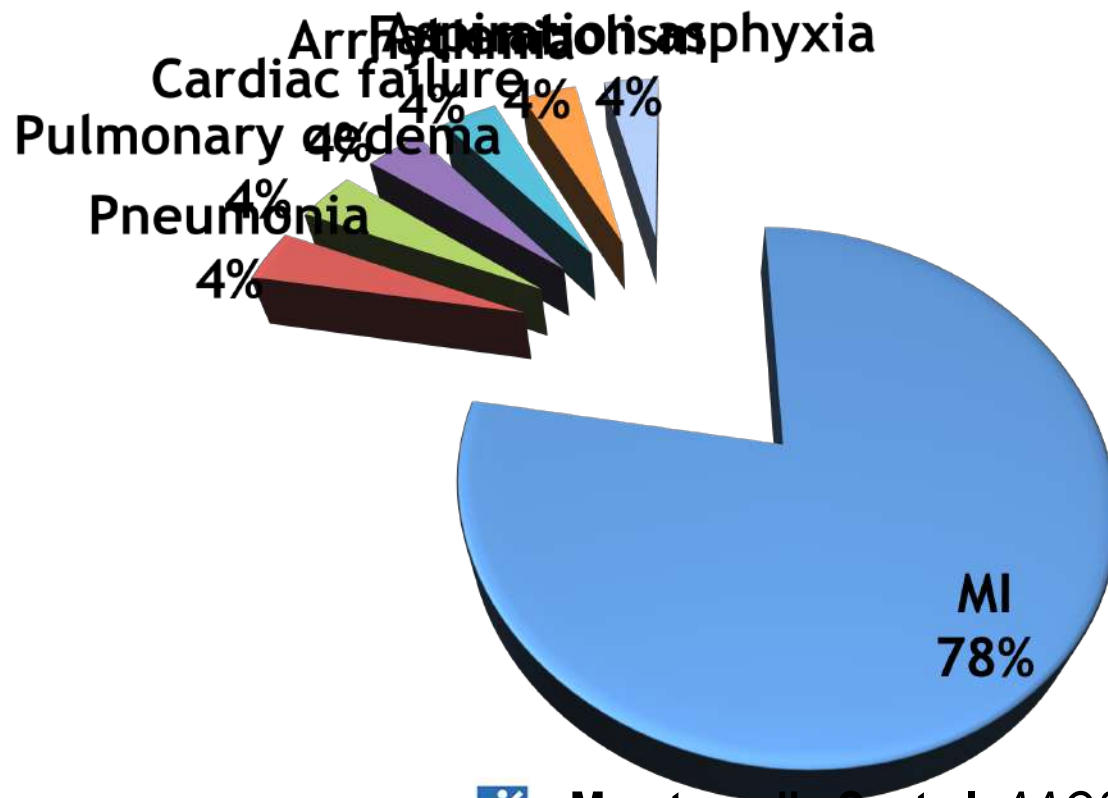
Mortality for known or suspected PE is no different with the use of potent anticoagulation



Autopsy proven deaths: 64 CP leading cause of mortality



Autopsy proven deaths in the cardiopulmonary group






Murray D, et al. Thromboprophylaxis and death after total hip replacement.

J Bone Joint Surg [Br] 1996;78(6):863-70

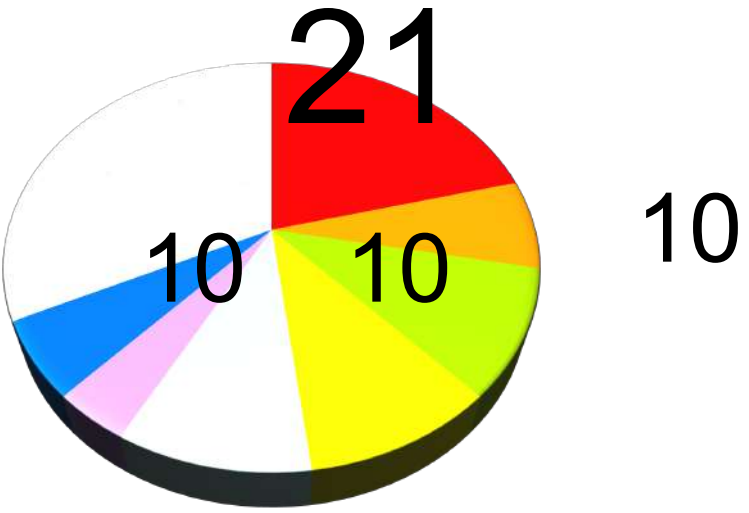
- Meta-analysis of prophylaxis after THA surgery
- 1970s to 1990s (130,000 pts)
- Fatal PE rate: 0.1% - 0.2%
- Mortality rate: 0.3% - 0.4%
- Not enough evidence in the literature to determine if pharmacologic thromboprophylaxis decreases the death rate after THA

 **Shepard M, et al.** Fatal pulmonary embolism following THA and TKA. A study of 2153 cases using routine mechanical prophylaxis and selective chemoprophylaxis. *Hip Int.* 2006;16:53-56.

- 2153 TKAs and THAs
- 8 autopsy-proven deaths
 - 5 due to ischemic heart disease

Pedersen et al. Short- and long-term mortality following primary total hip replacement for OA. *JBJS Br* 2011;93(2):172-7.

90-day - Danish Hip Arthroplasty Registry (209 pts)
44,558 patients operated on between 1995-2006



MI	CHF	PE	Stroke	Pneumonia
UGIB	Cancer	Other		

Theoretical benefits of aspirin

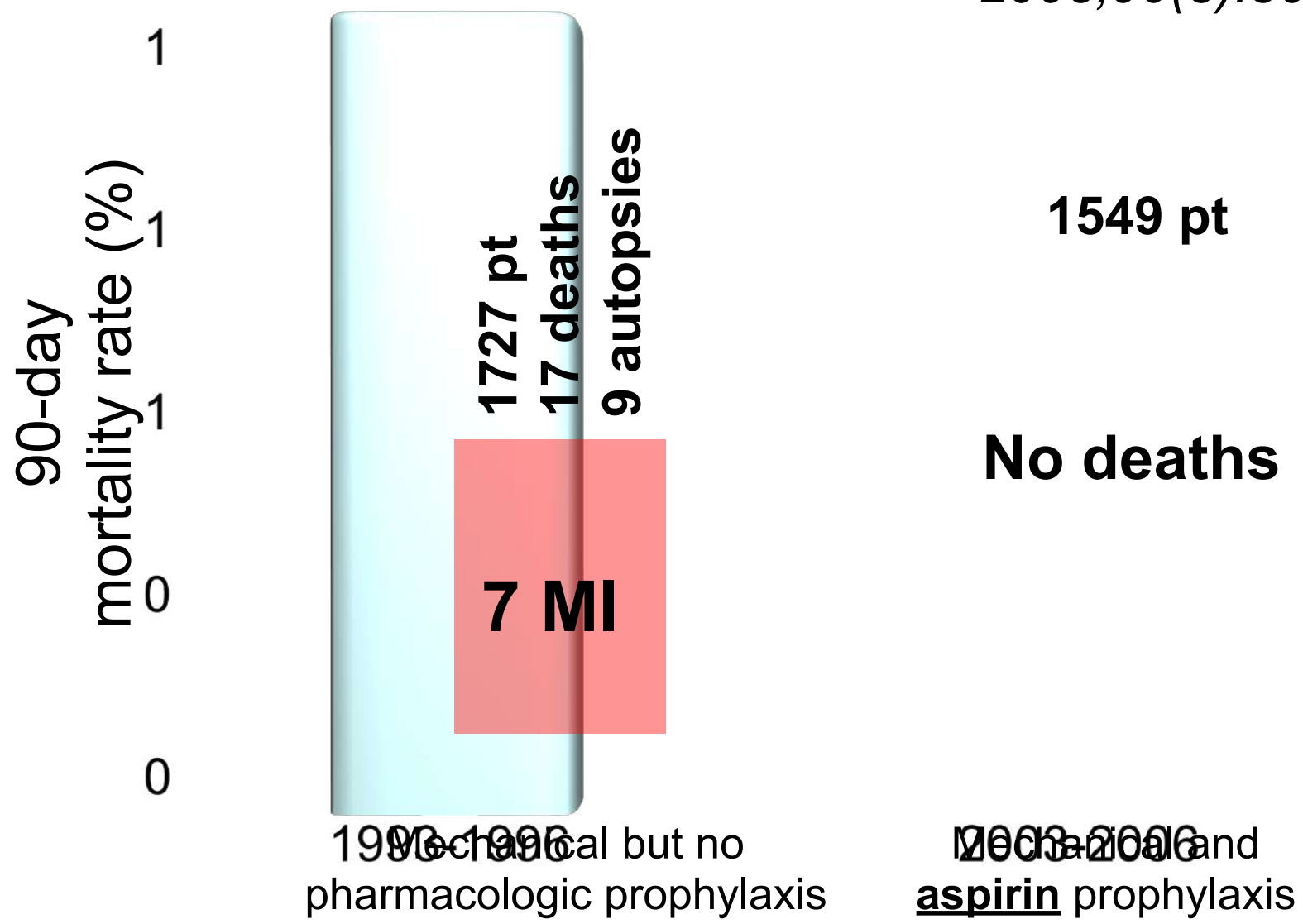
- Acceptable safety profile
- Inexpensive
- Requires no injections or monitoring
- Pain relief
- Anti-inflammatory
- Prevention of HO
- Prevention of acute CAD events



Bloom A, Bannister G, et al. Early death following primary THA. *Acta Orthopaedica* 2006;77(3):347-50.



Parry M, Bloom A, et al. 90-day mortality after elective THR. *J Bone Joint Surg Br* 2008;90(3):306-7.



Concerns with ACCP Guidelines

1

Rely on a reduction in the asymptomatic DVT rate to justify the systematic use of potent anticoagulation

... relegating major bleeding, re-operation, fatal PE, fatal bleeding and all-cause mortality.

DVT may be the incorrect surrogate to study the safety and efficacy of thromboprophylaxis

Dahl O, et al. Risk of clinical PE after joint surgery in patients receiving LMWH prophylaxis. *Acta Orthopaedica* 2003;74(3): 299-309.

- 3,954 patients (THR, TKR, NHF)
- LMWH during hospital stay
- 50 PE was confirmed
- **Only 6 of 50 pts (12%) had a DVT**

Concerns with ACCP Guidelines

2

Authors of clinical guidelines and supporting studies may have conflict of interest with the pharmaceutical industry



Choudhry N, et al. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *JAMA* 2002;287;5:612-617.

**Sharrock N, Salvati E, Gonzalez Della Valle A,
et al.** Response to letter to the Editor.
Clin Orthop 2008;466(8):2012–2014.



Concerns with ACCCP Guidelines

3

Validity of ACCCP
guidelines
methodology has
been recently
questioned

Brown G. Award paper by AAHKS. VTE prophylaxis after major orthopaedic surgery. A pooled analysis of RCT. *J of Arthroplasty* 2009;24(6 suppl):77-83.

- Pooled analysis of 14 RCT cited by ACCP
- Pentasaccharides, LMWH, warfarin, aspirin and placebo
- Rates of symptomatic VTE, fatal PE and bleeding.

- Symptomatic VTE

- Fatal PE

- Bleeding



NO DIFFERENCE



HIGHER WITH LMWH

Concerns with ACCP Guidelines

4

Safety and efficacy concerns are proliferating in the orthopaedic literature

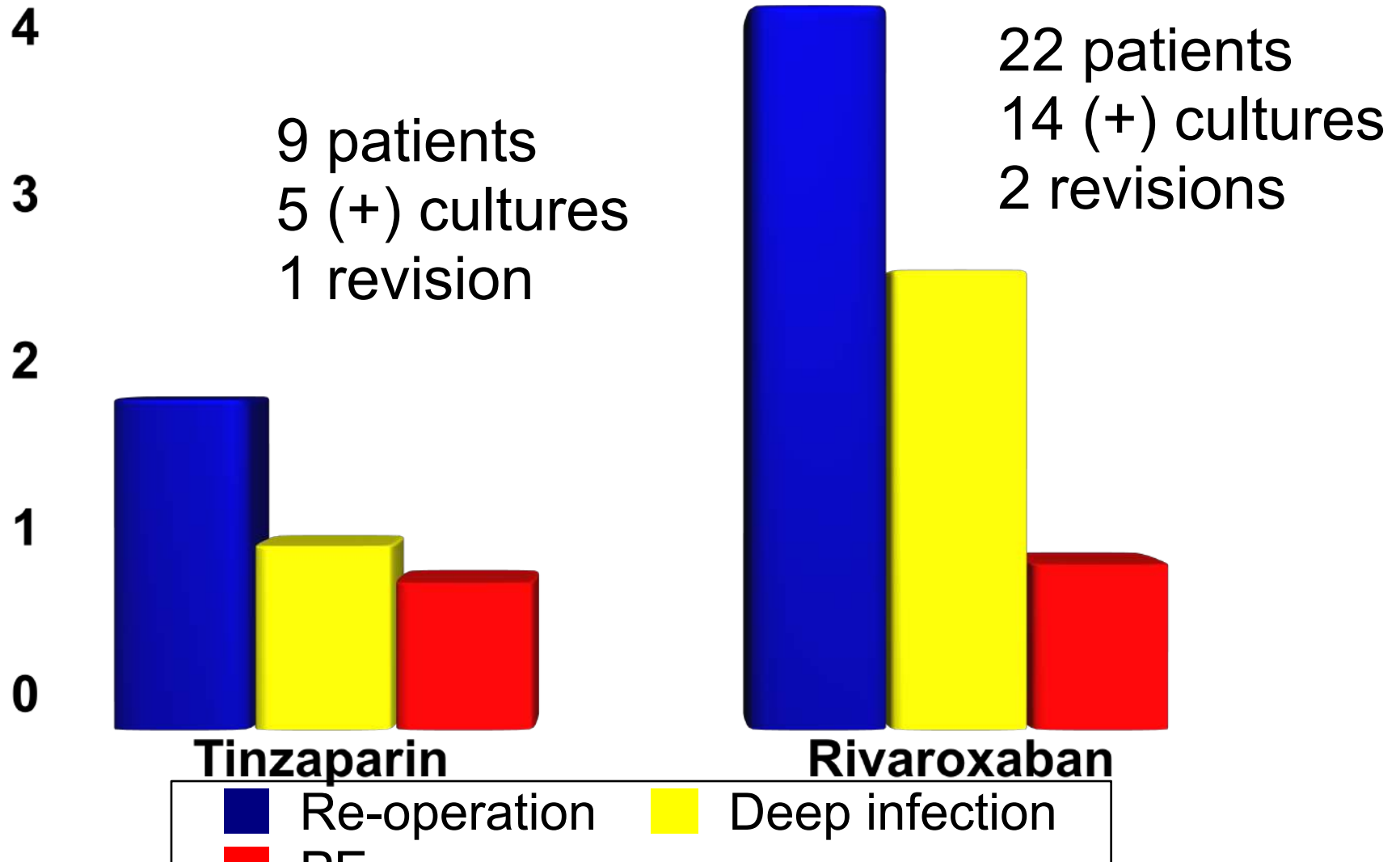
... persistent wound drainage, hematoma formation, neurological injury, reoperation, infection, and fatal bleeding.



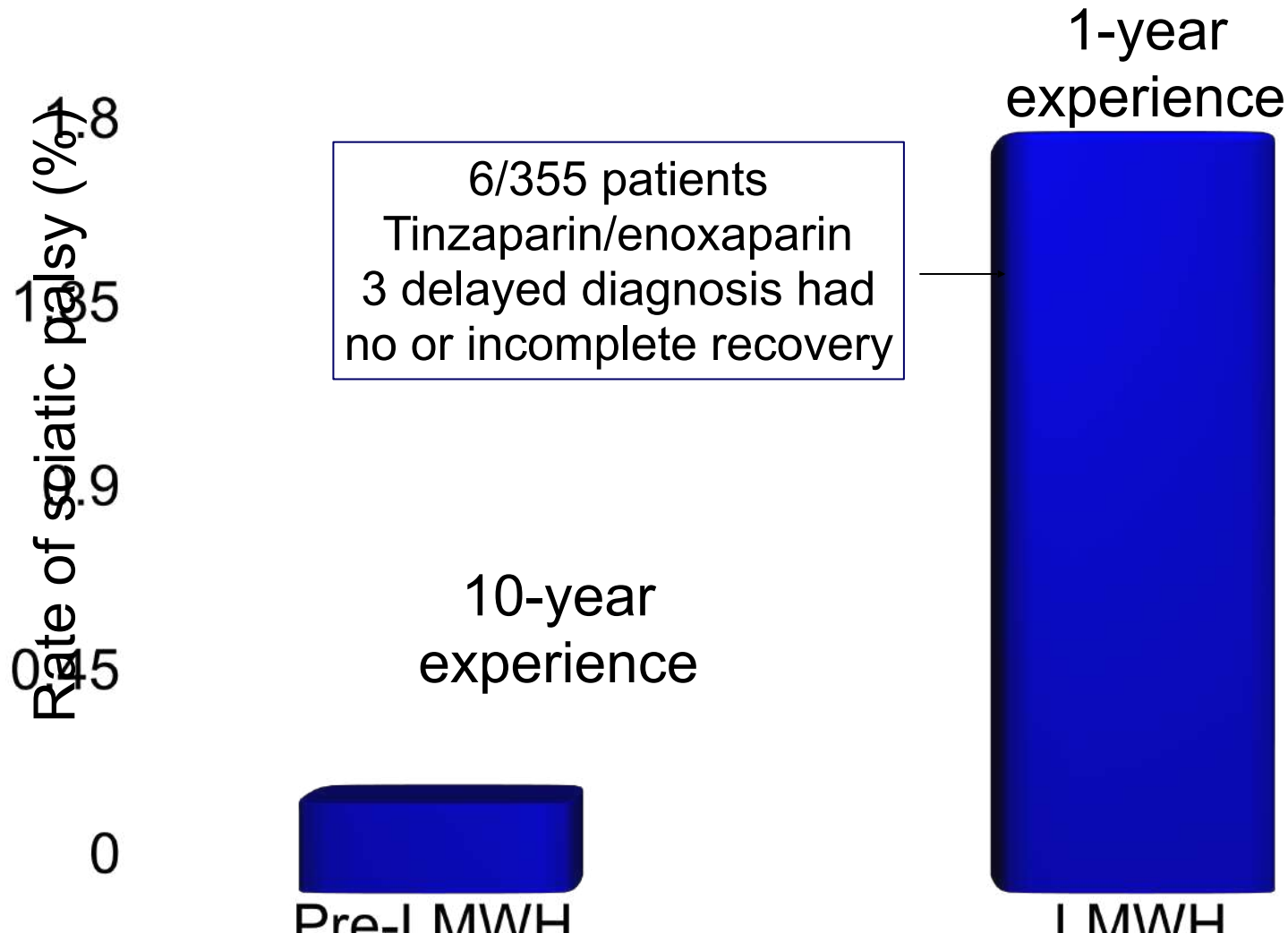
Jensen C, et al. Return to theatre following THR and TKR, before and after the introduction of rivaroxaban. *J Bone Joint Surg Br* 2011;93(1):91-5.

- 30-day reoperation rate for wound-related problems
- 489 patients on tinzaparin
- 599 patients on rivaroxaban
- Similar demographics and co-morbidities

Jensen C, et al. Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban. *J Bone Joint Surg Br* 2011;93(1):91-5.



Butt A, McCoy G, et al. Sciatic nerve palsy secondary to hematoma formation in primary THR. *J Bone Joint Surg (Br)* 2005;87(11)1465-7.



Routine potent anticoagulation as a sole means of thromboprophylaxis

- Increases bleeding risks
- Local complications of surgery
 - Hematoma formation – neurological injury
 - Superficial and deep infection
 - Reoperation
- May not diminish VTE risk or mortality
- INCREASE THE COST OF CARE

Conclusions

- Patients die rarely after elective TJR surgery despite adequate thromboprophylaxis.
- The majority of fatalities are unrelated to PE.
- Fatal PE rates are not improved by the use of potent anticoagulation in every case.
- Symptomatic PE and fatal PE should not be regarded as a fully preventable complication

Conclusions

Routine postoperative potent anticoagulation of patients undergoing elective TJR surgery

- ...does not diminish mortality or fatal PE
- ...may promote major bleeding, wound complications and increase re-operation rate
- ...should not be the regarded as the gold standard for thromboprophylaxis

Future efforts should focus on:

1. Risk stratification for rational utilization of prophylactic drugs and resources
2. Prevention of mortality for any cause