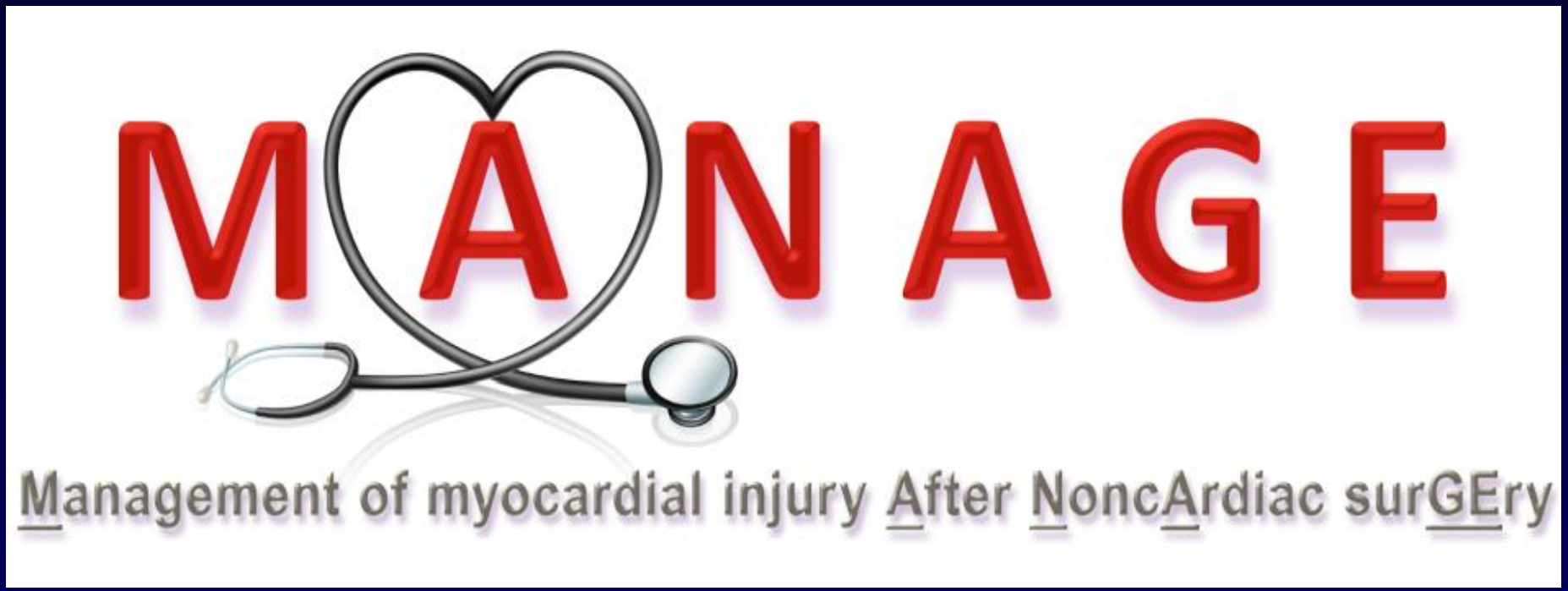

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Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): an international, randomised, placebo-controlled trial

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Background

- Myocardial injury after noncardiac surgery (MINS)
  - includes MI and isolated ischemic troponin elevation that occur within first 30 days after surgery
  - does not include non-ischemic myocardial injury
    - sepsis, rapid AF, PE, chronically elevated troponin
  - affects ≥8 million adults worldwide annually
  - is independently associated with increased risk of CV events and death over first 2 years after surgery
- No published trial has evaluated treatment for MINS

Rationale for MANAGE Trial

- Patients with MINS are at risk of thrombotic complications
- In non-operative patients high-quality evidence demonstrates benefits of anticoagulation therapy
- Dabigatran oral direct thrombin inhibitor
  - prevents VTE in perioperative setting
- In patients with MINS
  - dabigatran has potential to reduce broad range of vascular complications without causing substantial bleeding

MANAGE Trial design

- RCT of patients with MINS
  - randomized to dabigatran or placebo
- Partial 2X2 factorial design
  - patients not already on PPI
    - randomize to omeprazole or placebo
    - omeprazole results will be presented at later date
- Investigator initiated blinded trial

Eligibility criteria

- Included patients
  - ≥45 yrs of age, had undergone noncardiac surgery, ≤35 days of having MINS
    - MINS diagnostic criteria: Universal Definition of MI or isolated ischemic troponin elevation after surgery
- Excluded patients
  - with history of bleeding diathesis or prior intracranial, intraocular, or spinal bleeding
  - condition that required anticoagulation
  - eGFR <35 ml/min

Intervention and F/U

- On day of randomization, patients started taking
  - dabigatran 110 mg BID or matching placebo
  - patients in partial factorial took omeprazole 20 mg daily or matching placebo
- Patients took study drugs and were followed for
  - maximum of 2 years or until trial terminated on November 30, 2017

Design modification

- Initial design was to randomize 3200 patient
  - primary composite outcome of vascular mortality and nonfatal MI, stroke, peripheral arterial thrombosis, and symptomatic PE
- Recruitment slower than expected, during trial funding curtailed
- Without knowledge of trial results
  - sample size reduced to 1750 patients - 90% power to detect HR of 0.65 (2-sided $\alpha = 0.05$) assuming placebo Kaplan-Meier rate of 20%
  - based on COMPASS results, their relevance, and to enhance power
    - added amputation and symptomatic prox DVT to primary outcome

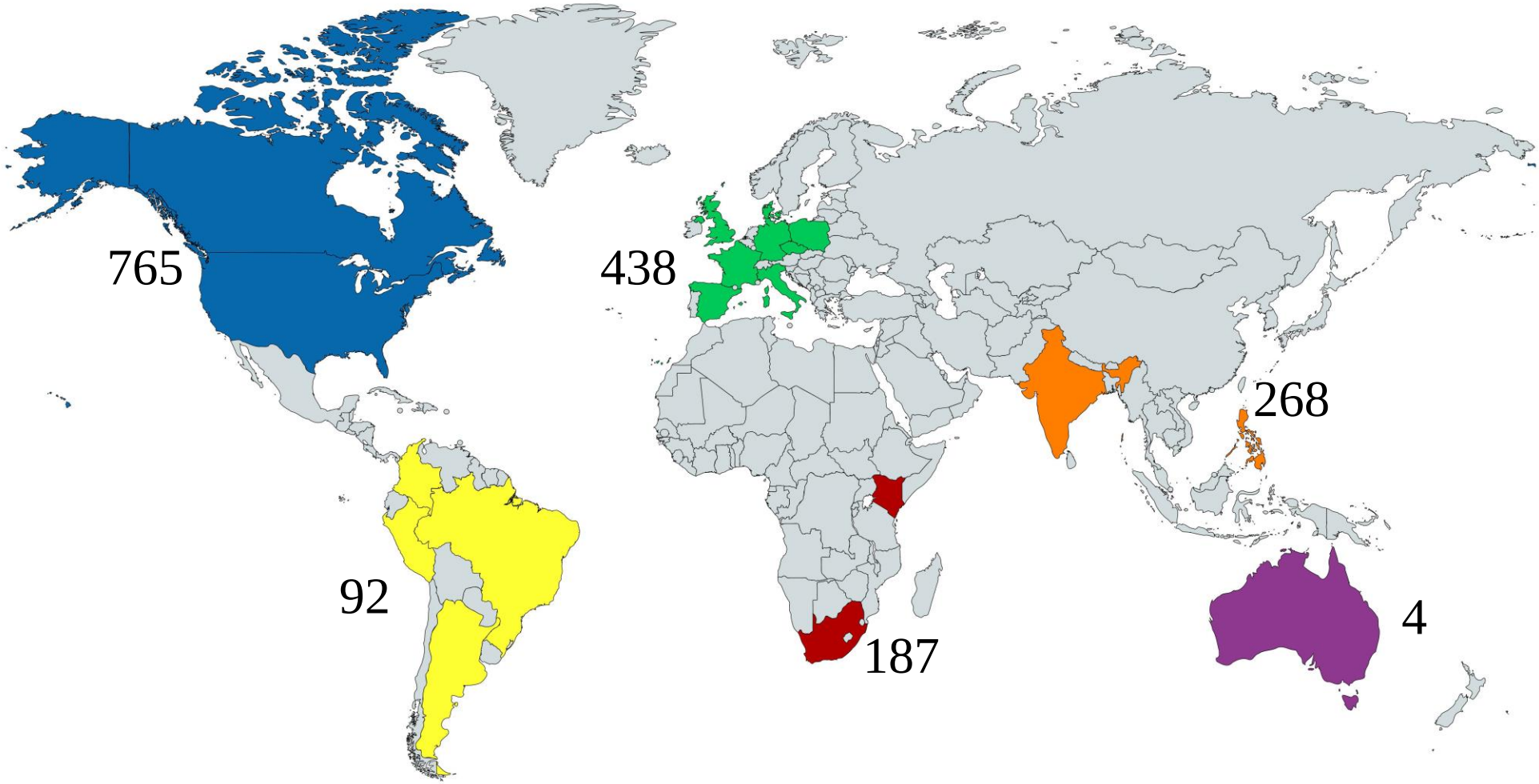
Outcomes

- Primary efficacy outcome (major vascular complication)
  - composite of vascular mortality and nonfatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic VTE
- Primary safety outcome
  - composite of life-threatening, major, and critical organ bleeding

Trial flow

- 1754 patients randomized to dabigatran or placebo
  - 556 randomized to omeprazole or placebo
- Patients were followed for mean of 16 months
- Follow-up complete for 99% of participants

Recruitment by region
84 centres in 19 countries



Baseline characteristics

Characteristics	Dabigatran (N=**877)**	**Placebo (N=877)**
Age – (mean yrs)	70	70
Male	52%	51%
MINS criteria		
MI	20%	20%
isolated isch trop elevation	80%	80%
Time from MINS diagnosis to randomization (days, IQR)	5 (2 – 14)	5 (2-14)

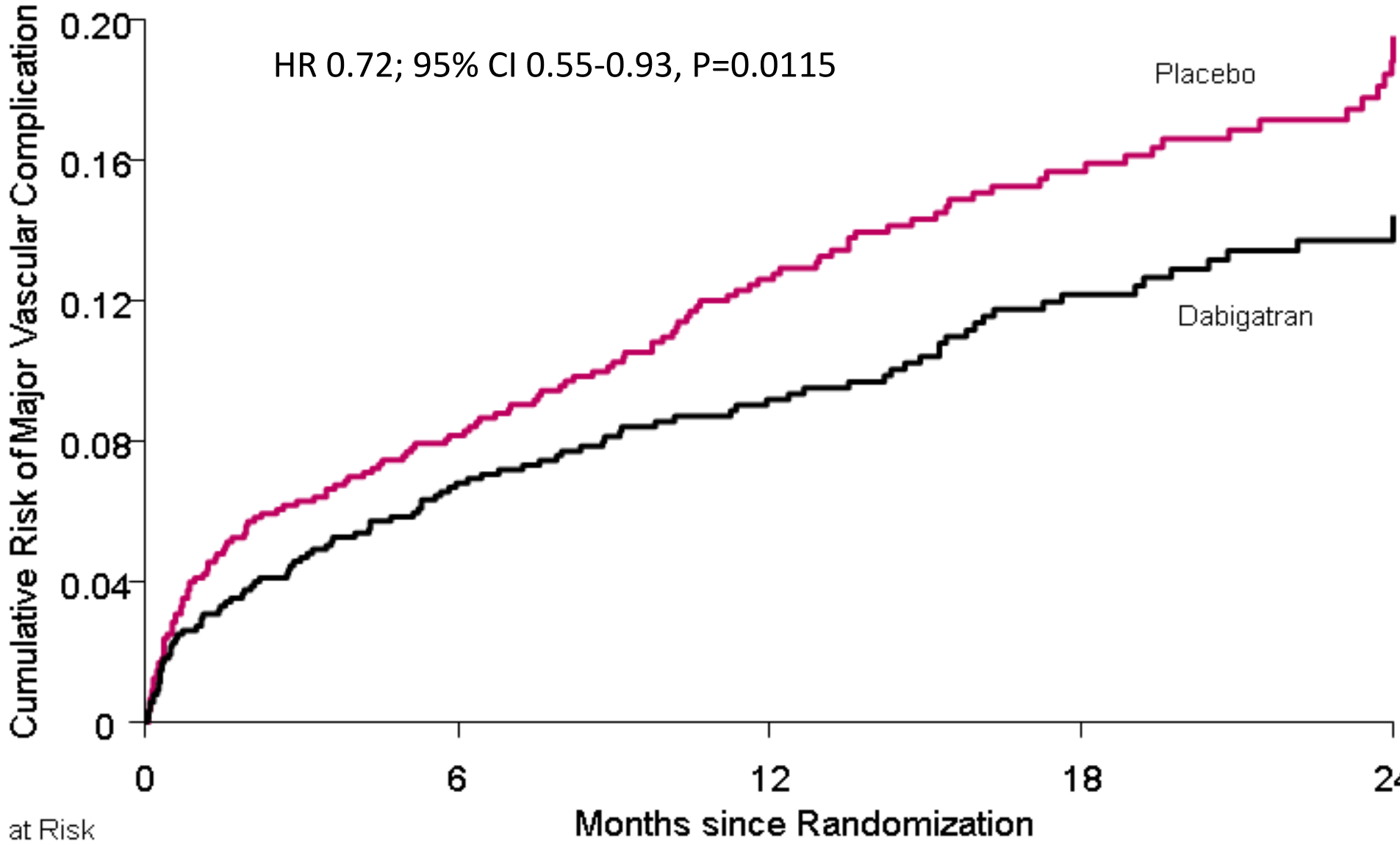
91% did not experience an ischemic symptom with MINS

Drug compliance

- Permanent study drug discontinuation
  - Dabigatran group 46%
  - Placebo group 43%
- Most common reason was patient request
  - 60% of discontinuations

Primary efficacy outcome

Outcome	Dabigatran n=877 no. (%)	Placebo n=877 no. (%)	HR (95% CI)	P value
Major vascular complication	97 (11)	133 (15)	0.72 (0.55-0.93)	0.0115



No. at Risk					
Placebo	877	751	550	386	225
Dabigatran	877	754	559	400	244

Secondary efficacy outcomes

Outcome	Dabigatran n=877 no. (%)	Placebo n=877 no. (%)	HR (95% CI)
Vascular mortality	52 (6)	64 (7)	0.80 (0.56-1.16)
All cause mortality	100 (11)	110 (13)	0.90 (0.69-1.18)
Myocardial infarction	35 (4)	43 (5)	0.80 (0.51-1.26)
Cardiac revascularization	32 (4)	21 (2)	1.53 (0.88-2.65)
Periph arterial thrombosis	0 (0)	4 (1)	-
Amputation	18 (2)	26 (3)	0.70 (0.38-1.27)
Symptomatic VTE	8 (1)	17 (2)	0.47 (0.20-1.08)
Vascular readmission	113 (13)	130 (15)	0.86 (0.67-1.11)
Non-hemorrhagic stroke	2 (<1)	10 (1)	0.20 (0.04-0.90)

Consistency efficacy outcomes

Outcome	Dabigatran n=877 no. (%)	Placebo n=877 no. (%)	HR (95% CI)
Arterial components of primary composite	89 (10)	121 (14)	0.73 (0.55-0.96)
Venous components of primary composite	8 (1)	17 (2)	0.47 (0.20-1.08)
Original efficacy composite	81 (9)	107 (12)	0.74 (0.56-0.99)
Per-protocol analysis censoring 7 days after drug discontinuation	54 (6)	94 (11)	0.57 (0.41-0.79)

Primary safety outcome

Outcome	Dabigatran n=877 no. (%)	Placebo n=877 no. (%)	HR (95% CI)	P Value
Composite of life-threatening, major, and critical organ bleed	29 (3)	31 (4)	0.92 (0.55-1.53)	0.78

- No significant effect of omeprazole study drug on dabigatran primary safety result (interaction P=0.37)

Secondary safety outcomes

Outcome	Dabigatran n=877 no. (%)	Placebo n=877 no. (%)	HR (95% CI)
Life-threatening bleed	9 (1)	8 (1)	1.11 (0.43-2.88)
Major bleed	21 (2)	25 (3)	0.83 (0.46-1.48)
Critical organ bleed	5 (1)	10 (1)	0.49 (0.17-1.43)
Intracranial bleed	4 (1)	3 (<1)	1.32 (0.30-5.90)
Hemorrhagic stroke	2 (<1)	2 (<1)	0.98 (0.14-6.96)
Significant lower GI bleed	15 (2)	6 (1)	2.50 (0.97-6.44)
Fracture	39 (4)	28 (3)	1.38 (0.85-2.24)
Non-sign lower GI bleed	33 (4)	7 (1)	4.77 (2.11-10.80)
Minor bleed	134 (15)	84 (10)	1.64 (1.25-2.15)
Dyspepsia	129 (15)	98 (11)	1.33 (1.02-1.73)

Consistency safety outcomes

Outcome	Dabigatran n=877 no. (%)	Placebo n=877 no. (%)	HR (95% CI)
International Society of Thrombosis and Hemostasis (ISTH) major bleed	59 (7)	43 (5)	1.38 (0.93-2.04)
Bleeding Academic Research Consortium (BARC) ≥Type 2 bleed	29 (3)	28 (3)	1.03 (0.61-1.73)
Major upper gastrointestinal complication	4 (<1)	4 (<1)	0.99 (0.25-3.96)
Per-protocol analysis censoring 7 days after drug discontinuation	21 (2)	21 (2)	1.04 (0.57-1.88)

Conclusions

- Among patients with MINS dabigatran 110 mg BID
  - decreased risk of major vascular complications
  - with no observed increased risk of major bleeding

Implications

- Patients with MINS are at high risk
  - 1 in 7 suffered major vascular complication at 16 month f/u
- 91% of MINS were only detected through troponin screening
  - clinicians will not recognize most MINS without routine perioperative troponin measurements
- MANAGE demonstrated NNT of 24 patients for dabigatran to prevent major vascular complication
- Potential for increased major harm substantially lower
  - even if assume primary safety outcome HR upper 95% CI (1.53) represents true effect NNH (54 patients) would be more than double NNT