Impact of a systematic review on subsequent clinical research

The case of the prevention of propofol injection pain

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Injection of propofol: why a concern?

Intravenous anesthetic, sedative hypnotic agent

Characteristics: quick and deep sedation, fast recovery, haemodynamic stability, less post-operative nausea and vomiting

Main uses: induction and maintenance of general anesthesia, hypnosis for endoscopic procedures, sedation during mechanical ventilation

Adverse effect: **pain on the site of injection** (etiology unclear)

→ **Trials testing interventions to prevent propofol inection pain are: simple, cheap and quick to perform**

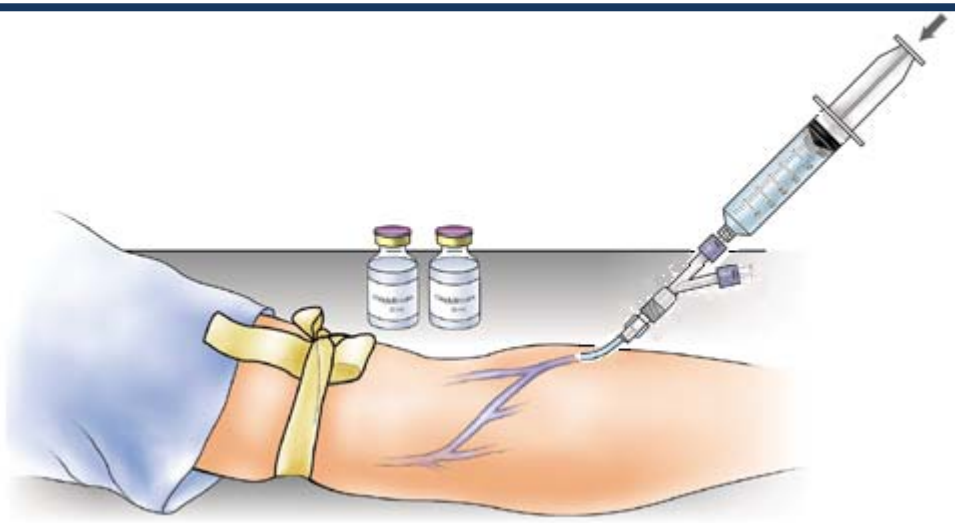
Prevention of Pain on Injection with Propofol: A Quantitative Systematic Review

Pascale Picard, MD*, and Martin R. Tramèr, MD, DPhil†

Anesth Analg 2000;90:963–9

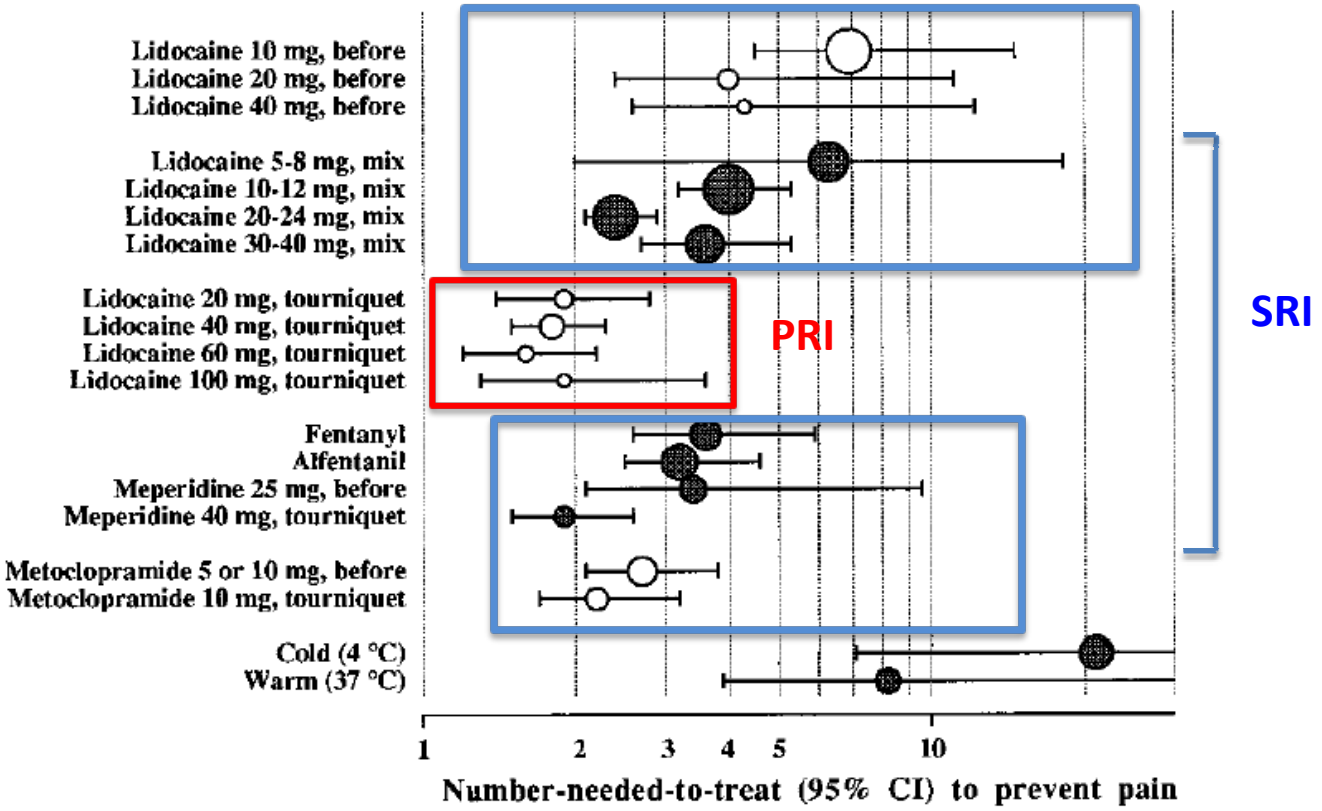
56 randomized controlled trials, 6'264 patients
12 drugs, 12 physical measurements, and combinations were tested
Baseline risk: 70% of the patients reported pain on injection

→ 30-120 s Bier's Block with lidocaine prior propofol (NNT 1.8, 95% CI 1.5-2.2)
= "gold-standard" = primary reference intervention (PRI)



Lidocaine without venous occlusion (NNT 4.0-6.9)
Mixture of lidocaine and propofol (NNT 2.4-6.3)
Opioid and non-opioid agents with or without venous occlusion

→Alternative but less efficacious interventions = secondary reference interventions (SRI)



Picard et al. *Anesth Analg* 2000;90:963-9

Other conclusions

Lack of data for further analgesic interventions to allow meaningful conclusions

Limited data on children

Blinding was often inadequate

The lidocaine-tourniquet method is undeniably effective and simple to perform. This begs the question as to the necessity of clinical studies that may identify yet another intervention with some analgesic efficacy to prevent pain on injection with propofol.

Picard et al. *Anesth Analg* 2000;90:963-9

Objective

To examine whether knowledge from the systematic review ("Picard review") had an impact on the design of subsequent trials

Hypotheses

1. The number of publications per year on the issue of pain on injection of propofol has decreased since 2000
2. A greater proportion of trials report on children
3. Subsequent trials are more often blinded
4. The lidocaine-tourniquet intervention (=PRI) is chosen as the control intervention
5. Authors of subsequent trials cite the Picard review
6. Methodological issues in trials citing the Picard review differ from those that do not

Methods: Search strategy

DESCRIPTIVE SYSTEMATIC REVIEW Comparison of **old** trials (published before the Picard review) with **new** trials (published afterwards)

INFORMATION SOURCES Electronic databases, bibliographies

SEARCH STRATEGY Key words used in the Picard review (« propofol », « pain », « injection », « random »)

LIMITS Full reports, humans (adults, children), no limit to language

SEARCH PERIOD From January 2002 (two years after publication of the Picard review) to January 2013

ELIGIBILITY CRITERIA Randomised, placebo-controlled trials, testing the analgesic efficacy of interventions to prevent pain on injection of propofol

Methods: Data extraction

STUDY CHARACTERISTICS

Year of publication, country of origin, journal, impact factor, open access, study population, number of subjects, quality of data reporting, funding

COMPARATOR GROUPS

- **Primary Reference Intervention (PRI):** Lidocaine-tourniquet prior to propofol
- **Secondary Reference Intervention (SRI):** Lido alone, mixture lido/propo, opioids
- **Experimental:** Any intervention without proven efficacy
- **Placebo/no treatment**

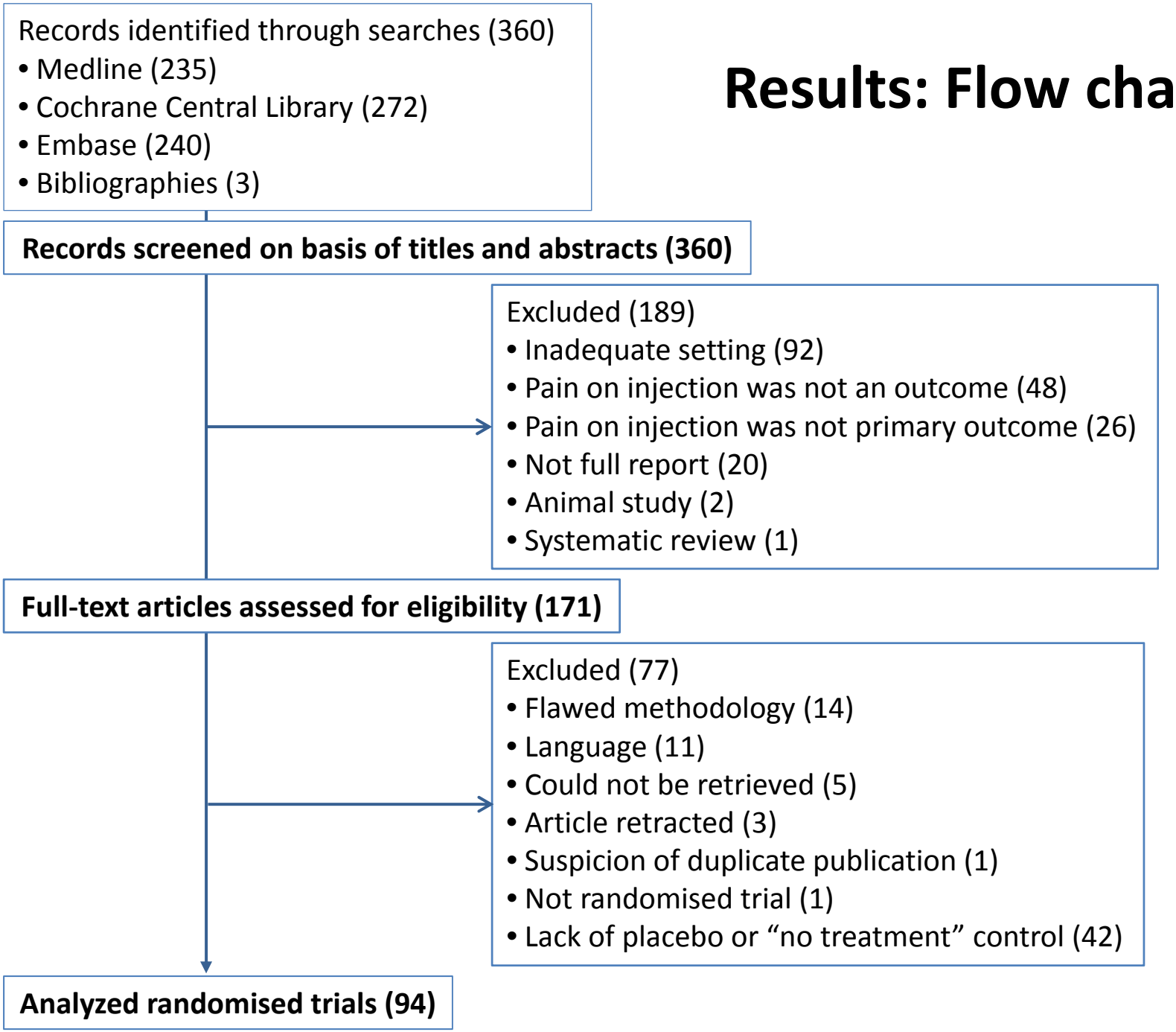
REFERENCE TO PICARD REVIEW

- **Yes or no**
- **Purpose of citation**

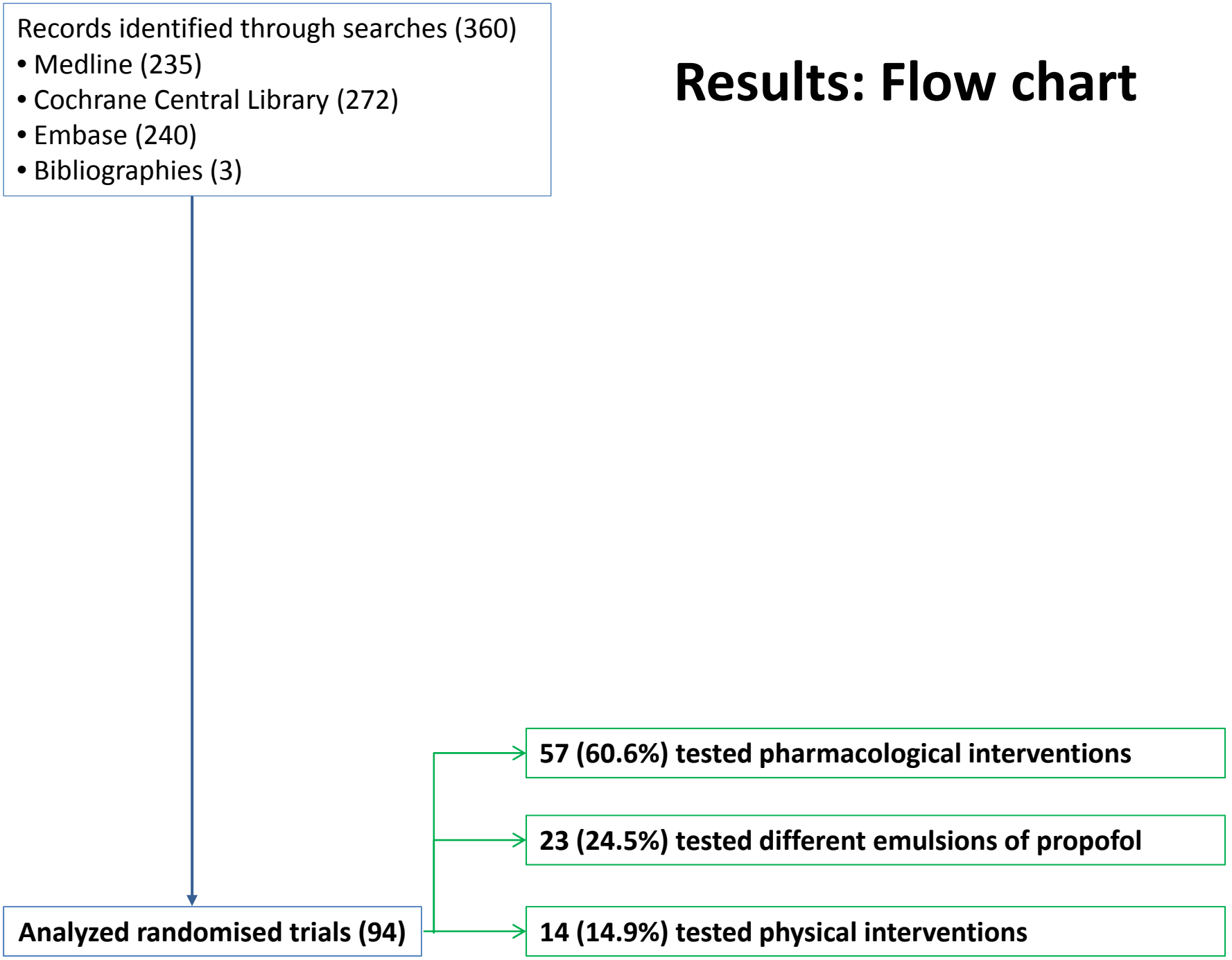
CLINICAL RELEVANCE OF COMPARISON

- **Clinically informative:** Experimental *vs* PRI
- **Not clinically informative:** All other comparisons

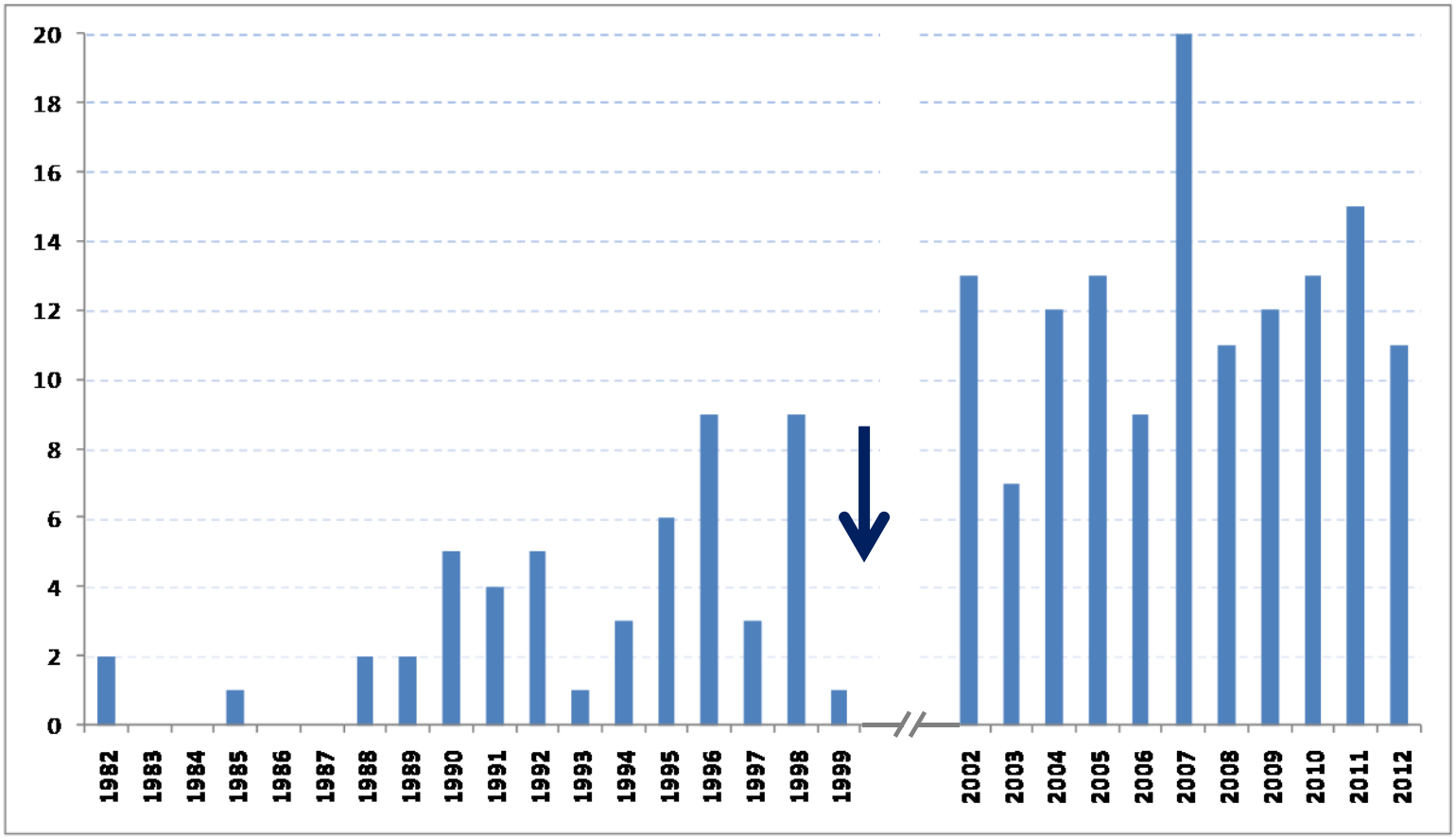
Results: Flow chart



Results: Flow chart



Results: Number of published trials per year



	Old trials	New trials	P
Year of publication, median (range)	**1995** (1982 to 1999)	**2007** (2002 to 2012)	
N° trials published per year, median (range)	**2.5** (0 to 9)	**8** (5 to 15)	<0.001

Results: Differences between old and new trials

Characteristics of studies	Old trials	New trials	P
N° of trials	56	94	
N° of subjects	6264	14068	
N° of subjects in trial	100 (28 to 368)	**133** (16 to 500)	<0.001
Trials published in journal without IF	9 (16.1%)	31 **(33%)**	0.024
Impact factor	2.96 (1.21 to 5.34)	**2.23** (0.03 to 4.24)	<0.001
Oxford quality score	2 (1 to 4)	2 **(1 to 5)**	0.012

Results: Main outcomes

Study characteristics	Old trials (n = 56)	New trials (n = 94)	P
Trials in children	3 (5.4%)	6 (6.4%)	0.803
Adequately blinded trials	38 (67.9%)	55 (58.5%)	0.251

Comparisons	Old trials (n = 56)	New trials (n = 94)	P
Primary reference intervention (PRI)	7 (12.5%)	28 (29.8%)	0.015
Secondary reference intervention (SRI) (no PRI)	35 (62.5%)	26 (27.6%)	<0.001
Experimental *vs* placebo (neither PRI nor SRI)	11 (19.6%)	40 (42.6%)	0.004

Clinical relevance of trial designs	Old trials (n = 56)	New trials (n = 94)	P
Clinically informative	n/a	24 (25.5%)	
Not clinically informative	n/a	70 (74.5%)	

Results: Characteristics of trials according to reference to Picard review

Characteristics of studies	Citation	No citation	P
N° of trials	65 (69.1%)	29 (30.9%)	
N° of subjects	9770	4298	
N° of subjects in trial	130 (22 to 500)	137 (16 to 335)	0.844
Trials published in journal without IF	18 (27.7%)	13 (44.8%)	0.103
Impact factor	2.23 (0.03 to 4.24)	1.70 (0.52 to 3.29)	0.485
Oxford quality score	3 (1 to 5)	2 (1 to 4)	0.047

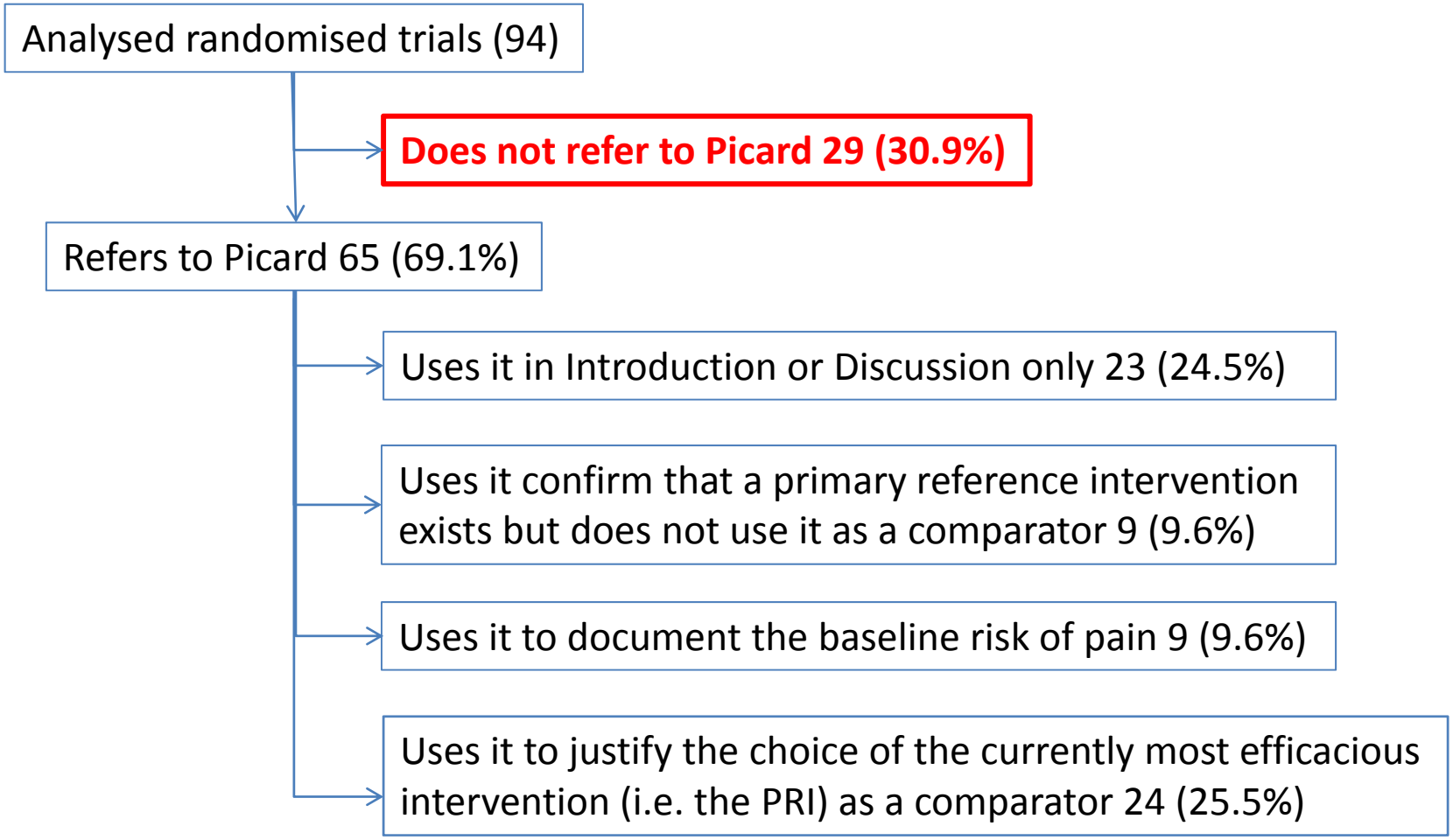
Results: Characteristics of trials according to reference to Picard review

Study features	Yes (n = 65)	No (n = 29)	P
Trials in children	4 (6.2%)	2 (6.9%)	0.898
Adequately blinded trials	43 (66.1%)	12 (41.4%)	0.025

Comparisons	Yes (n = 65)	No (n = 29)	P
Primary reference intervention (PRI)	19 (29.2%)	9 (30.9%)	0.868
Secondary reference intervention (SRI) (no PRI)	21 (32.3%)	5 (17.2%)	0.131
Experimental vs placebo (neither PRI nor SRI)	25 (38.5%)	15 (51.7%)	0.232

Clinical relevance of trial designs	Yes (n = 65)	No (n = 29)	P
Clinically informative	17 (26.2%)	7 (24.1%)	0.829
Not clinically informative	48 (73.8%)	22 (75.9%)	

Results: Reference to Picard review



Results: Additionnal findings

Additional findings	Clinically relevant (n = 24)	Clinically not relevant (n = 70)	P
Open-access journal			
yes	6 (25%)	13 (18.6%)	
no	18 (75%)	57 (81.4%)	0.499
Funding source			
Not declared	16 (66.7%)	46 (65.7%)	
No funding	4 (16.7%)	6 (8.6%)	
Academic funding	4 (16.7%)	12 (17.2%)	
Industry funding	0 (0.0%)	6 (8.6%)	0.367

Conclusions

The number of trials published per year has not decreased since the publication of the systematic review

Despite a clear research agenda, the systematic review had poor influence on designing new trials

The proportion of clinically informative trials that could have had an impact on clinical practice remained low

70% of new trials cited the Picard review but only 25% were using it to justify for methodological purposes

Conclusions

It is unethical to embark on new research without first analysing systematically what can be learned from existing literature.

Chalmers I. Academia's failure to support systematic reviews. *Lancet* 2005;365:469

Systematic reviews guide researchers in assessing the need for further investigations, and also to avoid unnecessary or redundant research.

Young C, Horton R. Putting clinical trials into context. *Lancet* 2005;366:107-8

The choice of a control intervention should be supported by a systematic review of the relevant literature.

Mann H, Djulbegovic B. Choosing a control intervention for a randomised clinical trial. *BMC Medical Res Methodol* 2003; 3:7

➔ **Our study emphasizes that systematic reviews are still not sufficiently used to inform future research**