Acute Cardiac Care 2010
Stent or Lysis? It's a matter of time

Incorporating randomised trials in guidelines

W. Wijns
Aalst, B

Saturday October 16, 2010

Evidence basis

	RCT The Gold standard	Registries (Propensity Matched)
Strengths	No Bias	Large Numbers Represent real clinical practice
Potential Weaknesses		Confounding/Bias

Levels of Evidence (LOE)

Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Evidence basis

	RCT The Gold standard	Registries (Propensity Matched)
Strengths	No Bias	Large Numbers Represent real clinical practice
Potential Weaknesses	Small numbers of patients Small % of eligible population Atypical patient populations Short duration of follow-up Large numbers of cross-overs	Confounding/Bias

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- Levels of evidence
- Endpoints of RCT
- Weight of RCT
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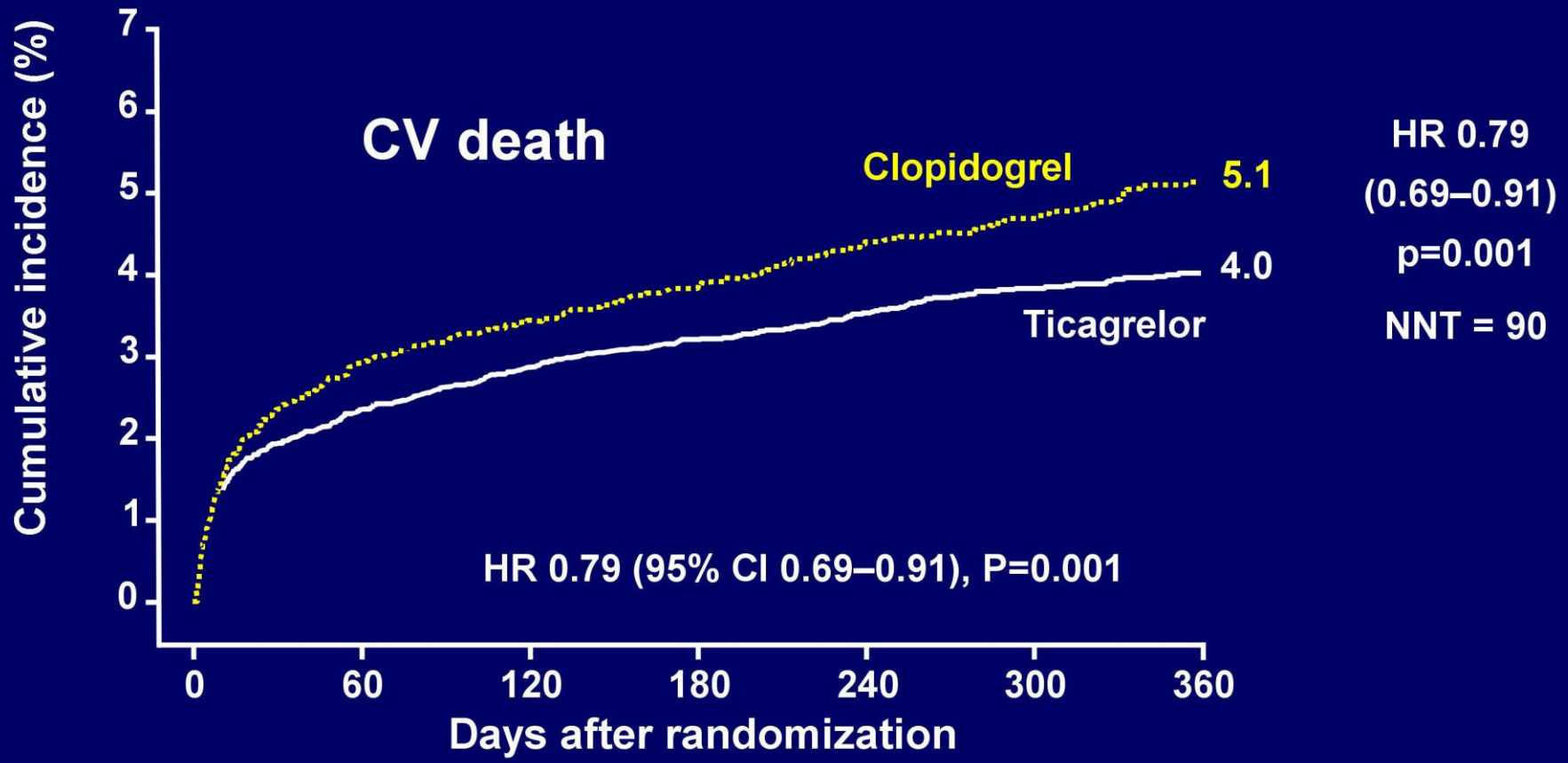
Endpoints for RCT

- Hard event endpoints: (cardiac) death, stroke, MI (wild type)
- Soft(er) endpoints: periprocedural MI, revascularization, ischaemia

PLATO

Cardiovascular death

18,624 ACS UA/NSTEMI or STEMI (if primary PCI)
All receiving ASA; clopidogrel-treated or -naïve



Wallentin L, et al. *N Engl J Med.* 2009;361:1045-57.

Endpoints for RCT

- Hard event endpoints: (cardiac) death, stroke, MI (wild type)
- Soft(er) endpoints: periprocedural MI, revascularization, ischaemia
- Surrogate endpoints, mostly angiographic:

  TIMI flow rate / infarct size / QCA metrics (late loss)

Validated drug-eluting stents (DES) for clinical use

DES	Eluted Drug	Trials and references
Clinical primary endpoint reached		
BioMatrix Flex	Biolimus A9	LEADERS
Cypher	Sirolimus	SIRIUS
Endeavor	Zotarolimus	ENDEAVOR-II, -III and -IV
Resolute	Zotarolimus	RESOLUTE-AC
Taxus Liberté/ Element	Paclitaxel	TAXUS-IV and -V/ PERSEUS-WH
Xience V	Everolimus*	SPIRIT-III and –IV
Angiographic primary endpoint reached		
Nevo	Sirolimus	NEVO RES I
Nobori	Biolimus A9	NOBORI-I Phase-I and -2
Yukon	Sirolimus	ISAR-Test

Selection is based on adequately powered RCT with a primary clinical or angiographic endpoint.

With the exception of LEADERS and RESOLUTE (all-comers trials), efficacy was investigated in selected de novo lesions of native coronary arteries.

* Promus Element device elutes everolimus from a different stent platform.

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- Intermediate endpoints, mostly mechanistic (imaging based)
- **Composite endpoints**

  Triple, quadruple, or multiple mix

  Issues are hierarchy, (in)consistency

Timing of Angiography and Intervention

Optimal timing for invasive treatment

Meta-analysis of 4 major trials (n = 4013)

EARLY (1.2-14 hours) vs DELAYED (20-86 hours)

ISAR-COOL

ABOARD

TIMACS

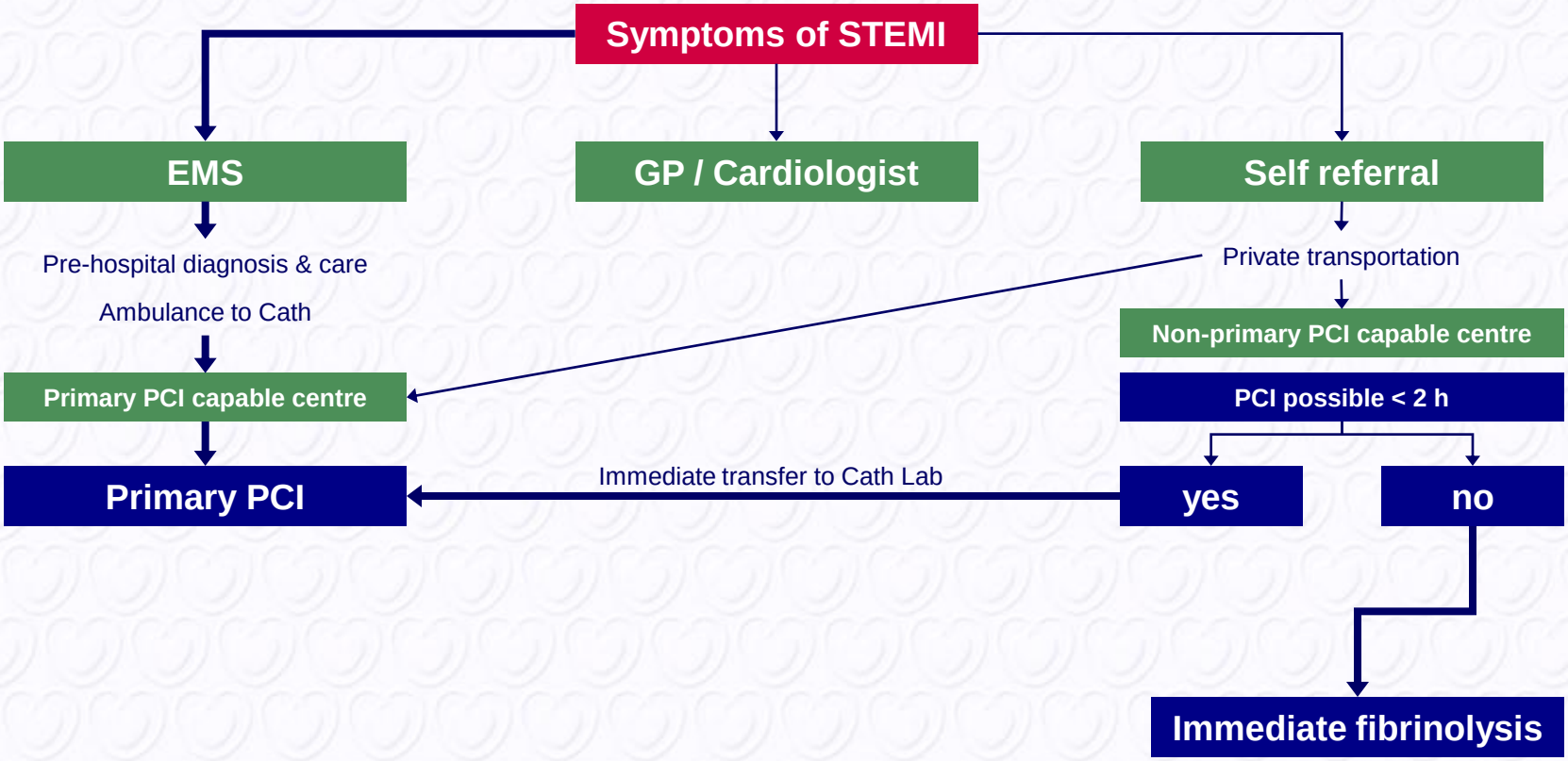
ELISA

Table 4 Summary risk ratios for major clinical outcomes

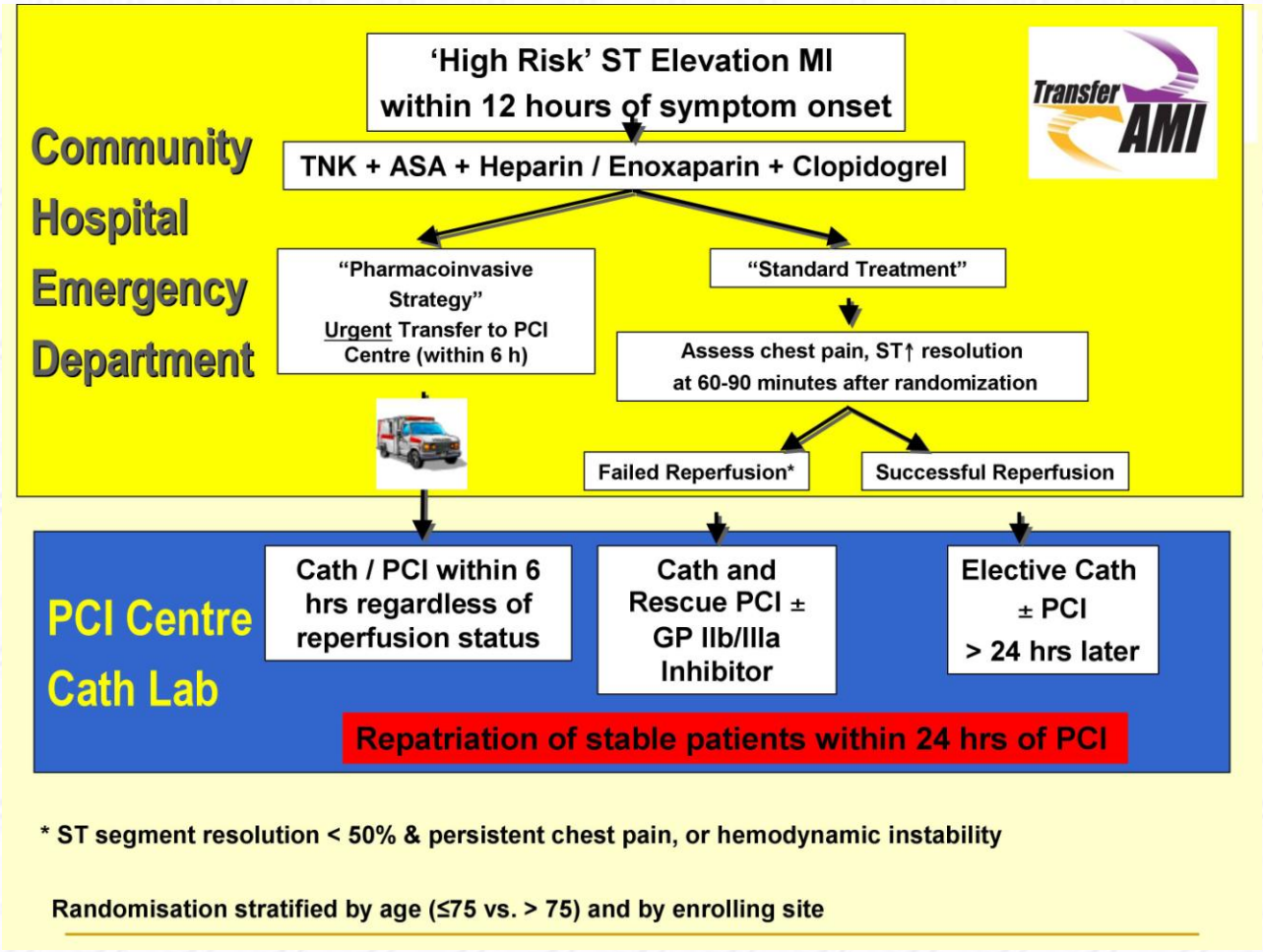
Outcomes	Random effects (95% CI)	*P* (RE)
Death	0.85 (0.64–1.11)	0.24
MI	0.94 (0.61–1.45)	0.79
Major bleeding	0.78 (0.57–1.07)	0.13
Recurrent ischaemia	0.59 (0.38–0.92)	0.02
Repeat intervention	0.96 (0.67–1.38)	0.84
Stroke	0.84 (0.47–1.49)	0.55
Death, MI, or stroke	0.91 (0.82–1.01)	0.09

Katritsis et al. Eur H J;2010, online August 13

Organization of STEMI patient disposal describing pre- and in-hospital management, and reperfusion strategies within 12 h of First Medical Contact (FMC)

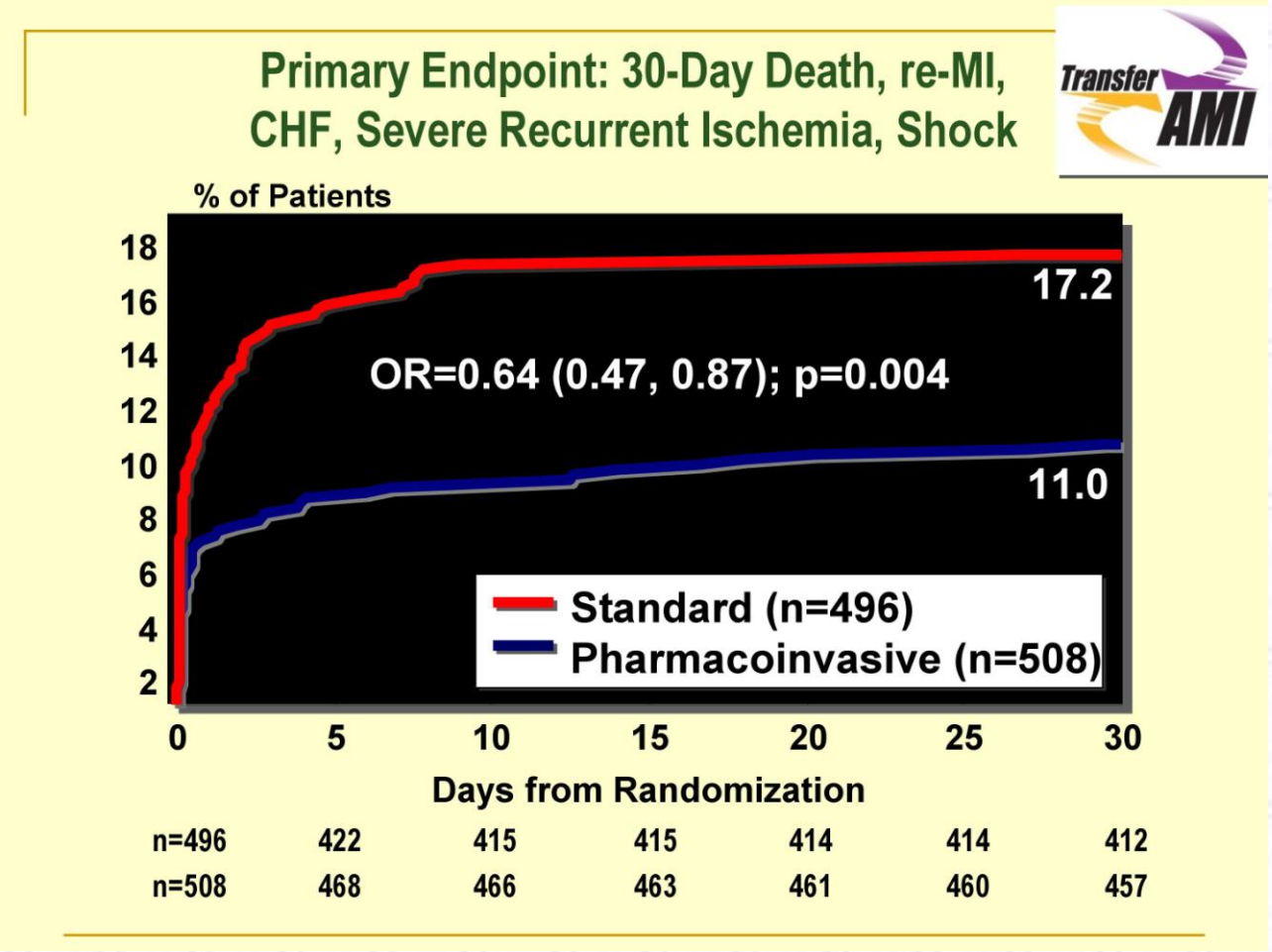


Reperfusion Strategies



Cantor WJ et al. N Engl J Med. 2009;360(26):2705-18.

Reperfusion Strategies



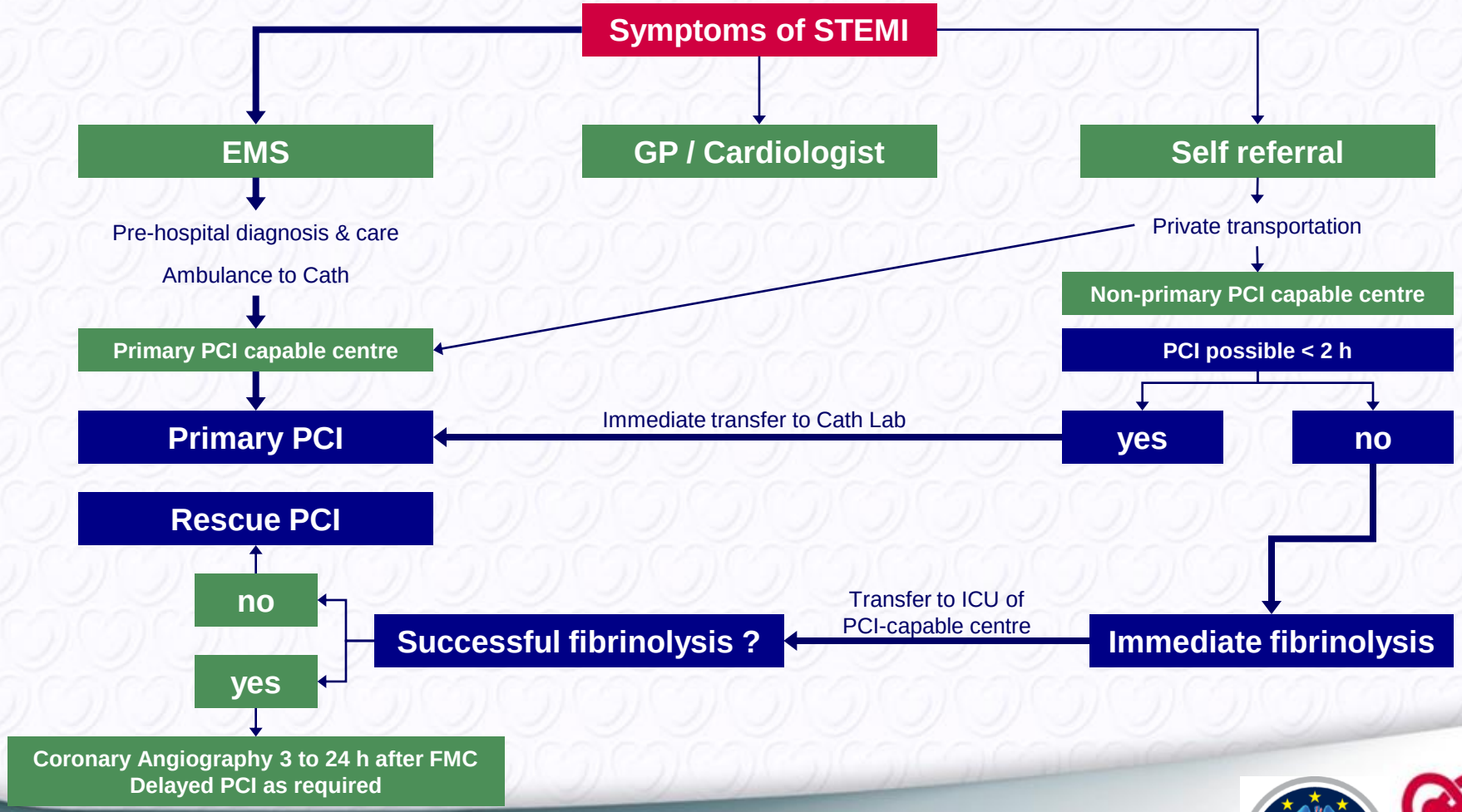
Cantor WJ et al. N Engl J Med. 2009;360(26):2705-18.

Recommendations for PCI in STEMI

Indication	Time from FMC	Class	Level
PCI after fibrinolysis:			
Routine urgent PCI is indicated after successful fibrinolysis (resolved chest pain/discomfort and ST-segment elevation).	Within 24 h	I	A
Rescue PCI should be considered in patients with failed fibrinolysis.	As soon as possible	IIa	A

In order to reduce delay for patients with no reperfusion, transfer to PCI center of all post-fibrinolysis patients is recommended.

Organization of STEMI patient disposal describing pre- and in-hospital management, and reperfusion strategies within 12 h of First Medical Contact (FMC)



www.escardio.org/guidelines

Joint 2010 ESC - EACTS Guidelines on Myocardial Revascularisation

EACTS

EUROPEAN SOCIETY OF CARDIOLOGY®

Endpoints for RCT

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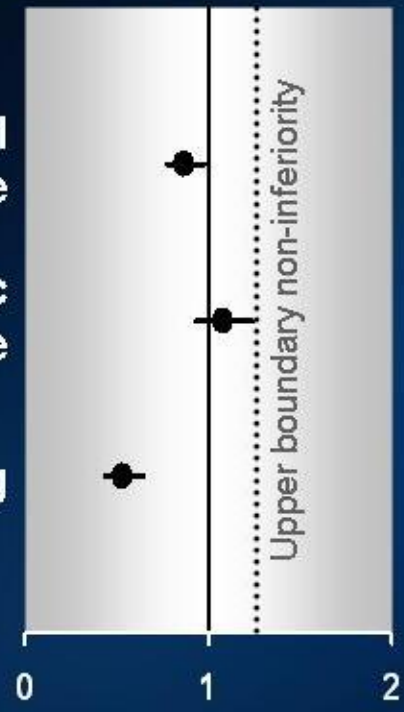
  Triple, quadruple, or multiple mix

  Benefit / Risk ratio

ACUITY: Primary Endpoint Measures

UFH/Enoxaparin + GPI vs. Bivalirudin Alone

Primary endpoint	Bival alone	UFH/Enox + IIb/IIIa	RR (95% CI)	p value (non inferior) (superior)
Net clinical outcome	10.1%	11.7%	0.86 (0.77-0.97)	<0.001 0.015
Ischemic composite	7.8%	7.3%	1.08 (0.93-1.24)	0.02 0.32
Major bleeding	3.0%	5.7%	0.53 (0.43-0.65)	<0.001 <0.001



NEJM 2006;355:2203

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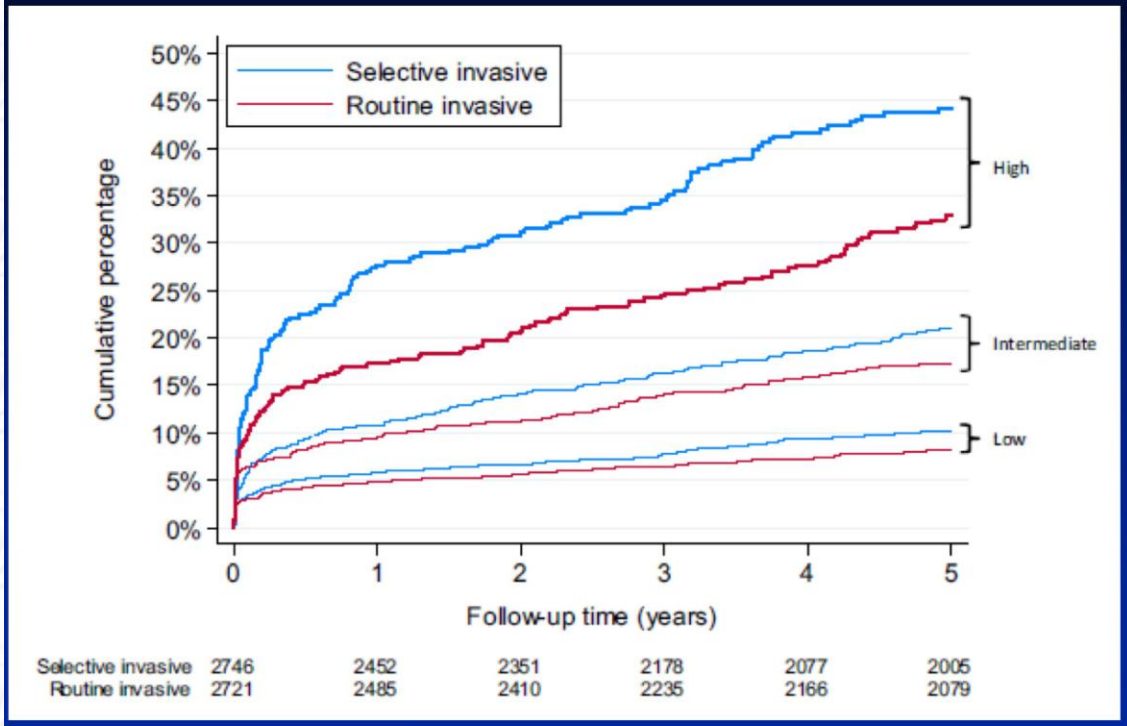
Weight of RCT

- Size: mega vs large vs small
- Relevance
  - Robust finding (p value)
  - Case selection
  - Generalisable
  - Subgroup analysis (absolute vs RRR)
  - Obsolescence

Intended Early Invasive vs. Conservative Strategy

Long term outcome by initial Risk Score

Meta-analysis of 3 major trials



FRISC2

RITA-3

ICTUS

Fox KA et al. JACC 2010;55(22):2435-45

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EACTS

EUROPEAN SOCIETY OF CARDIOLOGY®

15 RCT of PCI vs CABG in 'Multivessel' Disease (Pre-SYNTAX)

TRIAL	N	Stent	Included /Eligible	1 or 2 VD	EF >50%	Left Main	Proximal LAD	Diabetes	ITA
RITA	1011	-	4%	88	-	0	-	6	74
ERACI	127	-	9%	55	100	0	-	11	75
LAUSANNE	134	-	3%	100	-	0	100	12	100
GABI	359	-	4%	82	-	0	-	10	37
EAST	392	-	4%	60	100	0	70	25	-
CABRI	1054	-	3%	60	100	0	-	12	75
MASS	142	-	69%	-	100	0	100	21	100
BARI	1829	-	12%	59	100	0	36	24	80
TOULOSE	152	-	3%	71	-	0	-	14	58
SIMA	121	-	-	-	100	0	100	11	100
ERACI II	450	+	2%	44	-	0	-	17	88
AWESOME	454	+	-	55	-	0	-	-	70
MASS II	408	+	2%	59		0			
ARTS	1205	+	?5%	68	100	0	-	19	93
SOS	988	+	?5%	62	100	0	45	14	81
SUMMARY	8826	5/15	5%	65%	100%	0%	41%	16%	79%

RCT effectively excluded patients who are known to have the greatest benefit from CABG in favour of those who do not. Taggart, ATS 2006

Weight of RCT

- Size: mega vs large vs small
- Relevance
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New designs **“All-Comer” Trials**
Combined RCT & Registry arms

SYNTAX Trial Design

62 EU Sites + 23 US Sites

Heart Team (surgeon & interventional cardiologist)

Amenable for both treatment options

Amenable for only one treatment approach

Stratification: LM and Diabetes

Randomized Arms *N=1800*

Two Registry Arms *N=1275*

CABG n=897 *vs* TAXUS* n=903

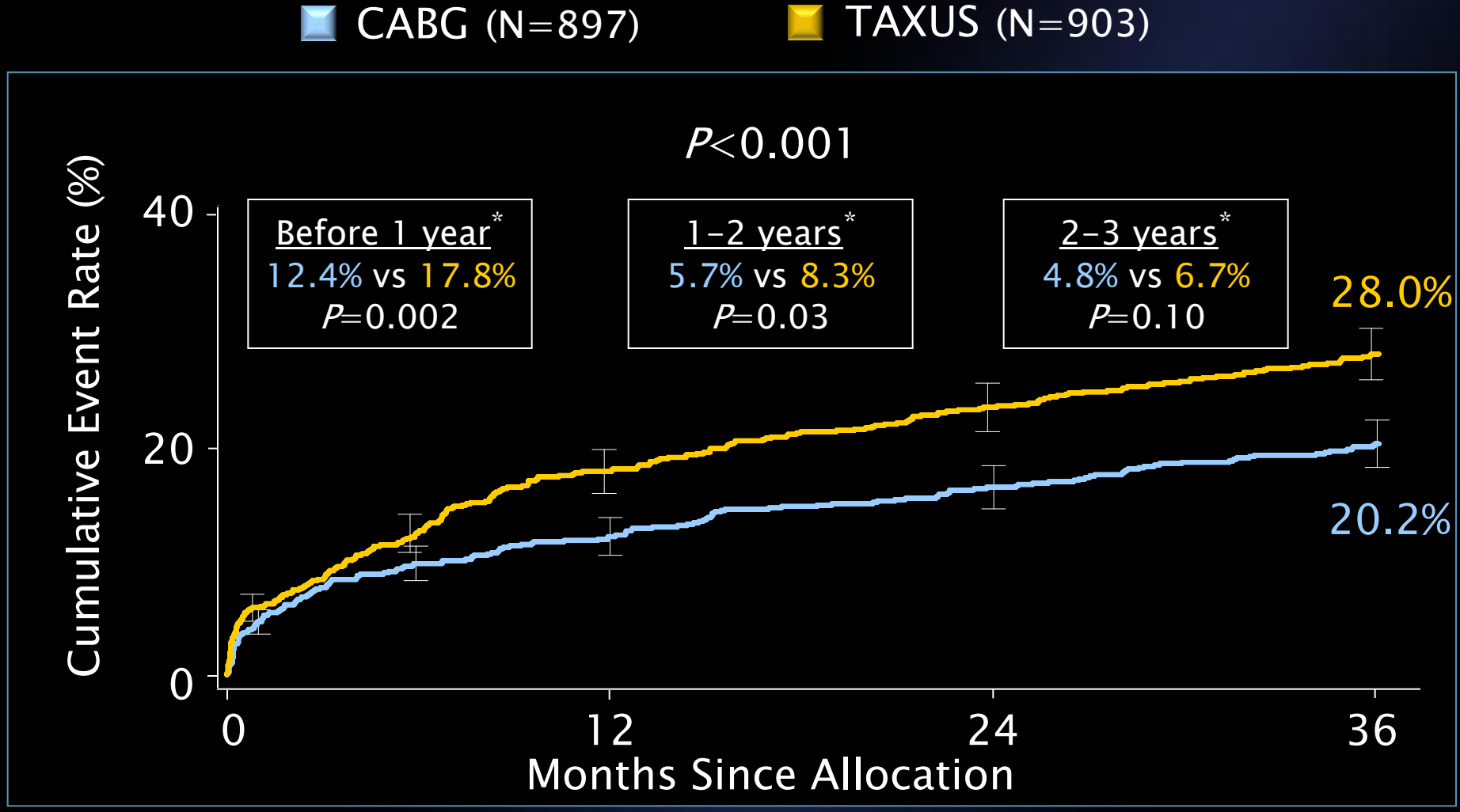
CABG n=1077

PCI n=198

3VD	LM	3VD	LM
n=549 (66.3%)	n=348 (33.7%)	n=546 (65.4%)	n=357 (34.6%)

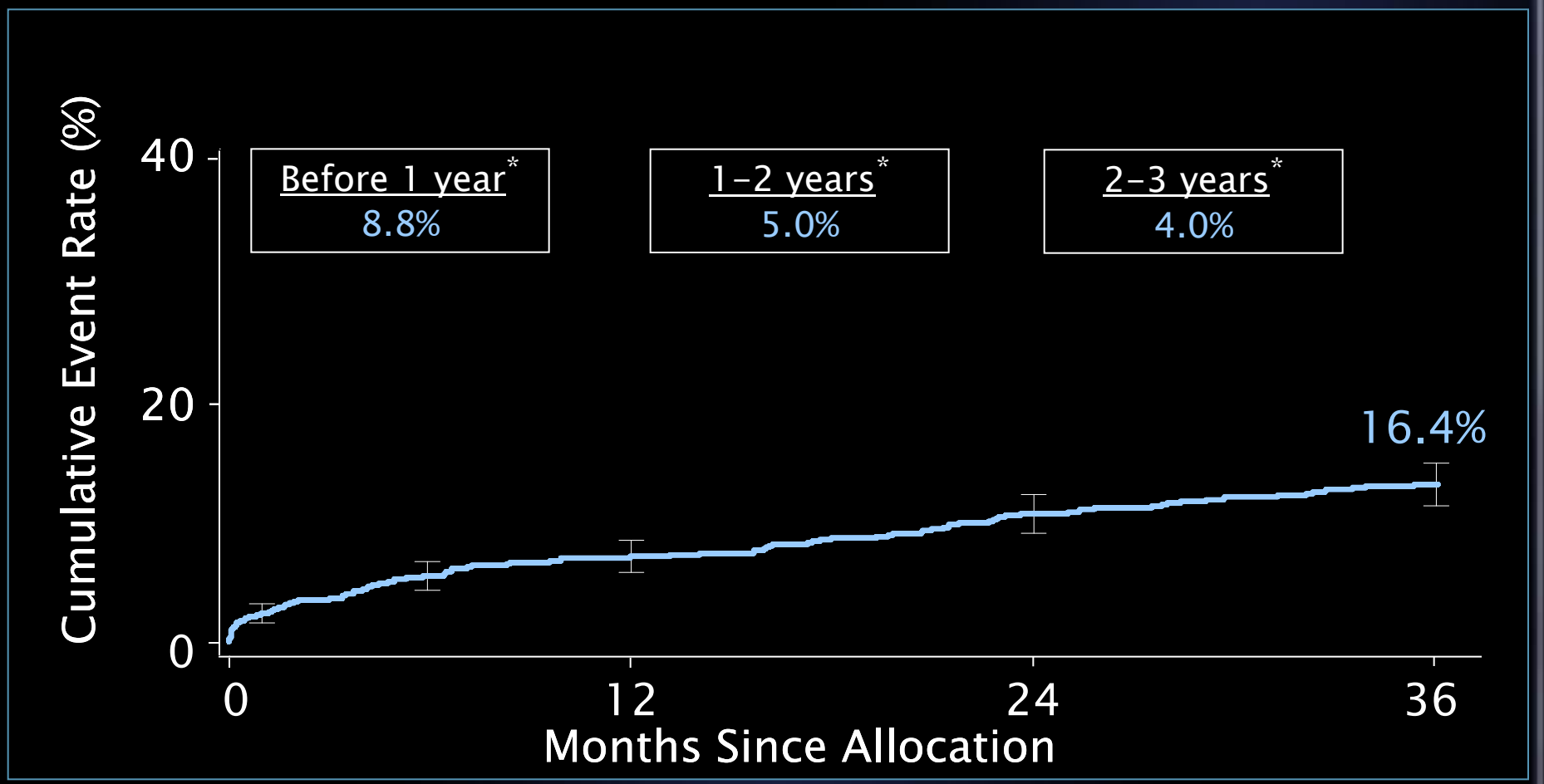
*TAXUS Express

MACCE to 3 Years



Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value;*Binary rates

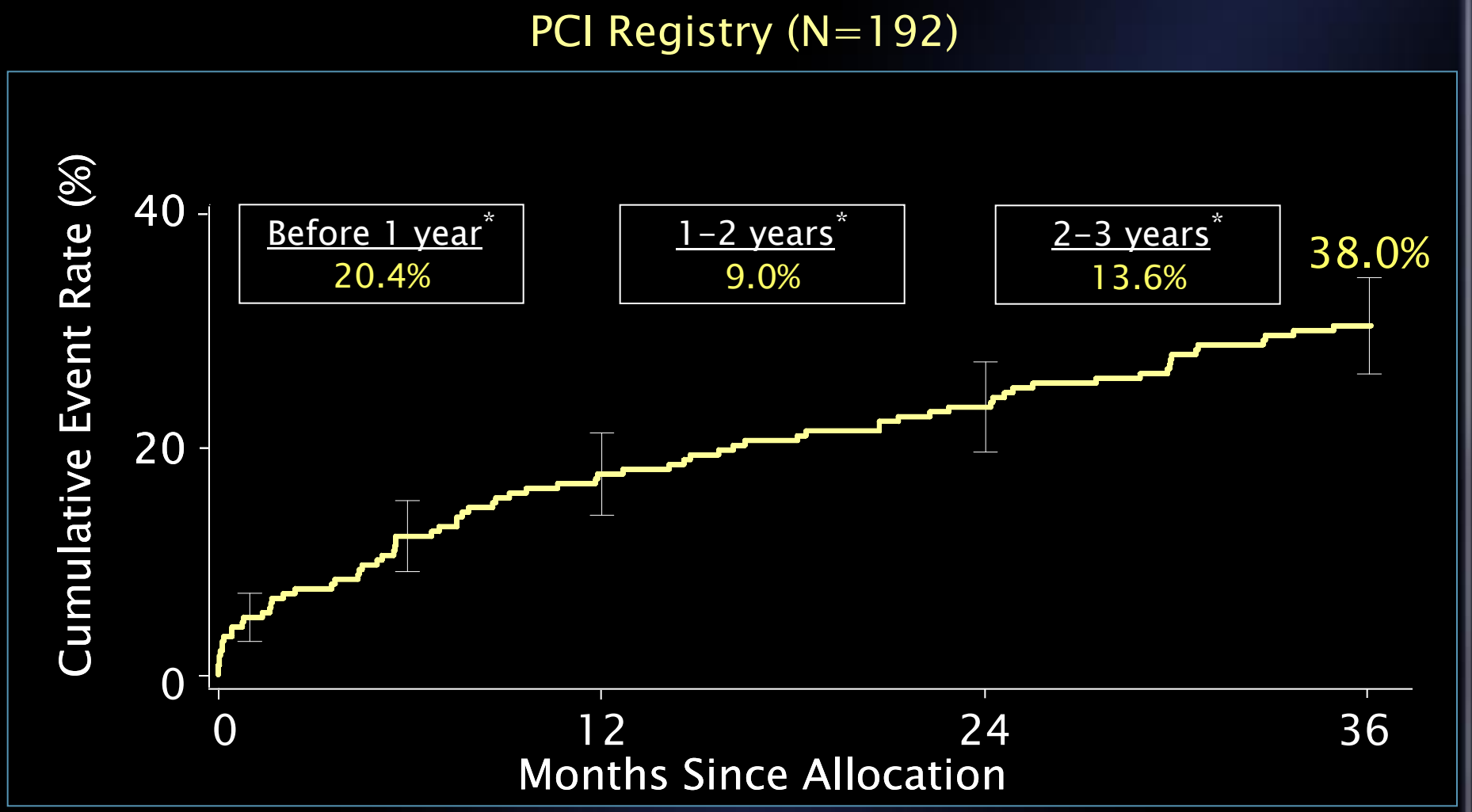
MACCE to 3 Years
SYNTAX CABG Registry



Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Calculated by core laboratory; ITT population

MACCE to 3 Years
SYNTAX PCI Registry



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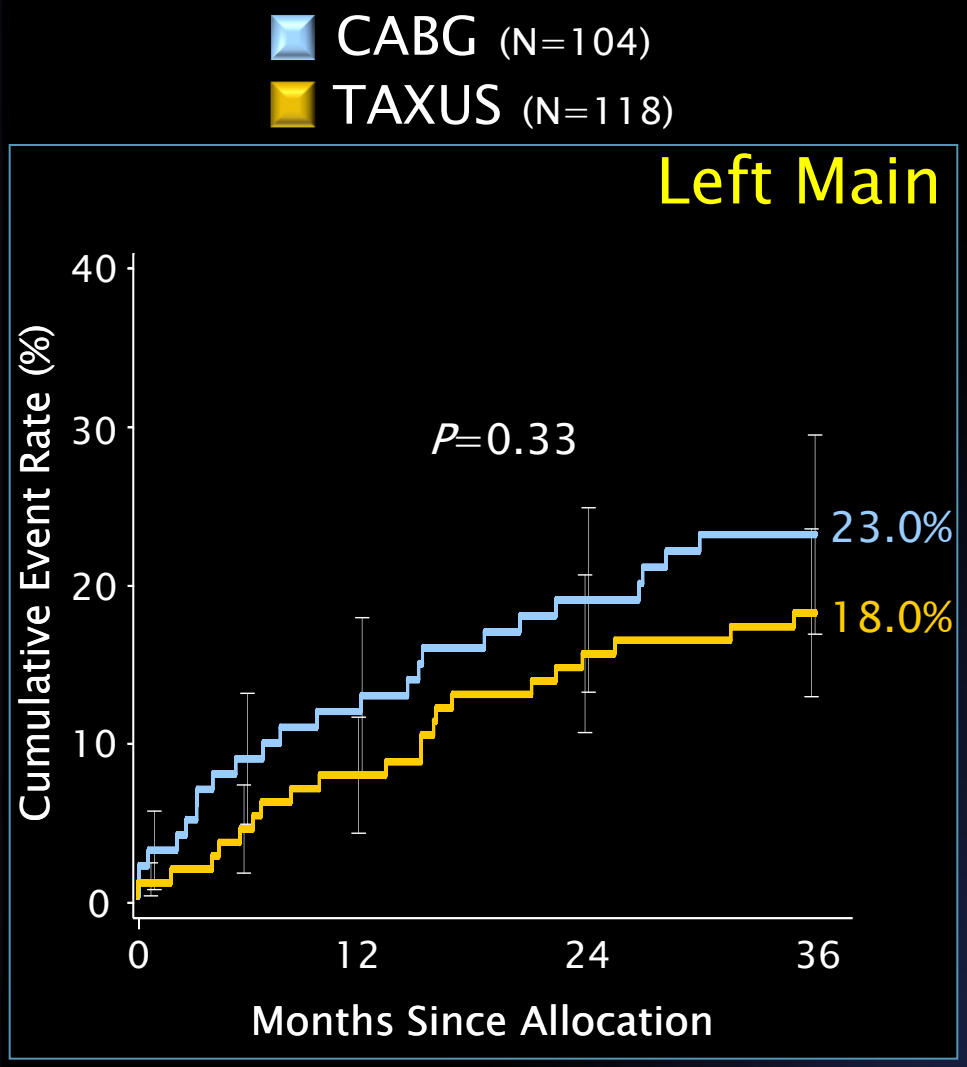
New Analyses "Delphi" Method

MACCE to 3 Years by SYNTAX Score Tercile *Low Scores (0–22)*

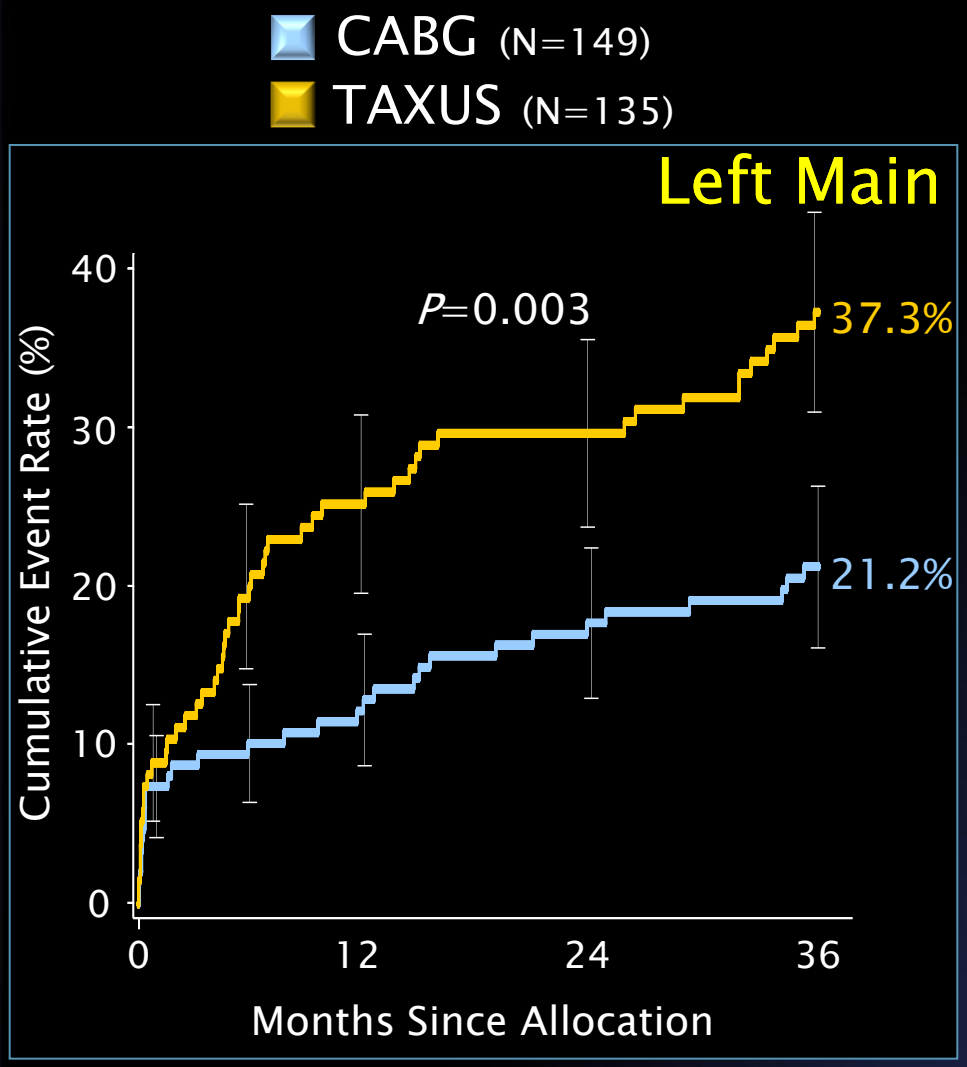


	CABG		PCI	*P* value
Death	6.0%	>	2.6%	0.21
CVA	4.1%	>	0.9%	0.12
MI	2.0%	<	4.3%	0.36
Death, CVA or MI	11.0%	>	6.9%	0.26
Revasc.	13.4%	<	15.4%	0.69

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

MACCE to 3 Years by SYNTAX Score Tercile *Left Main SYNTAX Score ≥33*



	CABG		PCI	*P* value
Death	7.6%	<	13.4%	0.10
CVA	4.9%	>	1.6%	0.13
MI	6.1%	<	10.9%	0.18
Death, CVA or MI	15.7%	<	20.1%	0.34
Revasc.	9.2%	<	27.7%	<0.001

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Site-reported Data; ITT population

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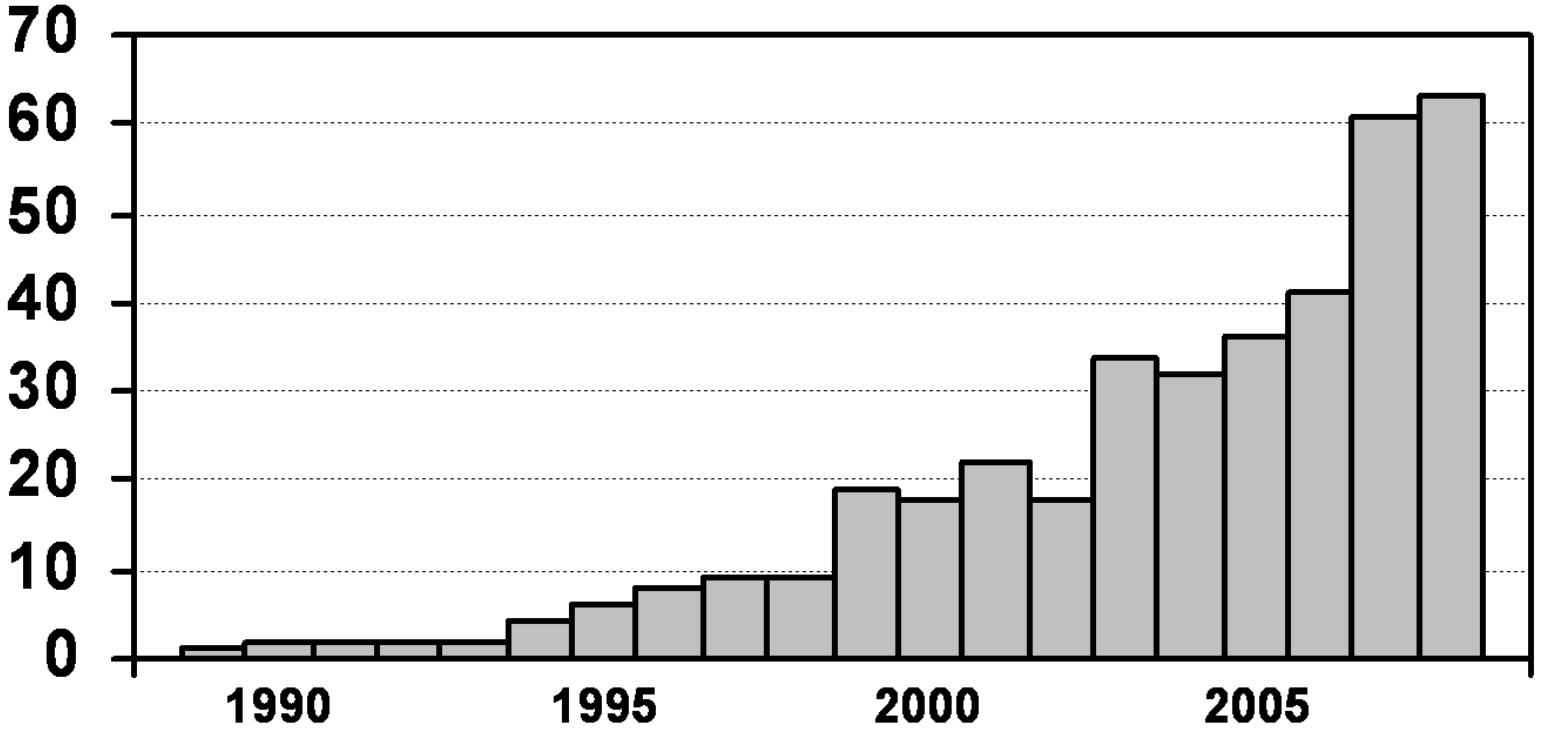
Meta-analyses



On the current epidemic outburst of meta-analytic rage in interventional cardiology.

Agostoni, Ribichini, Wijns. EuroIntervention 2009;5:1.

Specific PCI devices and pharmacotherapy

	Class	Level
Manual catheter thrombus aspiration should be considered during PCI of the culprit lesion in STEMI.	IIa	A
For PCI of unstable lesions, intravenous abciximab should be considered for pharmacological treatment of no-reflow.	IIa	B
Drug-eluting balloons* should be considered for the treatment of in-stent restenosis after prior BMS.	IIa	B

Based on registries, 1 positive RCT and meta-analyses

BUT

the TAPAS RCT is single-center, not powered for differences in mortality (n=1.071), there was no reduction in peak CK and aspirationwas performed in 84% of cases

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Antithrombotic treatment options in myocardial revascularisation

NSTE-ACS			
Antiplatelet therapy		**Class**	**Level**
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9-12 months after PCI)	I	B
	Prasugrel	IIa	B
	Ticagrelor	I	B
	+ GPIIb-IIIa antagonists (in high-risk patients with elevated Troponin)		
	Abciximab (with DAPT)	I	B
	Tirofiban, Eptifibatide	IIa	B
	Upstream GPIIb-IIIa antagonists	III	B

Depending on drug approval and availability.

Antithrombotic treatment options in myocardial revascularisation

NSTE-ACS			
Anticoagulation		**Class**	**Level**
very high-risk of ischaemia	UFH (+ GPIIb-IIIa antagonists)	I	C
	Bivalirudin (monotherapy)	I	B
medium-to-high-risk of ischaemia	UFH	I	C
	Bivalirudin	I	B
	Fondaparinux	I	B
	Enoxaparin	IIa	B
low-risk of ischaemia	Fondaparinux	I	B
	Enoxaparin	IIa	B

Antithrombotic treatment options in myocardial revascularisation

STEMI			
Anticoagulation		**Class**	**Level**
	Bivalirudin (monotherapy)	I	B
	UFH	I	C
	Fondaparinux	III	B

Antithrombotic treatment options in myocardial revascularisation

STEMI			
Antiplatelet therapy		**Class**	**Level**
	ASA	I	B
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel	I	B
	Ticagrelor	I	B
	+ GPIIb-IIIa antagonists (in patients with evidence of high intracoronary thrombus burden)		
	Abciximab	IIa	A
	Eptifibatide	IIa	B
	Tirofiban	IIb	B
	Upstream GPIIb-IIIa antagonists	III	B

Depending on drug approval and availability.

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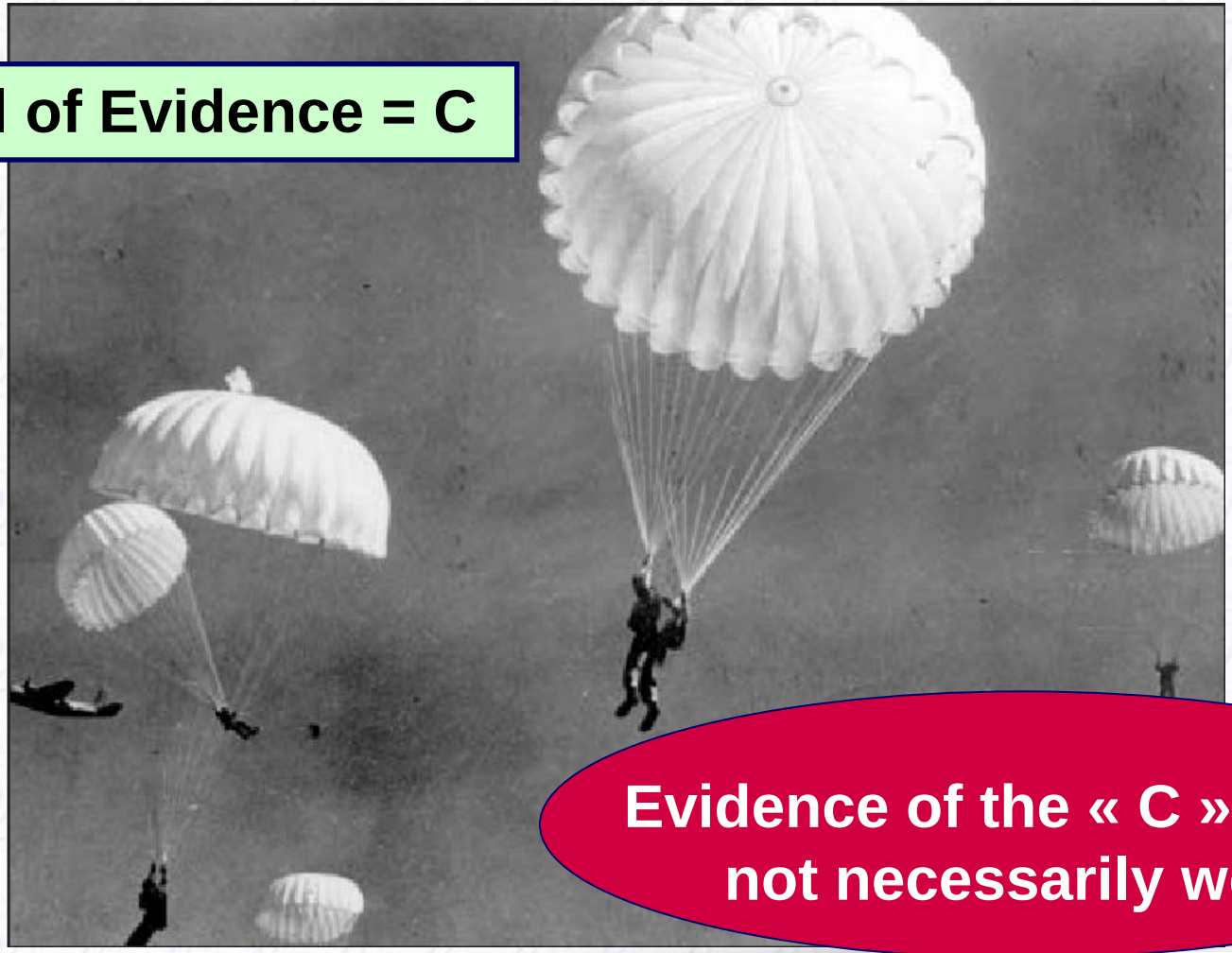
Out of 190 recommendations, 85 (44.7%) are LOE « C »

and *may* represent gaps in knowledge

Parachutes appear to reduce the risk of injury but ...
their effectiveness has not been proved with randomised controlled trials

Level of Evidence = C



Evidence of the « C » level is not necessarily weak!

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