Session 3 – Managing uncertainty in the post-launch phase

Piotr Szymanski
Associate Professor of Cardiology
European Society of Cardiology

Managing uncertainty in post-launch phase – key points

1. Evidence generation timeline
2. Uncertanity of evidence
3. Managing uncertainty

Managing uncertainty in post-launch phase – key points

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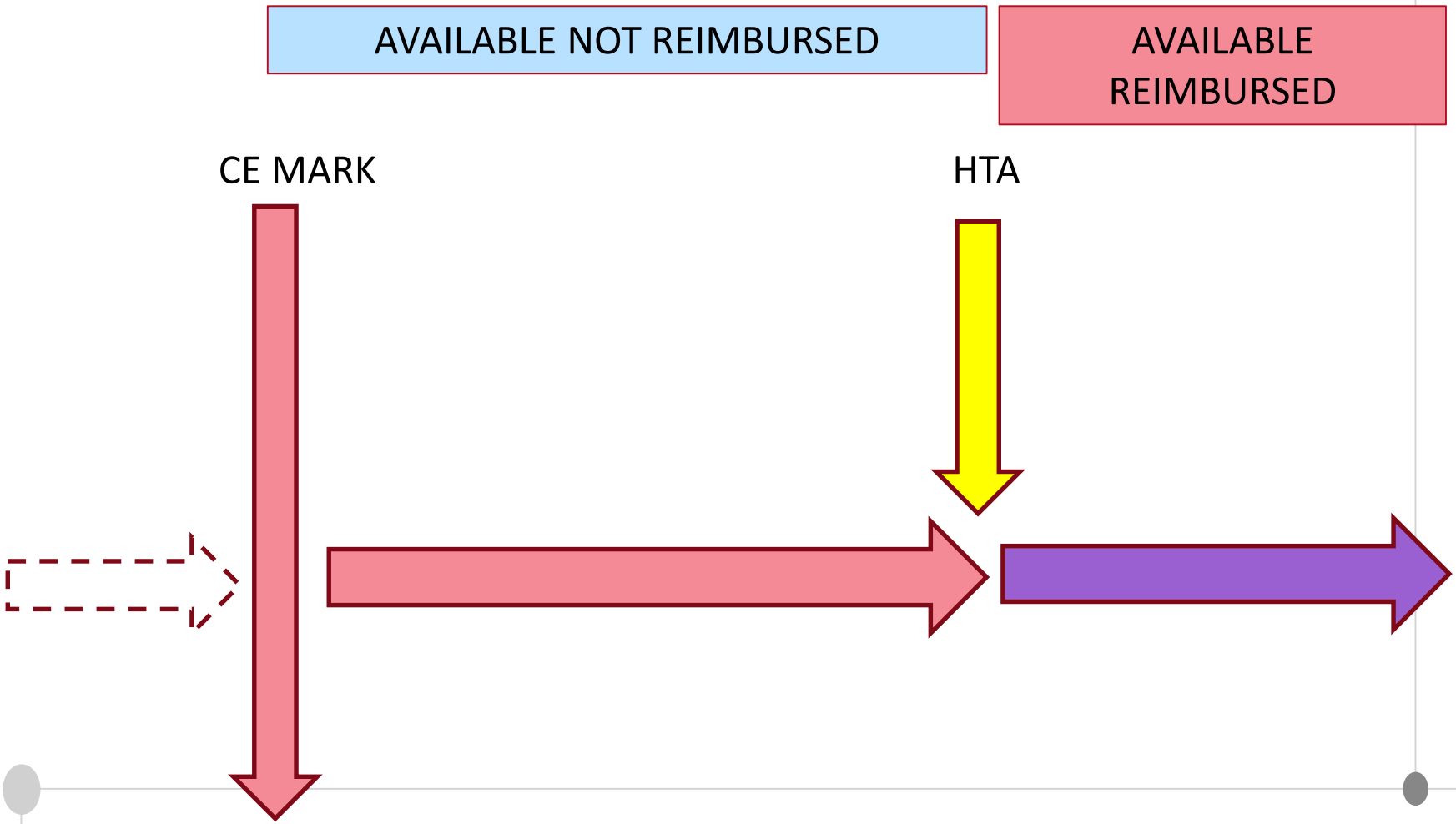
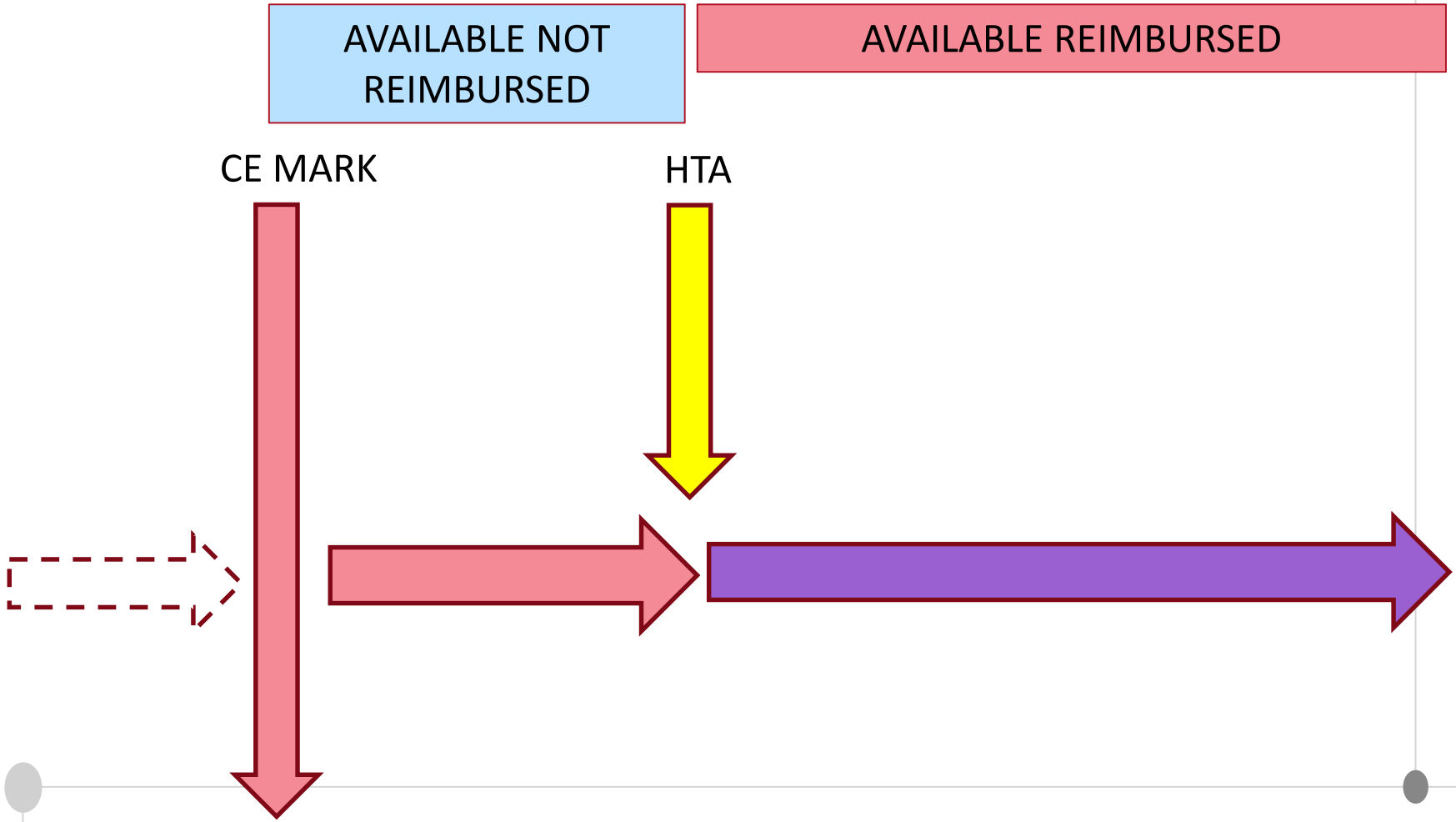
1. Evidence generation timeline
2. Uncertainty of evidence
3. Managing uncertainty

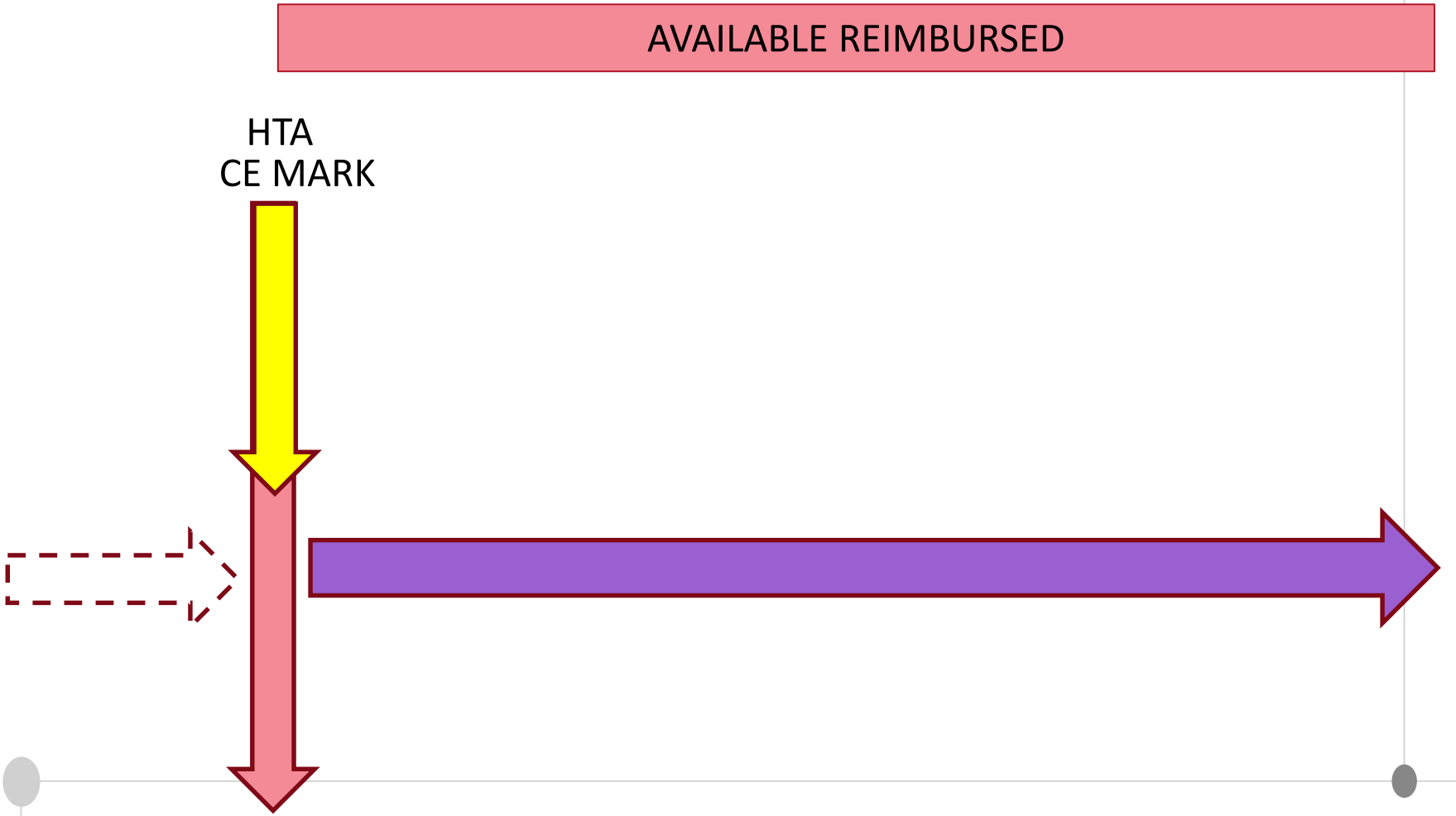
Launch of technology



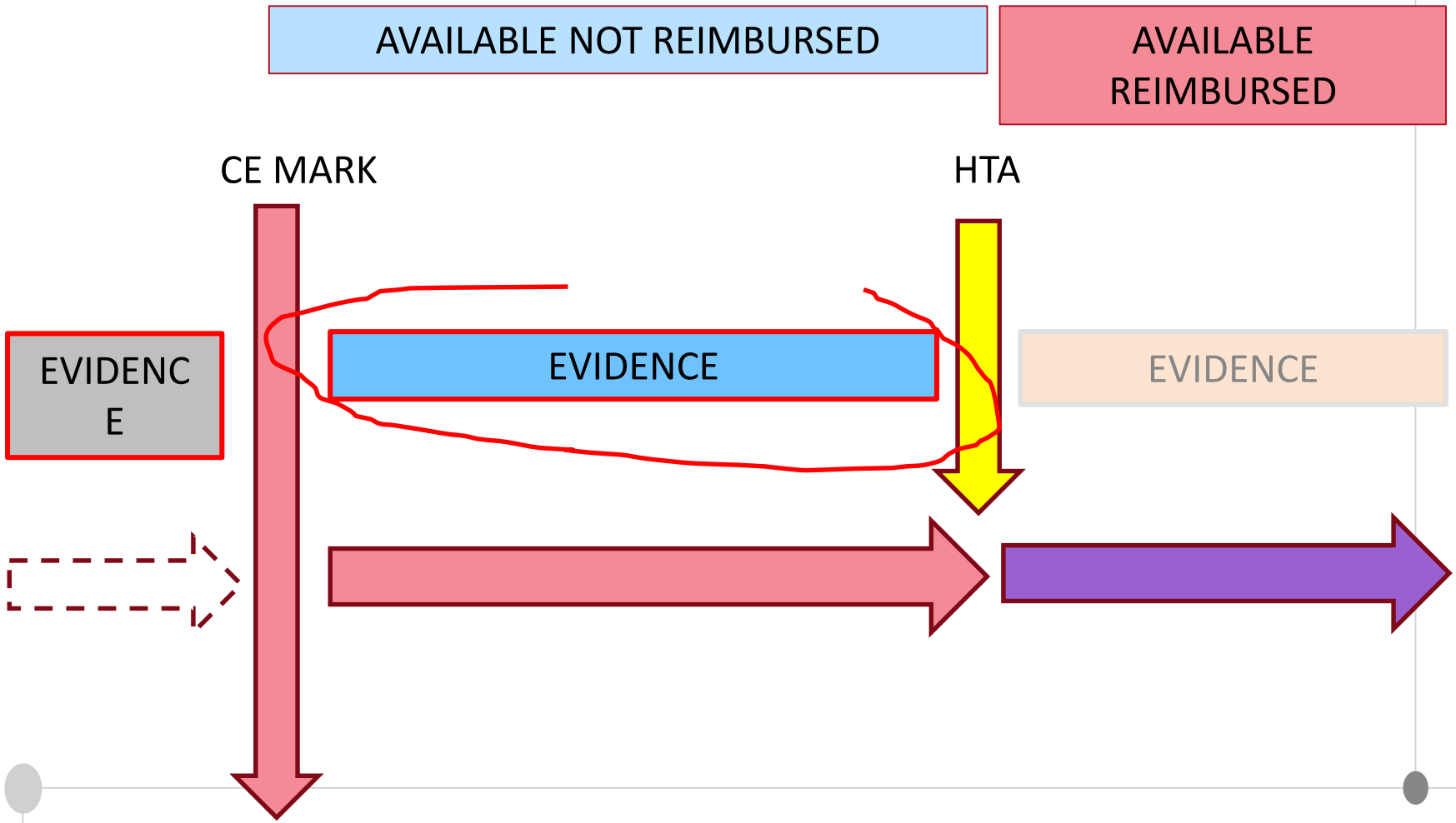
Launch of technology



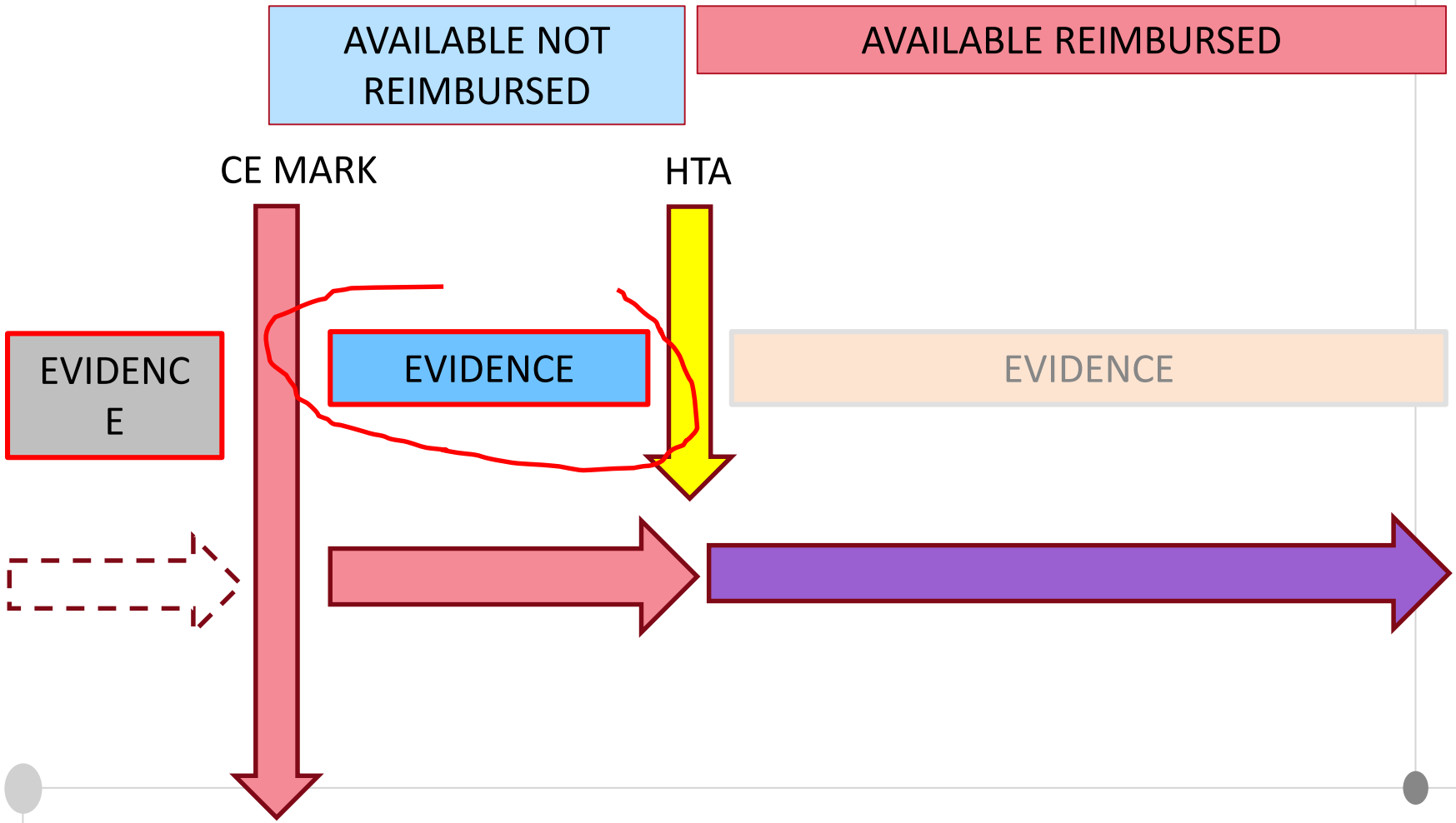
Launch of technology



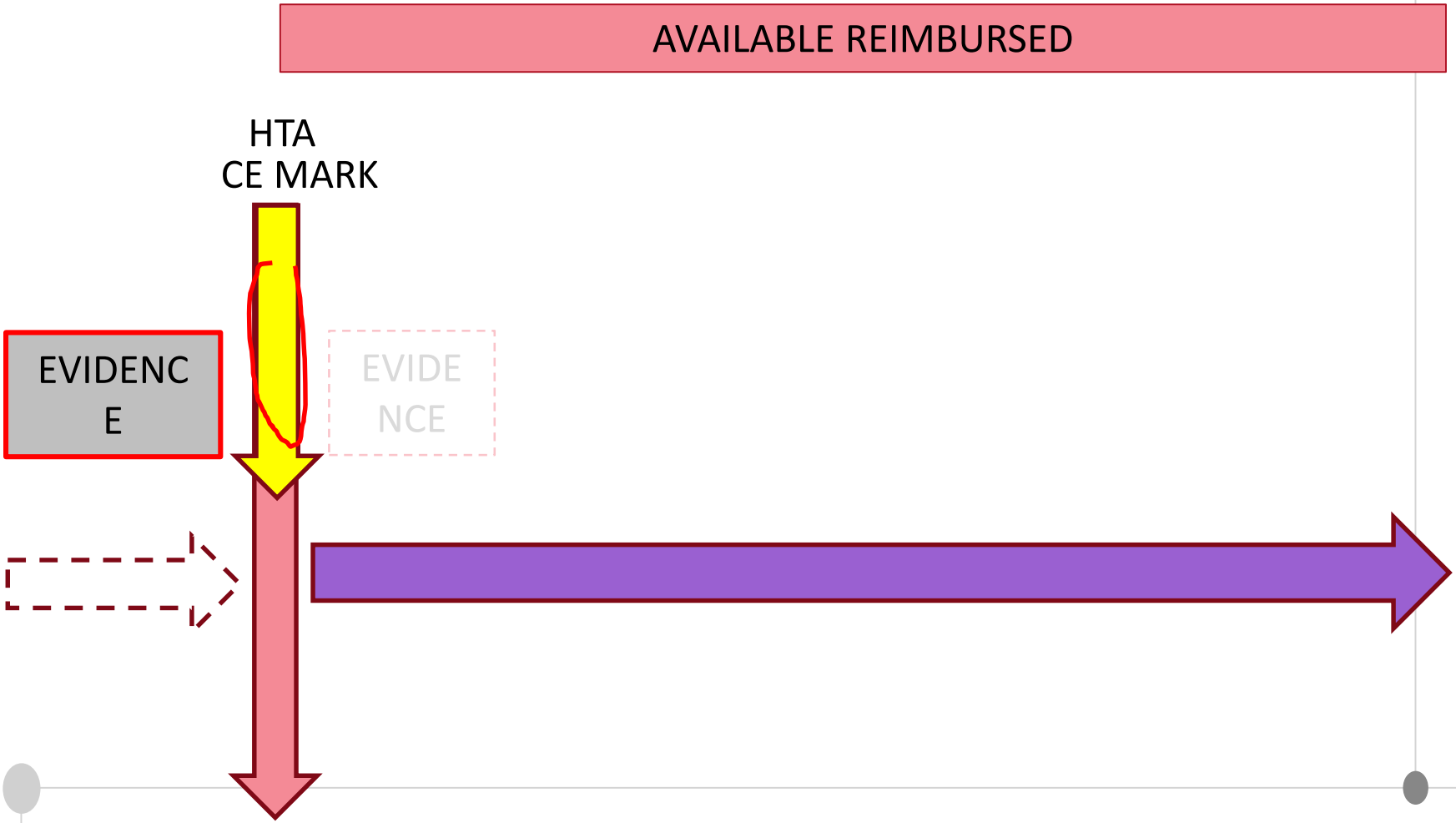
Evidence generation



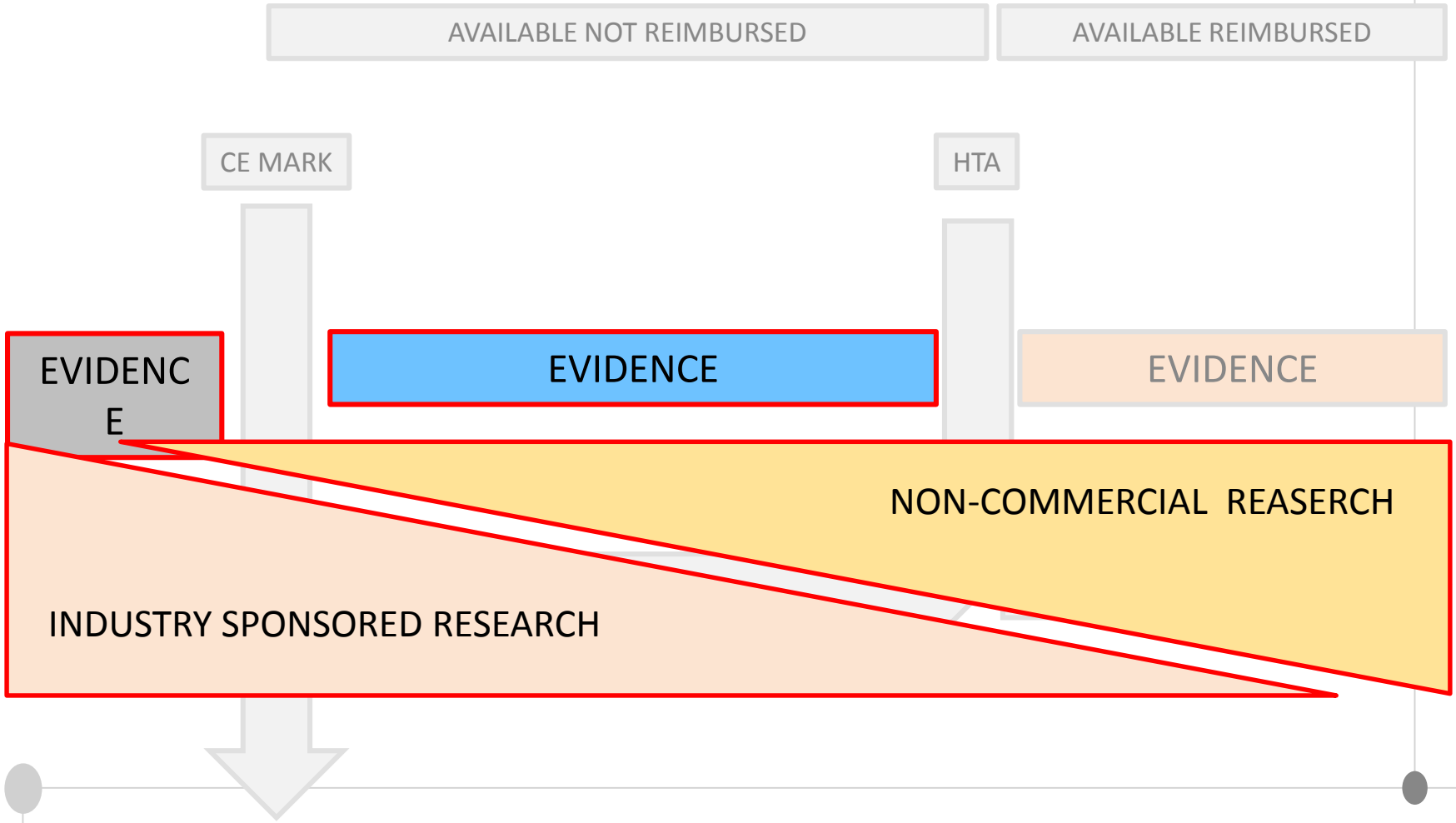
Evidence generation



Evidence generation



Evidence generation timeline vs source



Source of evidence

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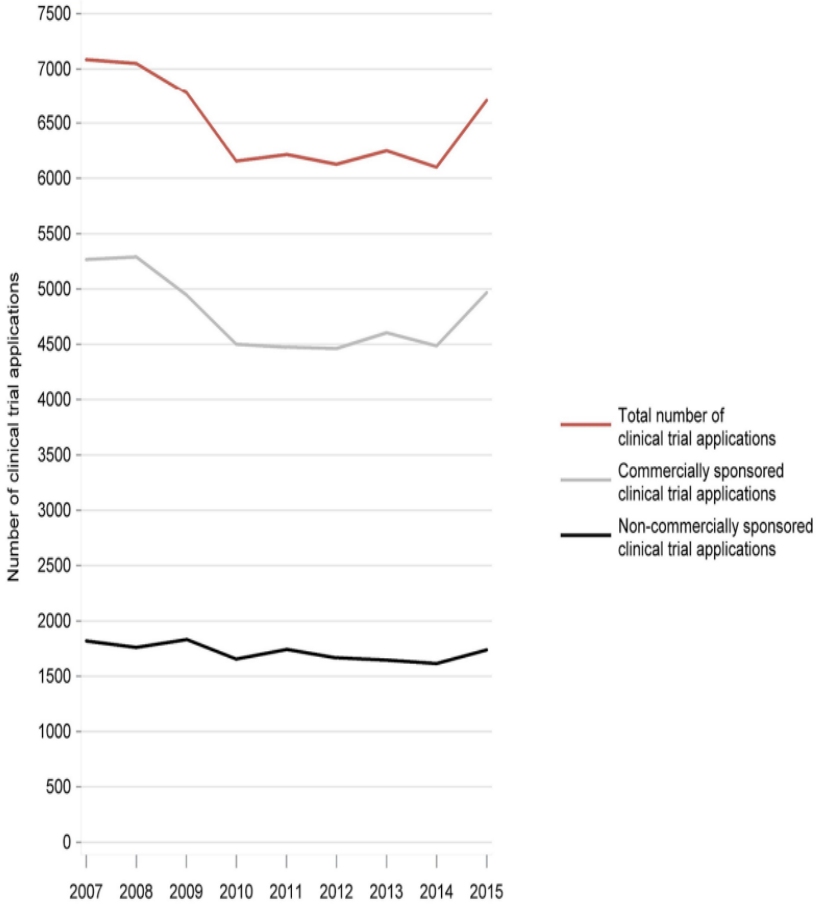

1/3
of clinical trials
non-commercial

BMJ Open

Development in the number of clinical trial applications in Western Europe from 2007 to 2015: retrospective study of data from national competent authorities

Tilde Dombernowsky,[1] Merete Hædersdal,[1] Ulrik Lassen,[2]

Managing uncertainty in post-launch phase – key points

1. Evidence generation
2. Uncertainty of evidence
3. Managing uncertainty

Evidence pyramid

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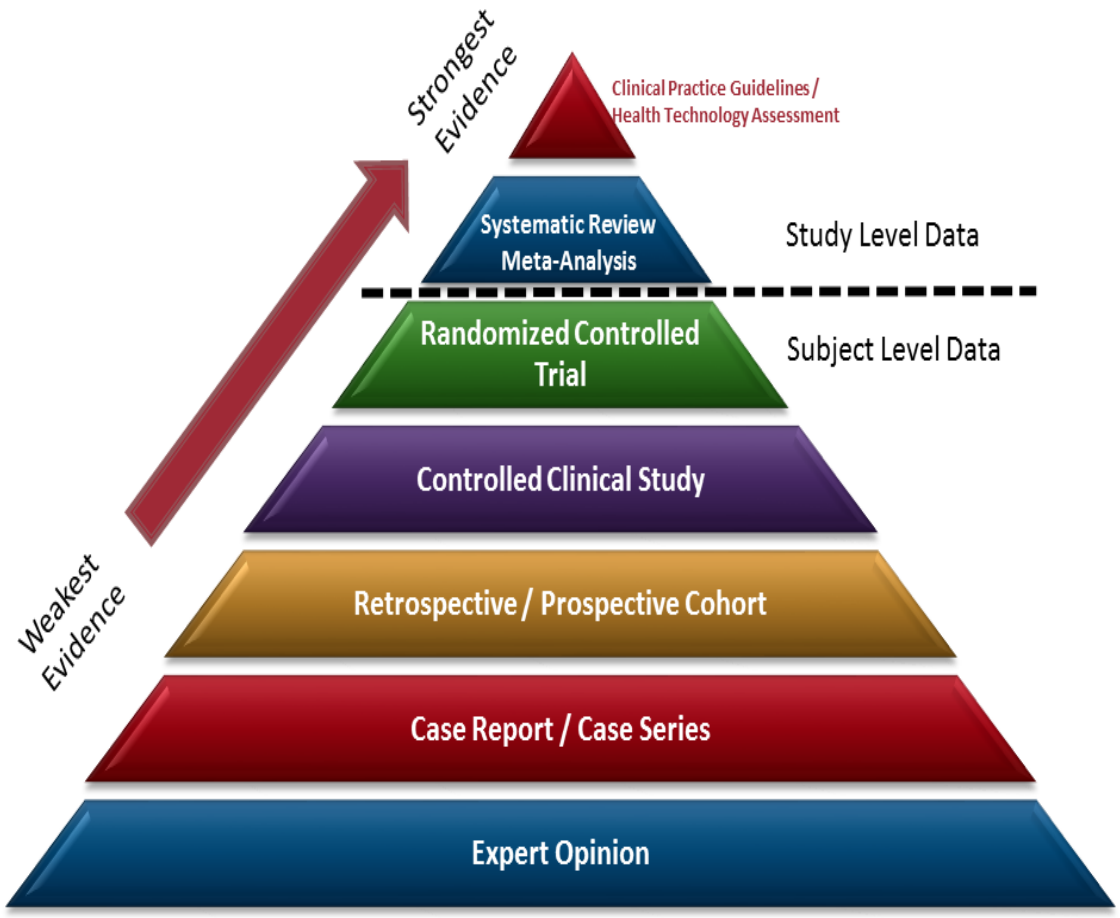

Evidence pyramid

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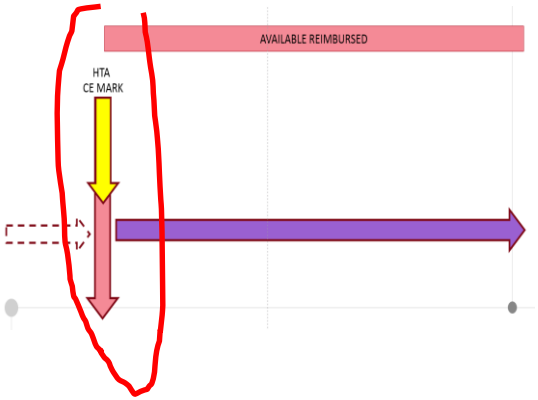

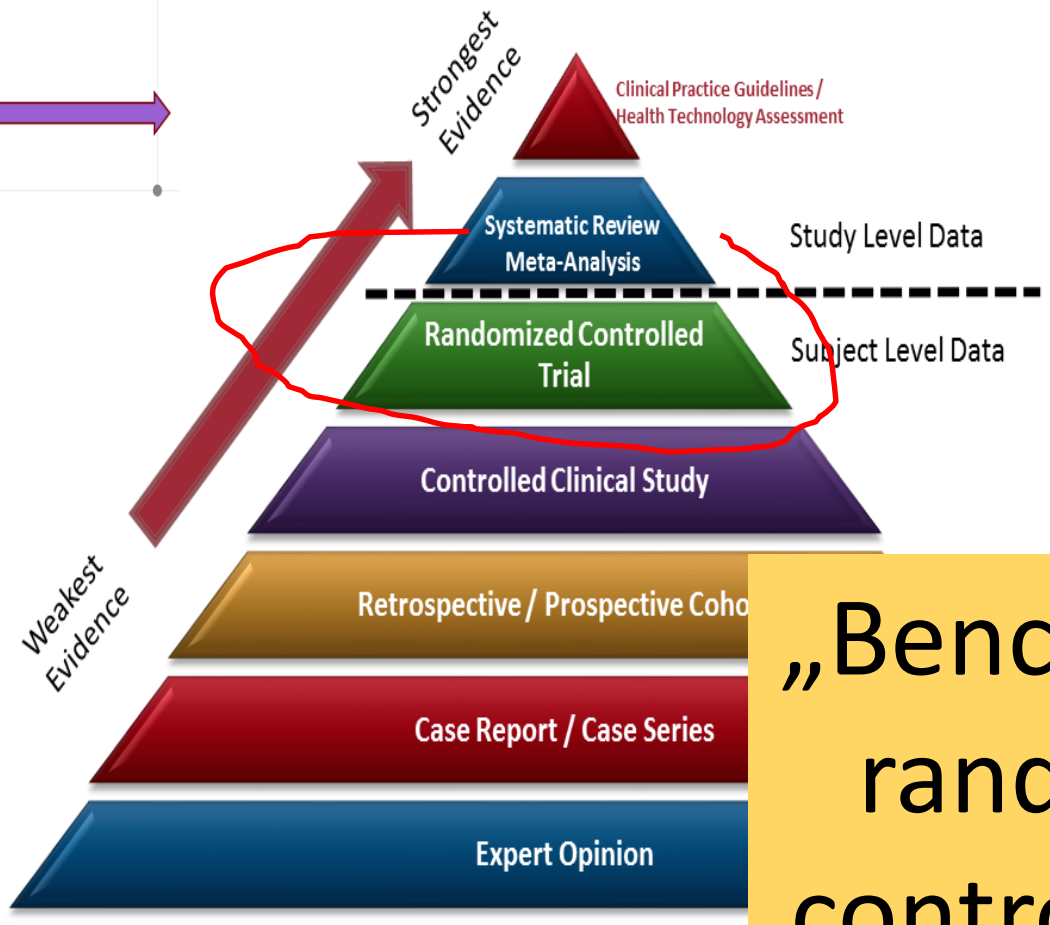

„Benchmark" – randomized controlled trial

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JAMA. 2014 Jan 22-29;311(4):368-77

Quality of Evidence

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Original Investigation

Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012

Nicholas S. Downing, AB; Jenerius A. Aminawung, MD, MPH; Nilay D. Shah, PhD; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

Table 2. Design of Pivotal Efficacy Trials Providing the Basis for Approval of Novel Therapeutic Agents by the US Food and Drug Administration Between 2005 and 2012, Stratified by Therapeutic Agent and Indication Characteristics

	No. (%) [95% CI]							
			Comparator			End Point		
Agent/Indication Characteristic (Pivotal Trials)	Randomized	Double-Blinded	Active	Placebo	None	Surrogate Outcome	Clinical Outcome	Clinical Scale
All (N = 448)	400 (89.3) [86.4-92.2]	356 (79.5) [75.7-83.2]	143 (31.9) [27.6-36.3]	247 (55.1) [50.5-59.8]	58 (12.9) [9.8-16.1]	219 (48.9) [44.2-53.5]	130 (29.0) [24.8-33.2]	99 (22.1) [18.2-26.0]
Therapeutic area								
Cancer (n = 55)	26 (47.3) [33.7-60.9]	15 (27.3) [15.1-39.4]	10 (18.2) [7.7-28.7]	16 (29.1) [16.7-41.5]	29 (52.7) [39.1-66.3]	46 (83.6) [73.5-93.7]	9 (16.4) [6.3-26.5]	0
Infectious disease (n = 57)	53 (93.0) [86.1-99.8]	45 (78.9) [68.0-89.9]	39 (68.4) [56.0-80.9]	13 (22.8) [11.6-34.0]	5 (8.8) [1.2-16.3]	33 (57.9) [44.7-71.1]	24 (42.1) [28.9-55.3]	0
Cardiovascular disease, diabetes mellitus, hyperlipidemia (n = 73)	72 (98.6) [95.9-100.0]	68 (93.2) [87.2-99.1]	26 (35.6) [24.4-46.9]	45 (61.6) [50.2-73.1]	2 (2.7) [0.0-6.6]	62 (84.9) [76.5-93.3]	11 (15.1) [6.7-23.5]	0

Quality of Evidence

ESC European Society of Cardiology

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Therapeutic area								
Cancer (n = 55)	26 (47.3) [33.7-60.9]	[1						
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Cardiovascular dise…, diabetes mellitus, hyperlipidemia (n = 73)	[95.9-100.0]	[87.2-99.1]						

Randomized trials in 9/10 cases (in cancer - 5/10 cases)

JAMA. …4;311:368-77

Quality of Evidence

ESC European Society of Cardiology

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			Comparator				
	Randomized	Double-Blinded	Active	Placebo		Surrogate Outcome	Clinical Scale
All (N = 448)	400 (89.3) [86.4-92.2]	356 (79.5) [75.7-83.2]	143 (31.9) [27.6-36.3]	247 (55.1) [50.5-59.8]	[	219 (48.9) [44.2-53.5]	99 (22.1) [18.2-26.0]
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Cardiovascular (diabetes mellitu hyperlipidemia (							

Surrogate outcomes in ½ of trials

2014;311:368-77

Quality of Evidence

ESC European Society of Cardiology

Original Investigation

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Table 3. Exposure to Novel Thera… During Pivotal Efficacy Trials That Provided the Basis fo…

Agent/Indication Characteristic (Pivotal Trials)	…erall Patients, Median (IQR)	Intervention Group	Duration Median (IQR), wk[a]	Duration ≥6	Overall Completion Rate, Median (IQR)
All trials (N = 448)	…5-678)	271 (133-426)	14.0 (6.0-26.0)	1… [2…	86.6 (77.9-93.1)
Therapeutic area					
					…(75.0-91.3)
					…(87.1-96.0)
					…(76.8-92.4)

Populations studied and duration of treatment are disproportionately small

JAMA. …14;311:368-77

Quality of Evidence – Medical Devices

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Characteristics of Clinical Studies Used for US Food and Drug Administration Approval of High-Risk Medical Device Supplements

Sarah Y. Zheng, MD; Sanket S. Dhruva, MD, MHS; Rita F. Redberg, MD, MSc

Table 2. Characteristics and Strength of Clinical Studies Supporting Premarket Approval Panel-Track Supplements

Characteristic	Value	Studies for Which Data Were Available, No. (%) (n = 83)
Study strength		
Randomized studies, No. (%)	37 (45)	
Blinded studies, No. (%)	25 (30)	
Single blinded	16 (19)	
Double blinded	9 (11)	
Studies stating No. of sites, No. (%)	74 (89)	
Single center	1 (1)	
Multicenter	73 (99)	
in age reporting, No. (%)		

JAMA Network

JAMA. 2017;318(7):6
625

Quality of Evidence – Medical Devices

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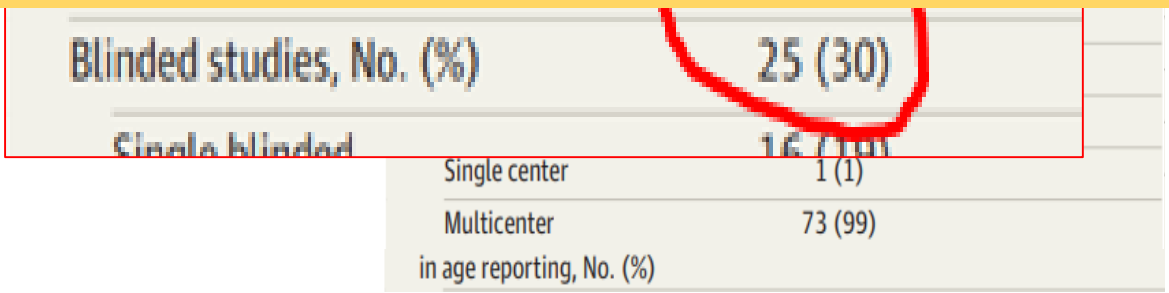
Characteristics of Clinical Studies Used for US Food and Drug Administration Approval

less than half of clinical studies submitted for approval of high-risk medical devices were randomized



Blinded studies, No. (%)	25 (30)
Single blinded	16 (19)
Single center	1 (1)
Multicenter	73 (99)
in age reporting, No. (%)	

JAMA Network

JAMA. 2017;318(7):6
625

Evidence available at technology approval

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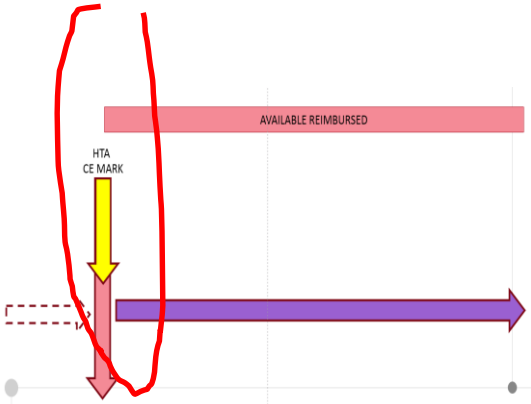

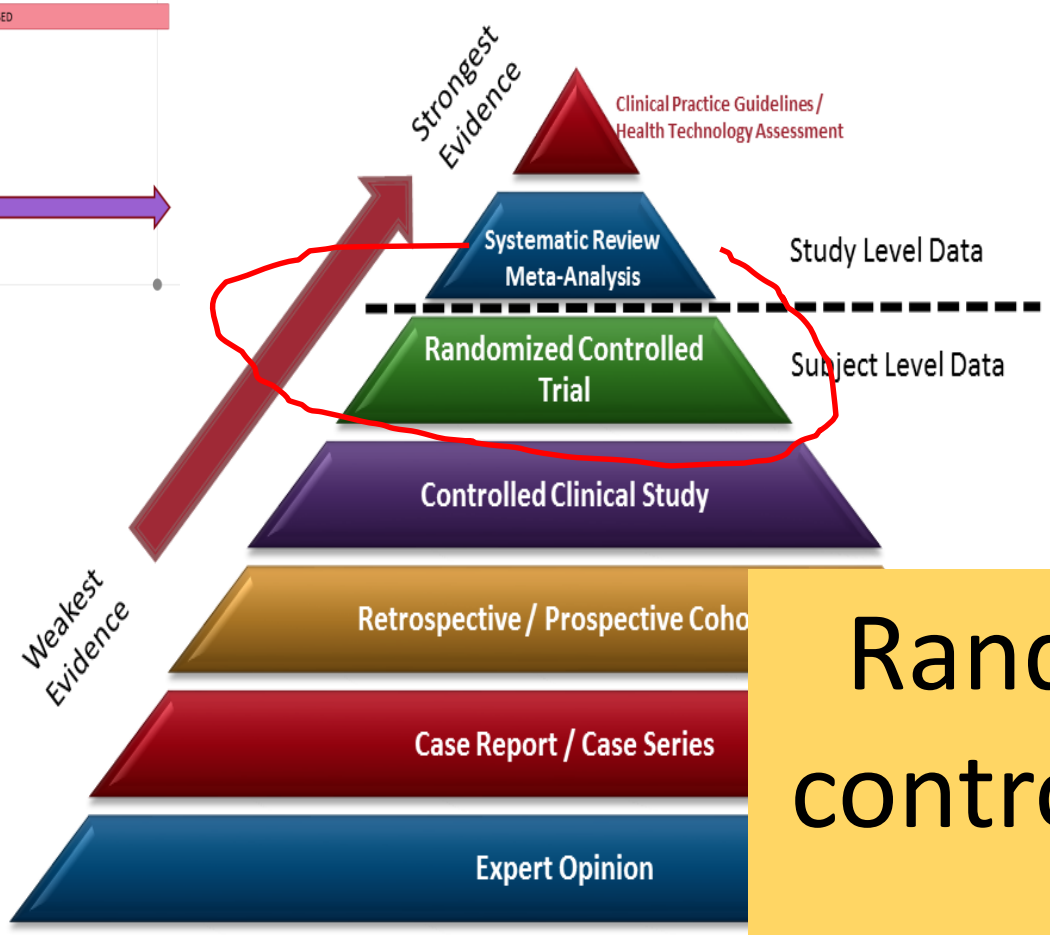

Randomized controlled trial is a

Quality of Evidence

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Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Randomized controlled trial is a „benchmark”
– but may be false

Quality of Evider

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

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Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

power	True/not true	bias	example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85

Even with good quality RCT, due to issues related to power, bias, pre-test probability, the proportion of true to false results is

PLoS Med. 2005;2:e124.

Quality of Evider

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

ESC European Society of Cardiology

Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

pow er	True/not true	bias	example	PPV
		0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
		0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
		0.40	Meta-analysis of small inconclusive studies	0.41
0.20		)	Underpowered, but well-performed phase I/II RCT	0.23
			epidemiological study	

True/not true

In case of underpowered RCT the risk rises 5-fold

PLoS Med. 2005;2:e124.

Quality of Evidence

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of Cardiology

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

ORIGINAL CONTRIBUTION

Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature were examined.

Main Outcome Measure The results of highly cited articles were compared against subsequent studies of comparable or larger sample size and similar or better controlled designs. The same analysis was also performed comparatively for matched studies that were not so highly cited.

Results Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly-cited nonrandomized studies had been contradicted or had found stronger effects vs 9 of 39 randomized controlled trials ($P = .008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($P = .009$) than replicated or unchallenged studies although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than highly cited studies, but they included more studies with "negative" results.

Conclusions Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes. The extent to which high citations may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones.

JAMA. 2005;294:218-228 www.jama.com

JAMA. 2005;294:2

Quality of Evidence

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of Cardiology

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Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000

Results

vention
ers (16%
(44%) w

1/4 of 49 highly cited clinical studies remained largely unchallenged by subsequent studies

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JAMA. 2005;294:218-228 www.jama.com

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Quality of evidence and postmarket safety

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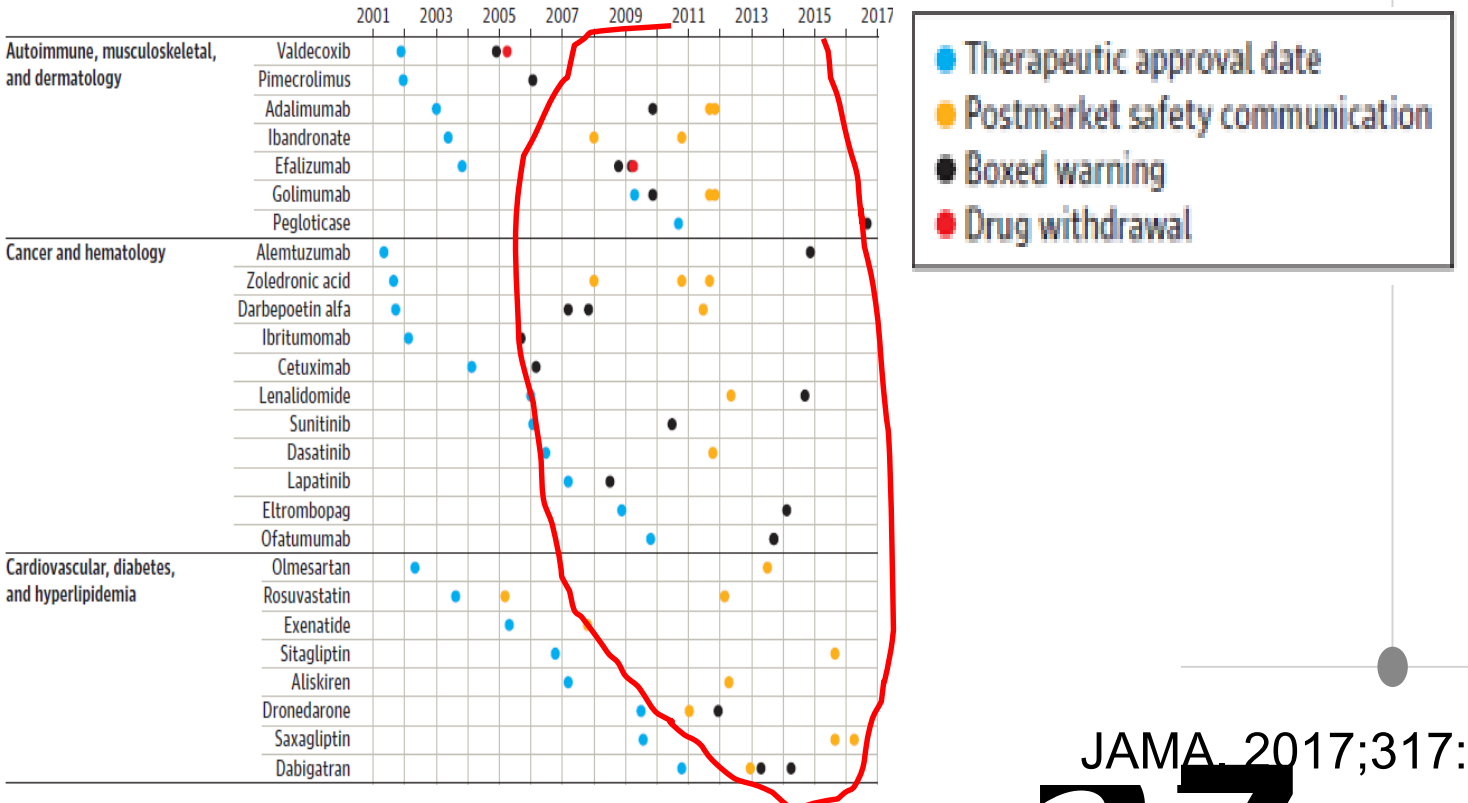
JAMA | Original Investigation

Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

Nicholas S. Downing, MD; Nilay D. Shah, PhD; Jenerius A. Aminawung, MD, MPH; Alison M. Pease, BS; Jean-David Zeitoun, MD, MHPM; Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS

Figure 1. Timeline of Novel Therapeutics Approved by the US FDA, 2001-2010, That Experienced Postmarket Safety Events, Grouped by Therapeutic Area



JAMA. 2017;317:185

Quality of evidence and postmarket safety

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JAMA | Original Investigation

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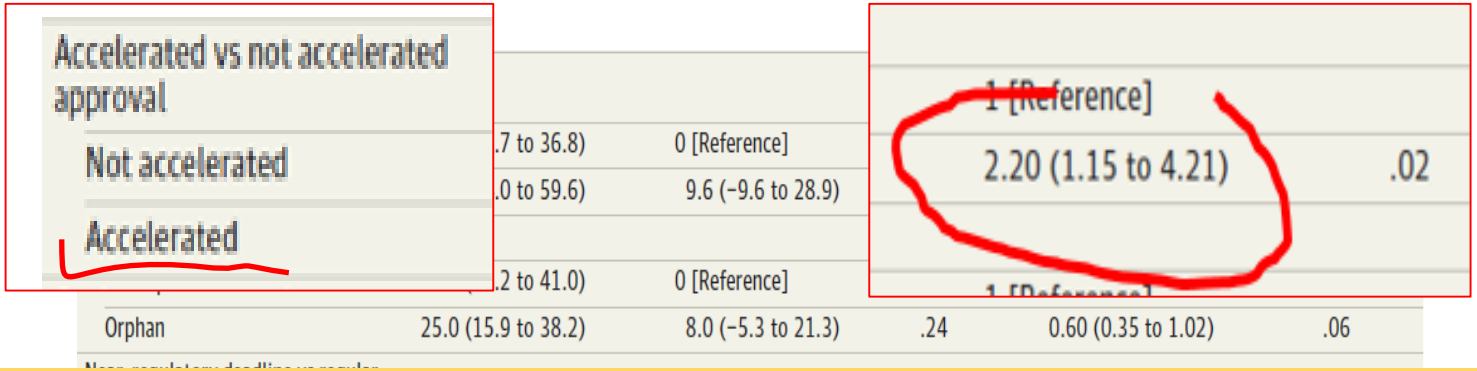
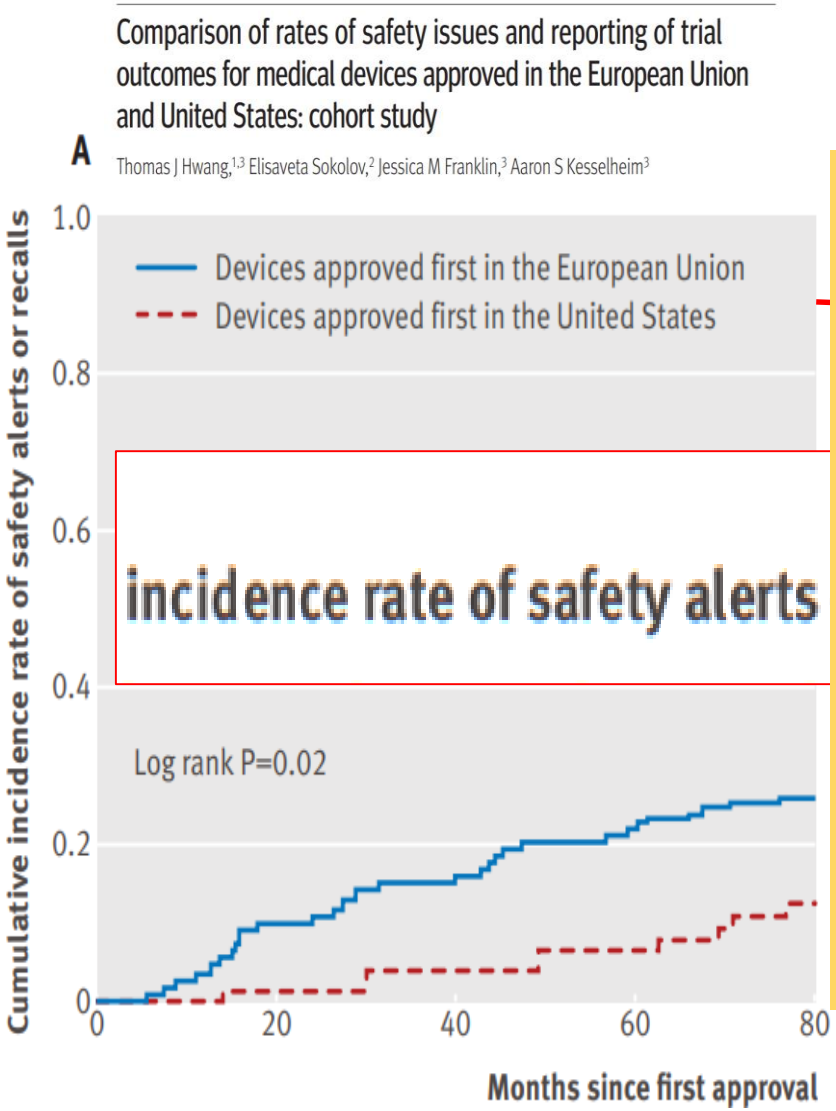


Accelerated vs not accelerated approval					
Not accelerated	.7 to 36.8)	0 [Reference]		1 [Reference]	
	.0 to 59.6)	9.6 (−9.6 to 28.9)		2.20 (1.15 to 4.21)	.02
Accelerated					
	.2 to 41.0)	0 [Reference]		1 [Reference]	
Orphan	25.0 (15.9 to 38.2)	8.0 (−5.3 to 21.3)	.24	0.60 (0.35 to 1.02)	.06

The risk of postmarket safety events is over two-fold higher with accelerated approval

JAMA. 2017;317:185

Quality of evidence and postmarket safety – medical devices



The risk of postmarket safety events was two-fold higher in EU vs US

BMJ. 2016

Missing evidence in the postapproval phase

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Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review

Alison M Pease,[1] Harlan M Krumholz,[2,3,4,5] Nicholas S Downing,[6] Jenerius A Aminawung,[7] Nilay D Shah,[8] Joseph S Ross[3,4,5,7]

ABSTRACT

OBJECTIVE

To characterize the prospective controlled clinical studies for all novel drugs that were initially approved by the Food and Drug Administration on the basis of limited evidence.

DESIGN

Systematic review.

DATA SOURCES

Drugs@FDA database and PubMed.

STUDY INCLUSION

All prospective controlled clinical studies published after approval for all novel drugs initially approved by the FDA between 2005 and 2012 on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease as primary endpoints, or both.

RESULTS

Between 2005 and 2012 the FDA approved 117 novel drugs for 123 indications on the basis of a single pivotal trial, pivotal trials that used surrogate markers of disease, or both (single surrogate trials). We identified 758 published controlled studies over a median of 5.5 years (interquartile range 3.4-8.2) after approval, most of which (554 of 758; 73.1%) were studies for indications approved on the basis of surrogate markers of disease. Most postapproval studies used active comparators—67 of 77 (87.0%) indications approved on the basis of single pivotal surrogate marker trials, and 100 of 127 (78.7%) approvals based on single surrogate trials—and examined surrogate markers of efficacy as primary endpoints—51 of 77 (66.2%), 512 of 554 (92.4%), and 110 of 127 (86.6%), respectively. Overall, no postapproval studies were identified for 43 of the 123 (35.0%) approved indications. The median total number of postapproval studies identified was 1 (interquartile range 0-2) for indications approved on the basis of a single pivotal trial, 3 (1-8) for indications approved on the basis of pivotal trials that used surrogate markers of disease as primary endpoints, and 1 (0-2) for single surrogate trial approvals, and the median aggregate number of patients enrolled in postapproval studies was 90 (0-509), 533 (122-3633), and 38 (0-666), respectively. The proportion of approved indications with one or more randomized, controlled, double blind study using a clinical outcome for the primary endpoint that was published after approval and showed superior efficacy was 18.2% (6 of 33), 2.0% (1 of 49), and 4.9% (2 of 41), respectively

CONCLUSIONS

The quantity and quality of postapproval clinical evidence varied substantially for novel drugs first approved by the FDA on the basis of limited evidence, with few controlled studies published after approval that confirmed efficacy using clinical outcomes for the original FDA approved indication.

BMJ 2017;357

Missing evidence in the postapproval phase

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Postapproval studies of drugs initially approved by the FDA on the basis of limited evidence: systematic review

Alison M Pease,[1] Harlan M Krumholz,[2,3,4,5] Nicholas S Downing,[6] Jenerius A Aminawung,[7] Nilay D Shah,[8] Joseph S Ross[3,4,5,7]

no postapproval studies were performed for 43 of the 123 (35%) indications approved on the basis of limited evidence (single pivotal trial or surrogate endpoints)

indications approved on the basis of single pivotal

7;357

Missing evidence for HTA

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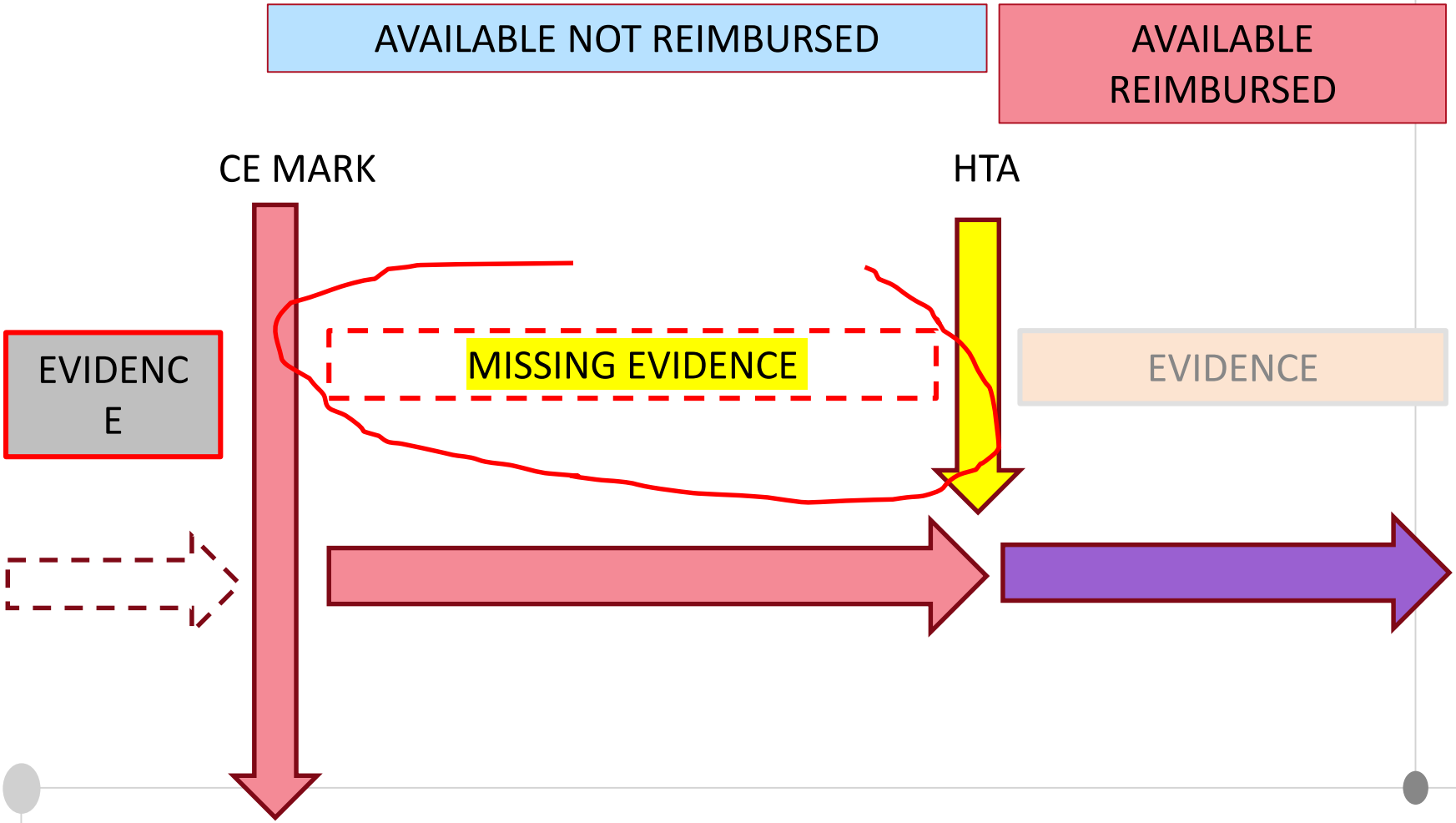

Managing uncertainity in post-launch phase – key points

1. Evidence generation
2. Uncertainity of evidence
3. Managing uncertainity

Clinical registries – technology comparisons

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Vascular complications more frequent with Mynx vs comparators

a prospective, propensity-matched analysis of the safety of the Mynx vascular-closure device, as compared with alternative approved vascular-closure devices, with data from the CathPCI Registry of the

Registry-Based Prospective, Active Surveillance of Medical-Device Safety

Frederic S. Resnic, M.D., Arjun Majithia, M.D., Danica Marinac-Dabic, M.D., Ph.D.,

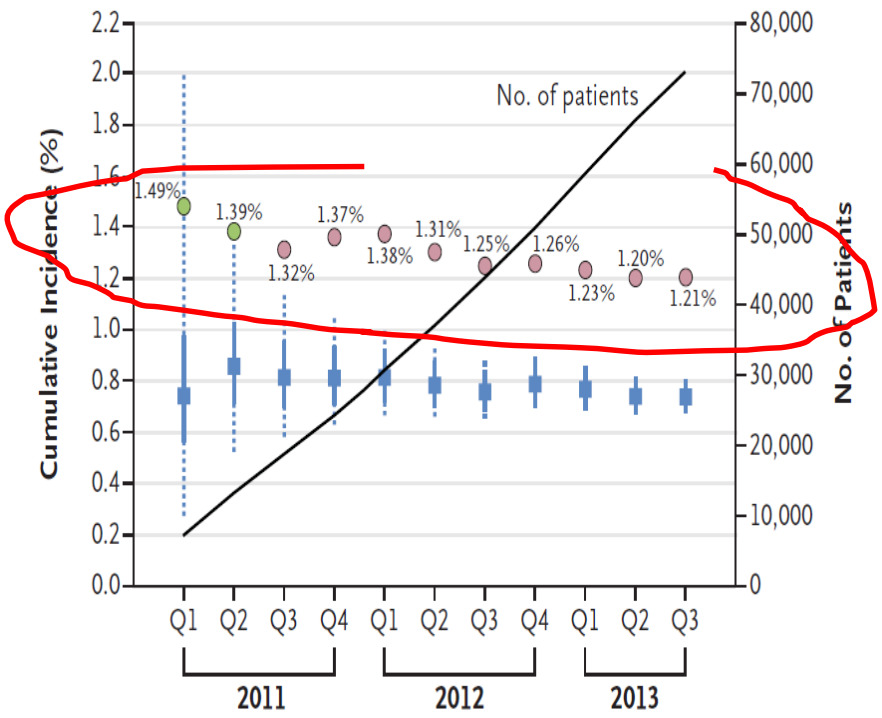

Figure 1. Cumulative Incidence of Any Vascular Complication among Recipients of the Mynx Device and Alternative Devices

N Engl J Med 2017; 3

Postmarket surveillance

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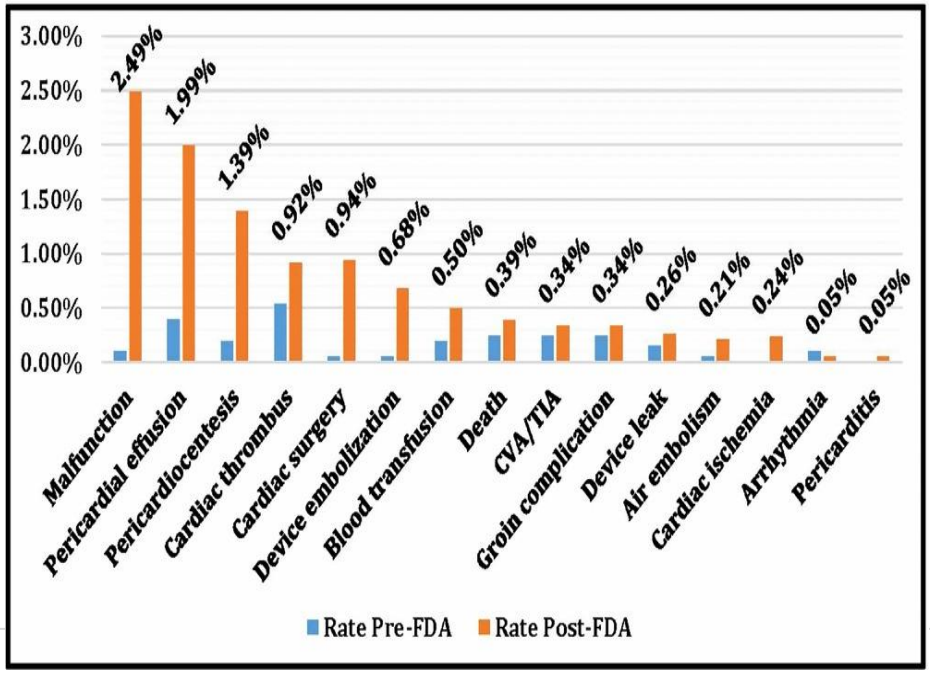
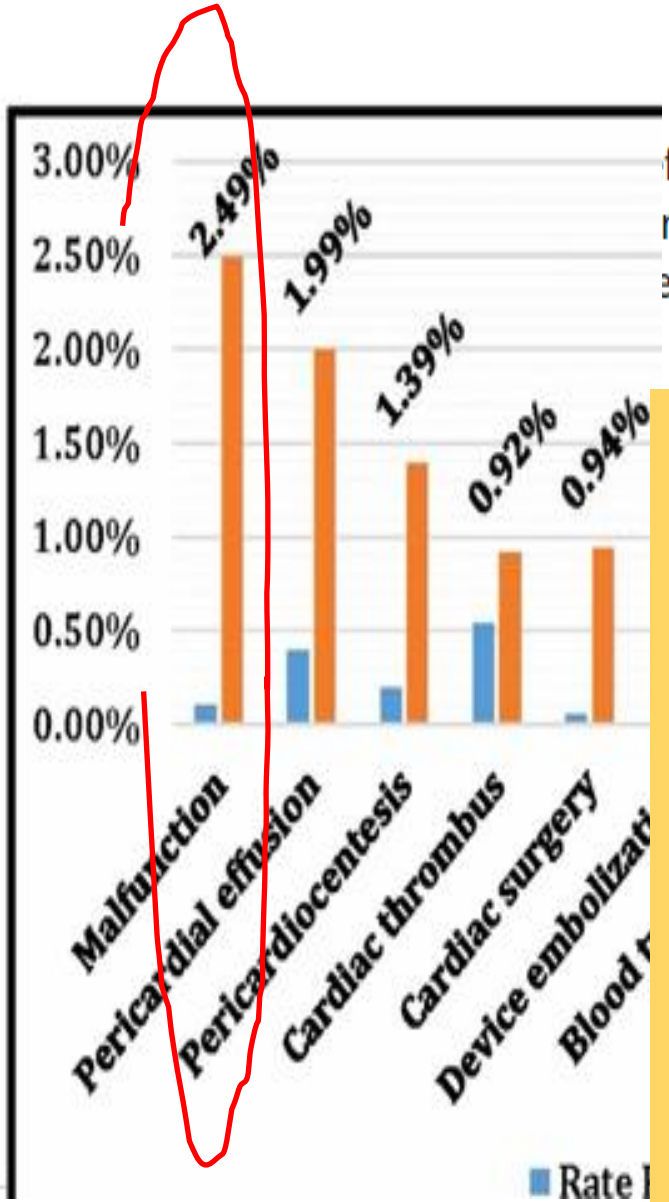
Safety profiles of percutaneous left atrial appendage closure devices: An analysis of the Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) database from 2009 to 2016

Mohammad-Ali Jazayeri MD, Venkat Vuddanda MD, Mohit K. Turagam MD, Valay Parikh MD,



J Card Electrophysiol. 20

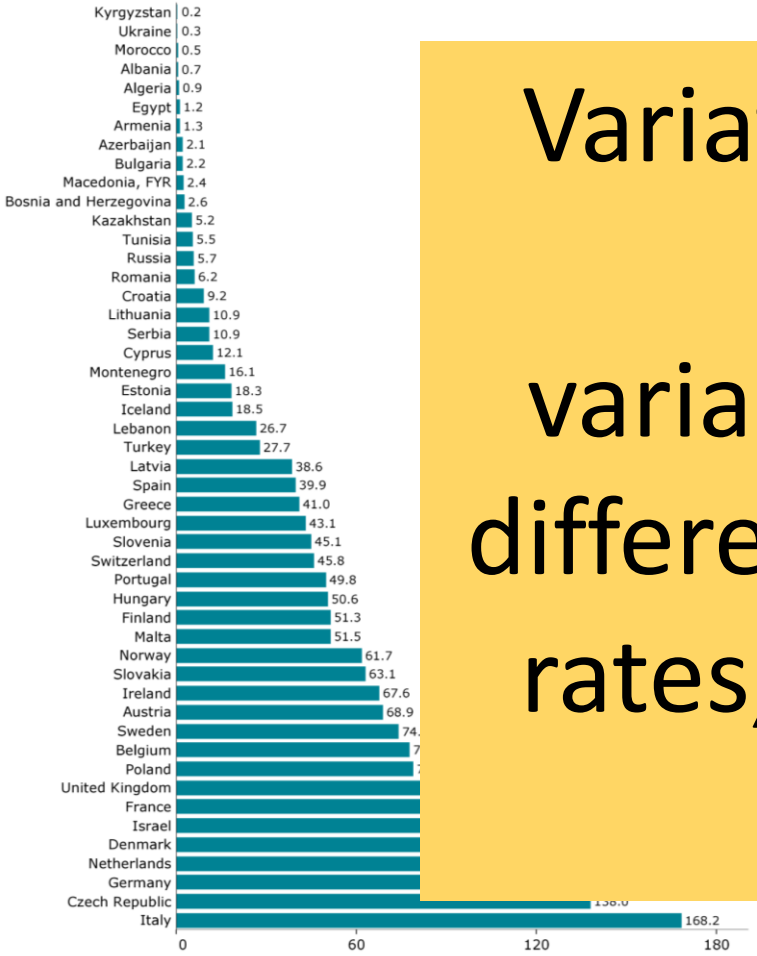
Postmarket surveillance



ft atrial appendage closure
nd Drug Administration
evice Experience (MAUDE)

Risk of malfunction several dozen higher post- as compared to pre-FDA approval

Variations in annual implant rates for CRTD/per million



Variations in uptake may result in variable learning curves, differences in complication rates, cost-effectiveness, etc.

ESC Atlas of Cardiology database, 2017

Quality of Evider

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

ESC European Society of Cardiology

Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

pow er	True/not true	bias	example	PPV
		0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
		0.40	Meta-analysis of small inconclusive studies	0.41
		0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.80		0.30	Adequately powered exploratory epidemiological study	0.20
			epidemiological study	
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12

True/not true

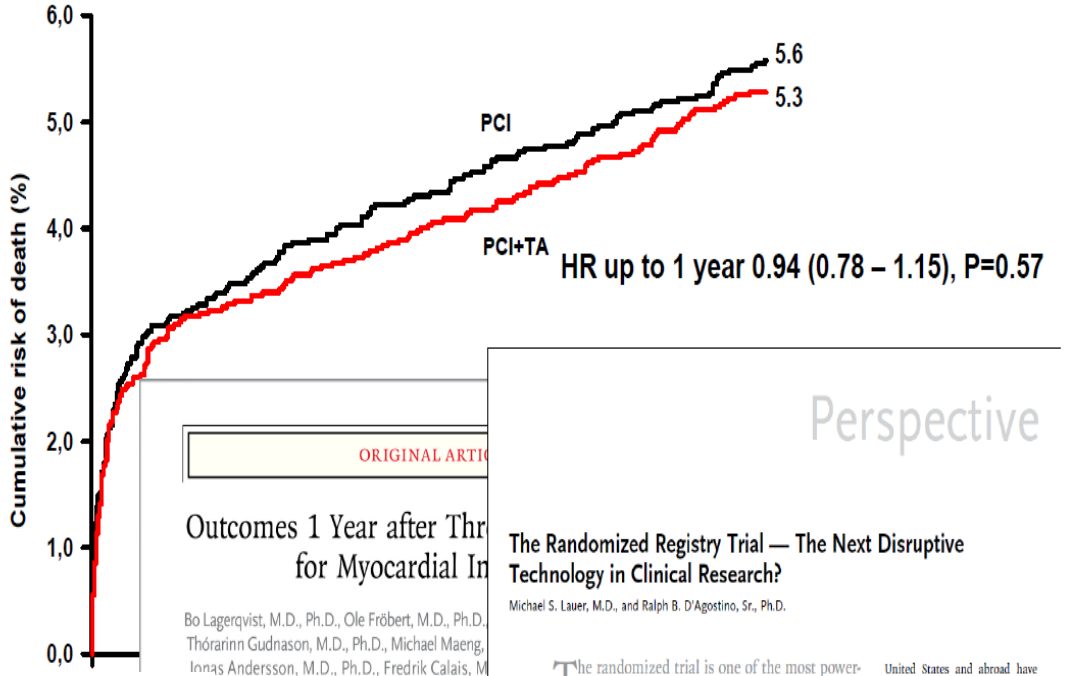
observational < randomized

LoS Med. 2005;2:e124.

Registry-based randomized trial

TASTE

All-cause mortality up to 1 year



ORIGINAL ARTICLE

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D., Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D.,

ORIGINAL ARTI

Outcomes 1 Year after Thr
for Myocardial In

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D.,
Thórarinn Gudnason, M.D., Ph.D., Michael Maeng,
Jonas Andersson, M.D., Ph.D., Fredrik Calais, M
Iv Collste, M.D., Matthias Götberg, M.D., Ph
Dan Ioanes, M.D., Anders Kallryd, M.D., R
Anders Lundin, M.D., Jacob Odenstedt, M.D.,
Verner Puskar, M.D., Tim Tödt, M.D., Ph.D., Eva Zelleroth, M.D.,
Ollie Östlund, Ph.D., and Stefan K. James, M.D., Ph.D.

Perspective

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for

United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as

Courtesy: Jonas Oldgren

A change in guidelines

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Title	Citation		Class	LOE
2012 ESC Guidelines ST-segment elevation myocardial infarction .	European Heart Journal 2012 Oct;33(20):2569-619	Routine aspiration should be considered	IIa	B
2014 ESC/EACTS guidelines on myocardial revascularization	Eur Heart J. 2014 Oct 1;35(37):2541-619	May be considered in selected patients	IIb	A
2015 ACC/AHA focused update PPCI	JACC	Routine thrombectomy not useful	III	A
2015 ACC/AHA focused update PPCI	JACC	Selective and bailout Thrombectomy not well established	IIb	C
2017 ESC Guidelines ST-segment elevation myocardial infarction	European Heart Journal 2017	Routine use of thrombus aspiration is not recommended.	III	A

CLASS IIa –USE

CLASS III – DO NOT use

Courtesy: Jonas Oldgren

A change in clinical practice

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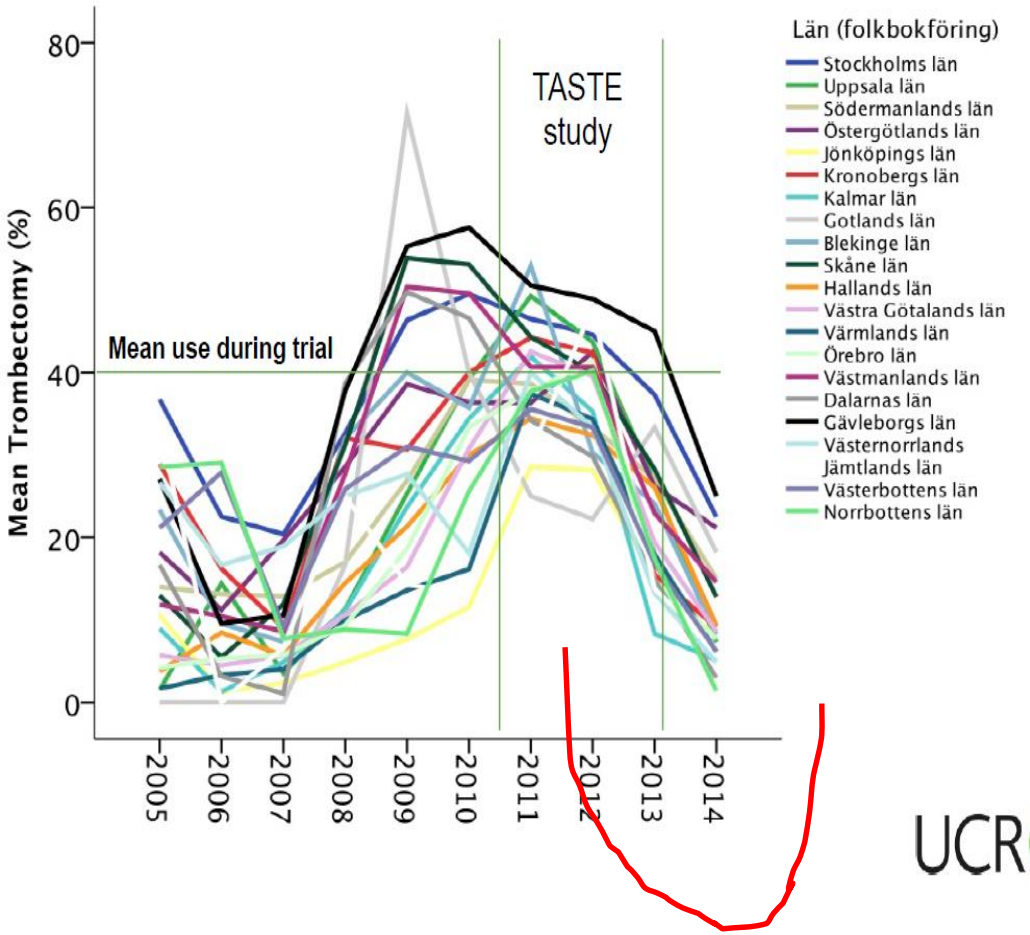
SWEDEHEART

Thrombus aspiration pre/post Taste



UCR

Courtesy: Jonas Oldgren

Conclusions

- The benefits of introduction of a new technology should be weighed against inevitable uncertainty of evidence
- Approval of new technologies on the basis of limited evidence should result in risk management plan, including systematic collection of real world data and pragmatic clinical trials, to reduce uncertainity.

Conclusions

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- Adequate quality real world data are fundamental to judge the clinical benefits related to the use of new health technologies compared to existing ones
- Joint clinical assessments should be coordinated, but not aligned with CE marking, to allow for the collection of real world data
- A coordinated effort should be

Piotr Szymanski
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7 June 2018

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