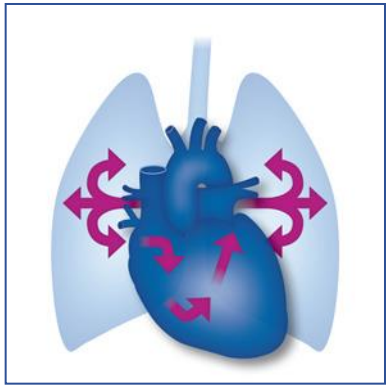
Pneumo Update Europe 2016

24-25 June, Prague

Pulmonary Vascular Diseases



Marc Humbert, France

Pulmonary Embolism

State of the Art

- Pulmonary embolism and venous thromboembolic disease are fast-moving fields of cardiopulmonary medicine
- ESC PE Guidelines endorsed by ERS have been published in 2014
- Novel information have been produced in the last year

Konstantinides et al. Eur Heart J 2014; 35:3033-80

Relevant new aspects

1. Couturaud F, at al. Six months vs extended anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized controlled trial. JAMA 2015; 314:31-40.

2. Carrier M. Screening for occult cancer in unprovoked venous thromboembolism. N Engl J Med 2015; 373:697-704.

3. Robin P, et al. Limited screening with versus without (18)F-fluorodeoxyglucose PET/CT for occult malignancy in unprovoked venous thromboembolism: an open-label randomised controlled trial. Lancet Oncol 2016; ; 17: 193–99.

4. Mismetti P, et al. Effects of a retrieval inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a rendomized clinical trial. JAMA 2015; 313:1627-35.

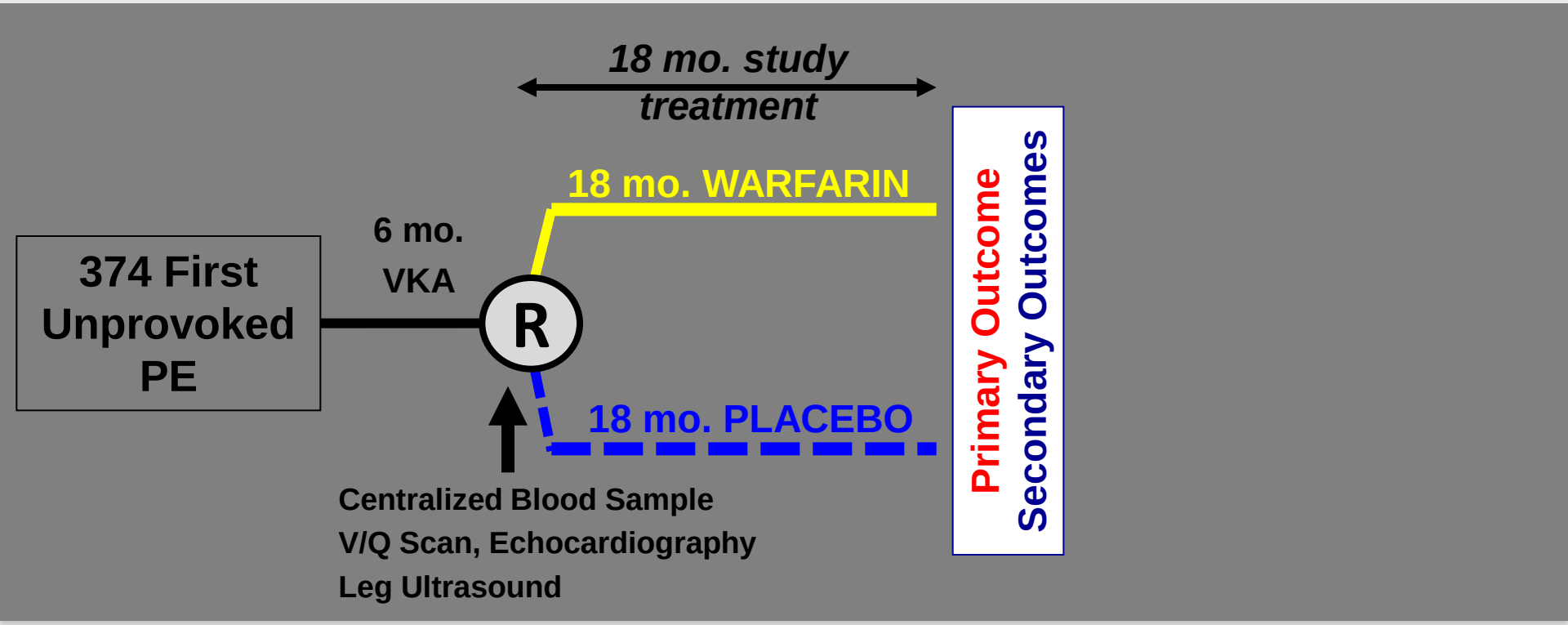
5. Kearon C, et a. Antithrombotic therapy for VTE disease: CHEST guidelines and expert panel report. Chest 2016; 149: 315-52.

Original Investigation

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD; Elisabeth Duhamel, MD; Karine Provost, MD; Claire Bal dit Sollier, MB; Emilie Presles, MS; Philippe Castellant, MD; Florence Parent, MD; Pierre-Yves Salaun, MD, PhD; Luc Bressollette, MD, PhD; Michel Nonent, MD, PhD; Philippe Lorillon, PharmD; Philippe Girard, MD; Karine Lacut, MD, PhD; Marie Guégan, MS; Jean-Luc Bosson, MD, PhD; Silvy Laporte, MS, PhD; Christophe Leroyer, MD, PhD; Hervé Décousus, MD; Guy Meyer, MD; Dominique Mottier, MD; for the PADIS-PE Investigators



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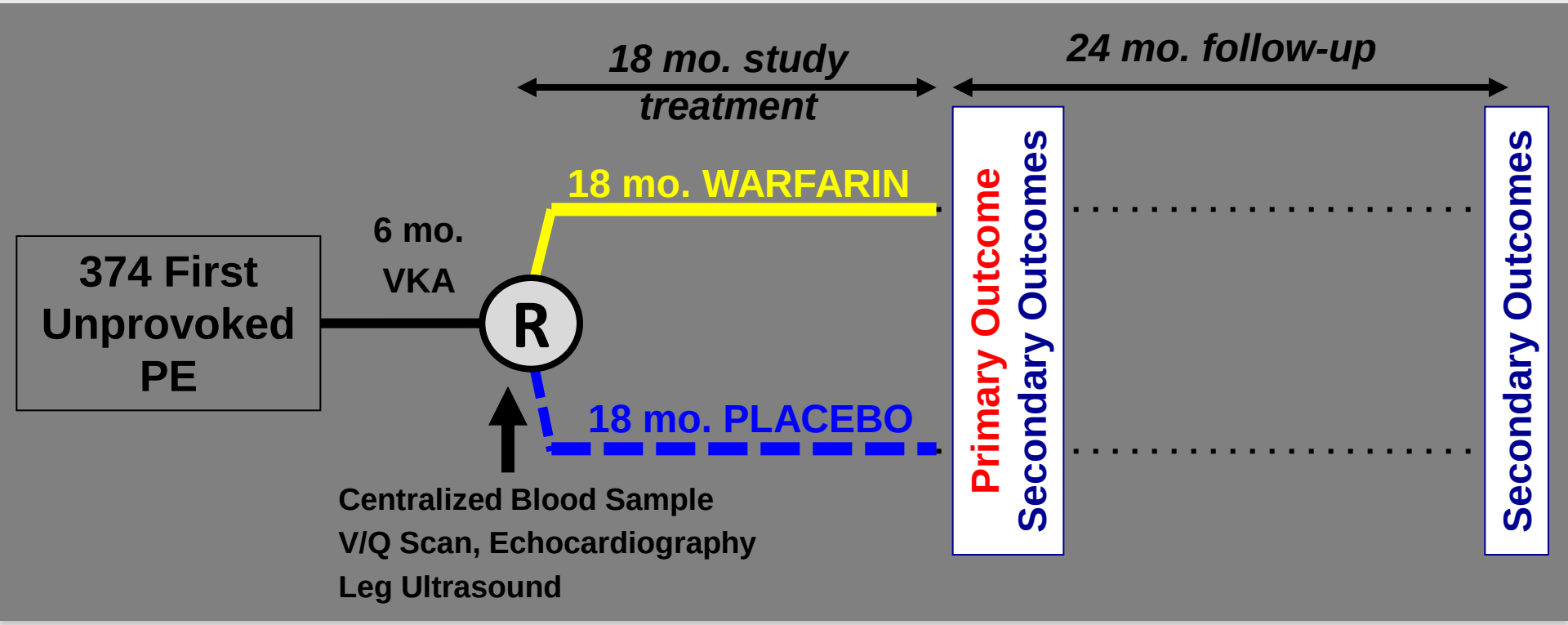


Couturaud F et al. JAMA 2015; 314:31–40

Outcomes

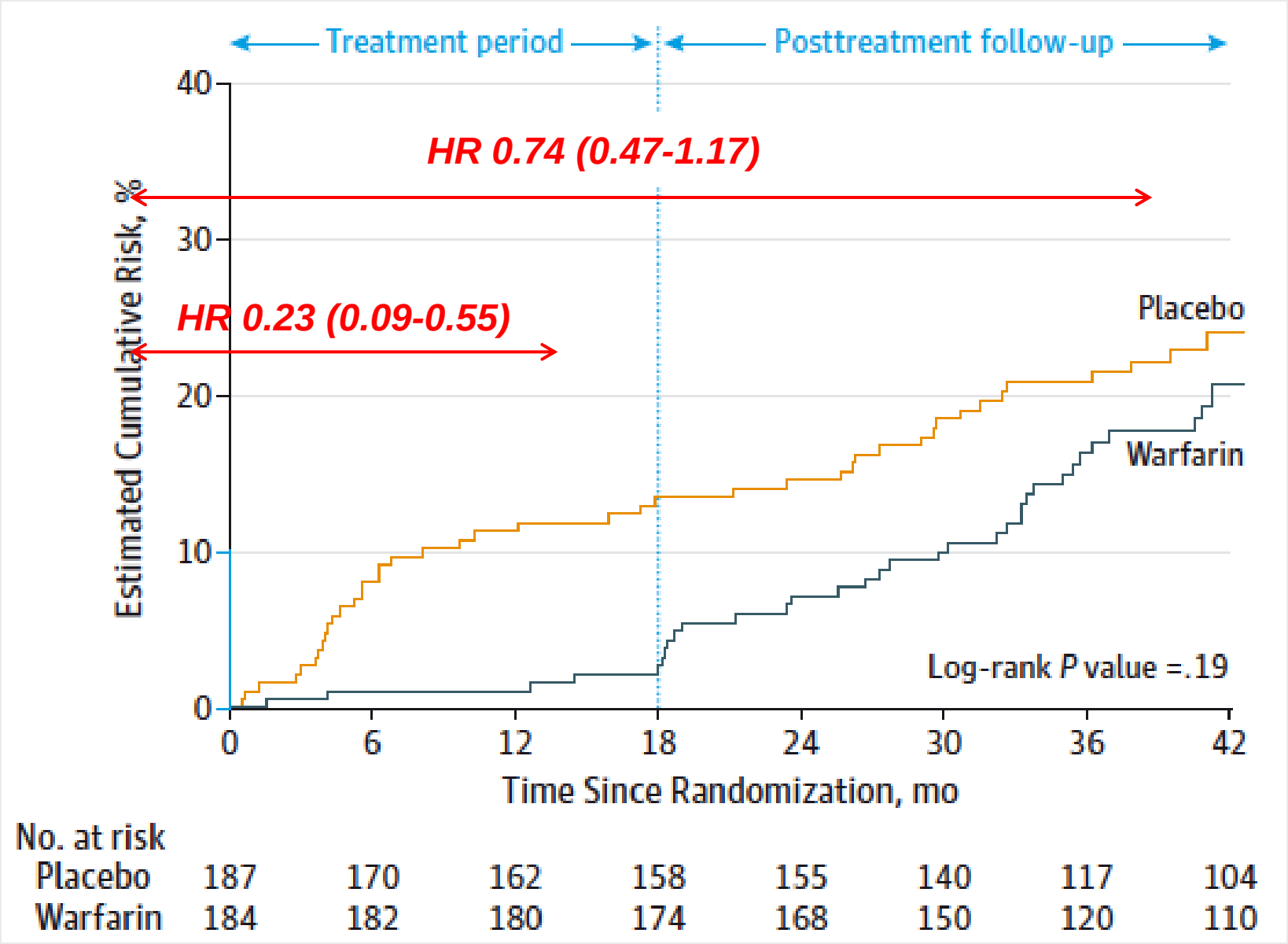
- **Primary outcome**:
  - **Composite of recurrent VTE or major bleeding during the 18 months study treatment period**

- **Secondary outcomes**:
  - Composite of recurrent VTE or major bleeding during the entire study period of 42 months
  - Recurrent VTE, major bleeding and deaths unrelated with the composite during the treatment period and the entire study period

All symptomatic events have been validated by the Critical Events Committee

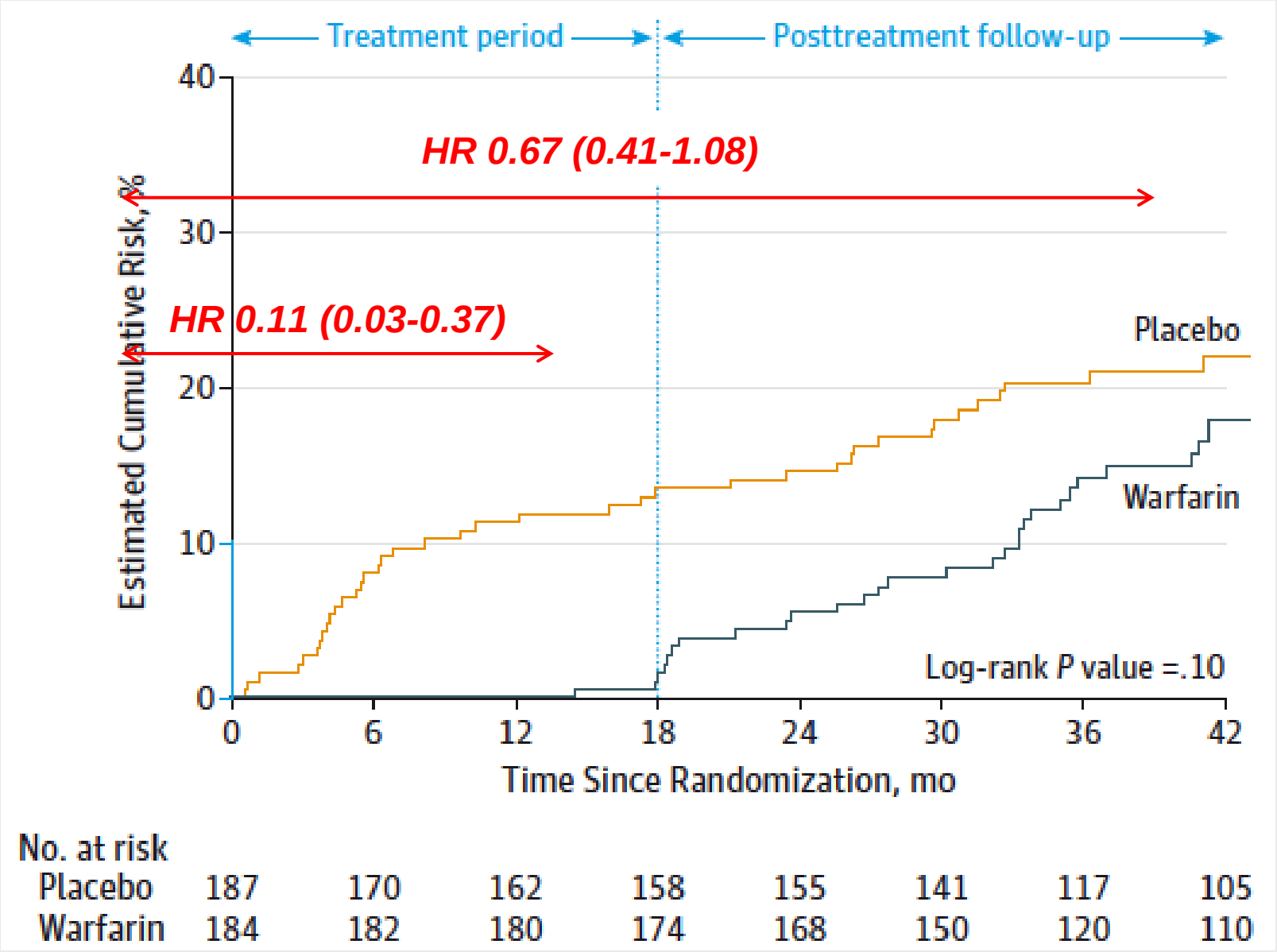
Couturaud F et al. JAMA 2015; 314:31–40

COMPOSITE: Recurrent VTE or Major Bleeding



Couturaud F et al. JAMA 2015; 314:31–40

Recurrent VTE



Couturaud F et al. JAMA 2015; 314:31–40

Clinical consequences of “PADIS-PE” trial

After a first episode of unprovoked PE initially treated during 6 months:

- **Major reduction of recurrent VTE** while anticoagulation is continued
- **Loss of benefit** after stopping anticoagulation

  → **No impact of an extended but limited duration of anticoagulation**

Recurrent VTE occurred:

- In **80%** of cases as **PE (8% fatal)**
- In **90%** of cases as **unprovoked VTE**

→ **Clinical presentation of recurrence = initial episode**

Couturaud F et al. JAMA 2015; 314:31–40

2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism

The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)

Endorsed by the European Respiratory Society (ERS)

Authors/Task Force Members: Stavros V. Konstantinides* (Chairperson) (Germany/Greece), Adam Torbicki* (Co-chairperson) (Poland), Giancarlo Agnelli (Italy), Nicolas Danchin (France), David Fitzmaurice (UK), Nazzareno Galiè (Italy), J. Simon R. Gibbs (UK), Menno V. Huisman (The Netherlands), Marc Humbert† (France), Nils Kucher (Switzerland), Irene Lang (Austria), Mareike Lankeit (Germany), John Lekakis (Greece), Christoph Maack (Germany), Eckhard Mayer (Germany), Nicolas Meneveau (France), Arnaud Perrier (Switzerland), Piotr Pruszczyk (Poland), Lars H. Rasmussen (Denmark), Thomas H. Schindler (USA), Pavel Svitil (Czech Republic), Anton Vonk Noordegraaf (The Netherlands), Jose Luis Zamorano (Spain), Maurizio Zompatori (Italy)

Konstantinides et al. Eur Heart J 2014; 35:3033-80

Clinical consequences

Reinforces recommendations ESC 2014 for indefinite anticoagulation

Recommendations for duration of anticoagulation after pulmonary embolism	Class[a]	Level[b]
For patients with PE secondary to a transient (reversible) risk factor, oral anticoagulation is recommended for 3 months.	I	B
For patients with unprovoked PE, oral anticoagulation is recommended for at least 3 months.	I	A
Extended oral anticoagulation should be considered for patients with a first episode of unprovoked PE and low bleeding risk.	IIa	B
Anticoagulation treatment of indefinite duration is recommended for patients with a second episode of unprovoked PE.	I	B
In patients who receive extended anticoagulation, the risk–benefit ratio of continuing such treatment should be reassessed at regular intervals.	I	C

Konstantinides et al. Eur Heart J 2014; 35:3033-80

Clinical consequences

Reinforces recommendations CHEST Guidelines for indefinite anticoagulation

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

Clive Kearon, MD, PhD; Elie A. Akl, MD, MPH, PhD; Joseph Ornelas, PhD; Allen Blaivas, DO, FCCP; David Jimenez, MD, PhD, FCCP; Henri Bounameaux, MD; Menno Huisman, MD, PhD; Christopher S. King, MD, FCCP; Timothy A. Morris, MD, FCCP; Namita Sood, MD, FCCP; Scott M. Stevens, MD; Janine R. E. Vintch, MD, FCCP; Philip Wells, MD; Scott C. Woller, MD; and COL Lisa Moores, MD, FCCP

Kearon C, et al. Chest 2016; 149: 315-52

Clinical consequences

Reinforces recommendations CHEST 2016 for indefinite anticoagulation

9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and

Kearon C, et al. Chest 2016; 149: 315-52

Clinical consequences

Only 2 treatment options:

1- Short Treatment = 3 (or 6 months)

2- Indefinite Anticoagulation

Based on what criteria ?

Couturaud F et al. JAMA 2015; 314:31–40

Screening for occult cancer in unprovoked VTE

SOME study

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, M.D., Sudeep Shivakumar, M.D., Vicky Tagalakis, M.D., Ryan Zarychanski, M.D., Susan Solymoss, M.D., Nathalie Routhier, M.D., James Douketis, M.D., Kim Danovitch, C.C.R.P., Agnes Y. Lee, M.D., Gregoire Le Gal, M.D., Philip S. Wells, M.D., Daniel J. Corsi, Ph.D., Timothy Ramsay, Ph.D., Doug Coyle, Ph.D., Isabelle Chagnon, M.D., Zahra Kassam, M.D., Hardy Tao, M.D., and Marc A. Rodger, M.D., for the SOME Investigators*

MVTEP study

Limited screening with versus without ^{18}F-fluorodeoxyglucose PET/CT for occult malignancy in unprovoked venous thromboembolism: an open-label randomised controlled trial

*Philippe Robin, Pierre-Yves Le Roux, Benjamin Planquette, Sandrine Accassat, Pierre-Marie Roy, Francis Couturaud, Nadia Ghazzar, Nathalie Prevot-Bitot, Olivier Couturier, Aurélien Delluc, Olivier Sanchez, Bernard Tardy, Grégoire Le Gal, Pierre-Yves Salaun, for the MVTEP study group**

Carrier M et al. N Engl J Med 2015; 373:697–704
Robin P. et al. *Lancet Oncol* 2016; 17: 193–99

Background

To compare limited screening strategy:

- History, physical examination,
- Blood counts, electrolytes, creatinine, liver function
- Chest-X Ray
- Sex-specific cancer (mammography, Papanicolaou test, PSA)

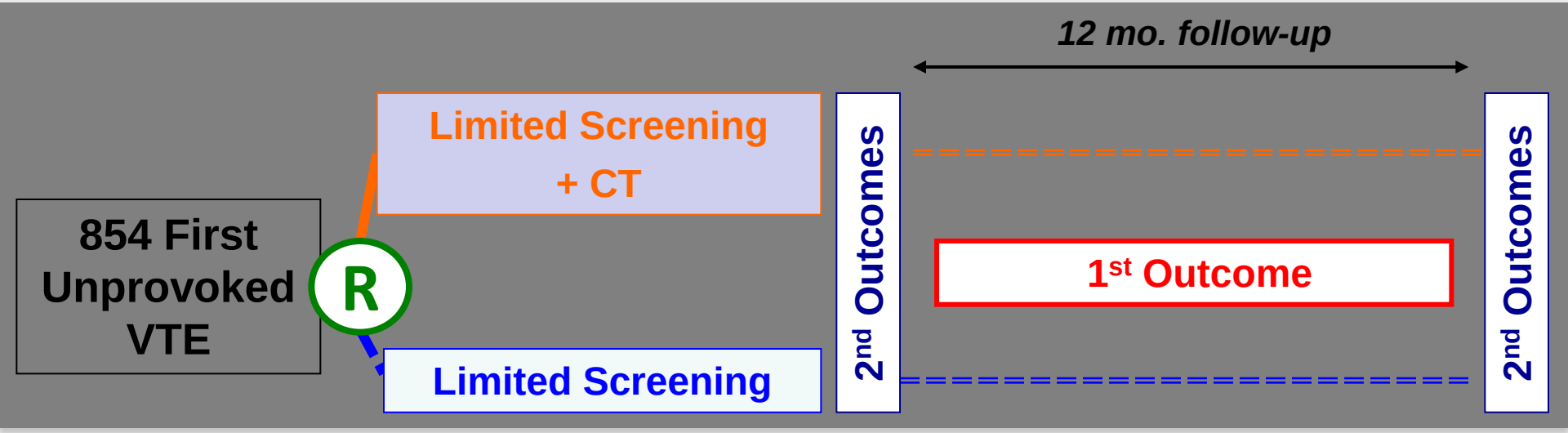
with:

- either comprehensive CT *(SOME study)*
- or PET/CT *(MVTEP study)*

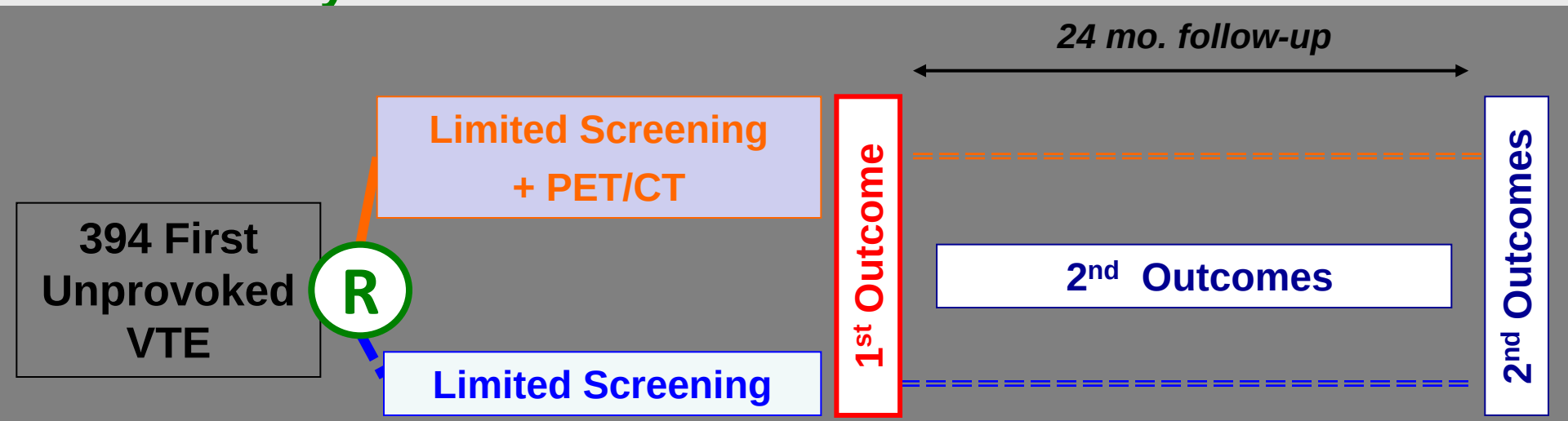
Carrier M et al. N Engl J Med 2015; 373:697–704
Robin P. et al. *Lancet Oncol* 2016; 17: 193–99

Screening for occult cancer

SOME study



MVTEP study



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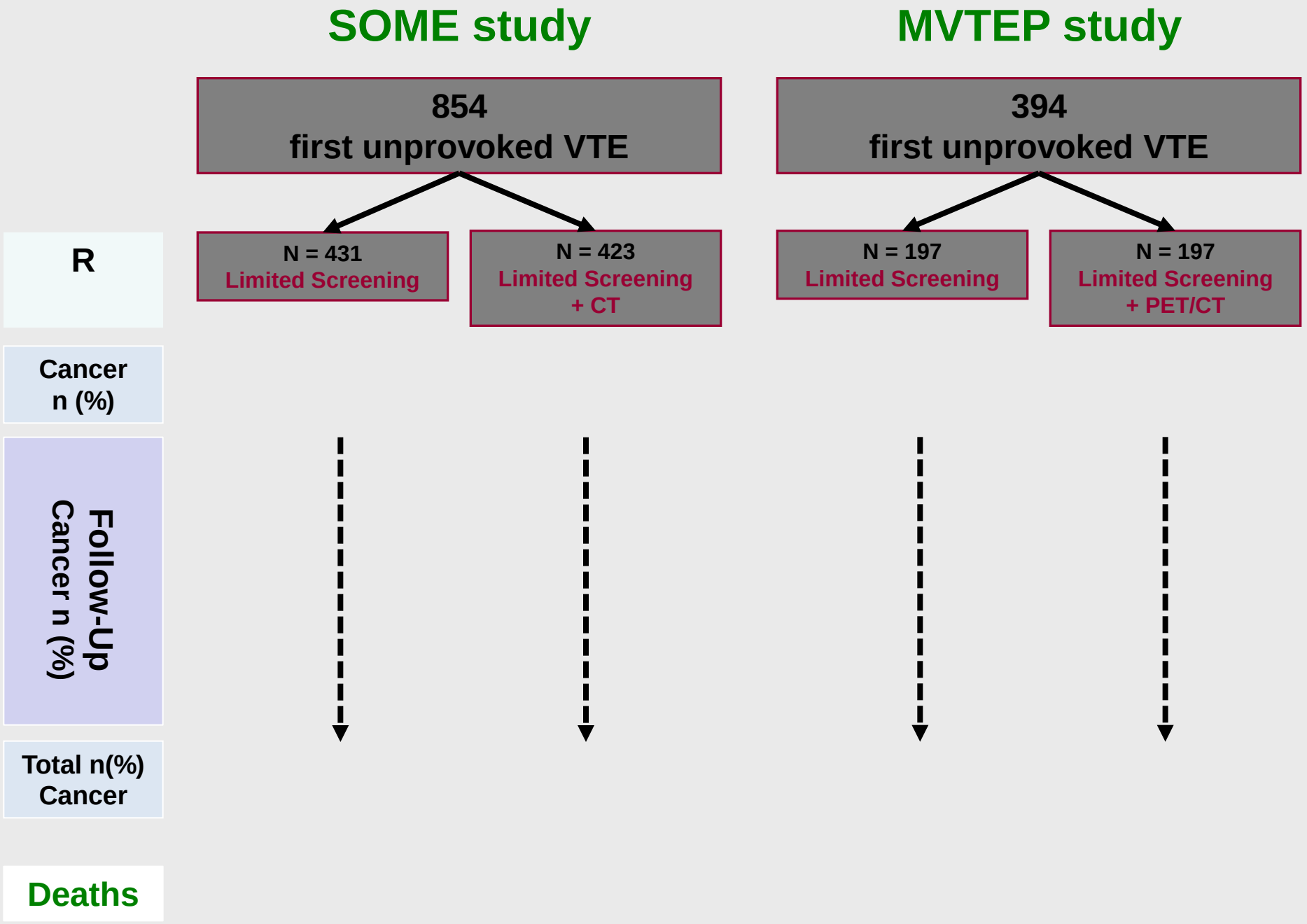

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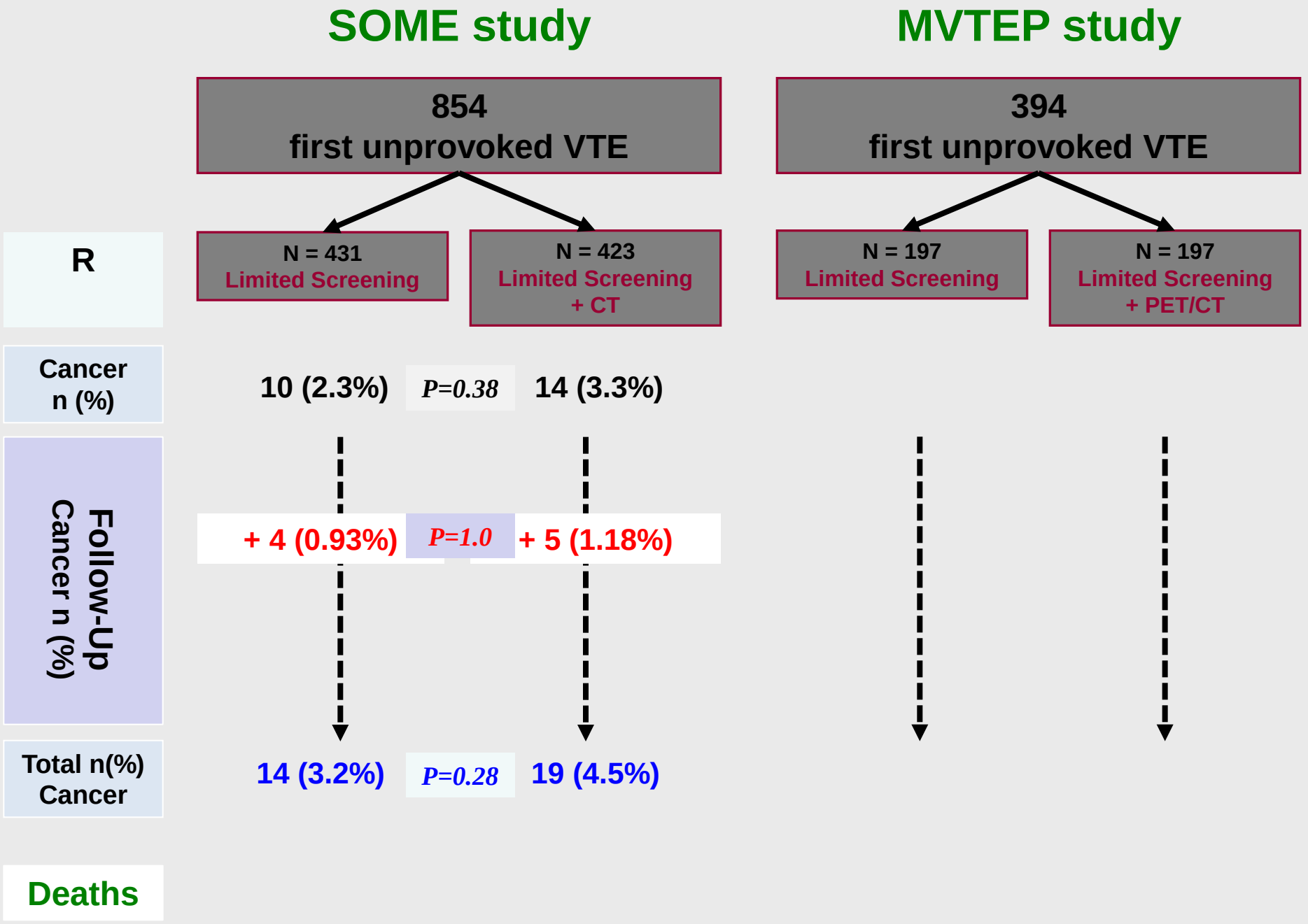

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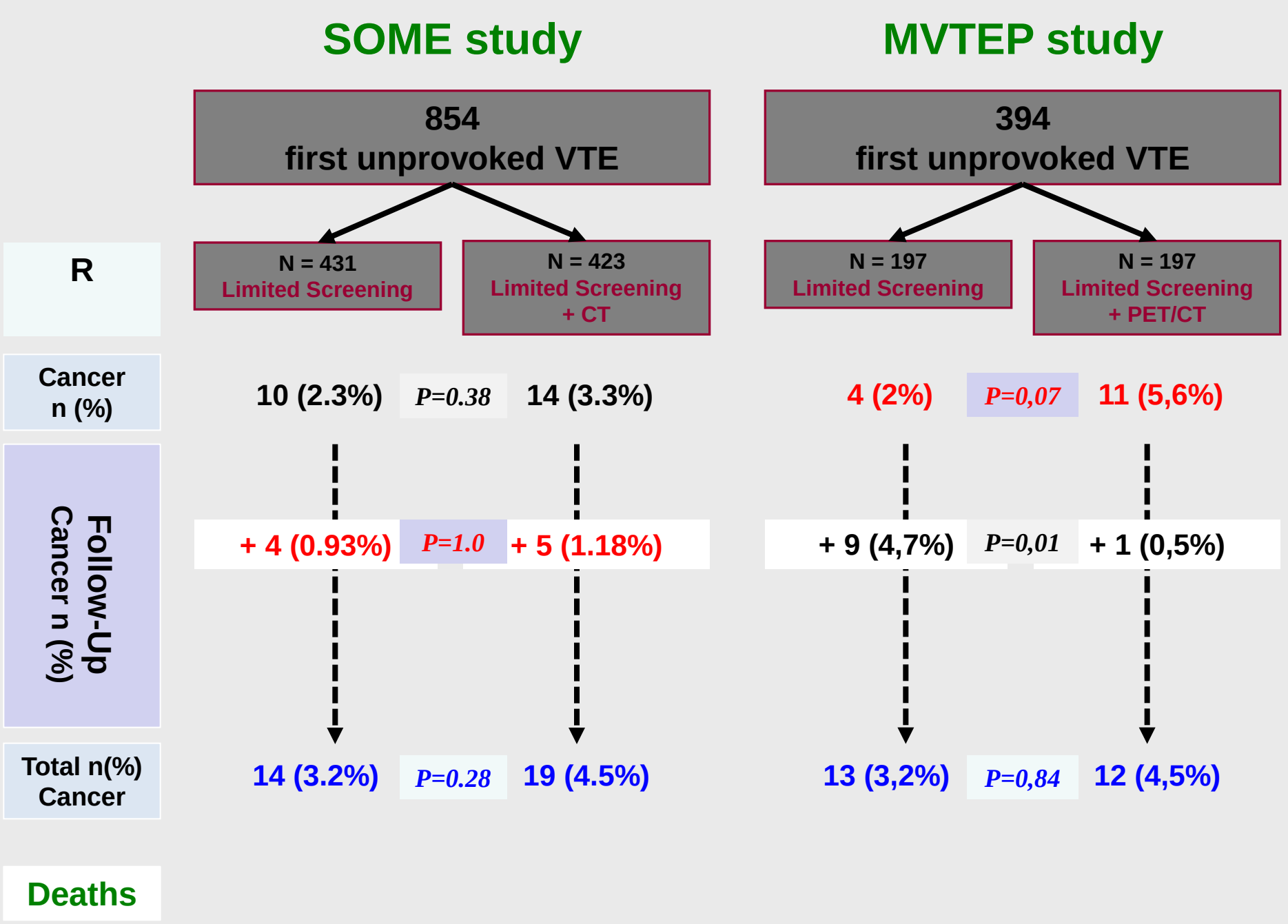

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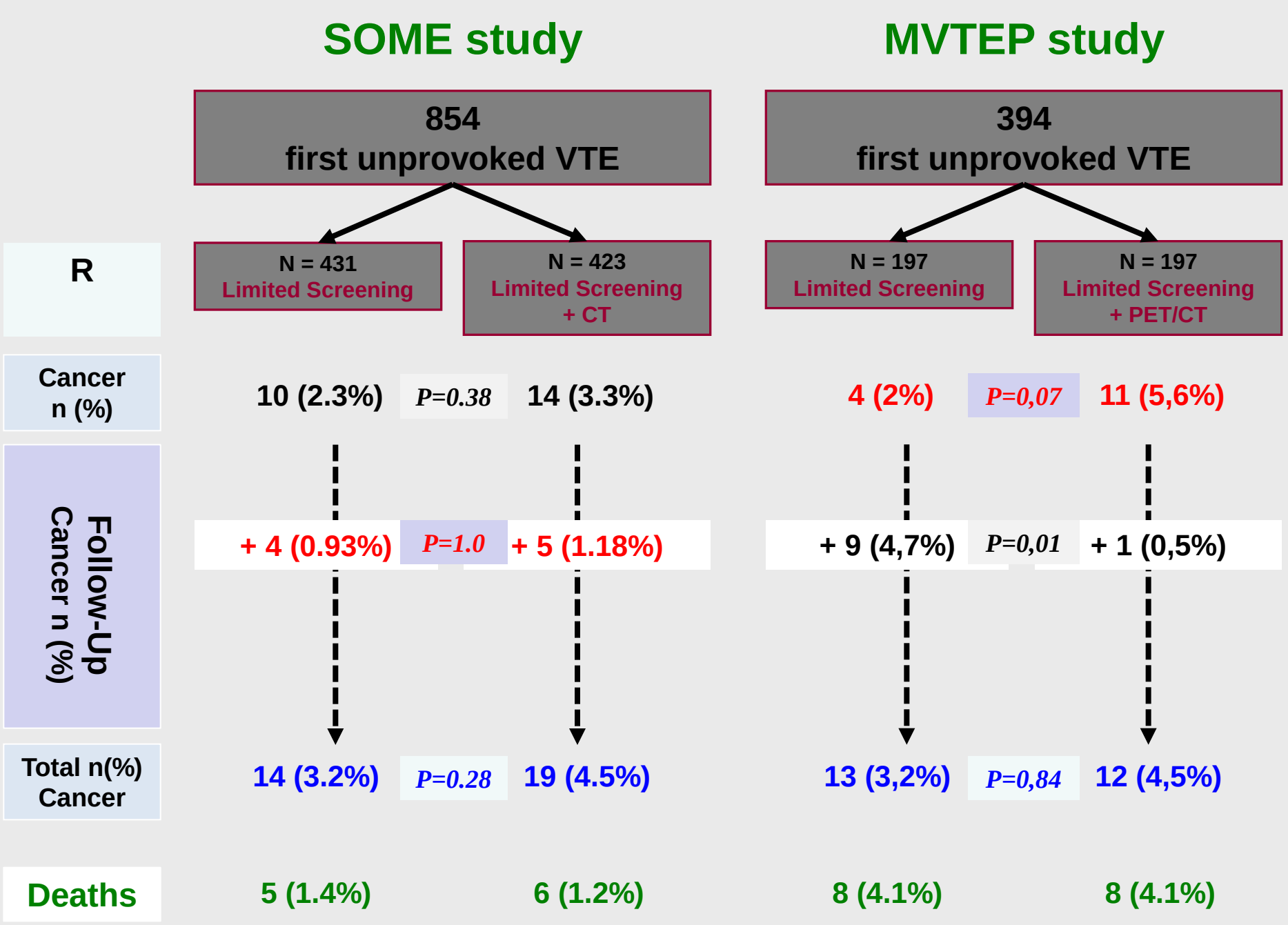


Carrier M et al. N Engl J Med 2015; 373:697–704
Robin P. et al. *Lancet Oncol* 2016; 17: 193–99

Clinical consequences of these trials

Among patients who had a first unprovoked venous thromboembolism, the **prevalence of occult cancer is low**

Routine screening with CT of the abdomen and pelvis or PET/CT did **not provide a clinically significant benefit** in terms of rate of diagnosed occult cancer and mortality

The risk of subsequent cancer diagnosis was, however, lower in patients who had negative initial screening that included ^{18}F-FDG PET/CT than in patients who had negative initial limited screening. Whether or not ^{18}F-FDG PET/CT might be useful in a more selected population of patients with a high risk of cancer remains to be determined

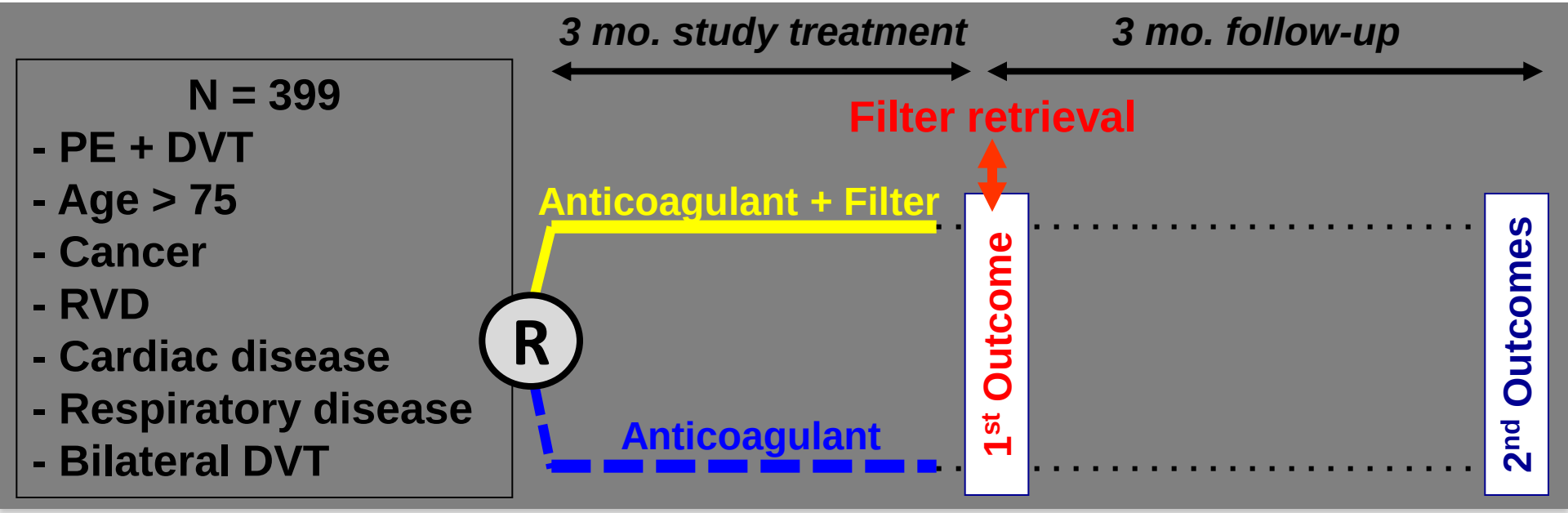
Carrier M et al. N Engl J Med 2015; 373:697–704
Robin P. et al. *Lancet Oncol* 2016; 17: 193–99

Original Investigation

Effect of a Retrievable Inferior Vena Cava Filter Plus Anticoagulation vs Anticoagulation Alone on Risk of Recurrent Pulmonary Embolism

A Randomized Clinical Trial

Patrick Mismetti, MD, PhD; Silvy Laporte, MS, PhD; Olivier Pellerin, MD, MSc; Pierre-Vladimir Ennezat, MD, PhD; Francis Couturaud, MD, PhD; Antoine Elias, MD, PhD; Nicolas Falvo, MD; Nicolas Meneveau, MD, PhD; Isabelle Quere, MD, PhD; Pierre-Marie Roy, MD, PhD; Olivier Sanchez, MD, PhD; Jeannot Schmidt, MD, PhD; Christophe Seinturier, MD; Marie-Antoinette Sevestre, MD; Jean-Paul Beregi, MD, PhD; Bernard Tardy, MD, PhD; Philippe Lacroix, MD; Emilie Presles, MSc; Alain Leizorovicz, MD; Hervé Decousus, MD; Fabrice-Guy Barral, MD; Guy Meyer, MD; for the PREPIC2 Study Group



Mismetti P, et al. JAMA 2015; 313:1627-35

Retrievable VCF with anticoagulants

	Filter N = 200	No Filter N = 199	RR
Recurrent PE 3 mo	**6** (3%)	**3** (1.5%)	**2.00 (0.51-7.89)**
Recurrent PE 6 mo	**7** (3.5%)	**4** (2%)	**1.75** (0.52-5.88)

Mismetti P, et al. JAMA 2015; 313:1627-35

Clinical consequences of the “PREPIC 2” trial

Among hospitalized patients with severe acute PE, the use of a **retrievable inferior vena cava filter** plus anticoagulation compared with anticoagulation alone **did not reduce** the risk of symptomatic recurrent PE at 3 months

These findings do not support the use of this type of filter in patients who can be treated with anticoagulation

Mismetti P, et al. JAMA 2015; 313:1627-35

Venous filters

Recommendations for venous filters	Class[a]	Level[b]
IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation.	IIa	C
IVC filters should be considered in case of PE recurrence despite therapeutic levels of anticoagulation.	IIa	C
Routine use of IVC filters in patients with PE is not recommended.	III	A

Eur Heart J 2014 Dec 1;35(45):3145-6

Pulmonary Hypertension

State of the Art

- Pulmonary hypertension is another fast-moving field of cardiopulmonary medicine
- ESC/ERS Guidelines have been released in 2015
- Novel information have been produced in the last year

PAH treatment: targeting 3 major dysfunctional pathways (2004 – 2014)

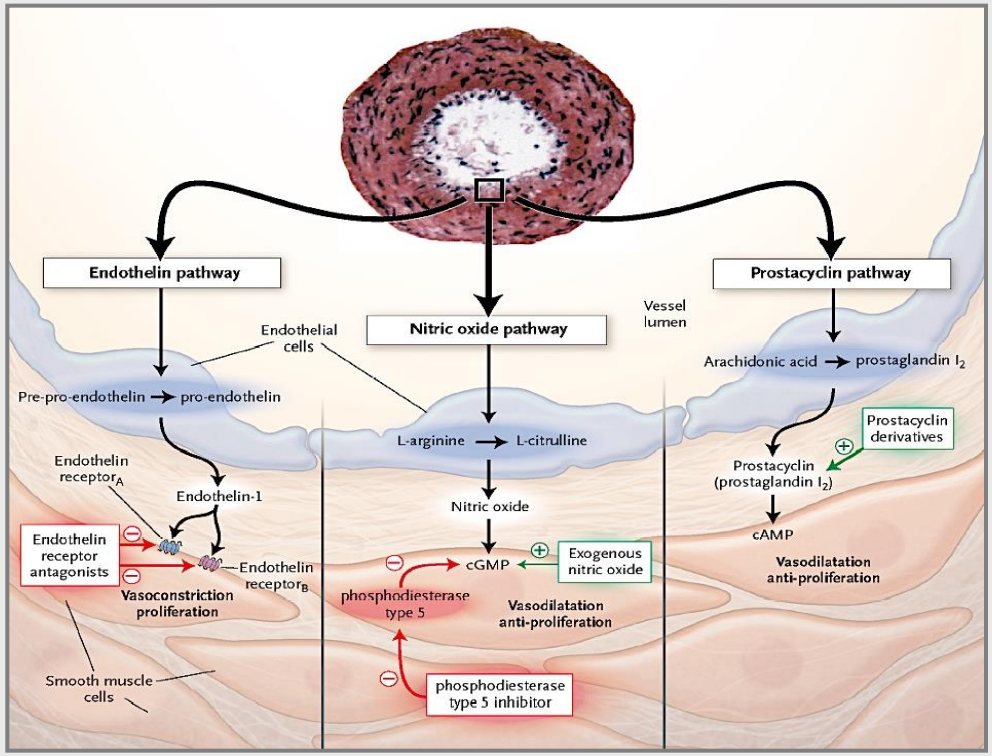
DRUG THERAPY

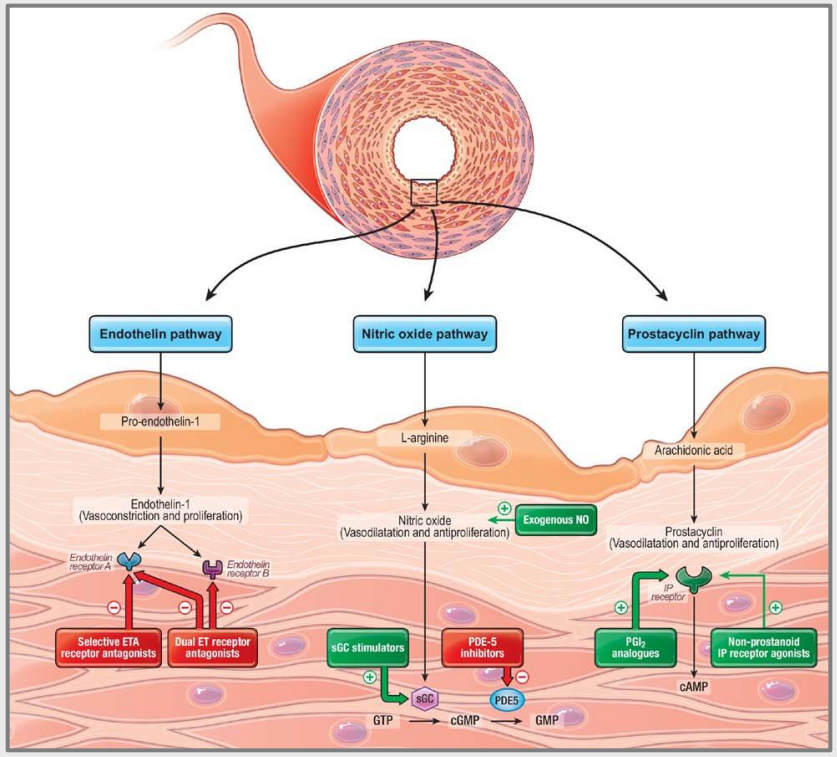
Treatment of Pulmonary Arterial Hypertension

Marc Humbert, M.D., Ph.D., Olivier Sitbon, M.D., and Gérald Simonneau, M.D.

Advances in Therapeutic Interventions for Patients With Pulmonary Arterial Hypertension

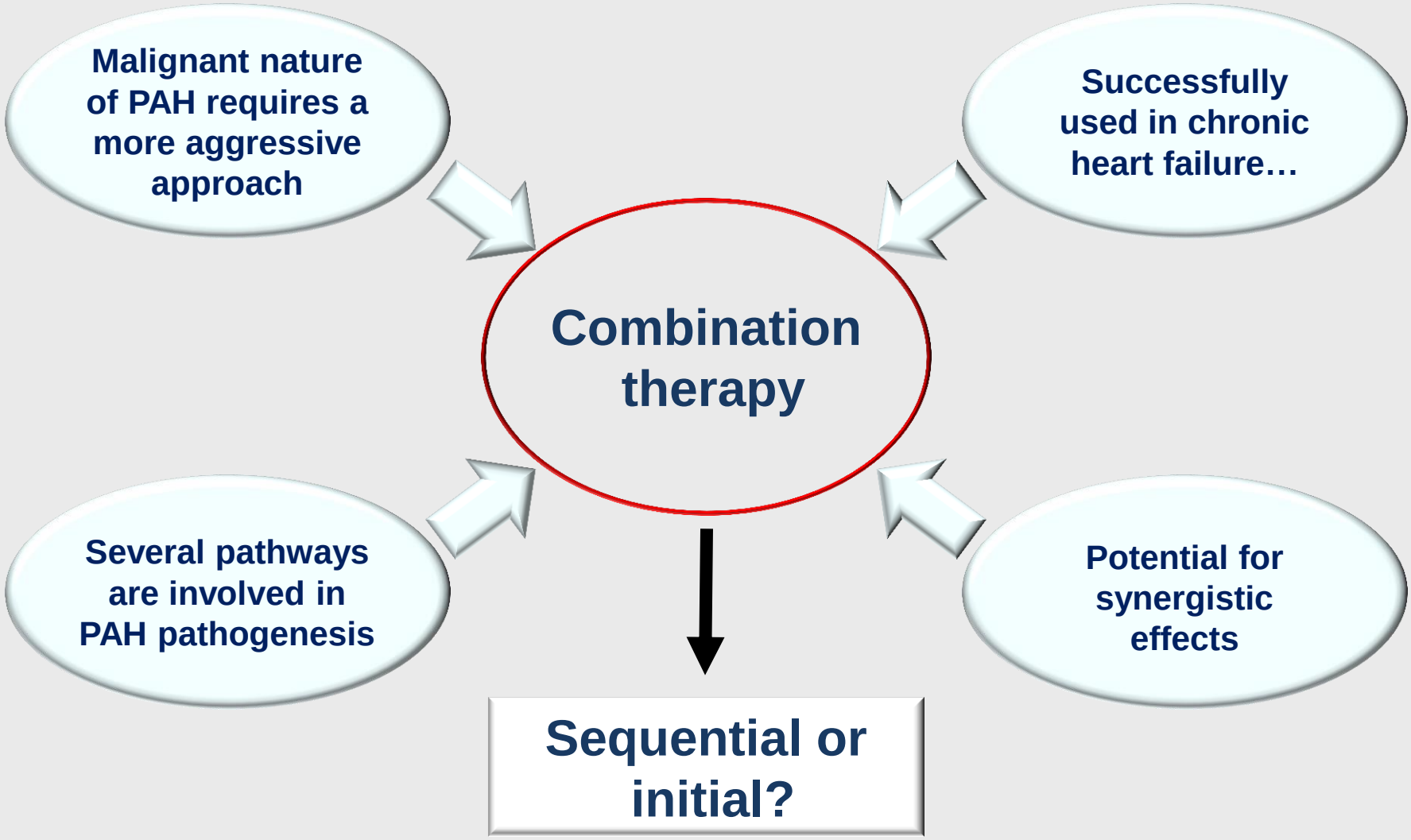
Marc Humbert, MD, PhD; Edmund M.T. Lau, MD, PhD; David Montani, MD, PhD; Xavier Jaïs, MD; Oliver Sitbon, MD, PhD; Gérald Simonneau, MD





 Humbert M, et al. N Engl J Med 2004 &Humbert M, et al. Circulation 2014

Rationale for combination therapy



Lajoie AC, *et al.* Lancet Respir Med 2016; 4: 291–305

Combination therapy: what is the evidence?

- Sequential combination therapy
  - Many studies (RCTs) are available
  - But results are not uniform
- Initial combination therapy
  - Only two RCTs: one negative (BREATHE-2), one positive (AMBITION)
  - Expanded experience in clinical practice (double, triple)
- Recent meta-analysis[1]: Combination therapy (all strategies, sequential and initial) is associated with significant risk reduction for clinical worsening compared with monotherapy

→ **No comparison between sequential and initial combination therapy**

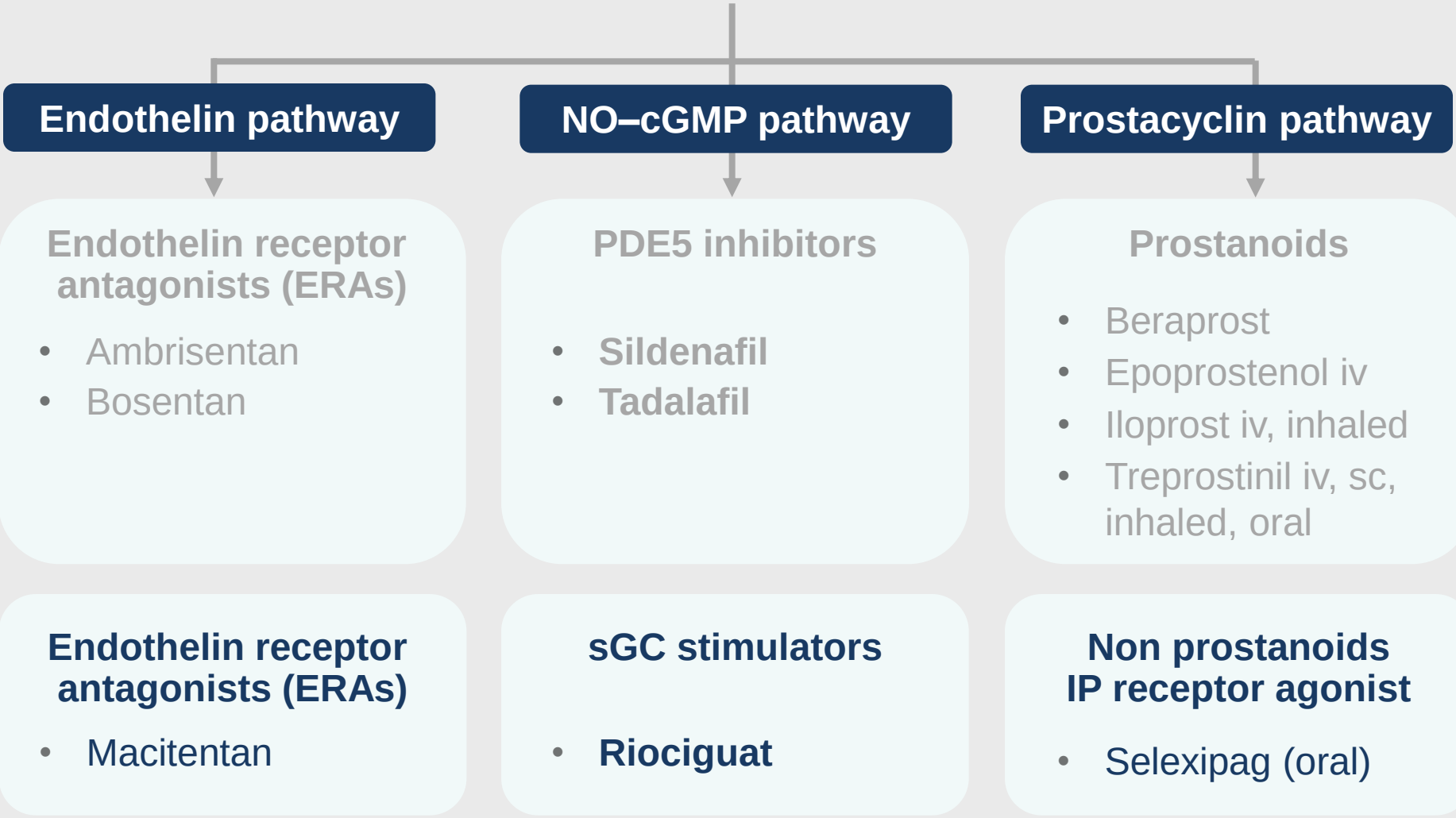
Lajoie AC, *et al.* Lancet Respir Med 2016; 4: 291–305

Meta-analysis: combination therapy is superior to monotherapy

- 17 studies (4095 patients), incl. 15 that assessed clinical worsening
- Main result: Combination therapy (sequential and initial) is associated with significant risk reduction for clinical worsening compared with monotherapy
  - combined therapy 17% [332 of 1940 patients]
    vs monotherapy 28% [517 of 1862 patients]
  - risk ratio [RR] 0.65 [95% CI 0.58–0.72], p<0.00001
- No heterogeneity between the studies (I.=18%, $p_{homogeneity}$=0.25).
- Main limitation: variable definition of clinical worsening among the trials and possible publication bias.
- Because many patients still had clinical worsening with combination therapy, identification of innovative therapeutic targets for PAH is urgently needed

Lajoie AC, *et al.* Lancet Respir Med 2016; 4: 291–305

PAH-specific therapies target the 3 signaling pathways involved in PAH: New drugs

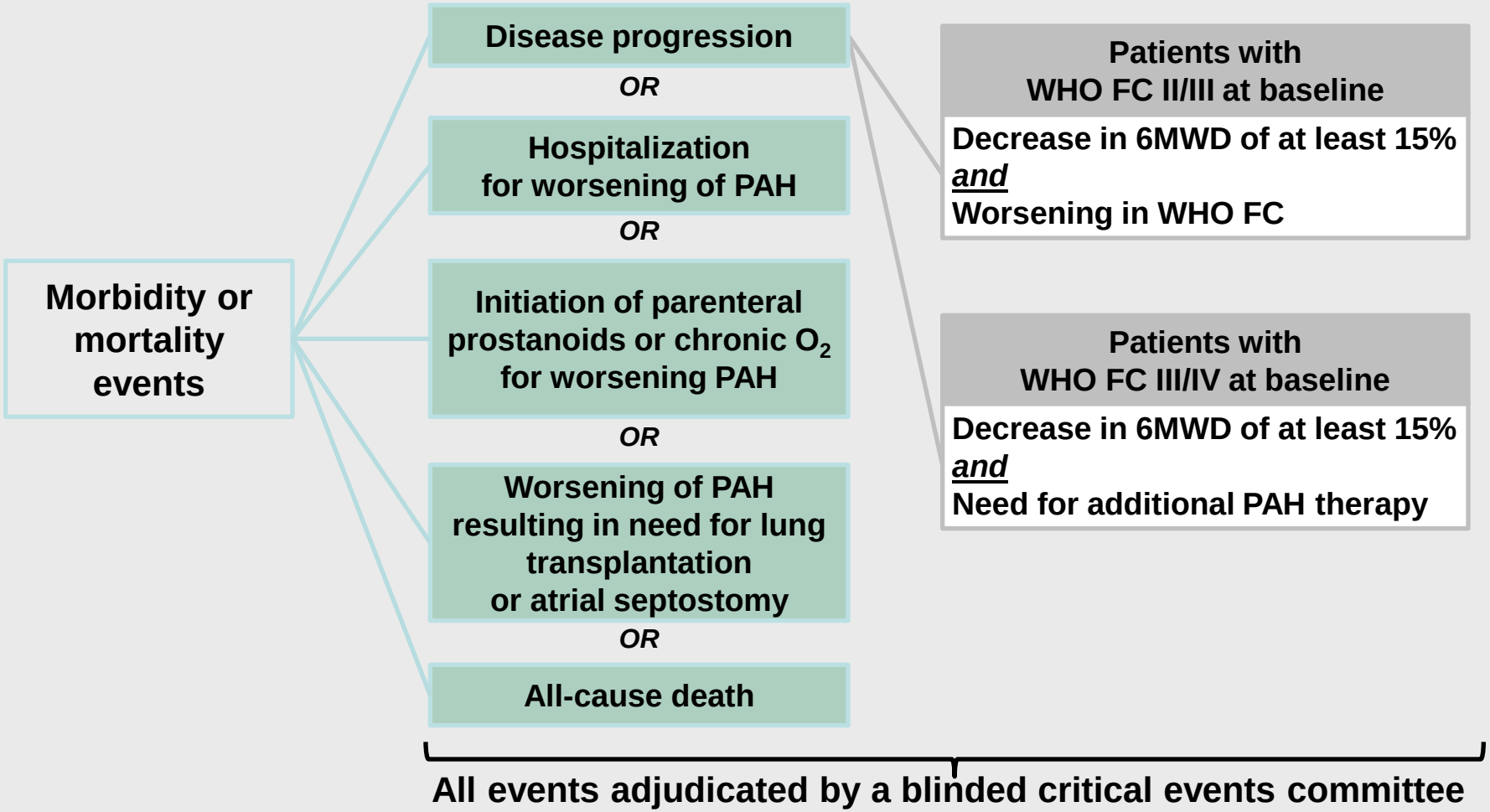


GRIPHON study : ProstaGlandin I_2 Receptor agonist In Pulmonary arterial HypertensiON

- Multicenter, double-blind, placebo-controlled event-driven study
- 1156 PAH adult patients
- 80% on background treatment with ERA and/or PDE-5i
- Composite primary outcome measure: time to the first occurrence of death or morbidity event

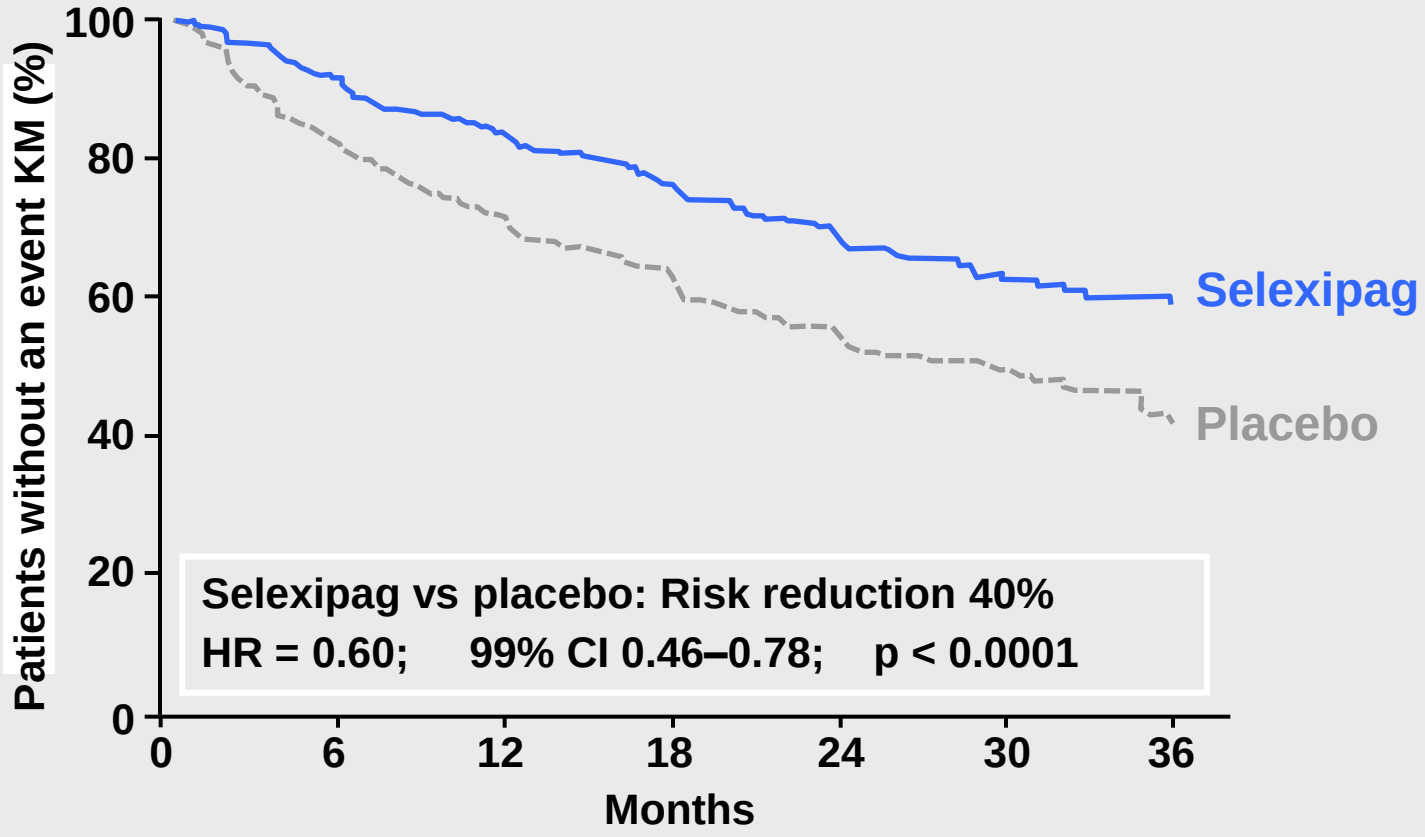
Sitbon O, et al. N Engl J Med 2015;373:2522-33

Primary endpoint: time to first occurrence of death or morbidity due to PH up to end of double-blind treatment



Sitbon O, et al. N Engl J Med 2015;373:2522-33

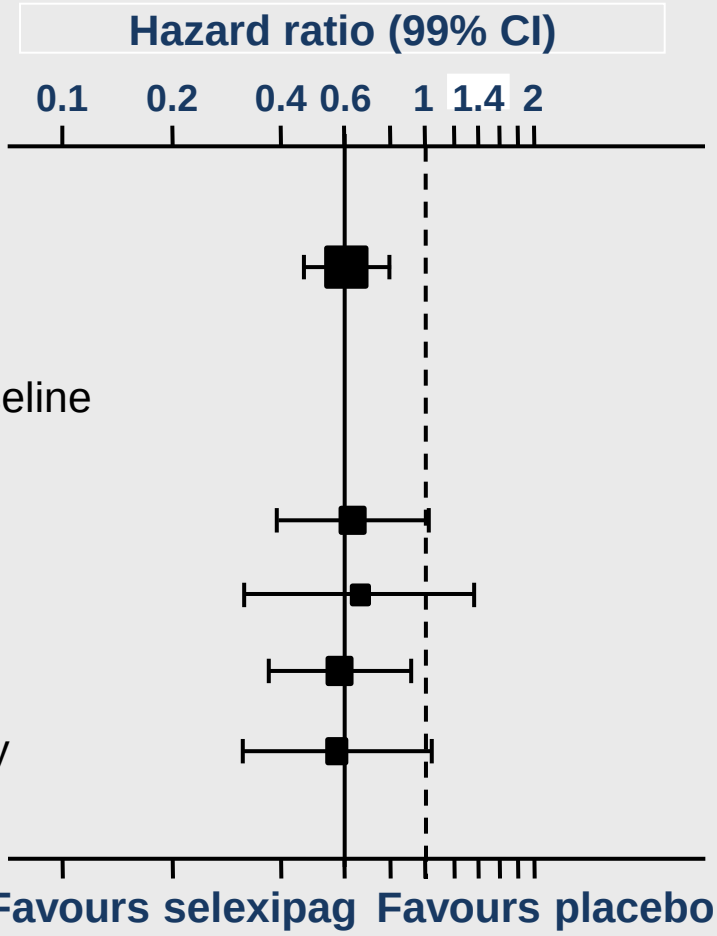
Selexipag reduced the risk of the primary outcome composite of death or morbidity due to PH



Hospitalisation for PAH worsening and disease progression were the main components of the primary endpoint

Sitbon O, et al. N Engl J Med 2015;373:2522-33

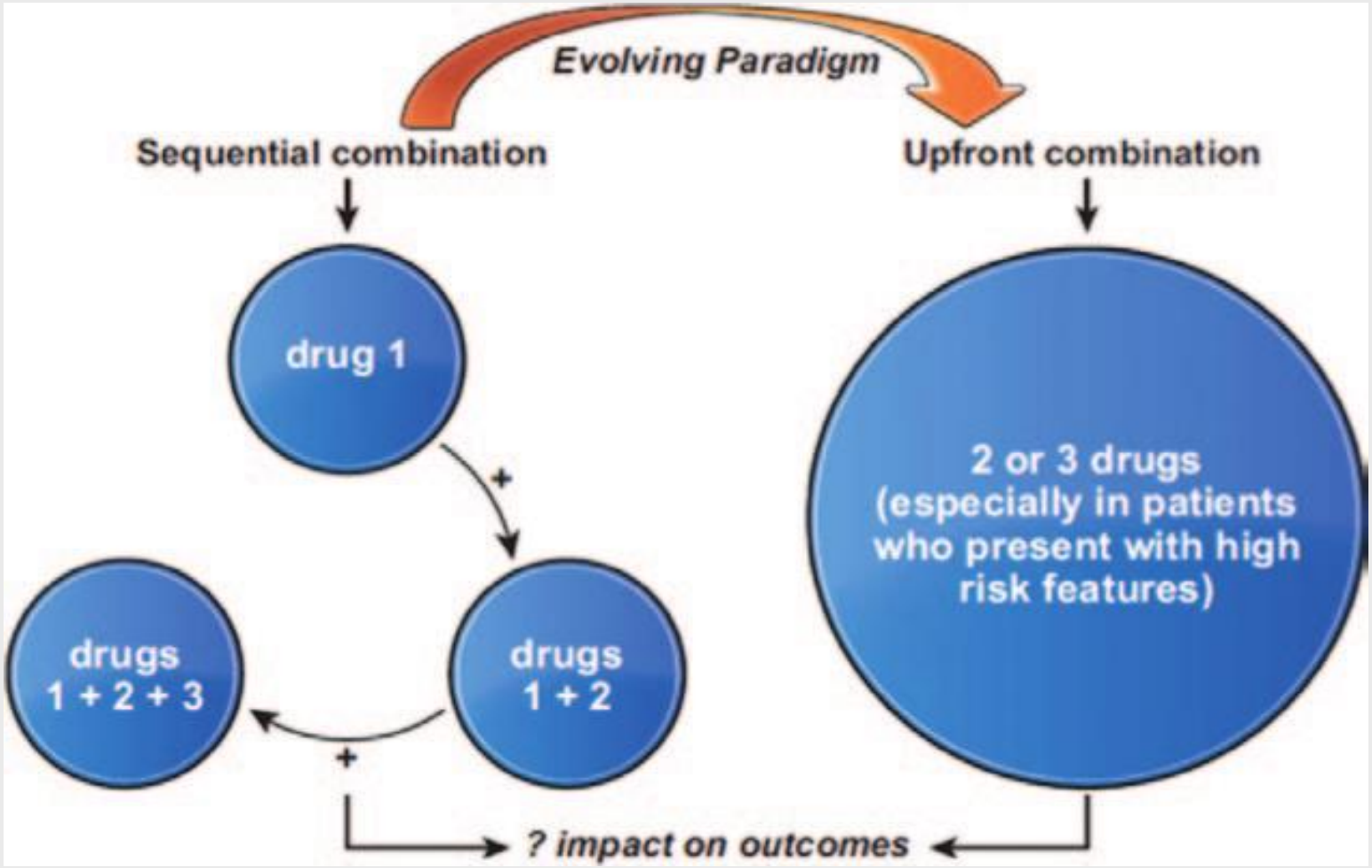
Consistent treatment effect of selexipag on primary composite endpoint according to background therapy



	Selexipag	Placebo
Selexipag vs placebo	No. of patients/ no. of events	
All patients	574/155	582/242
PAH specific therapy at baseline (interaction *p* value = 0.95)		
ERA + PDE-5i	179/47	197/80
ERA monotherapy	94/23	76/29
PDE-5i monotherapy	189/54	185/84
No PAH-specific therapy	112/31	124/49

Sitbon O, et al. N Engl J Med 2015;373:2522-33

Evolving paradigm
From sequential to initial combination therapy



Humbert M, et al. N Engl J Med 2004 & Circulation 2014

The AMBITION trial

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

- **Event-driven study**
- **Initial combo AMB+TADA vs monotherapy AMB or TADA**
- **N=500 treatment-naïve patients with PAH (31% FC II)**

Galiè N, et al. N Engl J Med 2015; 273:834:44

The AMBITION trial: Primary endpoint

Time to first clinical failure event

Death (all cause)

Hospitalization for worsening PAH

- Any hospitalization for worsening PAH
- Lung transplantation
- Atrial septostomy
- Initiation of parenteral prostanoid therapy

Disease progression

- Decrease in 6MWD > 15% vs baseline with FC III-IV (2 visits > 14 days)

Unsatisfactory long-term response

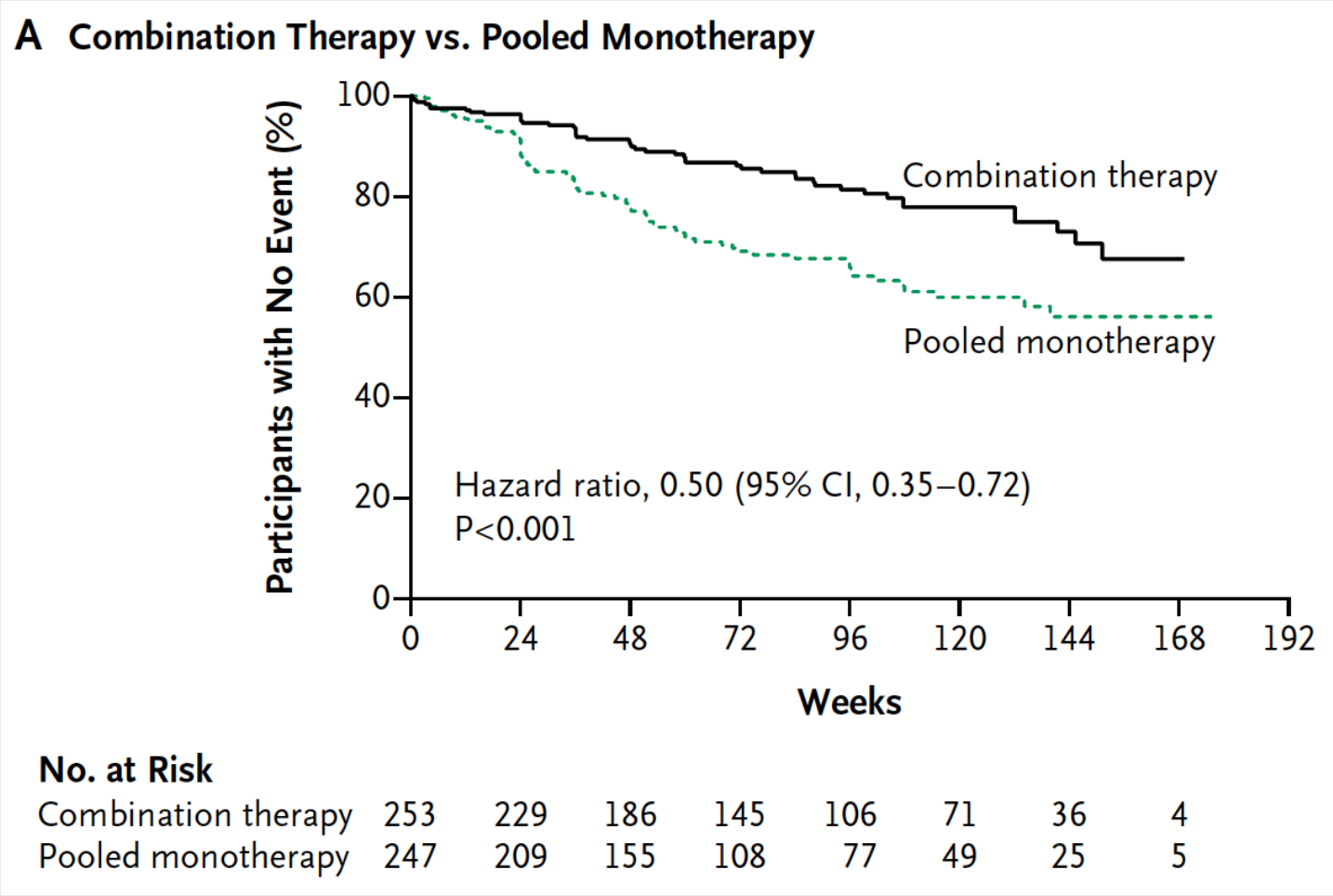
ALL

- 1 dose of IP and > 6 months in study
- Decrease in 6MWD (any amount)
- FC III at 2 visits separated by 6 months

All events were adjudicated

Galiè N, et al. N Engl J Med 2015; 273:834:44

The AMBITION trial: main result



Hospitalisation for PAH worsening was the main component of the primary endpoint

Galiè N, et al. N Engl J Med 2015; 273:834:44

Initial combination is also efficacious in SSc-PAH

- 36 week prospective multicentre open-label uncontrolled study
- Initial combination of ambrisentan & tadalafil
  - 24 treatment-naïve patients with PAH-SSc
  - FC II / III: 35% / 65%

	Baseline	36 weeks	*p*
mPAP (mmHg)	42 ± 12	30 ± 7	< 0.01
CI (L/min/m^2)	2.6 ± 0.7	3.3 ± 1.2	< 0.01
PVR (Wood units)	8.4 ± 5.1	4.1 ± 3	< 0.01

Hassoun P, et al. Am J Respir Crit Care Med 2015; 192:1102-10

Initial dual oral combination therapy

Initial dual oral combination therapy in pulmonary arterial hypertension

Olivier Sitbon[1,2,3], Caroline Sattler[1,2,3], Laurent Bertoletti[4,5], Laurent Savale[1,2,3], Vincent Cottin[6], Xavier Jaïs[1,2,3], Pascal De Groote[7], Ari Chaouat[8,9], Céline Chabannes[10], Emmanuel Bergot[11], Hélène Bouvaist[12], Claire Dauphin[13], Arnaud Bourdin[14], Fabrice Bauer[15], David Montani[1,2,3], Marc Humbert[1,2,3] and Gérald Simonneau[1,2,3]

- 97 incident patients with PAH
  - Mean age 54
  - NYHA FC II-III (88%) & IV (12%)
- Initial dual oral combination therapy with ERA and PDE5i
  - BOS-SIL (n=61)
  - BOS-TAD (n=17)
  - AMB-SIL (n=8)
  - AMB-TAD (n=11)
    - Median follow-up: 30 months [20 – 43]

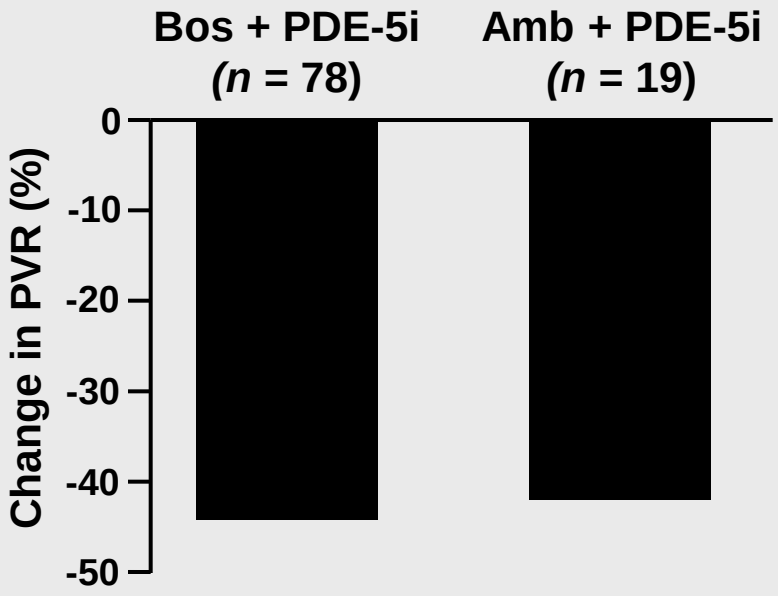
Sitbon O, et al. Eur Respir J 2016; 47:1727-36

Initial dual oral combination therapy
Effect on exercise capacity and haemodynamics

n=97	Baseline	*Median 4.1 months*	P-value[#]
NYHA FC (I : II : III : IV), *n*	0 : 15 : 70 : 12	4 : 57 : 31 : 5	<.001
6MWD, *m*	324 ± 132	395 ± 114	<.00001
BNP level, *ng/L* (n=42, median)	372	62	<.00001
Haemodynamics			
RAP, *mmHg*	9.5 ± 5.7	6.7 ± 4.5	<.00001
mPAP, *mmHg*	53.9 ± 10.4	45.1 ± 10.9	<.00001
CI, *L/min/m²*	2.14 ± 0.51	3.13 ± 0.79	<.00001
PVR, *dyn.s.cm⁻⁵*	1021 ± 357	565 ± 252	<.00001
Mean BP, *mmHg*	97.5 ± 17.7	87.2 ± 12.6	<.00001

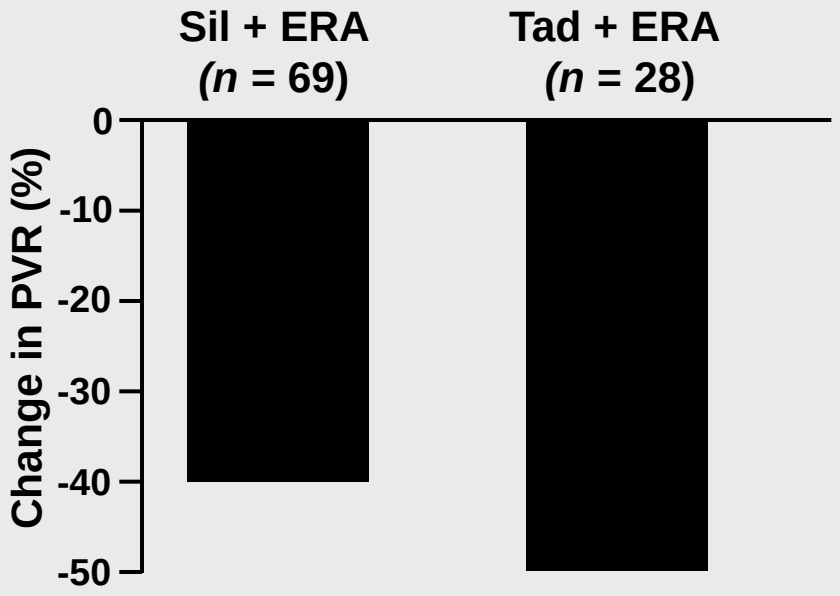
Sitbon O, et al. Eur Respir J 2016; 47:1727-36

The strategy works with different combinations



p = 0.74

Mean ± SD	-44% ± 20%	-42% ± 21%
95%CI	[-48%; -39%]	[-51%; -32%]



p = 0.03

-41% ± 20%	-49% ± 19%
[-45% ;-36%]	[-56%; -42%]

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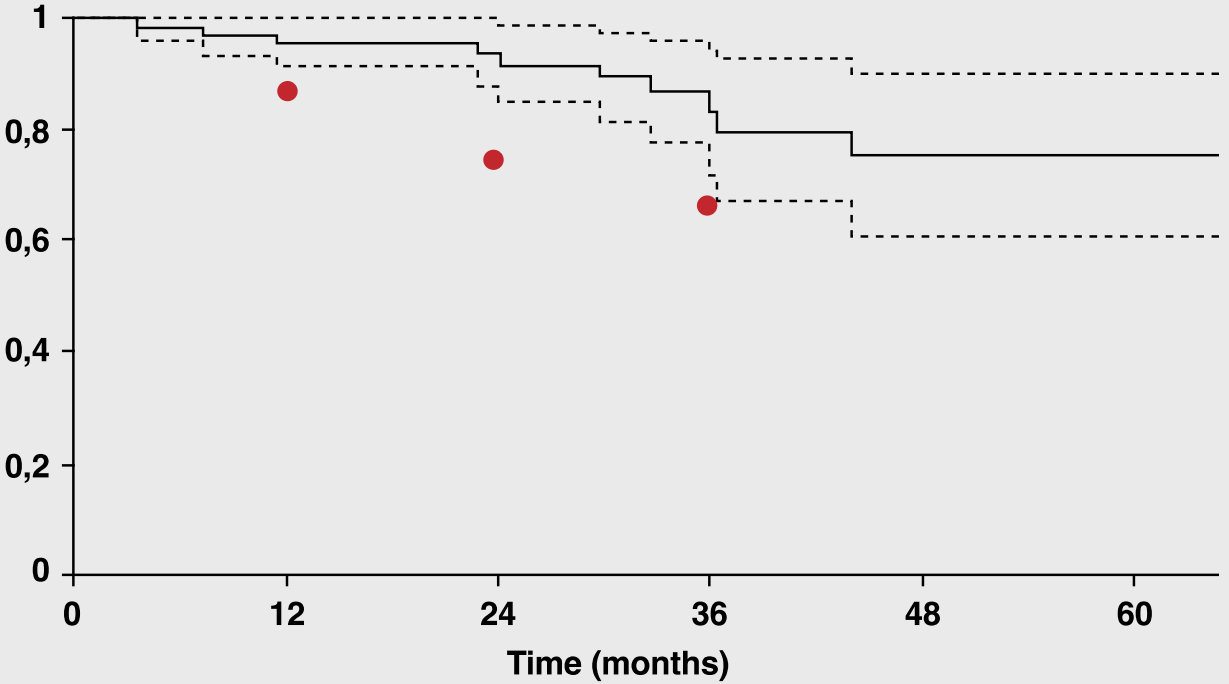
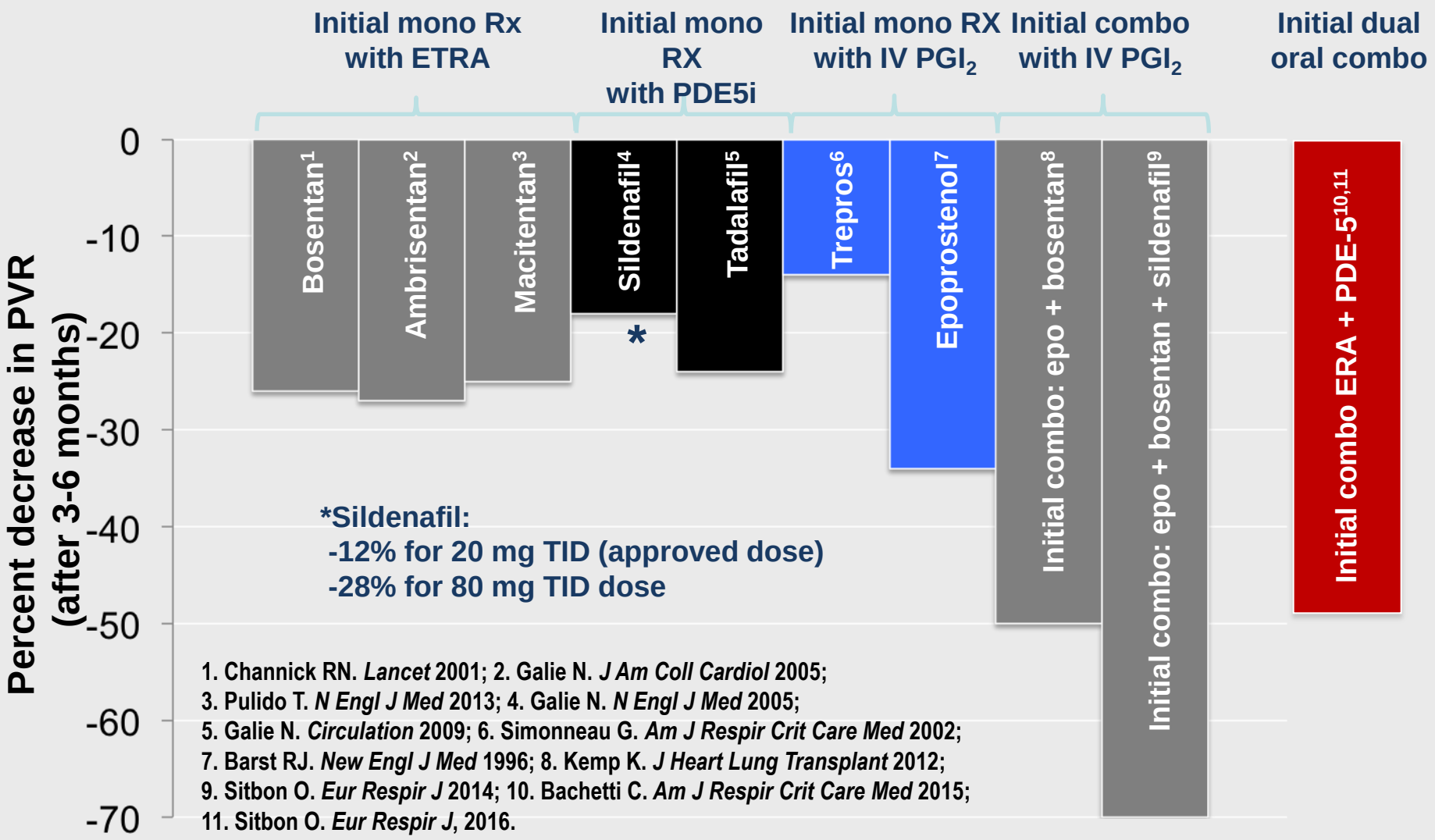
Survival of patients with idiopathic, heritable and anorexigen-associated PAH (n=74)



At risk, n	74	66	51	27	14	6
Actual survival [IC 95%]		96 [91-100]	94 [88-99]	84 [72-95]	75 [61-90]	
Expected survival [IC 95%]		86 [83-88]	75 [71-79]	66 [62-71]		

Sitbon O, et al. Eur Respir J 2016; 47:1727-36

Initial PAH therapy: effects on PVR



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Sitbon O, et al. Eur Respir J 2016; 47:1727-36

Clinical consequences
2015 ESC/ERS GUIDELINES

ESC/ERS GUIDELINES
PULMONARY HYPERTENSION

2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

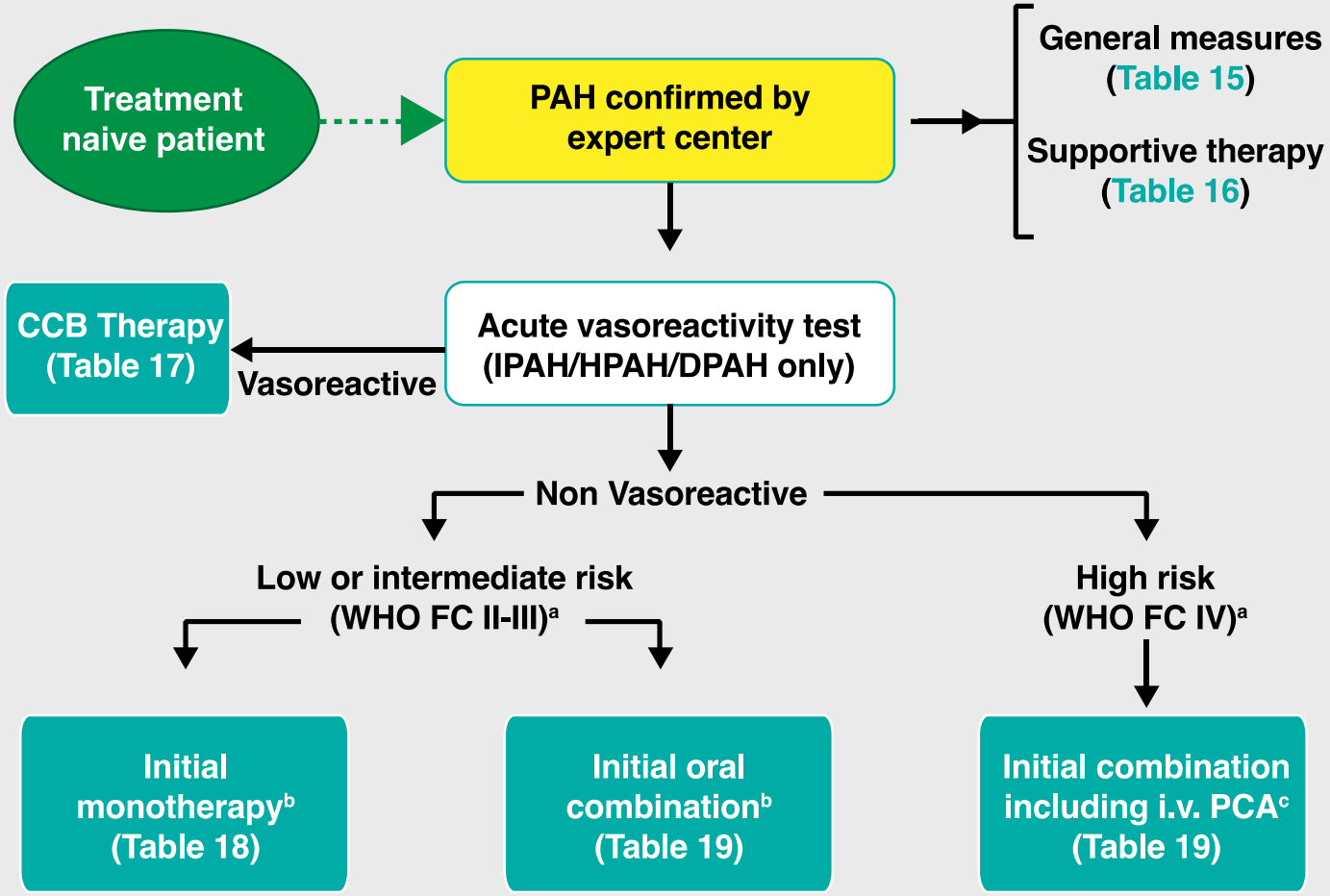
The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)

Nazzareno Galiè[1] (ESC Chairperson), Marc Humbert[2] (ERS Chairperson), Jean-Luc Vachiery[3], Simon Gibbs[1], Irene Lang[1], Adam Torbicki[1], Gérald Simonneau[2], Andrew Peacock[2], Anton Vonk Noordegraaf[2], Maurice Beghetti[4], Ardeschir Ghofrani[2], Miguel Angel Gomez Sanchez[1], Georg Hansmann[4], Walter Klepetko[3], Patrizio Lancellotti[1], Marco Matucci[5], Theresa McDonagh[1], Luc A. Pierard[1], Pedro T. Trindade[1], Maurizio Zompatori[6] and Marius Hoeper[2]

Galiè N, *et al. Eur Respir J 2015 & Eur Heart J* 2016

2015 ESC/ERS PH Guidelines treatment algorithm



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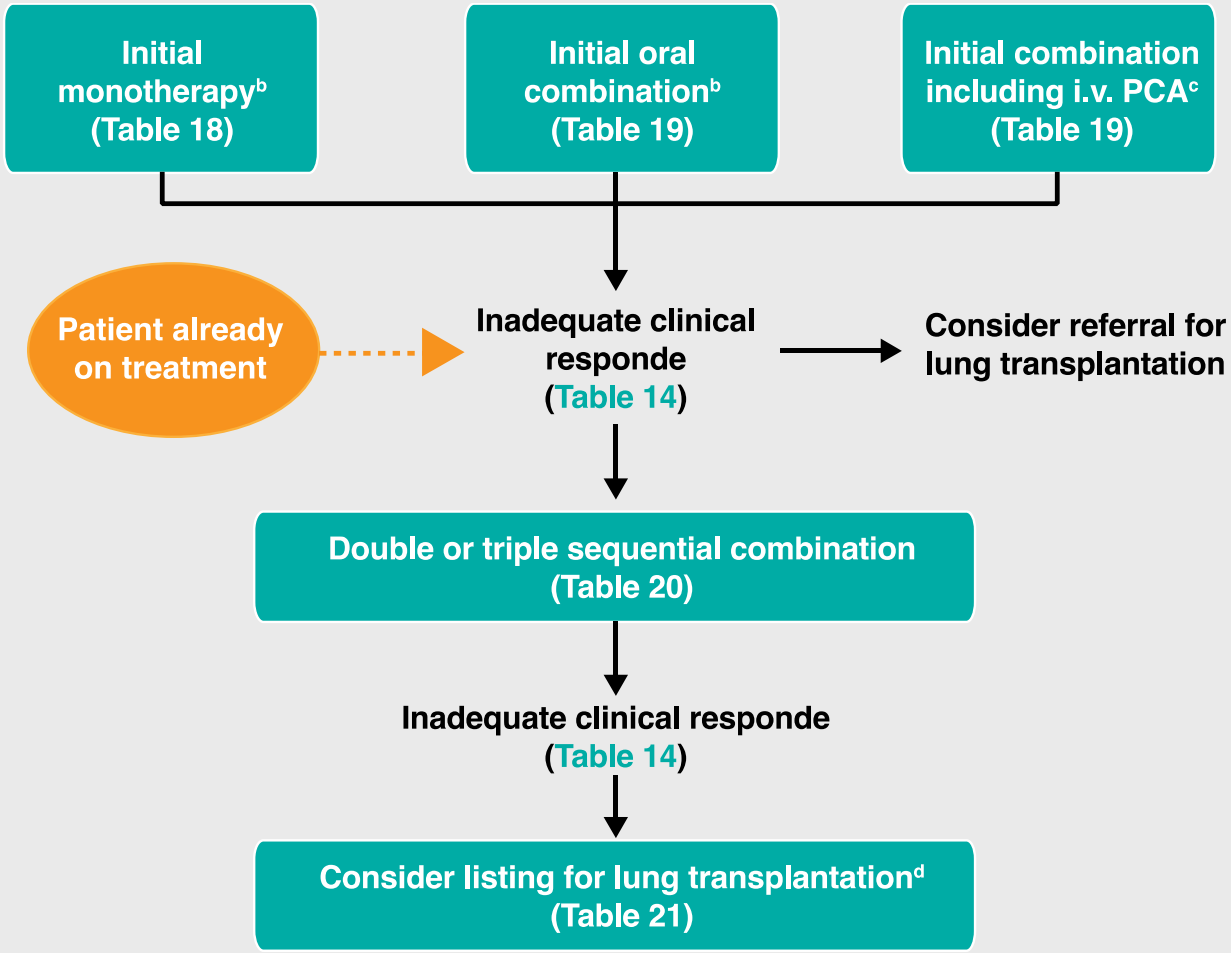
2015 ESC/ERS PH Guidelines treatment algorithm



Galiè N, *et al. Eur Respir J 2015 & Eur Heart J* 2016

2015 ESC/ERS PH Guidelines
The ten commandments

1. Right heart catheterization is recommended to confirm the diagnosis of pulmonary arterial hypertension (PAH - Group 1) and to support treatment decisions

2. Vasoreactivity testing performed during right heart catheterization is recommended in patients with idiopathic PAH, heritable PAH and PAH induced by drugs or toxins use to detect patients who can be treated with high doses of a calcium channel blocker

3. It is recommended to evaluate the severity of PAH patients with a panel of data derived from clinical assessment, exercise tests, biochemical markers, and echocardiographic and haemodynamic evaluation and to perform regular follow-up assessments every 3-6 months in stable patients.

4. It is recommended to avoid pregnancy in patients with PAH

5. It is recommended for referral centres to provide care by a multi-professional team (cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, appropriate on-call expertise)

Galiè N, *et al. Eur Respir J 2015 & Eur Heart J* 2016

2015 ESC/ERS PH Guidelines
The ten commandments

6. Initial drugs monotherapy or initial oral drugs combination therapy is recommended in treatment naïve, low or intermediate risk patients with PAH

7. Sequential drugs combination therapy is recommended in PAH patients with inadequate treatment response to initial monotherapy or to initial oral drugs combination therapy

8. Initial combination therapy including an intravenous prostacyclin analogue is recommended in high risk PAH patients

9. The use of PAH approved therapies is not recommended in patients with pulmonary hypertension due to left heart disease or lung diseases

10. Surgical pulmonary endarterectomy in deep hypothermia circulatory arrest is recommended for patients with CTEPH and it is recommended that the assessment of operability and decisions regarding other treatment strategies (drugs therapy or balloon pulmonary angioplasty) be made by a multidisciplinary team of experts

Galiè N, *et al. Eur Respir J 2015 & Eur Heart J* 2016

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