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University of Glasgow

Triple upfront combination therapy for Pulmonary Arterial Hypertension: are we ready for it?

Andrew Peacock

Torino 26th October 2018

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Message

- **Treatment for Pulmonary hypertension particularly in sick patients has evolved from *monotherapy* to *sequential combination* to *upfront combination***
- ***Triple upfront therapy* makes sense especially in young sick patients but:**
  - No randomised trials
  - Very expensive


Orkney Islands
Shetland Islands
Mainland
Hoy
Sanday
Outer Hebrides
Lewis
North Uist
South Uist
Skye
Barra
Rhum
Coll
Tiree
Mull
Jura
Islay
Arran
The Minch
The Little Minch
ATLANTIC
OCEAN
NORTH
SEA
SCOTLAND
Aberdeen
Glasgow
Edinburgh
NORTHERN IRELAND
Belfast
North Channel
ISLE OF MAN
Isle of Man
IRISH SEA
Dublin
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Leeds
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Sheffield
Newcastle upon Tyne
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Nottingham
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LONDON
Southampton
Exeter
Plymouth
Isles of Scilly
Portsmouth
Brighton
Strait of Dover
ENGLISH CHANNEL
Guernsey
Jersey
CHANNEL ISLANDS
FRANCE

Scottish Referendum for Independence from UK after 300 years!

Scottish Referendum for Independence from UK after 300 years! Referendum lost but now that EU vote has gone for separation Scotland may leave UK

Nota Bene……Italy Lega Norte; Spain Catalonia; Belgium: Flanders vs Wallonia

EU Referendum June 23rd 2016

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The BREXIT campaign run by these two……..

And gathered momentum…

Leaving a devavasted population of young people

EU Referendum June 23rd 2016

- **Voted to *Leave* 52% to 48%. PM resigns**
- **Only 36% of total population voted. Young people voted 60% to 40 % to *Remain***
- **If over 65 had not voted then UK *Remains***
- **Scotland voted 62% to 38% to *Remain* and once again talks of separation**

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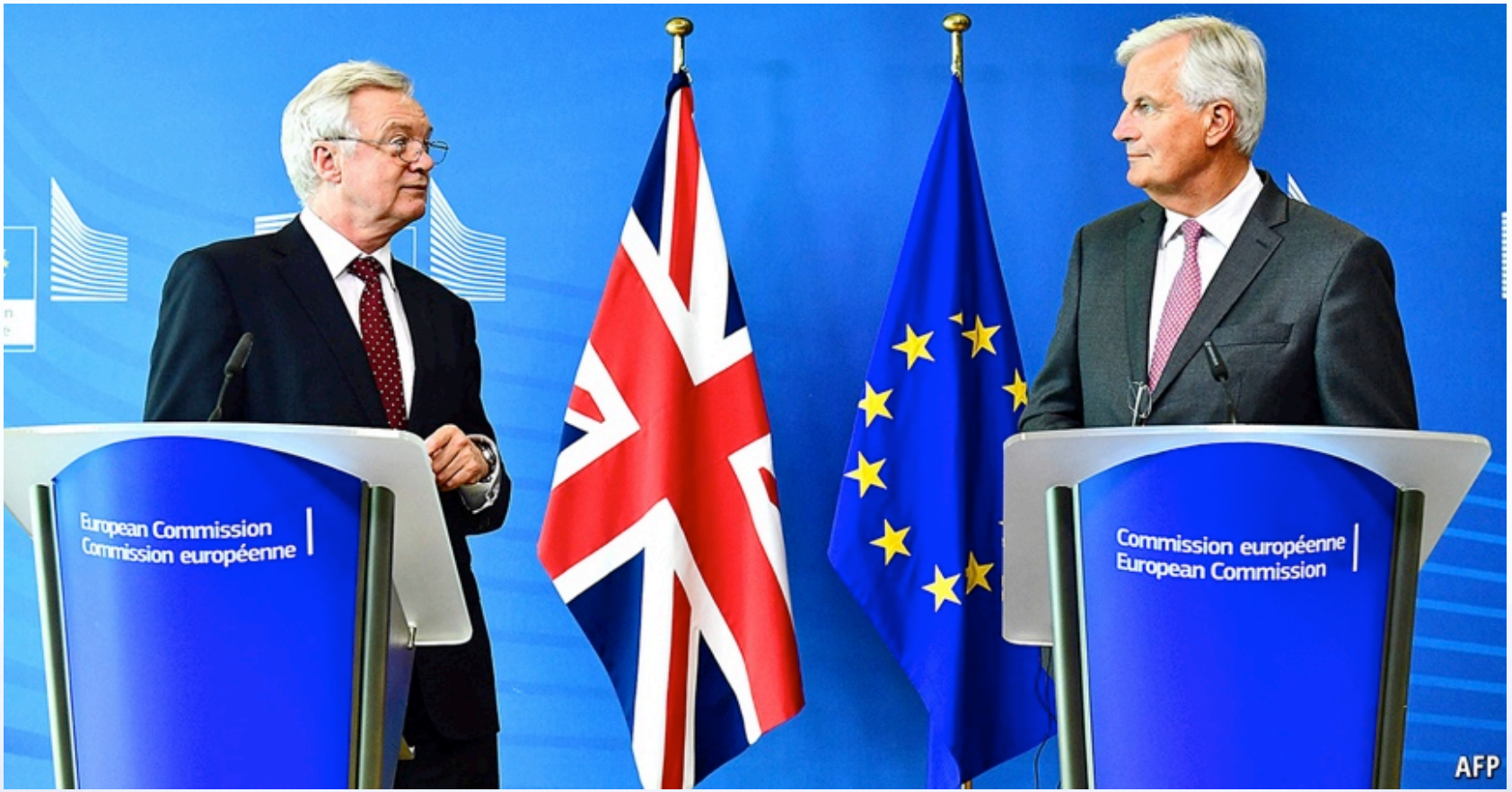
Why did UK (England and Wales) vote BREXIT?

- Poor white people frightened of *immigration*
- Rich white people concerned about *sovereignty*
- Non white people ignored
- No-one thought about *economic* consequences



David Davis (UK) vs Michel Barnier (EU)

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What happens now?

- **March 29th 2019 is exit day but some hope for extension because of economic catastrophe**
- **Trade negotiations stalled until problems of:**
  - Exit bill
  - Irish border
  - Status of EU citizens in UK resolved (eg 17000 EU doctors in the UK)
  - >1000 pieces of new UK legislation

We are likely to leave with no deal
Don't do it Italy!

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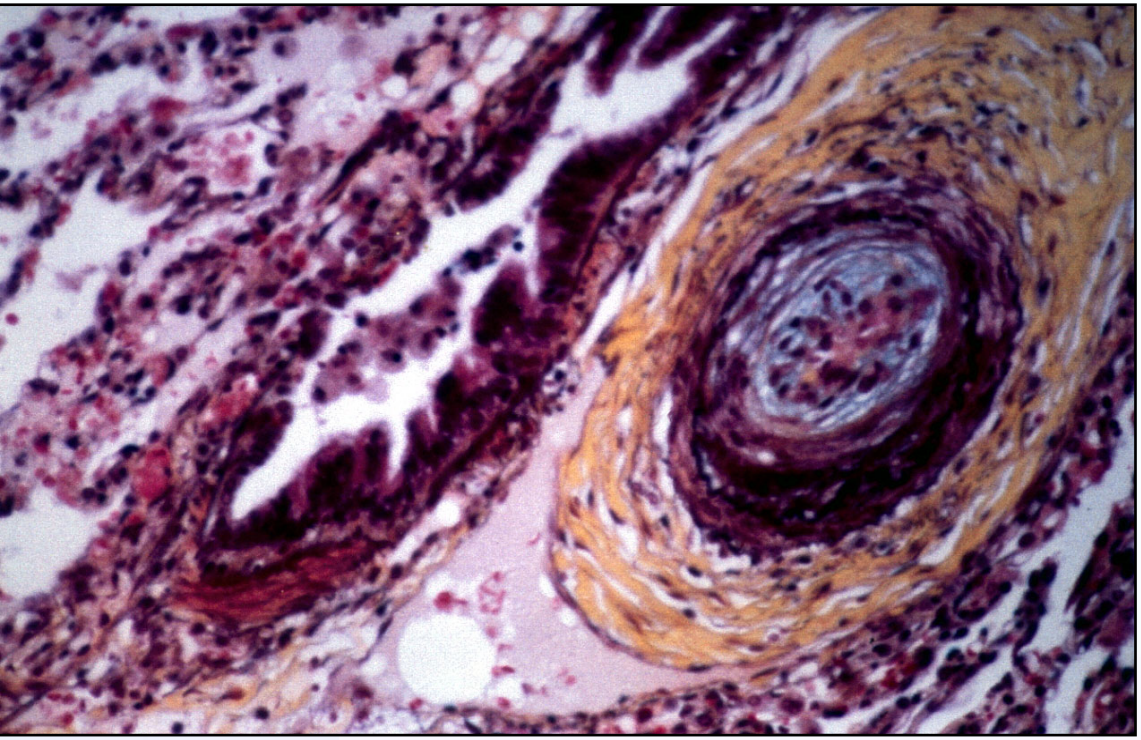
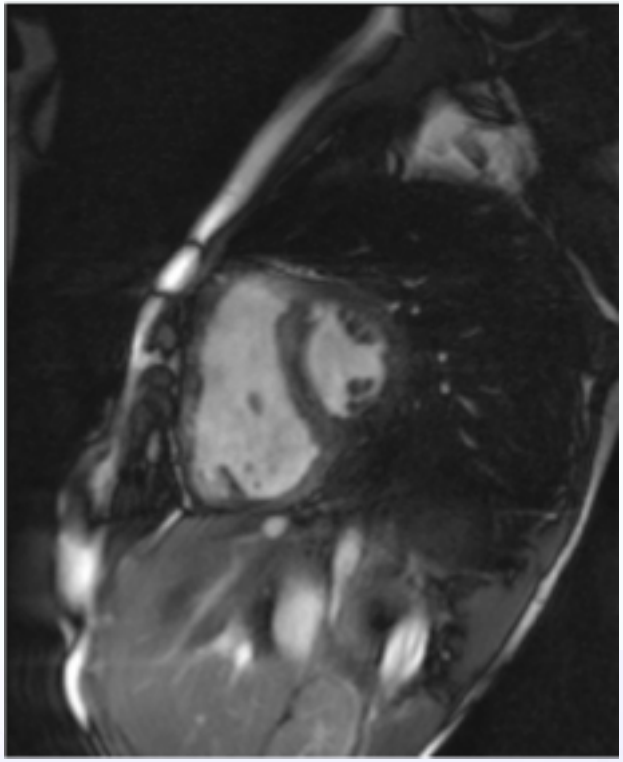
What is Pulmonary Arterial hypertension?

What is Pulmonary arterial Hypertension?





ie Vessels *and* Heart

PAH: how do we treat it?

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The 3 *Current* Therapeutic Pathways for PAH

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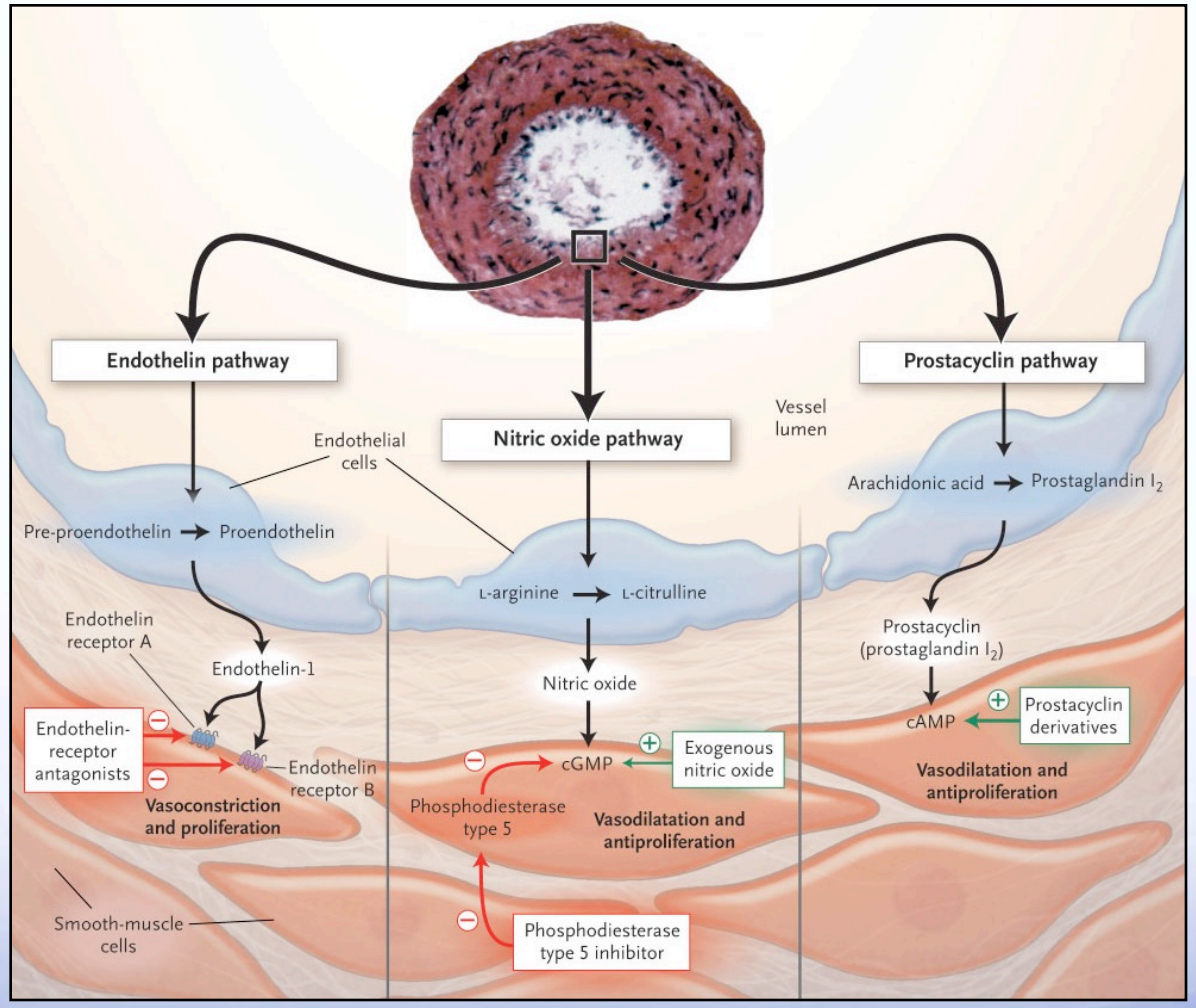
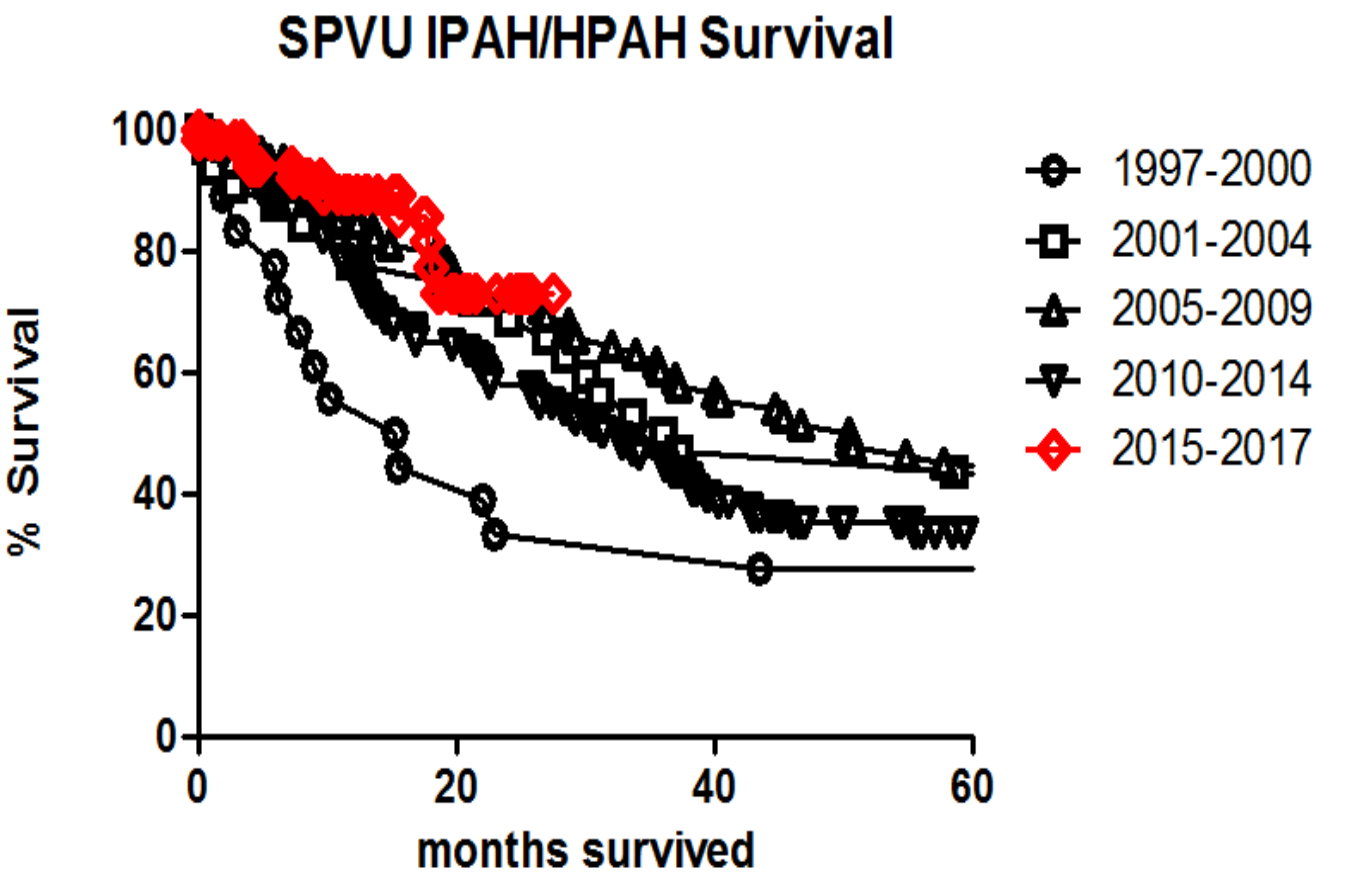


cAMP=Cyclic adenosine monophosphate; cGMP=Cyclic guanosine monophosphate.
Humbert M, et al. *N Engl J Med* 2004;351:1425–1436.

..but…….survival for IPAH…still not good enough!



What can we do?

- **New drugs**

  VIP agonists, Statins, TK inhibitors, Prostacyclin receptor agonists, Guanylate cyclase activators, p38 MAPK inhibitors

- **Non Drug Rx**
  - **Exercise training**

- **Treating the RV**

  Beta Blockers, PDE5i

- **Old drugs new tricks**

  Mode of delivery (oral, inhaled, s/c), Combination Rx, Tissue penetration

Old drugs new tricks
Combination therapy

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Combination Therapies Using the 3 Classes We Have Now

Lessons from other disease areas

- HIV
- Heart failure
- Asthma

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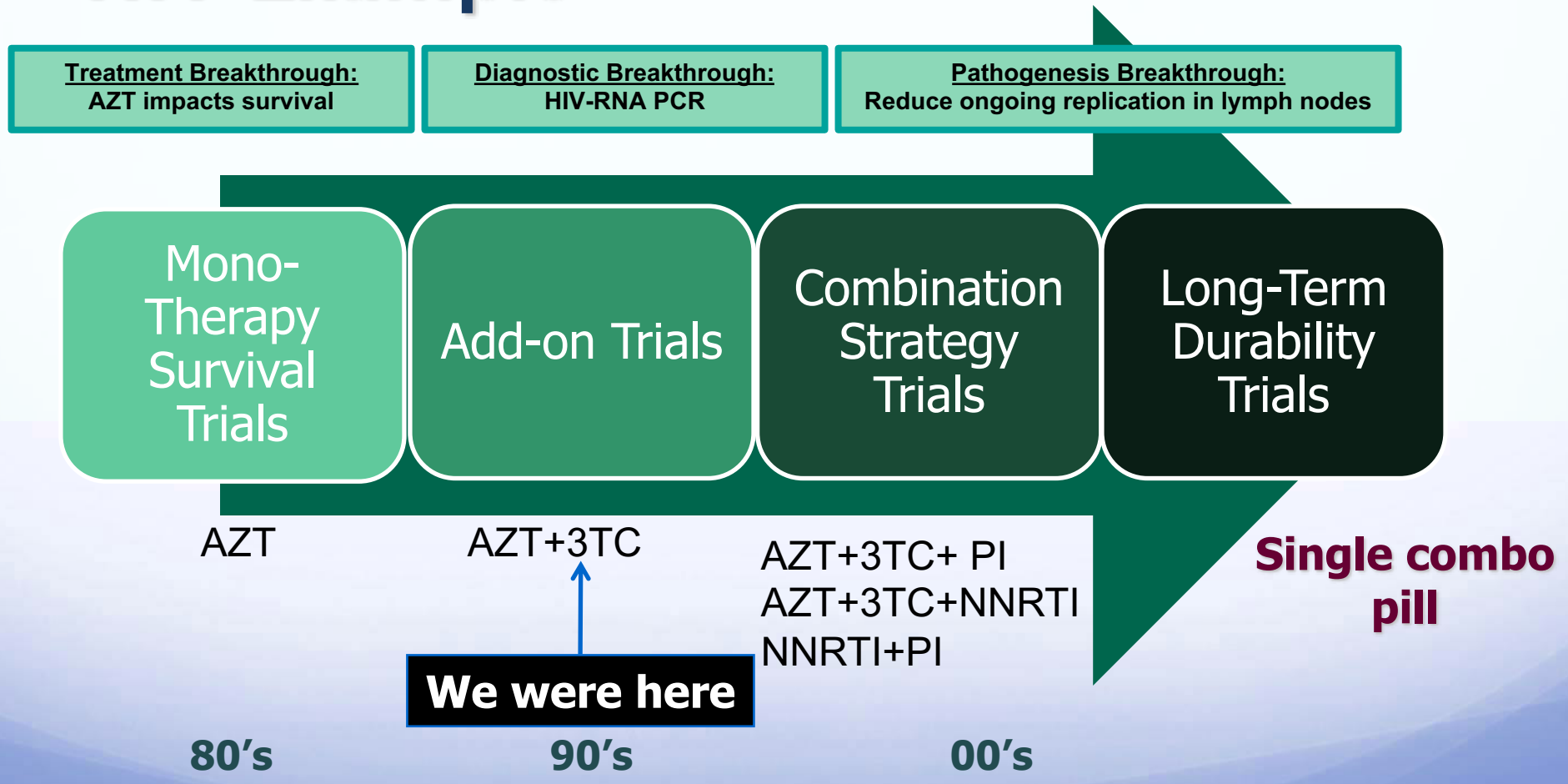
HIV=Human immunodeficiency virus.

What can we learn from other chronic, life-threatening diseases?

HIV Example

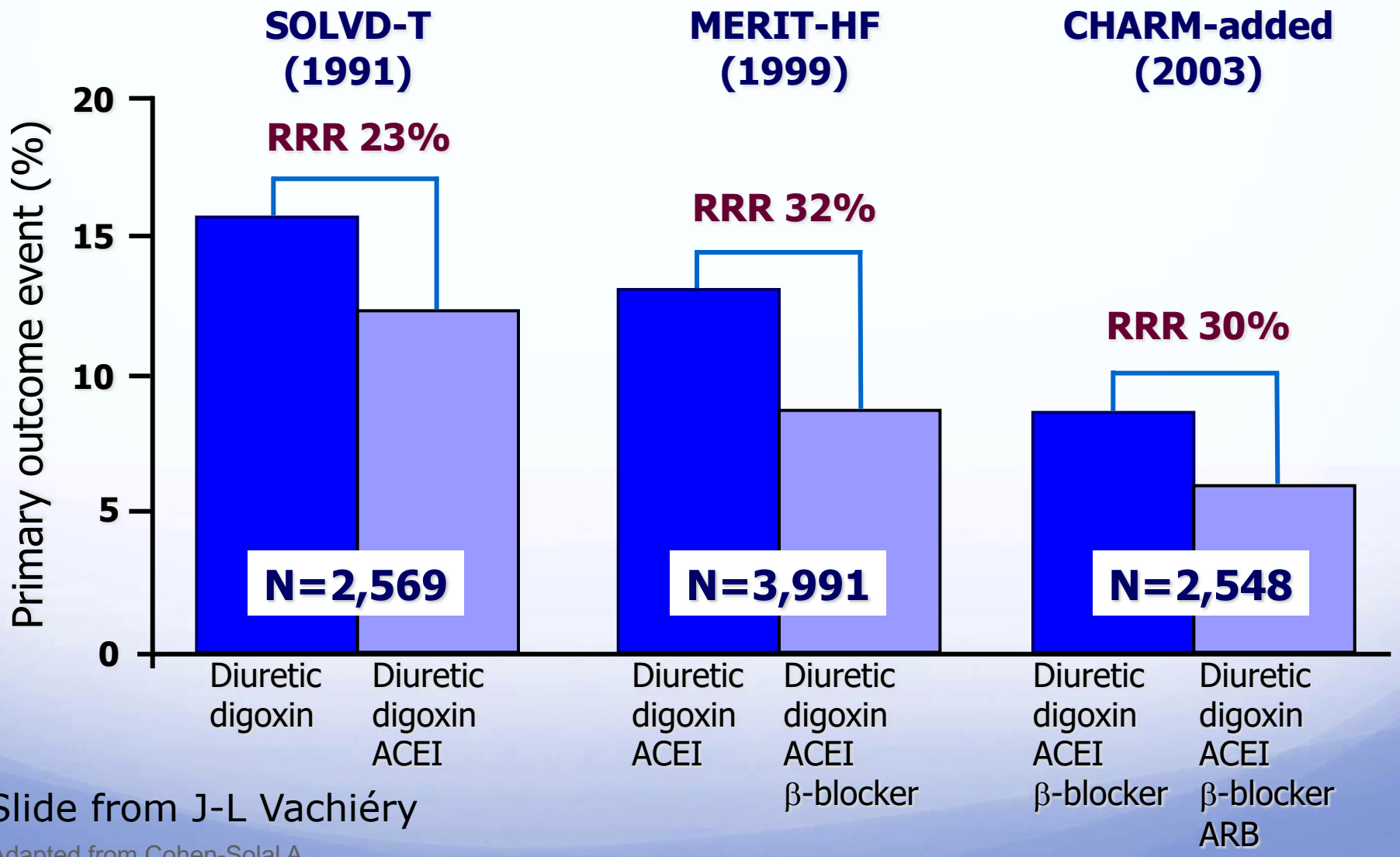


Slide courtesy of Prof. Jean-Luc Vachiery

AZT, zidovudine; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; 3TC, lamivudine.

Heart Failure

From Mortality to Composite Endpoint



Slide from J-L Vachiéry

Adapted from Cohen-Solal A.

ACEI=Angiotensin-converting enzyme inhibitors; ARB=Angiotensin receptor blocker; RRR=Relative risk reduction.

Asthma

Beta Agonists → Inhaled/Oral Steroids → Steroids and LABA/LAMA

We are here

Aggressive early management

70s **80s** **90s**

LABA=Long-acting beta agonist.

Pulmonary Arterial Hypertension

The evidence for combination therapy

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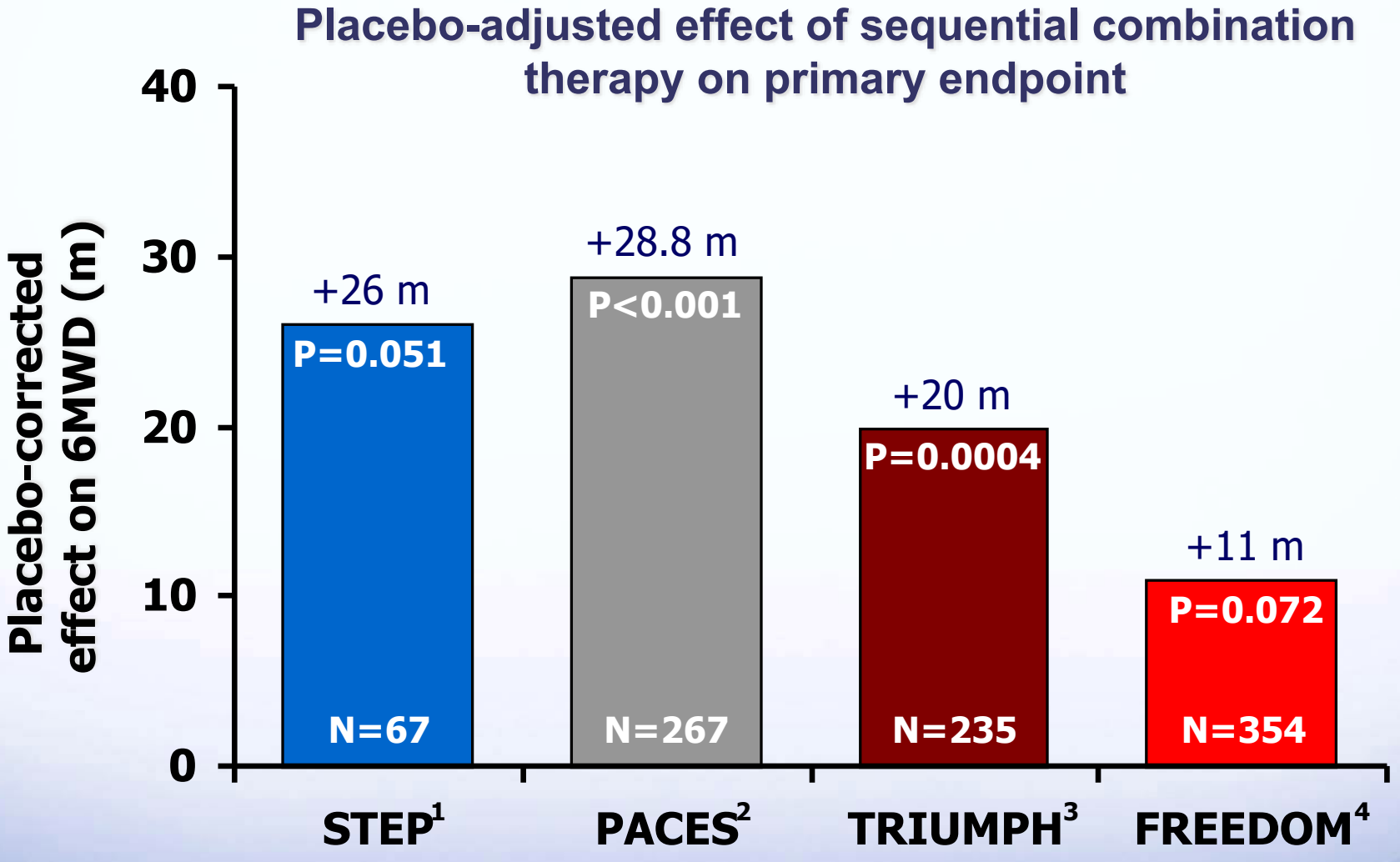
Evidence in Combination Therapy for PAH (3)



Slide from J-L Vachiéry

1. McLaughlin V, et al. *Am J Respir Crit Care Med* 2006;174:1257–1263;
2. Simonneau G, et al. *Ann Intern Med* 2008;149:521–530; 3. McLaughlin V, et al. *J Am Coll Cardiol* 2010;55:1915–1922;
4. Tapson V. ATS 2009.

Interim Summary

- **Reasonable evidence for benefit of *sequential* combination therapy in PAH (6MWD vs Time to Clinical Worsening)**

- **What about benefits of *initial* combination therapy for PAH?**

Initial Combination Therapy

- Co-administration of PAH drugs should provide synergistic effects
- Initial combination therapy: the simultaneous administration of more than one drug ("hit hard and early") to a drug-naïve patient is attractive

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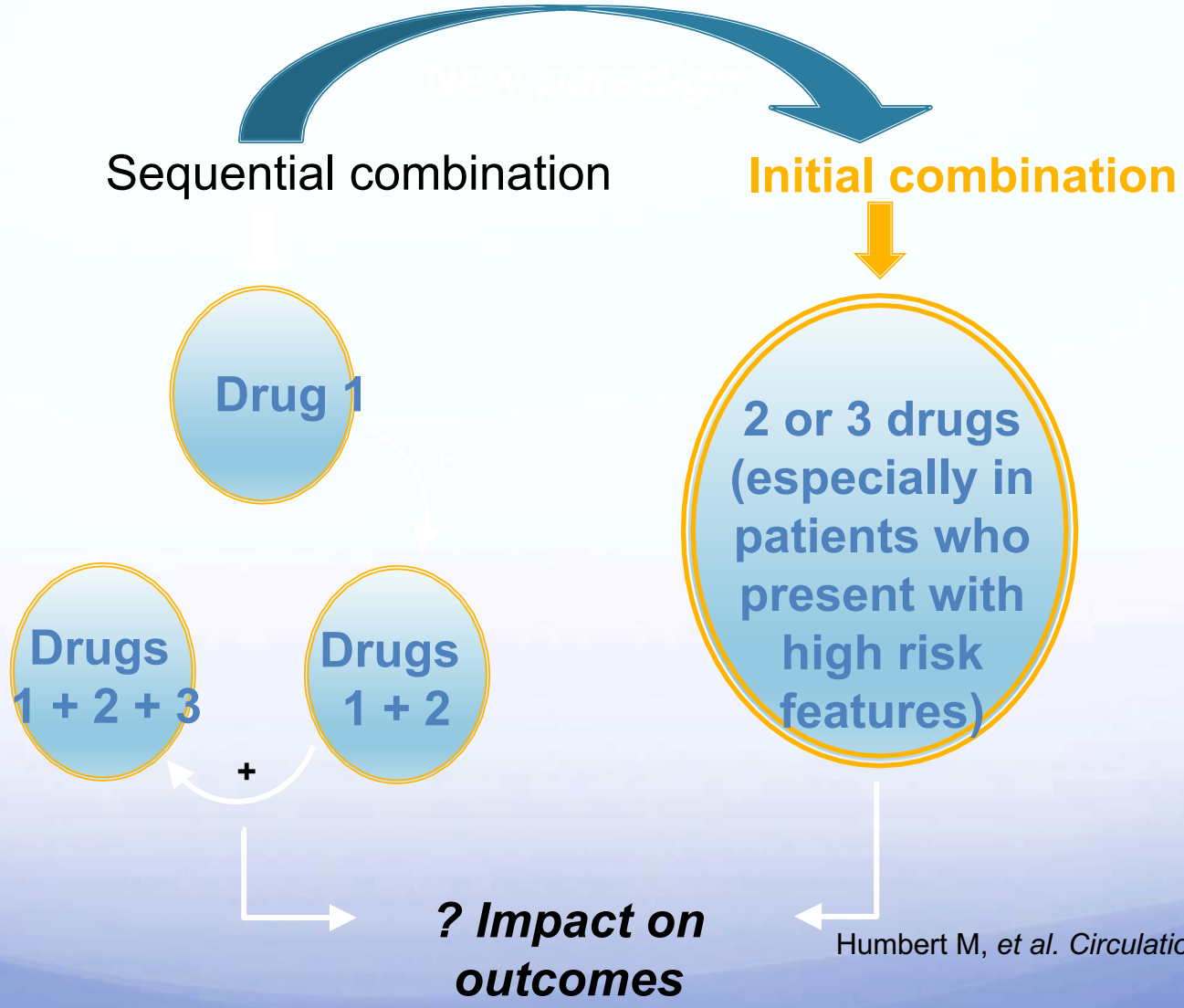
Beyond the Guidelines: for new incident PAH patients initial combination therapy well established.



Humbert M, *et al. Circulation* 2014;130:2189-208.

The AMBITION trial

Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension

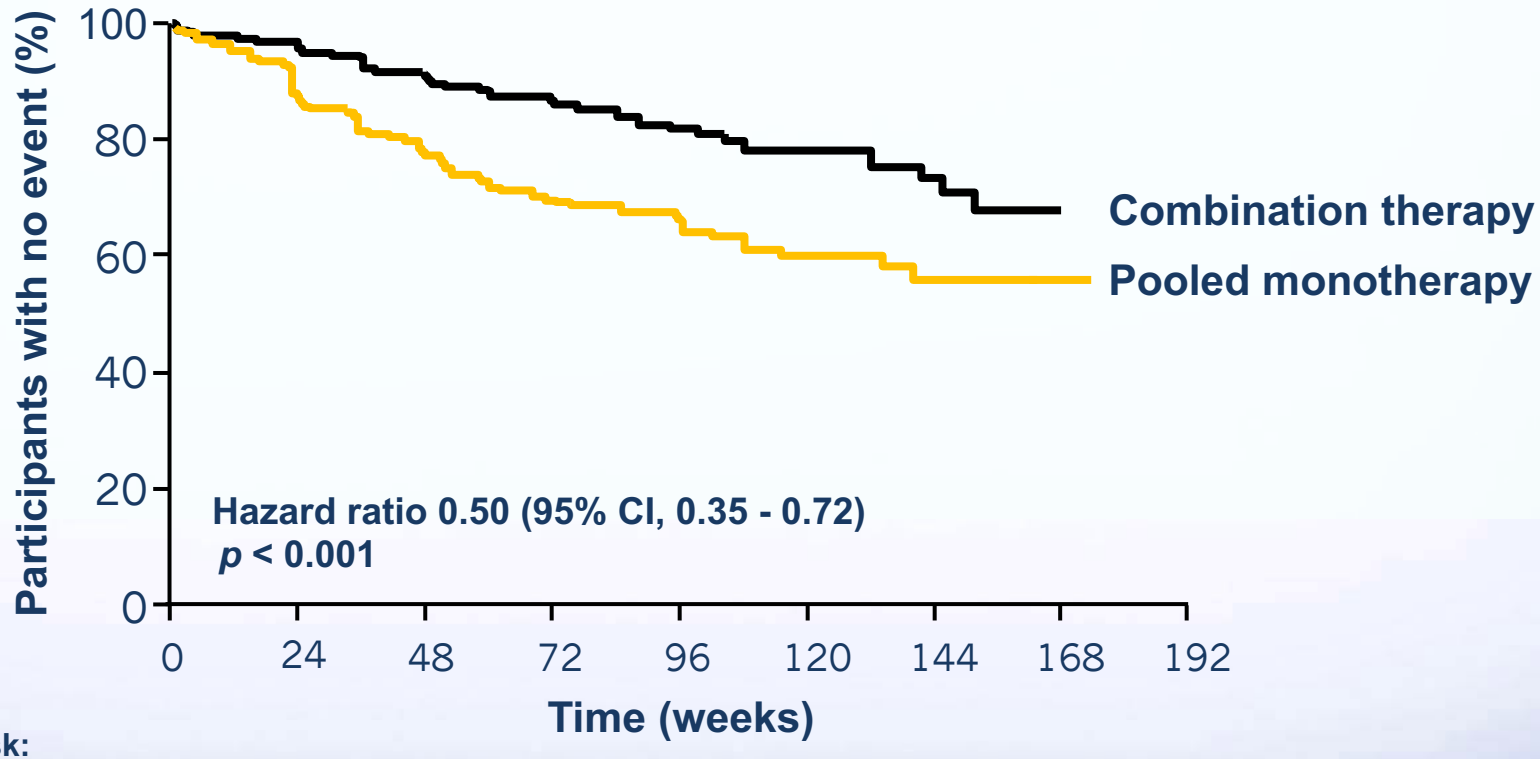
N. Galiè, J.A. Barberà, A.E. Frost, H.-A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, A.J. Peacock, G. Simonneau, J.-L. Vachiery, E. Grünig, R.J. Oudiz, A. Vonk-Noordegraaf, R.J. White, C. Blair, H. Gillies, K.L. Miller, J.H.N. Harris, J. Langley, and L.J. Rubin, for the AMBITION Investigators*

- 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.

Initial combination is better than monotherapy

Combination vs pooled monotherapy



Number at risk:

Combination therapy	253	229	186	145	106	71	36	4
Pooled monotherapy	247	209	155	108	77	49	25	5

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

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

Question?

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....if double combination is good would triple upfront be better?

What is severe PAH?

- **Severe signs and symptoms**
  - NYHA FC IV
  - Also NYHA FC III with severe haemodynamic impairement
  - Recurrent syncope (except children and acute responders)
  - Right heart failure
- **Impaired exercise capacity**
  - 6MWT / CPET
- **Severe RV dysfunction**
  - RHC / Echo / Biomarkers (BNP or NT-pro-BNP)
- **Reduced life expectancy +++**

Initial triple combination therapy in severe PAH

Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study

Olivier Sitbon[1,2,3], Xavier Jaïs[1,2,3], Laurent Savale[1,2,3], Vincent Cottin[4], Emmanuel Bergot[5], Elise Artaud Macari[1,2,3], Hélène Bouvaist[6], Claire Dauphin[7], François Picard[8], Sophie Bulifon[1,2,3], David Montani[1,2,3], Marc Humbert[1,2,3] and Gérald Simonneau[1,2,3]

- Prospective, observational analysis of incident patients with idiopathic or heritable PAH (n = 19) treated with initial combination therapy (epoprostenol, bosentan and sildenafil)
- Mean age 39 ± 14 years (18 – 63)
- NYHA FC III (n=8) or IV (n=11)
- Severe hemodynamics: CI < 2.0 L/min/m^2 or PVR > 1000 d.s.cm^{-5}

Sitbon O, *et al. Eur Respir J.* 2014;43:1691–7.

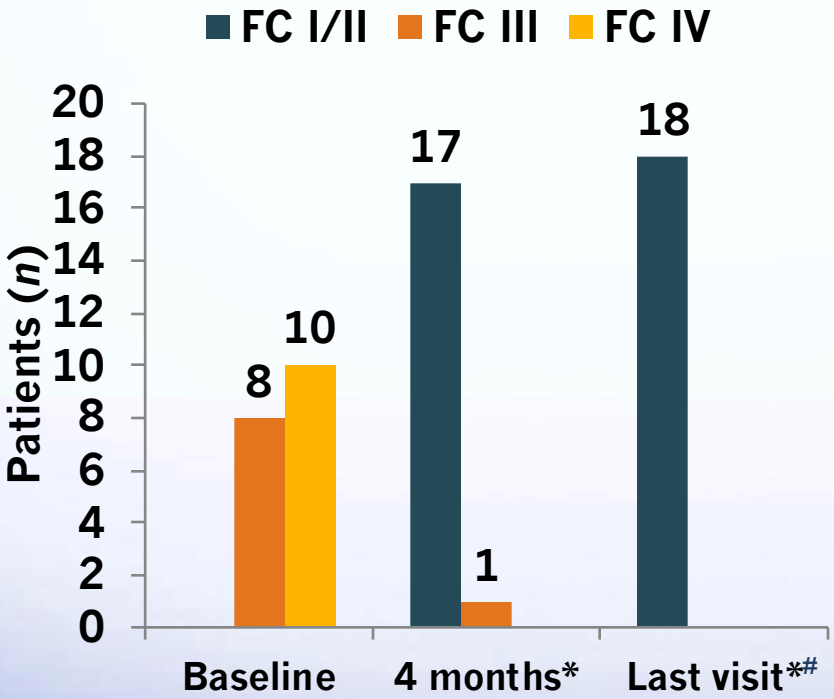
Baseline characteristics

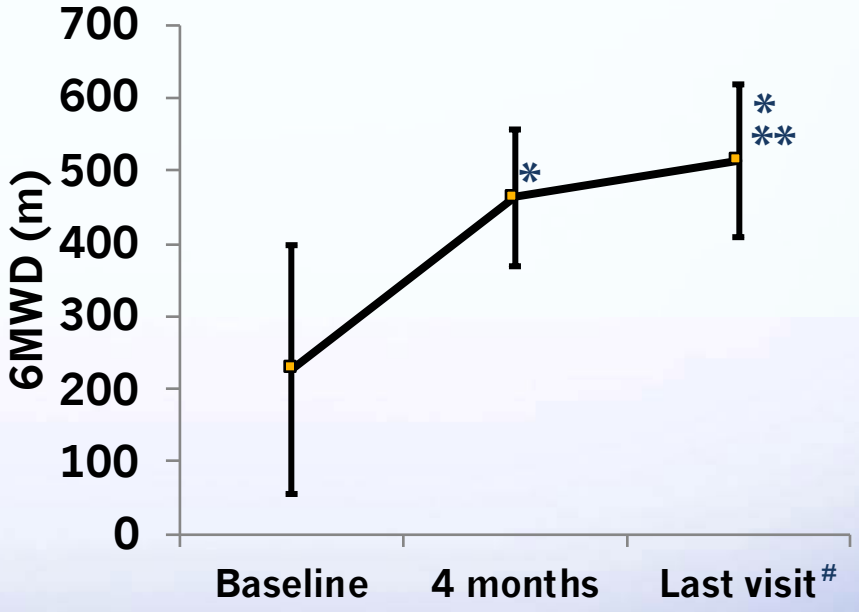
Age, years (mean ± SD, range)	39 ± 14 (18 – 63)
Female, n (%)	17 (89%)
Idiopathic : Heritable PAH, n	9 : 10
NYHA FC III : IV, n (%)	8 (42%) : 11 (58%)
6MWD, m	215 ± 174 m
Haemodynamics	
RAP, mmHg	12 ± 5
mPAP, mmHg	68 ± 16
PCWP, mmHg	8 ± 3
CI, $L.min^{-1}.m^{-2}$	1.6 ± 0.3
PVR, $dyn.s.cm^{-5}$	1807 ± 722
SvO_2, %	50 ± 9

Sitbon O, *et al. Eur Respir J.* **2014;43:1691–7.**

Upfront triple combination therapy: Effect on FC and 6MWD

Prospective, observational analysis of idiopathic or heritable PAH patients (*n* = 19) treated with upfront combination therapy (epoprostenol, bosentan and sildenafil)

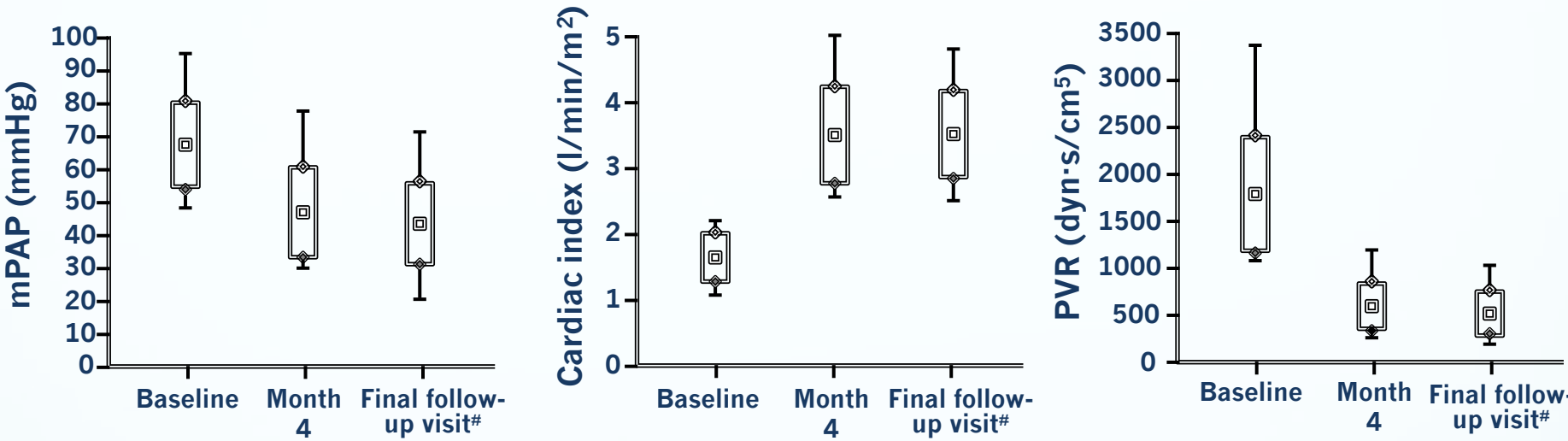




#32 ± 19 months
*$p < 0.01$ versus baseline; ** $p < 0.01$ versus 4 months

Sitbon O, *et al. Eur Respir J.* 2014;43:1691–7.

Upfront triple combination therapy: Effect on haemodynamics



	Baseline	Month 4	Final follow-up#
RAP (mmHg)	11.9 ± 5.2	4.9 ± 4.9*	5.2 ± 3.5*
mPAP (mmHg)	65.8 ± 13.7	45.7 ± 14.0*	44.4 ± 13.4*
CI (l/min/m^2)	1.66 ± 0.35	3.49 ± 0.69*	3.64 ± 0.65*
PVR (d.s.cm^{-5})	1718 ± 627	564 ± 260*	492 ± 209*

#32 ± 19 months
*$p < 0.01$ versus baseline

Sitbon O, *et al. Eur Respir J.* **2014;43:1691–7.**

Upfront triple combination therapy: Long-term outcome / survival

- **Long-term follow-up *(n=18)***
  - Median follow-up: 39.2 months (range: 13.7 – 73.3 months)
  - All patients well and alive in NYHA FC I-II
  - 6 patients with mPAP < 30 mmHg (incl. one < 20 mmHg)

- **Survival *(n=19)***

	1-year	2-year	3-year
Actual	100%	100%	100%
Transplant-free	94%	94%	94%
Expected* [95% CI]	75% [68%-82%]	60% [50%-70%]	49% [38%-60%]

Sitbon O, *et al. Eur Respir J.* **2014;43:1691–7.**

Conclusions

- Upfront **double** combination therapy now well established and trialed in PAH
- Upfront **triple** combination therapy appears to have dramatic benefits in young and sick but:
  - No randomised trials yet
  - Very expensive

Watch this space!

2018

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Simon Kerridge • Katryn Wilson• Fiona Johnstone • Val Pollock • Veronica Ferry • Geesh Jawasekara•Tim Crowe Colin Church