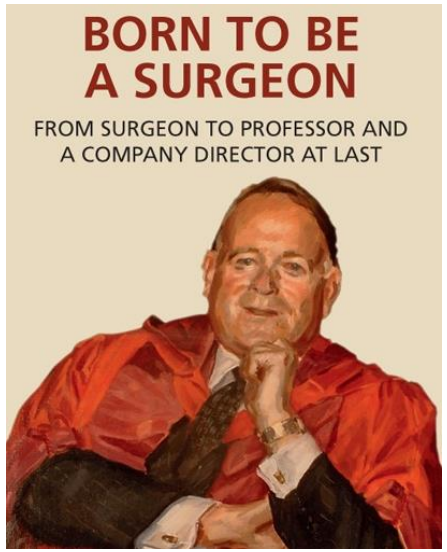
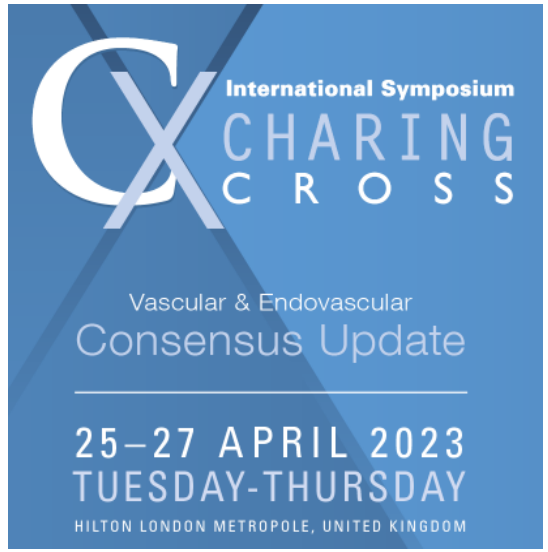
Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) 2 Trial

On behalf of the BASIL-2 Investigators





We have no disclosures

FUNDED BY
NIHR | National Institute for Health and Care Research

Birmingham Clinical Trials Unit

A vein bypass first versus a best endovascular treatment first revascularisation strategy for patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion: Bypass versus Angioplasty for Severe Ischaemia of the Leg (BASIL)-2, an open-label, randomised, multicentre, phase III trial

THE LANCET

On behalf of the BASIL-2 Investigators

Andrew W Bradbury, Catherine A Moakes, Matthew Popplewell, Lewis Meecham, Gareth R Bate, Lisa Kelly, Ian Chetter, Athanasios Diamantopoulos, Arul Ganeshan, Jack Hall, Simon Hobbs, Kim Houlind, Hugh Jarrett, Suzanne Lockyer, Jonas Malmstedt, Jai V Patel, Smitaa Patel, S Tawqeer Rashid, Athanasios Saratzis, Gemma Slinn, D Julian A Scott, Hany Zayed, Jonathan J Deeks, on behalf of the BASIL-2 Investigators

Summary

Background Chronic limb threatening ischaemia is the severest manifestation of peripheral arterial disease and presents with ischaemic pain at rest or tissue loss (ulceration, gangrene, or both), or both. We compared the effectiveness of a vein bypass first with a best endovascular treatment first revascularisation strategy in terms of preventing major amputation and death in patients with chronic limb threatening ischaemia who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure to restore limb perfusion.

Journey from BASIL-1 to BASIL-2

Lewis Meecham

Consultant Vascular Surgeon

University Hospital of Wales, Cardiff

And

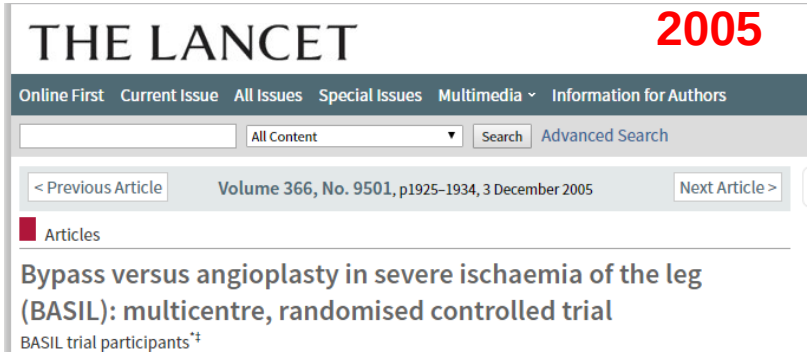
NIHR BASIL Research Fellow

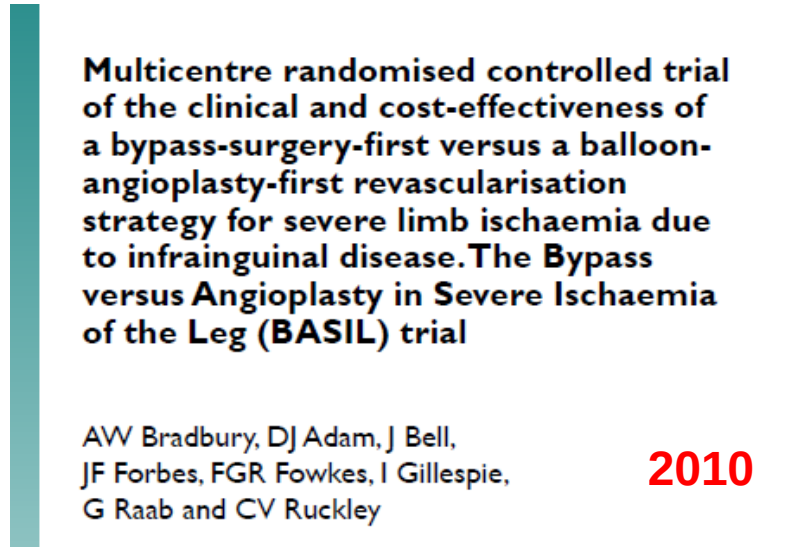
2016-2018

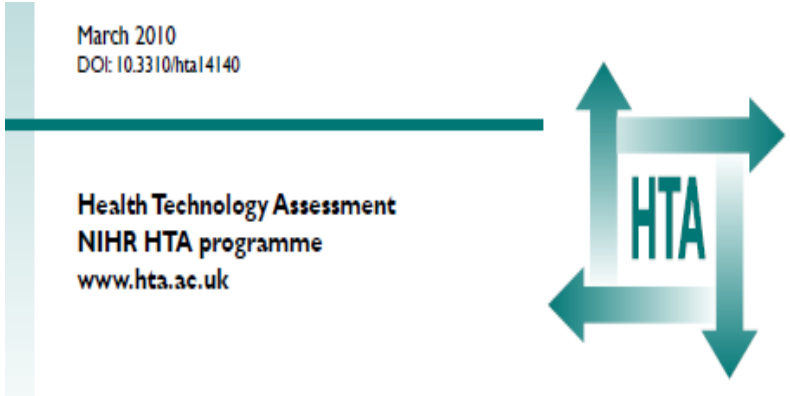
BASIL-1 Trial

- All started > 25 years ago - grant application 1997
- In BASIL-1, between 1999 and 2003, 452 CLTI patients were randomised to either a:
  - Bypass *first* or a
  - Plain Balloon Angioplasty (PBA)

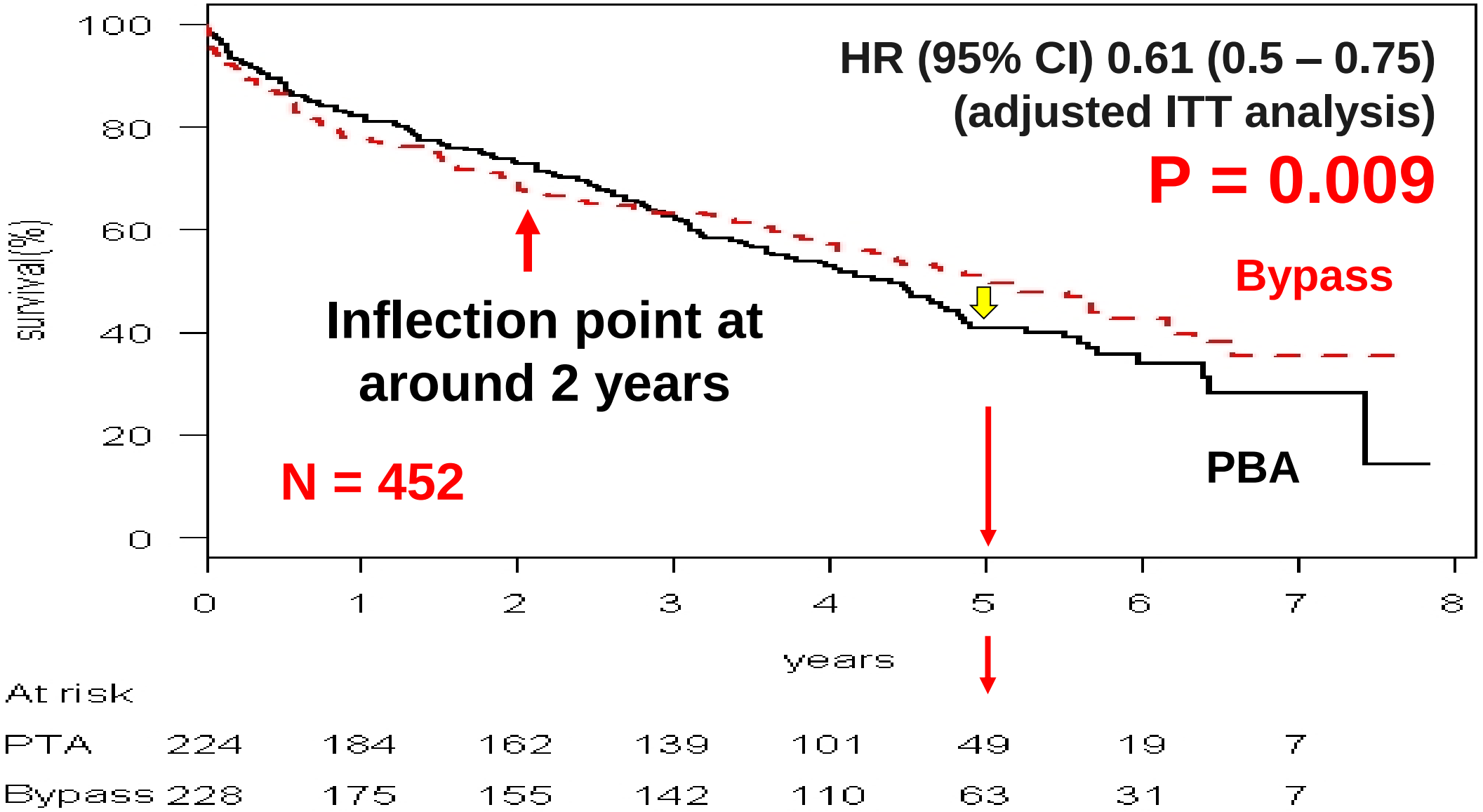
  - *first* revascularisation (6 SFA stents)
- 75% interventions confined to FP segment
- In the short term there was no significant difference between the two arms
- However, in patients who lived for ≥ 2 years, bypass was better than PBA in terms of:
  - Overall survival (**p = 0.009**)
  - Amputation free survival (trend, p = 0.11)



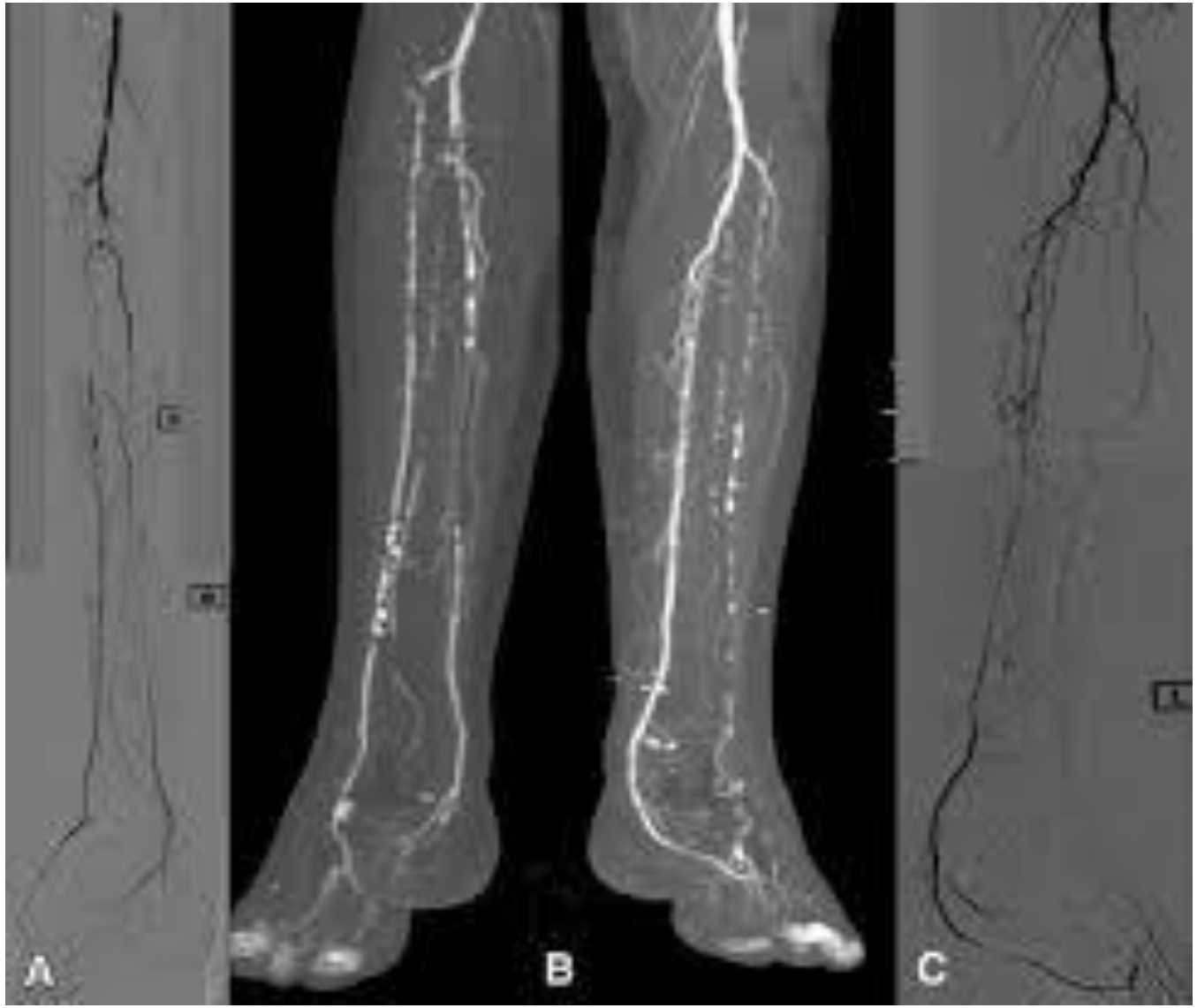




BASIL-1: Overall Survival



BASIL-1: IP revascularisation?



Only **25%** of the revascularisations in BASIL-1 were infra-popliteal

Part-way through BASIL-2 recruitment we did a BASIL-1 sub-group analysis comparing IP vein bypass with PBA

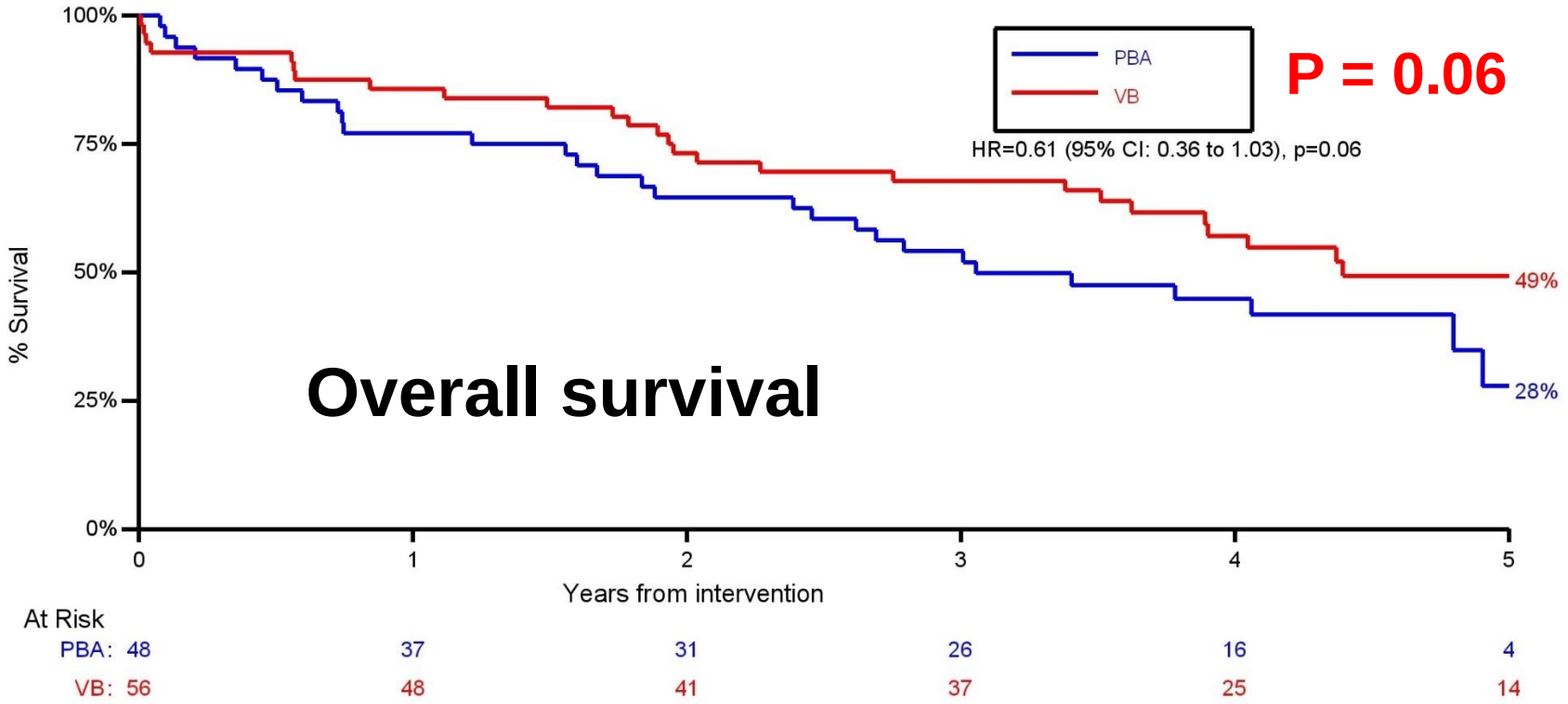
EJVES 2017

BASIL-1 IP sub-group analysis: vein bypass vs PBA

Supports BASIL-1 whole cohort results?

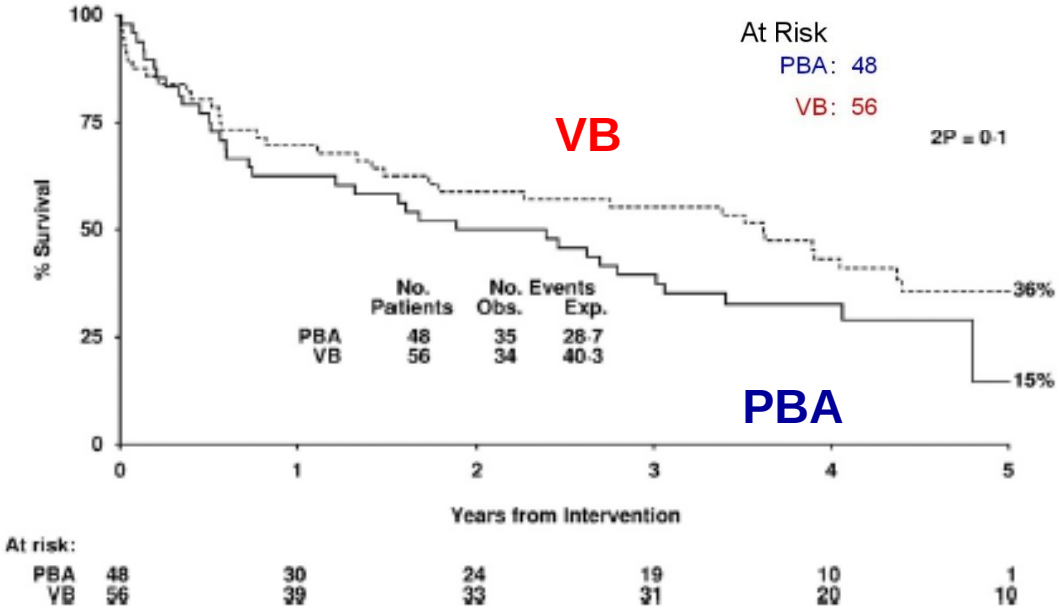
But imperfect methodology and small patient numbers - high levels of uncertainty

Clear need to complete BASIL-2



P = 0.06

Overall survival



Amputation free survival

P = 0.1

BASIL-2 Methodology Statistical Considerations

Catherine Moakes

Senior BASIL-2 Trial Statistician

Birmingham Clinical Trials Unit (BCTU)

University of Birmingham, UK

BASIL-2 Trial design and PICO

Pragmatic, open-label, parallel, multicentre, superiority, two-arm, RCT

Participants: Patients with CLTI who required an infra-popliteal, with or without an additional more proximal infra-inguinal, revascularisation procedure

Intervention: Vein Bypass (VB)

Comparator: Best Endovascular Treatment (BET)

Outcome (primary) - Amputation Free Survival (AFS) - time to first major (above ankle) amputation of the trial leg, or death from any cause, whichever occurs first

Secondary outcomes included time to major amputation, OS, MALE, MACE, 30-day morbidity and mortality, relief of ischaemic pain (VAS, opiate usage), HRQoL, further interventions, healing of tissue loss (PEDIS, WIfI), and haemodynamics

BASIL-2 Original Sample Size

- Based on a time-to-event analysis to be performed after the last participant had been followed up for two years.
- Anticipated recruitment: 20%, 40% and 40% in years 1-3
- Comparator (BET) event rates were obtained from BASIL-1
- Allowing for a 10% attrition rate
- 600 participants required to observe 247 primary events
- One third reduction in AFS (hazard ratio [HR] 0·66)
- With 90% power
- At the 5% significance level

BASIL-2 Revised Sample Size

- In early 2018 it became apparent that recruitment would continue beyond 3 years such that median follow-up would be longer than originally planned
- The number of participants required to observe 247 primary events would now be lower than 600 due to the increased time spent at risk of having an primary event
- With support from the funder and DMC, recruitment rates, length of follow-up, and pooled event rates over time were modelled to predict the number of participants needed to observe 247 primary events, with 24 months minimum follow-up
- Modelling updated around every 6 months based on emerging data up to 2020
- Due to ongoing challenges, mainly related to COVID-19, recruitment closed on 30 November 2020 with 345 participants randomly assigned
- While we realised it was unlikely that we would observe the 247 primary events needed for 90% power we were confident that we would observe the 184 primary events required to exceed 80% power

BASIL-2 Methodology: Clinical Considerations

Gareth Bate

Senior BASIL-2 Research Nurse

University Hospitals Birmingham NHS Foundation Trust

Birmingham, UK

BASIL-2 Pragmatic Trial

- Vascular surgeons and interventional radiologists performed VB and BET using their preferred equipment, devices, and techniques
- Any vein deemed suitable by the surgeon could be used for VB
- If, at operation, vein could not be used, then composite or prosthetic grafts could be inserted at the surgeon's discretion
- For BET, any device used as part of standard of care in that country was permissible
- All further management was at the responsible clinicians' discretion

BASIL-2 Follow-up

Patient data were collected locally at centres:

- 1 month after first revascularisation
- 6, 12, and 24 months after randomisation
- then annually until the last recruited participant had been followed for 24 months

From March 2020 onwards, data collection that required a face-to-face assessment was substantially adversely affected by the COVID-19 pandemic

In England and Wales, primary outcome data were also obtained from NHS Digital

In Stockholm, the Regional Electronic Health Data system was also used to check for amputations, hospitalisations, and deaths

BASIL-2 Oversight

Trial Steering Committee (TSC)

- Chair: Professor Jonathan Michaels, University of Sheffield
- Members: Dr Ian Gillespie, Prof. Michael Gough, Mr Andrew Beech, Mr Martin Fox, Mr James Griffin, and Mr Peter Maufe and Mr Barry Attwood (both patient representatives)

Provided independent supervision of the trial, and advice to the Chief and Co- Investigators and Sponsor on all aspects of the trial throughout the study

Data Monitoring Committee (DMC)

- Chair: Professor Charles McCollum, University of Manchester
- Members: Dr Michael Flynn (deceased), Prof. Peter Gaines, Prof. Doug Altman (deceased), Ms. Lisa Smith, Dr Louise Longworth, Mr Richard Jackson, Dr Sam Chakraverty

DMC reviewed the interim safety and effectiveness data, and adopted the DAMOCLES charter to define its terms of reference and operation

BASIL Prospective Cohort Study

Matt Popplewell

ST8 NIHR Academic Lecturer

University of Birmingham, UK

And

NIHR BASIL Research Fellow

2014-2016

BASIL-2: generalisability?

CLTI is a very clinically and anatomically heterogeneous condition

RCT have to have inclusion and exclusion criteria that

Create a more homogenous cohort so as to facilitate analysis

But, this can lead to problems with generalisability…

So, how generalisable will the BASIL-2 trial be to:

- The whole CLTI population?
- Other CLTI patient cohorts requiring IP revascularisation?

BASIL-2 Prospective Cohort Study (PCS)

Between June 2014 and July 2018

Birmingham Heartlands Hospital

BASIL-2 trial CRFs were used to document the:

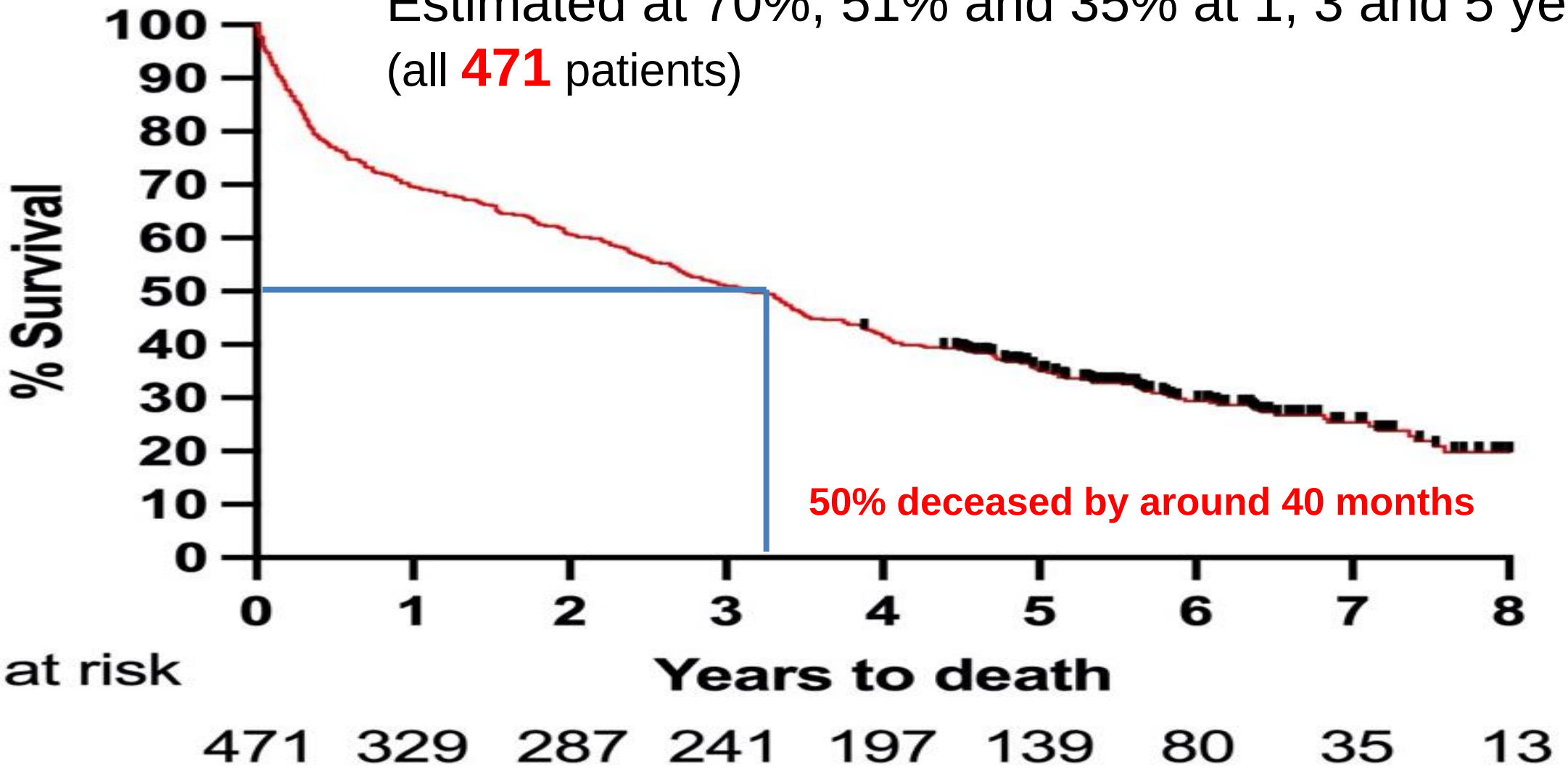
- Characteristics
- Management
- Clinical outcomes

of **471** consecutive patients admitted with CLTI

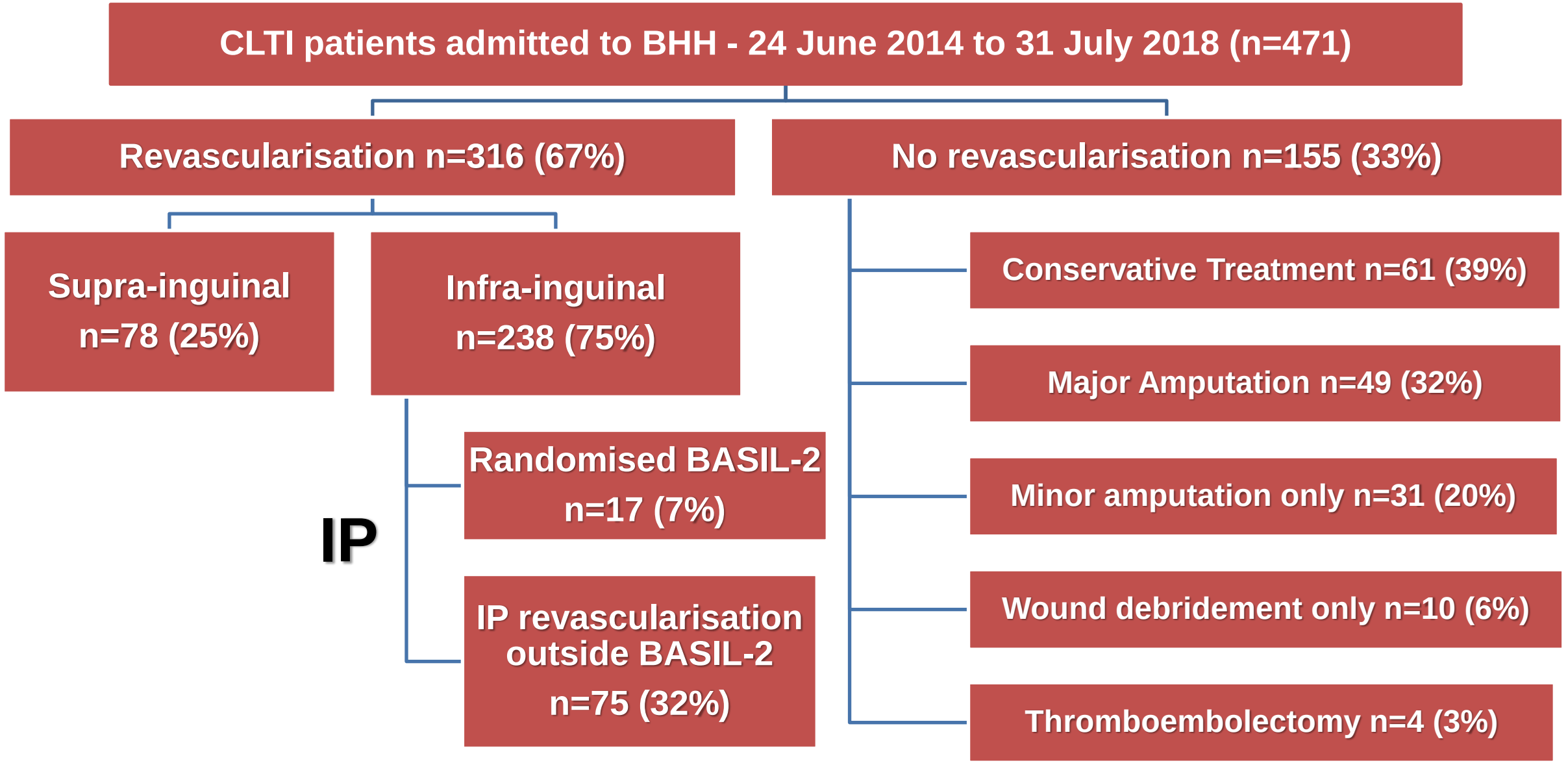
Follow up stopped in December 2022

BASIL-2 PCS: Overall Survival (OS)

Estimated at 70%, 51% and 35% at 1, 3 and 5 years
(all **471** patients)



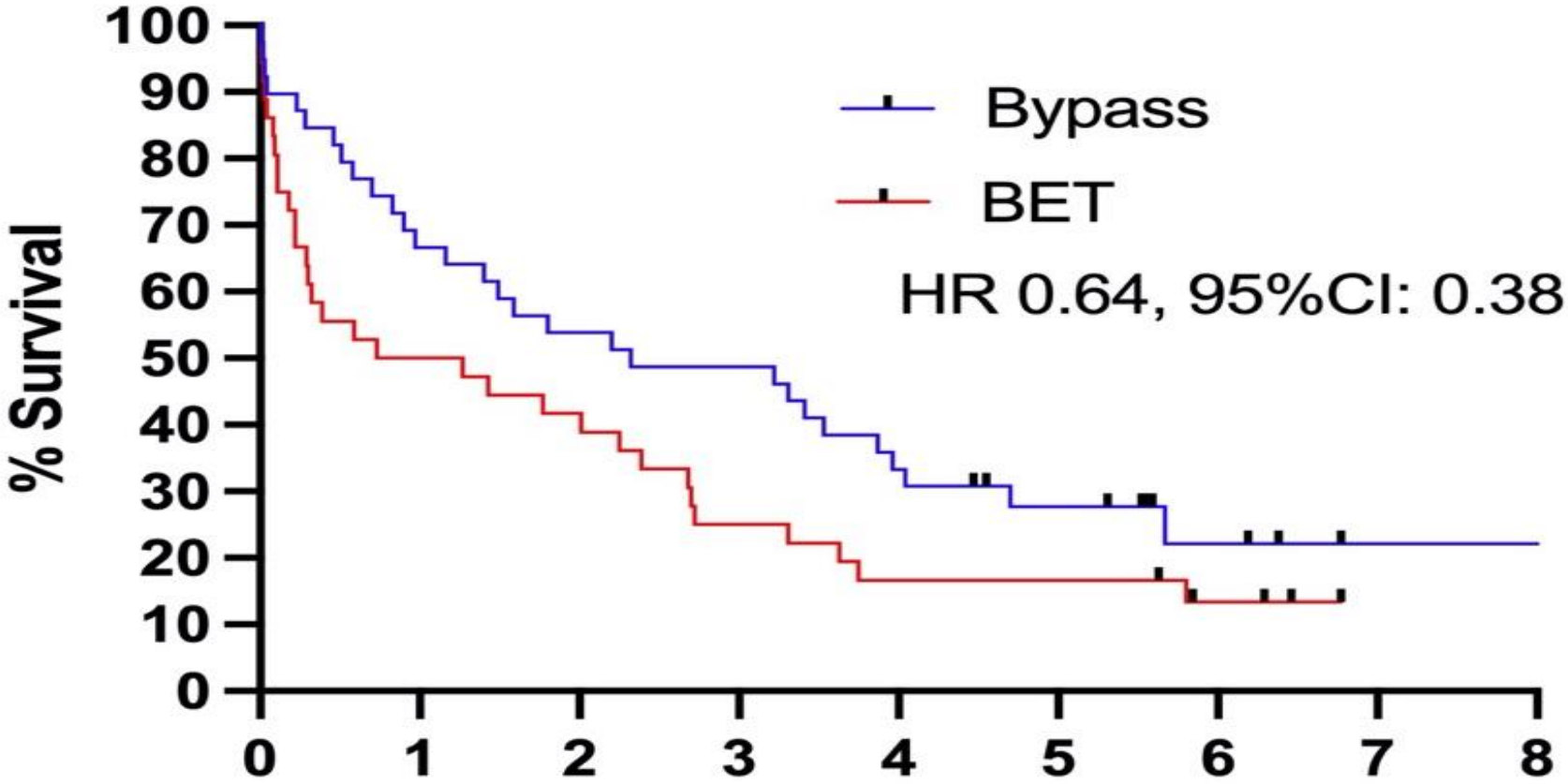
BASIL-2 PCS Initial Management



BASIL-2 PCS MDT Reasons for no Equipoise

Bypass n=39	N (%)	Endovascular Treatment n=36	N (%)
Long occlusive disease (SFA)	24 (61%)	Short stenotic or occlusive disease	14 (39%)
Redo bypass < 6 months	5 (13%)	No distal target / poor run off	7 (19%)
Acute on chronic	4 (10%)	Considered unfit for surgery	4 (11%)
Aneurysmal Occlusive disease	3 (8%)	Tissue loss over potential target IP vessel	2 (5%)
Composite sequential	1 (2%)	Inadequate venous conduit	1 (3%)
Significant CFA disease	1 (2%)	Planned DSA only - treated	1 (3%)
Patient choice	1 (2%)	Randomised to BASIL-3 for concurrent FP disease	1 (3%)
		Lack of capacity – least restrictive option	1 (3%)
		Previous bypass – treatment of native vessels	1 (3%)

BASIL-2 PCS AFS in patients undergoing IP bypass or endovascular treatment *outside* BASIL-2



Number at risk

Bypass	39	27	22	20	14	10	5	2	1
BET	36	19	16	10	7	7	4	1	0

Not randomised or matched

BASIL-2 Clinical Results

Andrew Bradbury

BASIL-2 Chief Investigator

And

Sampson Gamgee Professor of Vascular Surgery

University of Birmingham, UK

Further clinical data and analyses are available in the Lancet paper and in the accompanying supplementary material on line

Health Economic analysis currently underway

Ambitious programme of further work planned

BASIL-2 Recruitment

Between 22 July 2014 and 30 November 2020

We randomised **345** CLTI patients

Who required an infra-popliteal, with or without additional more proximal infra-inguinal, revascularisation procedure to either a:

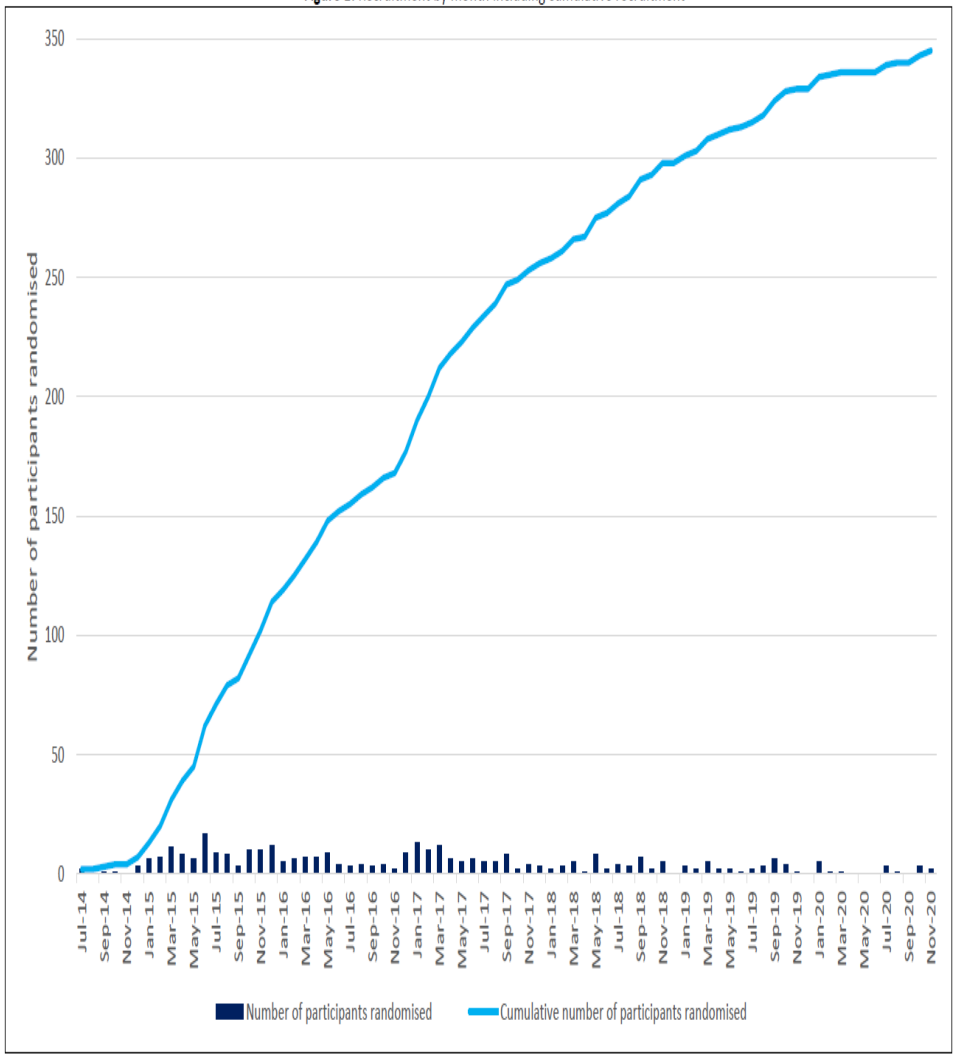
- Vein bypass (VB) *first*, n = **172**
- Best endovascular therapy (BET) *first*, n = **173**

- revascularisation *strategy*

In 41 centres (39 UK + Stockholm + Kolding)

Median [IQR] follow-up was **40** [21-61] months

Figure 1: Recruitment by month including cumulative recruitment



Co-applicants, Principal Investigators (PI), hospitals, and number of participants recruited (non-UK centres)

1. Sodersjukhuset, Stockholm, Sweden, Dr Jonas Malmstedt, Dr Peter Gillgren (36)
2. Hull & East Yorkshire NHS Trust, ***Professor Ian Chetter**, ***Dr Duncan Ettles** (**34**)
3. Guy's and St Thomas' NHS FT, Mr Hany Zayed, Dr Athanasios Diamantopoulos (**28**)
4. Black Country Vascular Unit (Russell's Hall Hospital), Mr Simon Hobbs (**23**)
5. University Hospitals Birmingham NHS FT (Heartlands Hospital), ***Mr Martin Claridge, *Dr Arul Ganeshan** (**20**)
6. Leeds Teaching Hospitals NHS Trust, ***Professor Julian Scott, *Dr Jai Patel** (**20**)
7. Manchester University NHS FT, Mr Tawqeer Rashid, Dr Ray Ashleigh, Dr Stephen Butterfield (**20**)
8. **Kolding Hospital of University of South Denmark, Professor Kim Houlind (16)**
9. Aneurin Bevan University Health Board, Dr Rebecca Wallace, Mr Christopher Twine (**11**)
10. Royal Free London NHS FT, Mr Toby Richards, Mr Lim Chung (**10**)
11. East Kent Hospitals NHS FT, Mr Thomas Rix (**10**)
12. University Hospitals of Leicester NHS Trust, Mr Robert Davies, Mr Athanasios Saratzis, ***Dr Will Adair** (**8**)
13. NHS Greater Glasgow and Clyde, Mr Wesley Stuart (**8**)
14. Frimley Health NHS FT, Mr Patrick Chong (7)
15. University Hospitals Coventry and Warwickshire, Professor Chris Imray (**7**)
16. North Bristol NHS Trust, Mr William Neary (**7**)
17. Imperial College Healthcare NHS Trust, ***Professor Alun Davies** (**7**)
18. St George's Healthcare NHS Trust, ***Mr Robert Hinchliffe** (moved to Bristol), Mr Peter Holt (**6**)
19. Newcastle upon Tyne Hospitals NHS FT, ***Professor Gerard Stansby** (**6**)
20. Oxford University Hospitals NHS FT, ***Dr Raman Uberoi, *Mr Jeremy Perkins** (**6**)
21. Royal Bournemouth and Christchurch NHS Trust, Mr Lasantha Wijesinghe (**5**)
22. United Lincolnshire Hospitals NHS Trust, Mr Nityanand Arya (**5**)
23. Sheffield Teaching Hospitals NHS Foundation Trust, Dr Stephen Goode. Professor Jonathan Beard, ***Dr Trevor Cleveland** (**4**)
24. University Hospitals Birmingham NHS FT (Queen Elizabeth Hospital), Professor Rajiv Vohra, Mr Radu Rogoveanu (**4**)
25. Sandwell & West Birmingham NHS Trust, Mrs Rachel Sam (**4**)
26. East Suffolk and North Essex NHS FT, Mr Sohail Choksy (3)
27. Cambridge University Hospitals NHS FT, Mr Manjit Gohel (**3**)
28. North Cumbria University Hospitals NHS Trust, Mr Thomas Joseph, Mr Ron Eifell (**3**)
29. Doncaster and Bassetlaw Hospitals NHS FT, Mr Woolagasen Pillay (**3**)
30. Worcestershire Acute Hospitals NHS Trust, Mr Isaac Nyamekye (**3**)
31. Pennine Acute Hospitals NHS Trust, Mr Damian Kelleher, Mr Georgios Antoniou (**3**)
32. University Hospitals Sussex NHS FT, Mr Mario Caruana (3)
33. Tayside Health Board, Mr Murray Flett (**3**)
34. Royal Cornwall Hospitals NHS Trust, Dr Harvey Chant, Miss Rachel Barnes (**2**)
35. Bradford Teaching Hospitals NHS FT, Mr Kevin Mercer (**1**)
36. York Teaching Hospitals NHS FT, Mr Marco Baroni (**1**)
37. University Hospital Southampton NHS FT, Miss Nandita Pal (**1**)
38. Portsmouth Hospitals NHS Trust, Mr Mark Pemberton (1)
39. London North West University Healthcare NHS Trust, Mr Tahir Hussain (**1**)
40. NHS Forth Valley, Mr Mike Yapanis (**1**)
41. Bart's Health NHS Trust, Mr Sandip Sarkar (**1**)

The roughly one quarter of centres that each recruited 10 or more patients contributed around two-thirds of the patients

Very similar to BASIL-1

85% patients recruited in the UK

10% Sweden (Stockholm)

5% Denmark (Kolding)

Funding: £2 million

NIHR | National Institute for Health and Care Research

Research Award | Active Award | Award ID: 12/35/45 | Shortlist:

Multicentre randomised controlled trial to compare the clinical and cost-effectiveness of a 'vein bypass first' with an 'endovascular first' revascularisation strategy for severe limb ischaemia due to infrageniculate arterial disease (Bypass v Angioplasty in Severe Ischaemia of the Leg, BASIL-2)

Chief Investigator(s):
Professor Andrew Bradbury

Co-investigators:
Dr Arul Ganeshan, Dr Jai Patel, Dr Margaret Grant, Dr Raman Uberoi, Dr Trevor Cleveland, Dr Will Adair, Mr Jeremy Perkins, Mr Martin Claridge, Mrs Smitaa Patel, Professor Alun Davies, Professor Duncan Ettles, Professor Gerard Stansby, Professor Ian Chetter, Professor Jonathan Deeks, Professor Julian Scott, Professor Robert Hinchliffe, Professor Tracy Roberts

Award:
£2,024,094.79

Start Date:
February 2014

End Date:
May 2023

Contracting Organisation:
University of Birmingham

BASIL-2 Baseline Characteristics

At baseline the two groups were very well matched due randomisation with minimisation

Participant Baseline Characteristics (selected, see Lancet)	VB (n = 172)	BET (n = 173)
Male	81%	82%
Median age [IQR]	72.4 [64.3 - 78.7]	72.5 [62.7 - 79.7]
White	91%	91%
Diabetes	68%	69%
Mean BMI (SD, range)	27.1 (4.9, 17-43)	26.8 (5.5, 16-58)
Smoking: current / ex / never	22% / 44% / 34%	19% / 53% / 28%
Tissue Loss	87%	89%
Dialysis	6%	3%
Previous CV event: stroke / MI / CABG / PCI	15% / 2% / 13% / 13%	20% / 13% / 9% / 10%
Any previous revascularisation (trial / non-trial leg leg)	31% / 17%	39% / 31%
Major amputation (non-trial leg)	5%	11%
Any antiplatelet / lipid lowering agent	76% / 75%	80% / 80%

BASIL-2 Adherence

	VB (N=172)	BET (N=173)
Adherent (received randomised treatment)	145 (84%)	165 (95%)
First revascularisation - N (%)		
BET	10 (6)	165 (95)
Bypass	145 (84)	5 (3)
Non-bypass surgery	2 (1)	1 (1)
None	15 (9)	2 (1)
Reason for no revascularisation		
Deterioration / improvement of condition	5 / 2	1 / 0
Participant declined intervention	3	0
No reason provided	5	1
Median [IQR] weeks to revascularisation	0.9 [0.3-1.7]	0.6 [0.3-1.6]

BASIL-2 Surgical bypass (first revascularisation)

	VB	BET
Surgical bypass received-N	145	5
Technical success-N (%)	137 (96)	4 (80)
Missing	2	0
Conduit-N (%)		
Ipsi-GSV reversed / non-reversed	70 (49) / 48 (34)	1 (20) / 4 (20
Contra-GSV reversed / non-reversed	7 (5) / 2 (1)	-
Ipsi-SSV reversed / non-reversed	-	-
Contra-SSV reversed / non-reversed	- / 1 (1)	-
Arm reversed / non-reversed	5 (4) / 1(1)	-
Composite	5 (4)	-
Prosthetic	2 (1)	-
Missing	4	-
Proximal anastomosis-N (%)		
CFA	37 (26)	3 (60)
SFA	46 (33)	2 (40)
AKPA	11 (7)	-
BKPA	46 (33)	-
Previous Bypass	1 (1)	-
Missing	4	0

	VB	BET
Surgical bypass received-N	145	5
Distal anastomosis-N (%)		
SFA	-	-
AKPA	-	-
BKPA	2 (1)	-
ATA 1 / 2 / 3 [any]	13 (9) / 9 (6) / 11 (8) [23]	-
PTA 1 / 2 / 3 [any]	6 (4) / 20 (14) / 33 (23) [59]	- / - / 2
PerA 1 / 2 / 3 [any]	8 (6) / 8 (6) / 4 (3) [20]	1 (25) / - / 1 (25)
Dorsalis Pedis	24 (17)	-
Plantar Artery	1 (1)	-
Missing	6	1

BASIL-2 BET (first revascularisation)

Describing BET is more difficult than VB because almost every patient had a different intervention

	VB	BET
BET received – N	10	165
Technical success - %	78	87
Missing	1	15
Segments treated - N		
SFA – Proximal / Distal	3 / 3	24 / 51
AKPA / BKPA	3 / 5	57 / 60
PTA – 1 / 2 / 3	2 / 0 / 0	42 / 26 / 27
ATA – 1 / 2 / 3	4 / 2 / 2	78 / 51 / 47
PerA – 1 / 2 / 3	0 / 0 / 1	44 / 24 / 10
DP	0	17
Other	2	23
Missing	1	6

	VB	BET
BET received – N	10	165
Devices used - N		
PBA	6	**136**
DCB	0	21
BMS	1	28
DES	0	21
Missing	4	21
Number of crural arteries treated - N (%)		
One	5 (83)	86 (65)
Two	1 (17)	**43 (33)**
Three	0 (-)	2 (2)
Missing	4	33

84% BET performed by interventional radiologists

BASIL-2 30-day outcomes

N (%)	VB (172)	BET (173)	Risk ratio (95% CI)	Risk difference (95% CI)
30-day mortality	10 (6)	5 (3)	2.45 (0.84-7.20)	0.03 (-0.01-0.07)
30-day morbidity	79 (46)	73 (42)	1.11 (0.89-1.39)	0.06 (-0.04-0.16)
Major amputation	8 (5)	7 (4)		
Minor amputation	35 (20)	31 (18)		
MI	4 (2)	2 (1)		
TIA	-	2 (1)		
Stroke	1 (1)	1 (1)		
Other	27 (16)	11 (6)		
Any SAE	29 (17)	23 (13)		
Cross-over intervention	12 (7)	20 (12)		
Re-intervention	1 (1)	8 (5)		

BASIL-2 Further Interventions

N (%)	VB (172)	BET (173)	Risk ratio (95% CI)	Risk difference (95% CI)
Further intervention (any)	50 (29)	56 (32)	0.94 (0.68 to 1.28)	-0.03 (-0.13 to 0.06)
Re-intervention	9 (5)	33 (19)	0.27 (0.13 to 0.55)	-0.14 (-0.21 to -0.07)
Endovascular	5	62		
Surgical bypass	6	1		
Cross-over intervention	46 (27)	33 (19)	1.43 (0.94 to 2.18)	0.08 (-0.01 to 0.17)
Endovascular	66	3		
Surgical bypass	2	28		
Non-bypass surgery	10	8		

Planning a more detailed analysis – participants in both groups had complex journeys through the trial

BASIL-2: AFS (ITT analysis)

Primary outcome analysed in the intention to treat population

108 of 172, 63%, patients randomised to a VB

Vs

92 of 173, 53%, patients randomised to a BET

first revascularisation strategy

Underwent major amputation or died

(No-AFS)

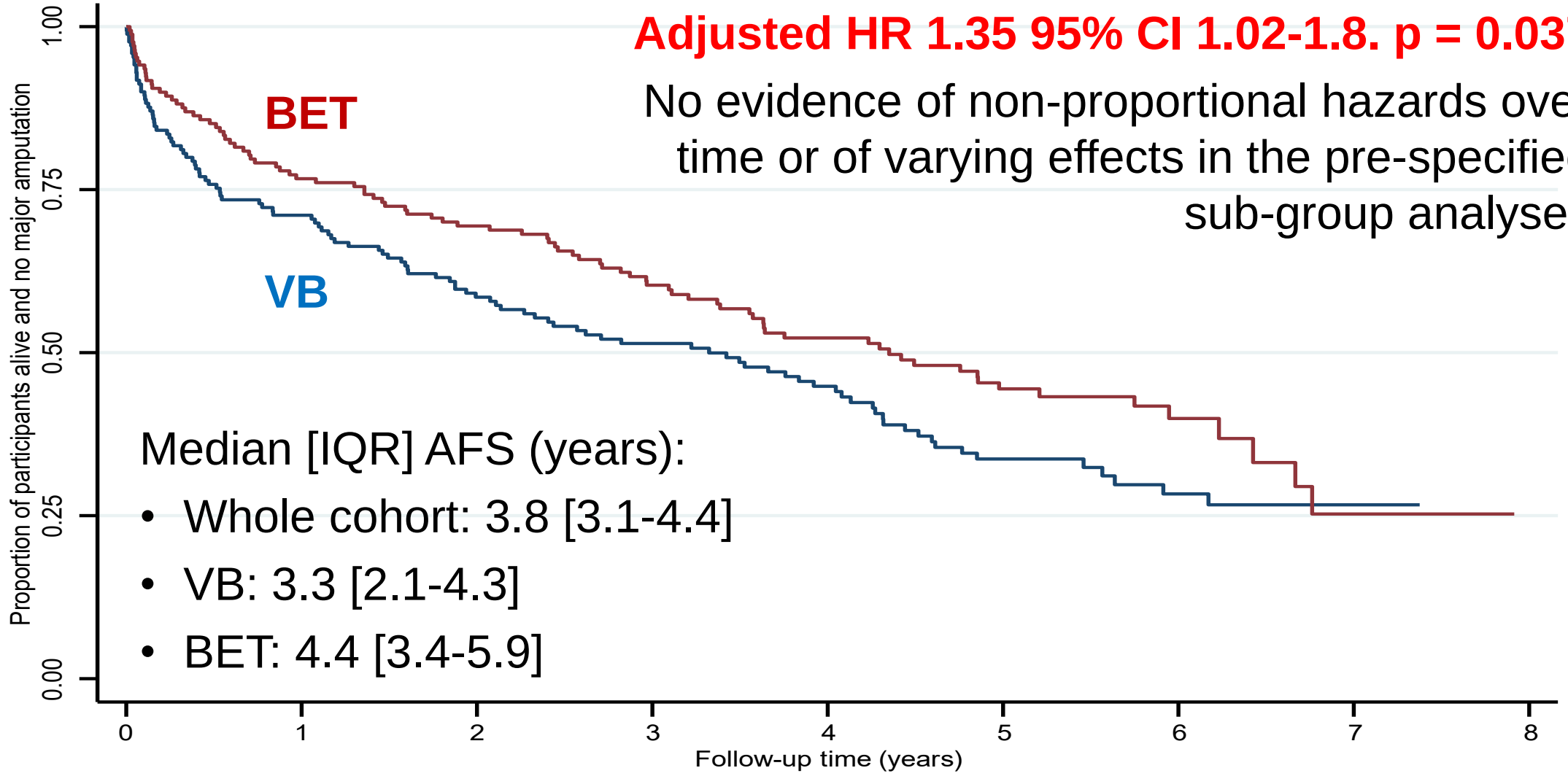
[35 patients (18 VB, 17 BET) had a major amputation then died]

BASIL-2: AFS Hazard Ratio (ITT analysis)

N (%)	VB (172)	BET (173)	Adjusted HR (95% CI)	P value
AFS	64 (37)	81 (47)	1.35 (1.02 to 1.80)	0.037
No AFS-N (%)	108 (63)	92 (53)		
Major amputation	35 (20)	32 (19)		
Death	91 (53)	77 (45)		

This means that, in this cohort, a VB first revascularisation strategy resulted in a **35%** increased risk of major amputation or death during follow-up compared with a BET first revascularisation strategy

BASIL-2: AFS (ITT analysis)



Adjusted HR 1.35 95% CI 1.02-1.8. p = 0.037

No evidence of non-proportional hazards over time or of varying effects in the pre-specified sub-group analyses

Median [IQR] AFS (years):

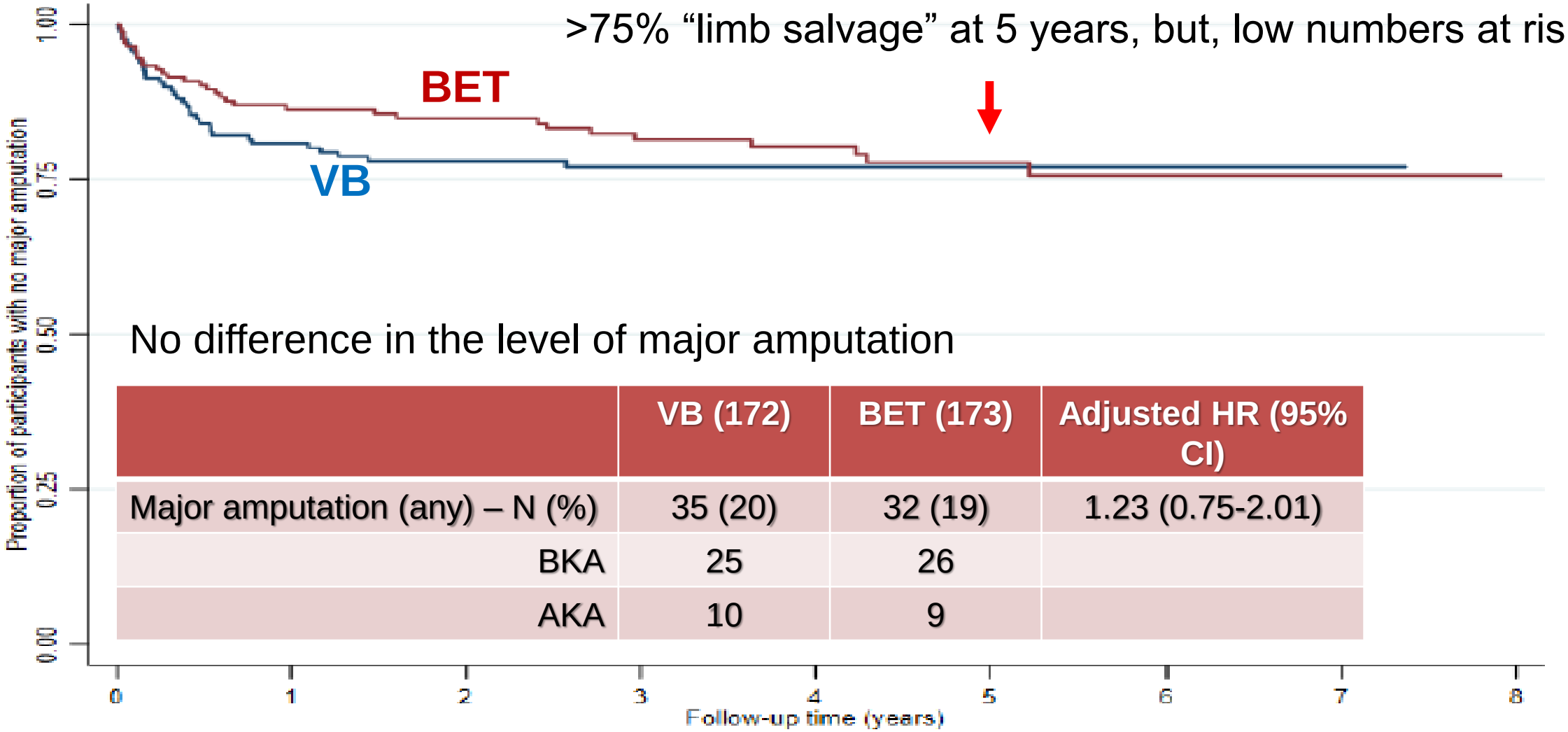
- Whole cohort: 3.8 [3.1-4.4]
- VB: 3.3 [2.1-4.3]
- BET: 4.4 [3.4-5.9]

Number at Risk

VB	172	120	94	78	58	37	19	8	0
BET	173	127	112	91	67	47	19	5	0

BASIL-2 Time to First Major Amputation (ITT)

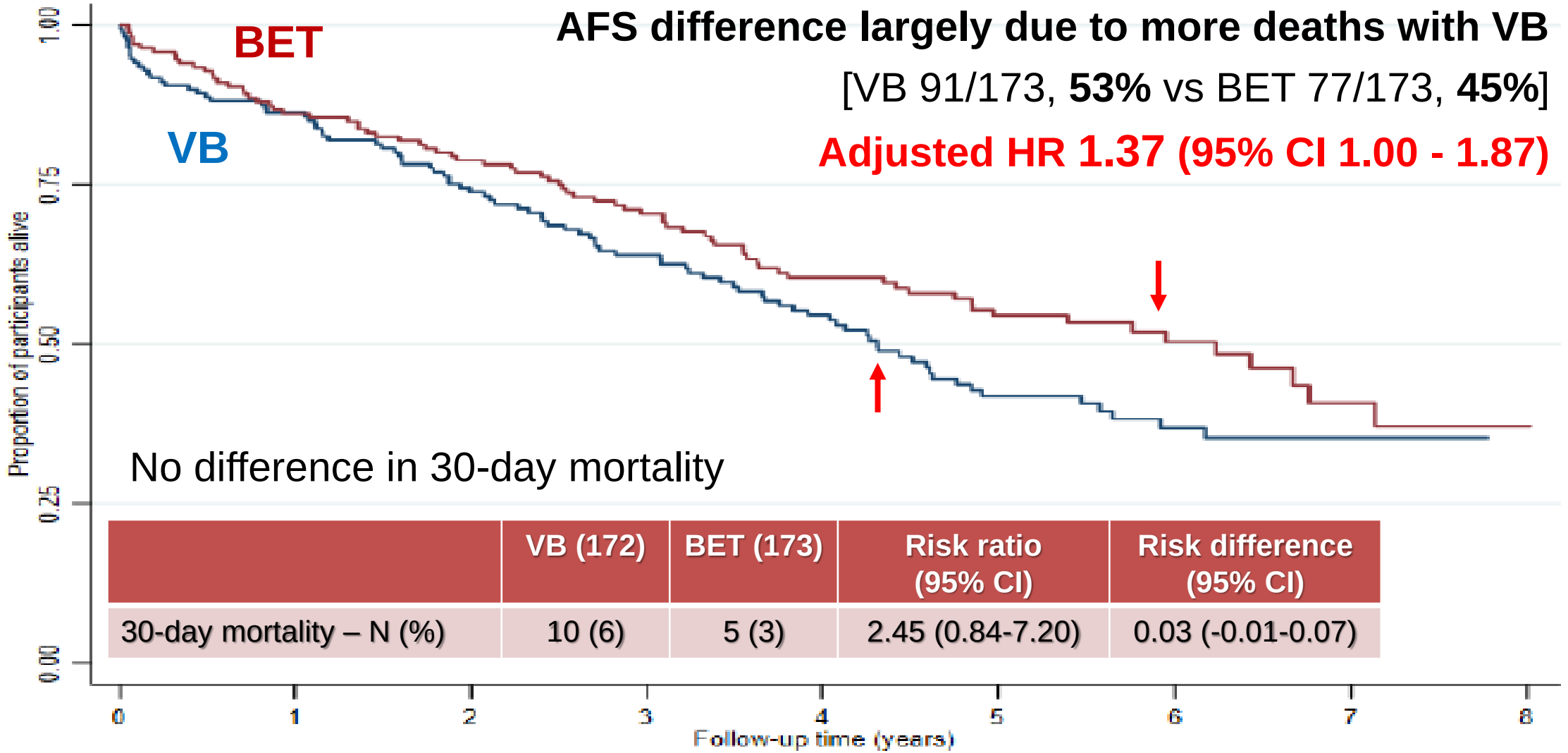
>75% “limb salvage” at 5 years, but, low numbers at risk



No difference in the level of major amputation

	VB (172)	BET (173)	Adjusted HR (95% CI)
Major amputation (any) – N (%)	35 (20)	32 (19)	1.23 (0.75-2.01)
BKA	25	26	
AKA	10	9	

BASIL-2 Overall Survival (ITT analysis)



AFS difference largely due to more deaths with VB

[VB 91/173, **53%** vs BET 77/173, **45%**]

Adjusted HR 1.37 (95% CI 1.00 - 1.87)

No difference in 30-day mortality

	VB (172)	BET (173)	Risk ratio (95% CI)	Risk difference (95% CI)
30-day mortality – N (%)	10 (6)	5 (3)	2.45 (0.84-7.20)	0.03 (-0.01-0.07)

SAEs and Deaths

- 29 (17%) patients in the VB group and 23 (13%) in the BET had a SAE
- One SAE in the BET group was considered to be related to the intervention and to be unexpected (biliary sepsis, GS, pancreatitis)
- Most deaths were reported as multifactorial and were often related to multiple pre-existing co-morbidities
- Cardiovascular (61 VB, 49 BET) and respiratory (25 VB, 23 BET) events predominated
- No specific causes of death were identified that would explain the difference in overall survival between the arms (COVID-19, 4 VB, 5 BET)

BASIL-2: AFS Sensitivity Analyses

Per-protocol – only adherent participants included

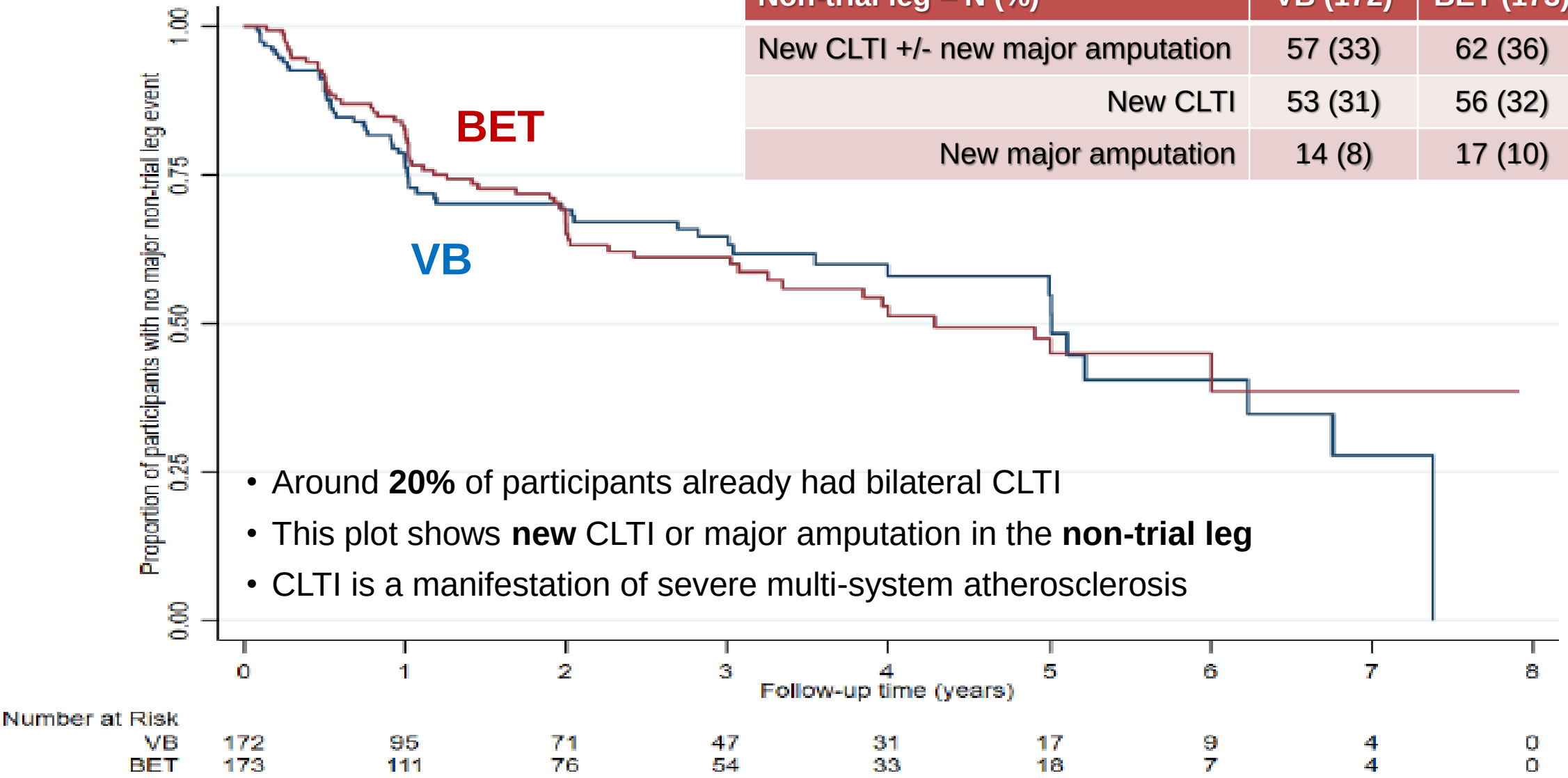
As treated - first revascularisation received post-randomisation

Both trended towards reduced AFS in the VB first group

No AFS-N/N (%)	VB	BET	Adjusted HR (95% CI)
ITT Analysis	108/172 (63)	92/173 (53)	1.35 (1.02 to 1.80)
Per-protocol analysis	88/145 (61)	90/165 (55)	1.30 (0.94 to 1.80)
As-treated analysis	89/150 (59)	98/175 (56)	1.16 (0.87 to 1.56)

BASIL-2 Major non-trial leg event

Non-trial leg – N (%)	VB (172)	BET (173)
New CLTI +/- new major amputation	57 (33)	62 (36)
New CLTI	53 (31)	56 (32)
New major amputation	14 (8)	17 (10)



- Around **20%** of participants already had bilateral CLTI
- This plot shows **new** CLTI or major amputation in the **non-trial leg**
- CLTI is a manifestation of severe multi-system atherosclerosis

BASIL-2: Statistical Interpretation

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Hazard Ratio Interpretation

Our hazard ratio from our ITT analysis of AFS was:

1.35 (95% CI of 1.02 to 1.80)

An increase in risk of No-AFS with VB of 35% is the most likely value with 2% and 80% increases the least likely

Most of this range covers point estimates that are likely to be considered clinically important differences in favour of BET

Especially as VB is a more invasive procedure

Overall survival and amputation

The difference in AFS in favour of BET is largely driven by improved OS (adjusted HR 1.37, 95% CI 1.00 -1.87).

As the number, and time to major amputations were very similar between the two arms (adjusted HR 1.23, 95% CI 0.75-2.01).

We saw no evidence of non-proportional hazards.

The favourable limb salvage rate (around 80% at 5 years in both groups) is largely because around half of the participants were already deceased and so not at risk.

BASIL-2: Reflections and Future Work

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And

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BASIL-2 compared with BASIL-1

Overall, BASIL-2 outcomes were no better than in BASIL-1 (15 years ago)

CLTI outcomes remain very poor overall, especially regarding mortality (PCS 35% 5 years survival)

Patients still presenting with, often quite advanced, “gangrene”

Are there still “missed opportunities” for public health and in primary care?

Earlier diagnosis, referral and treatment of CLTI patients leading to:

- lifestyle changes - smoking, obesity
- “best medical therapy”

May be a larger determinant of outcomes than revascularisation strategy?

BASIL-2 Generalisability and Applicability

CLTI is an extremely heterogenous condition: patient characteristics, degree of limb threat, and anatomic severity and extent of disease

RCT can only ever study CLTI sub-groups that have been defined by reasonably strict inclusion and exclusion criteria

BASIL-2 can only try to answer questions regarding the optimal management of CLTI patients who require an IP revascularisation, and, very importantly, who are deemed (equally) suitable for both VB and BET

This was always likely to be a relatively small sub-group of the CLTI population as a whole

But we probably did not realise just how small at the outset

BASIL-2 Generalisability and Applicability

The BASIL PCS suggests that in the UK NHS only 20% of people admitted with CLTI will probably be offered an IP +/- more proximal revascularisation

In order for such patients to be randomised in BASIL-2, *three* forms of equipoise had to be present:

- Clinical (intellectual)
- Logistical (operational)
- Patient (choice)

These may vary between centres, countries and healthcare systems?

BASIL-2 Key Message

Notwithstanding these important issues, BASIL-2 has provided a clear answer to the specific question it set out to address

In patients who required an IP, with or without an additional more proximal infra-inguinal revascularisation, and in whom “triple equipoise” was present, randomisation to a VB first revascularisation strategy was associated with a **one third** increase in major amputation/death

It is very unlikely that, in this cohort of patients, VB could be associated with better amputation free survival

VB is more invasive and may consume greater resources (HE awaited)

So, even if clinical outcomes were equivalent, would clinicians/patients choose an IP VB over an IP BET first revascularisation strategy?

BASIL-2 Going Forward

Health Economic analysis on-going

Further exploration of possible reasons for better AFS (OS) with BET

GLASS scoring of pre-randomisation angiograms

Analysis of WIfI data

Data sharing agreement with BEST-CLI Investigators

Individual patient data (IPD) BASIL-2 / BEST-CLI meta-analysis

BASIL-3 results expected late 2023 / early 2024

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The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care

Thank you

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