The Randomized Study of Endovascular Therapy With versus Without Intravenous Tissue Plasminogen Activator in Acute Stroke With ICA and M1 Occlusion (SKIP Study)

Kentaro Suzuki (Nippon Medical School), Yuji Matsumaru and Kazumi Kimura, for the SKIP study investigators

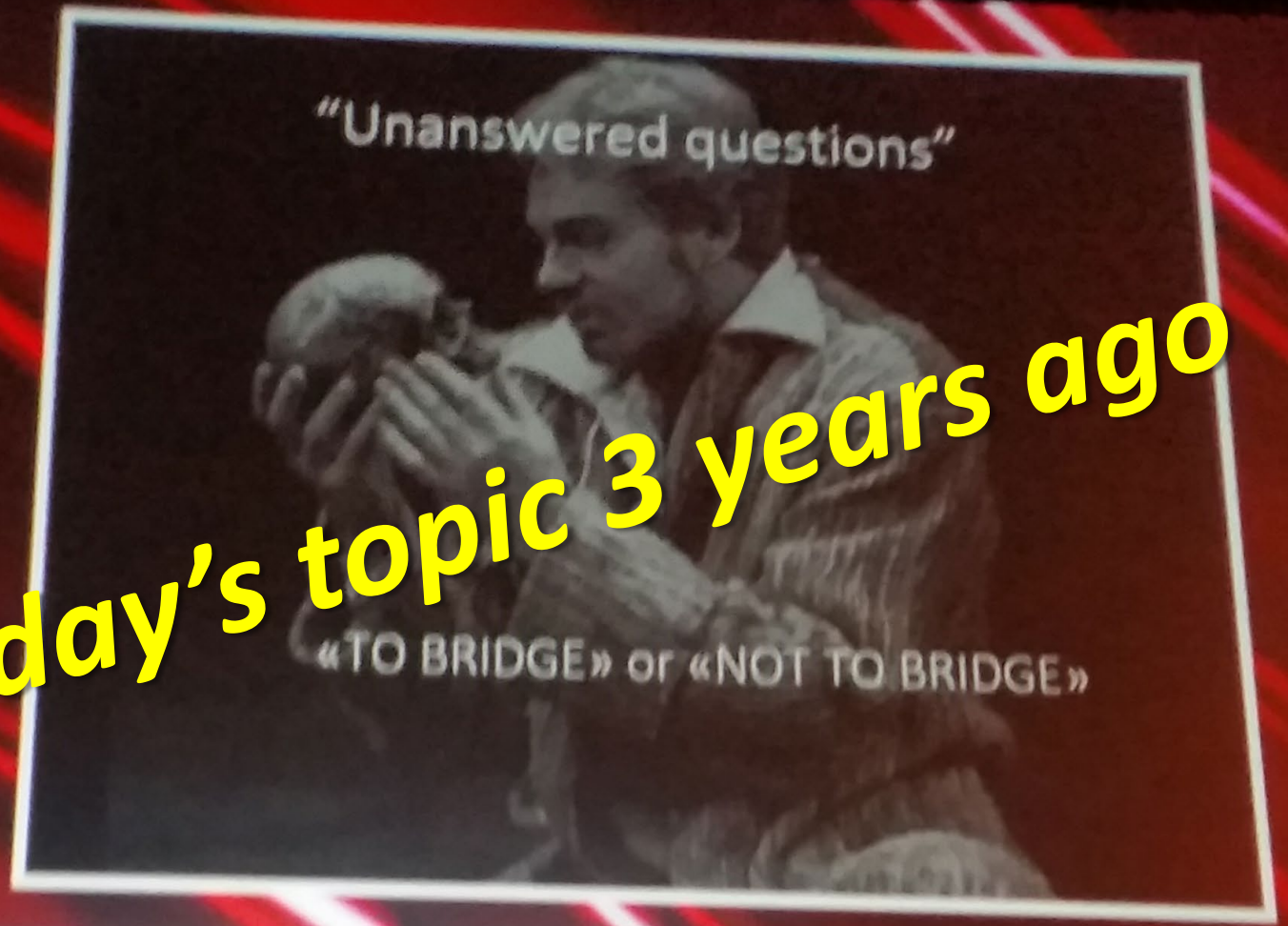
International Stroke Conference 2020, 21th Feb, 2019 Los Angeles

COI

- ✓SKIP study received funding for trial implementation and management from the Japanese society for neuroendovascular therapy (JSNET).
- ✓The authors and each committee member received lecture fees and research funding.

Yasuyuki Iguchi received lecture fees from Bayer Healthcare Co. Ltd., Pfizer Japan Inc., Nippon Boehringer Ingelheim Co. Ltd., Takeda Pharmaceutical Co. Ltd. Otsuka Pharmaceutical Co. Ltd. and Daiichi Sankyo Co. Ltd. And research funding from Sanofi Co. Ltd. Shigeru Fujimoto received lecture fees from Nippon Boehringer Ingelheim Co. Ltd., Daiichi Sankyo Co. Ltd., Pfizer Japan Inc., Bristol-Myers Squibb Co. Ltd., Bayer Healthcare Co. Ltd. And Takeda Pharmaceutical Co. Ltd. Kazumi Kimura received lecture fees from Bristol-Myers Squibb Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Bayer Healthcare Co. Ltd., Daiichi Sankyo Co. Ltd, Nippon Boehringer Ingelheim Co. Ltd. and Daiichi Sankyo Co. Ltd. Yuki Kamiya received lecture fees from Daiichi Sankyo Co. Ltd. And research funding from Bristol-Myers Squibb Co. Ltd., Teruyuki Hirano received lecture fees from Bayer Healthcare Co. Ltd., Daiichi Sankyo Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Bristol-Myers Squibb Co. Ltd., Medtronic Co. Ltd, Sanofi Co. Ltd. Otsuka Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Co., CSL Behring K.K., Astellas Pharma Inc. and Pfizer Japan Inc. Yuji Matsumaru received lecture fees from Medtronic Co. Ltd, Stryker Co. Ltd, Sanofi Co. Ltd., Daiichi Sankyo Co. Ltd., Otsuka Pharmaceutical Co. Ltd. and Biomedical solutions

ISC2017.2 Closing session at Houston



ISC discussed today's topic 3 years ago

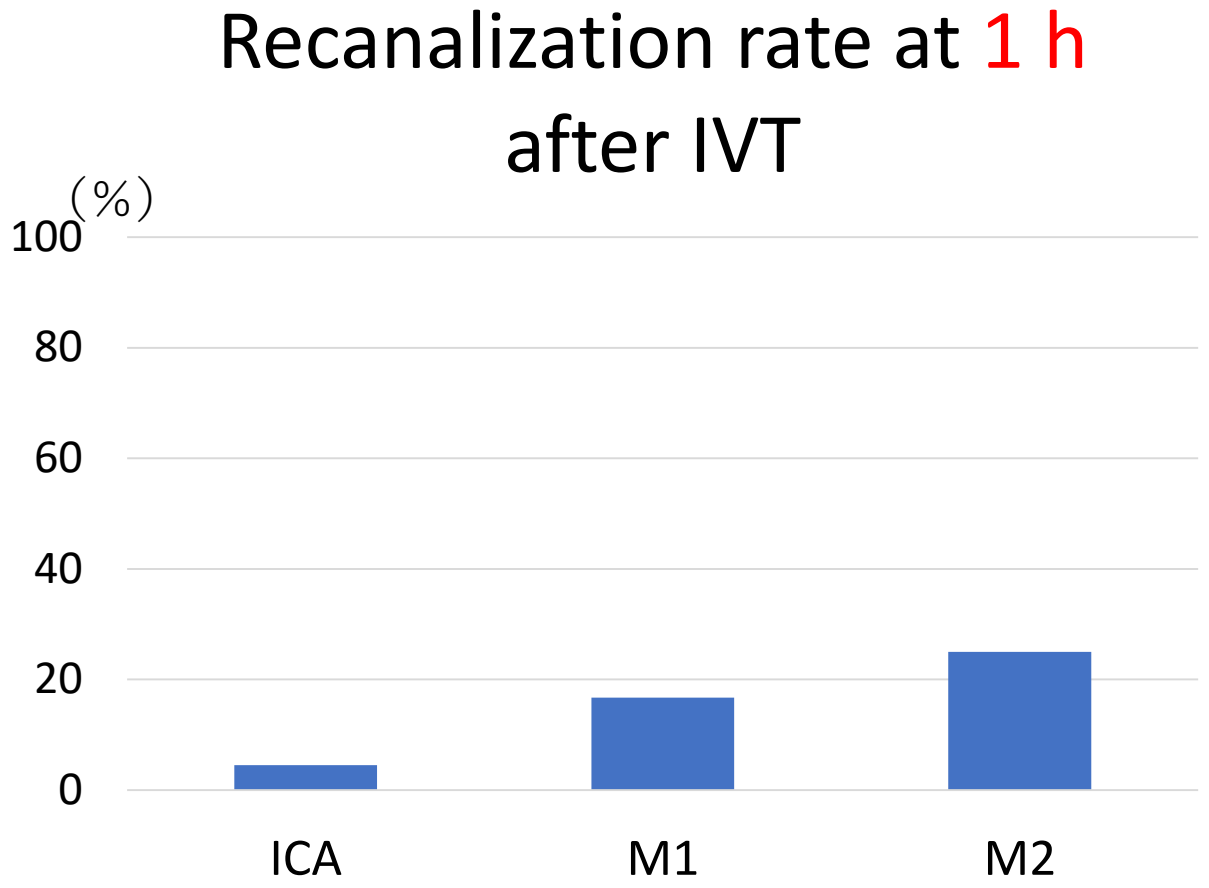
Background

- ✓Both IV tPA (IVT) and Mechanical Thrombectomy (MT) have an evidence for benefits in ischemic stroke patients.

Background

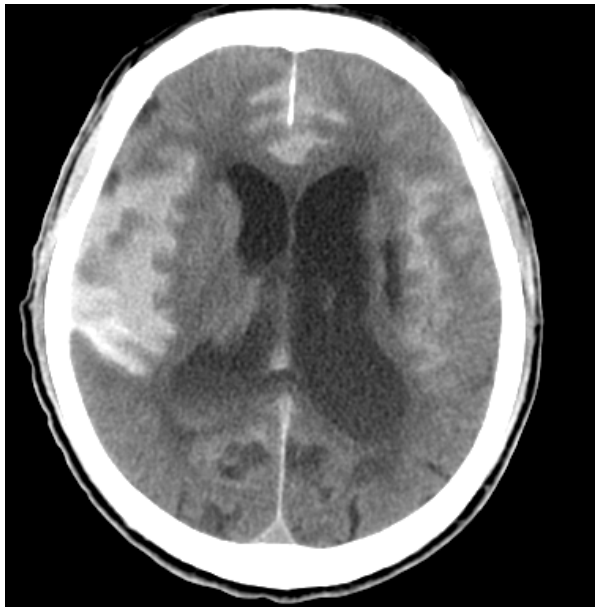
- ✓Both IV tPA (IVT) and Mechanical Thrombectomy (MT) have an evidence for benefits in ischemic stroke patients.
- ✓We really don’t know whether IVT before MT is needed for LVO patients.

IVT early recanalization rate in LVO patients



Kimura K et al. European Neurology 2009.

Recanalization rate of IVT in LVO patients is low



Hemorrhagic risk of IVT

The rate of blood clot exceeding 30% of the infarct volume

1.7 %

Placebo

5.9 %

IVT

IV tPA in LVO patients is still beneficial?

The ATLANTIS, ECASS, and NINDS rt-PA study Group Investigators. LANCET 2004.

Severe hemorrhagic risk of IVT becomes 3 times

Why did we conduct SKIP study?

✓We would like to know the ANSWER

※If we skip IV tPA・・・

- Lower hemorrhagic risk
- No prohibition of antithrombotic agents
- Low cost

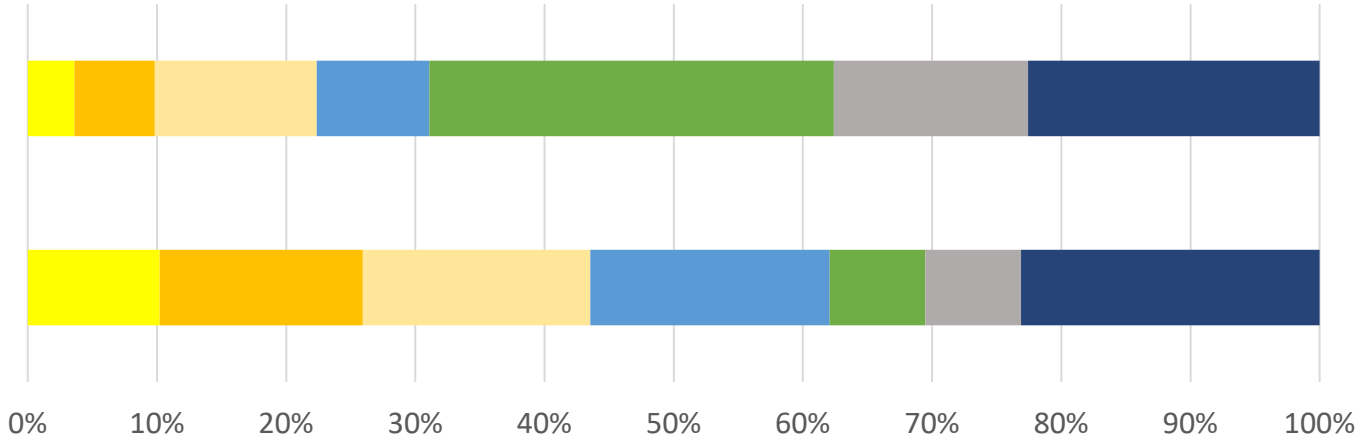
- Missing reperfusion opportunity
- Delaying the initial therapy

How was the HERMES collaboration?

※Ineligible for IVT

Best Medical treatment n=80

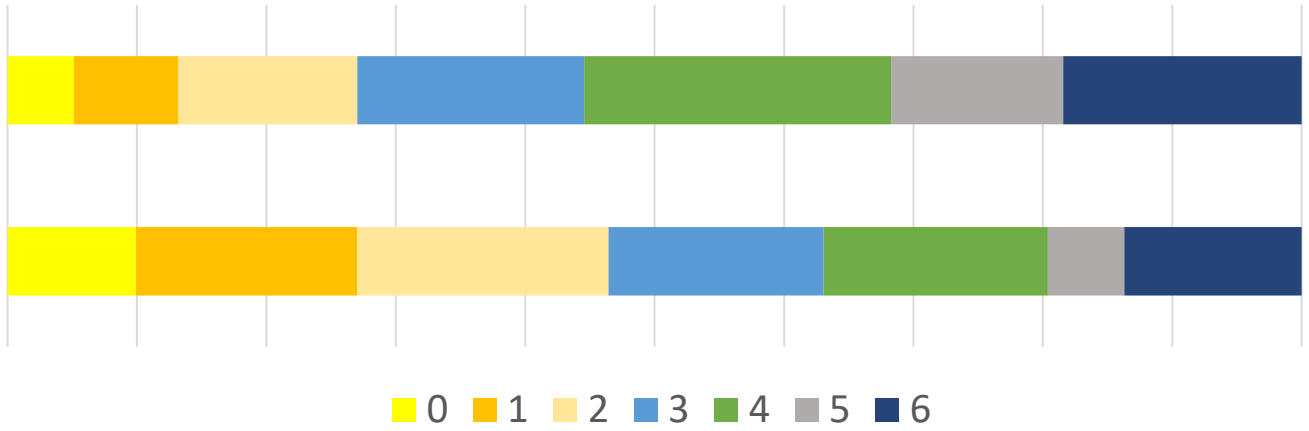
Best Medical treatment + MT n=108



※Eligible for IVT

Best Medical treatment n=565

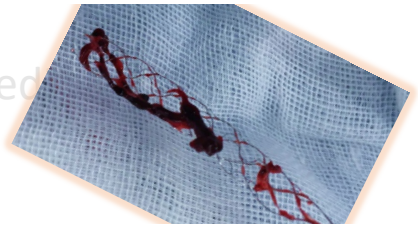
Best Medical treatment + MT n=525



HERMES collaboration (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA) Mayank Goyal et al. LANCET 2016.

How was the HERMES collaboration?

※Ineligible for IVT

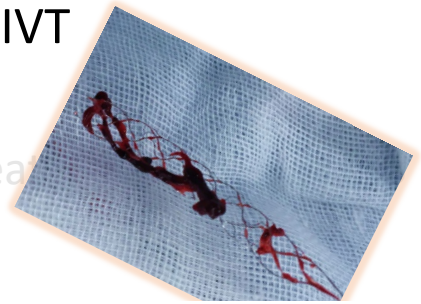


Best Medical treatment + MT n=108

≒Direct MT therapy

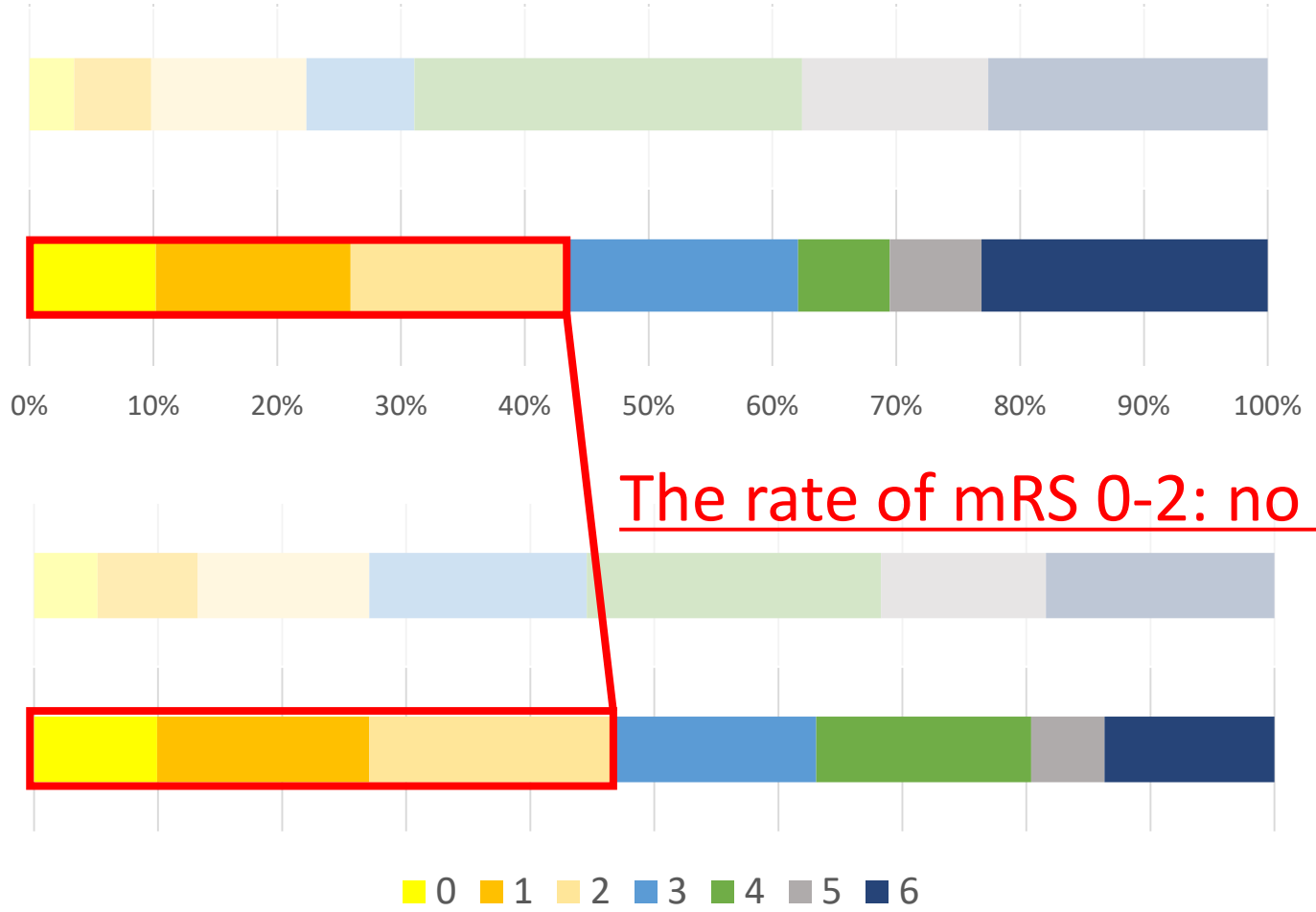
※Eligible for IVT

＋



Best Medical treatment + MT n=525

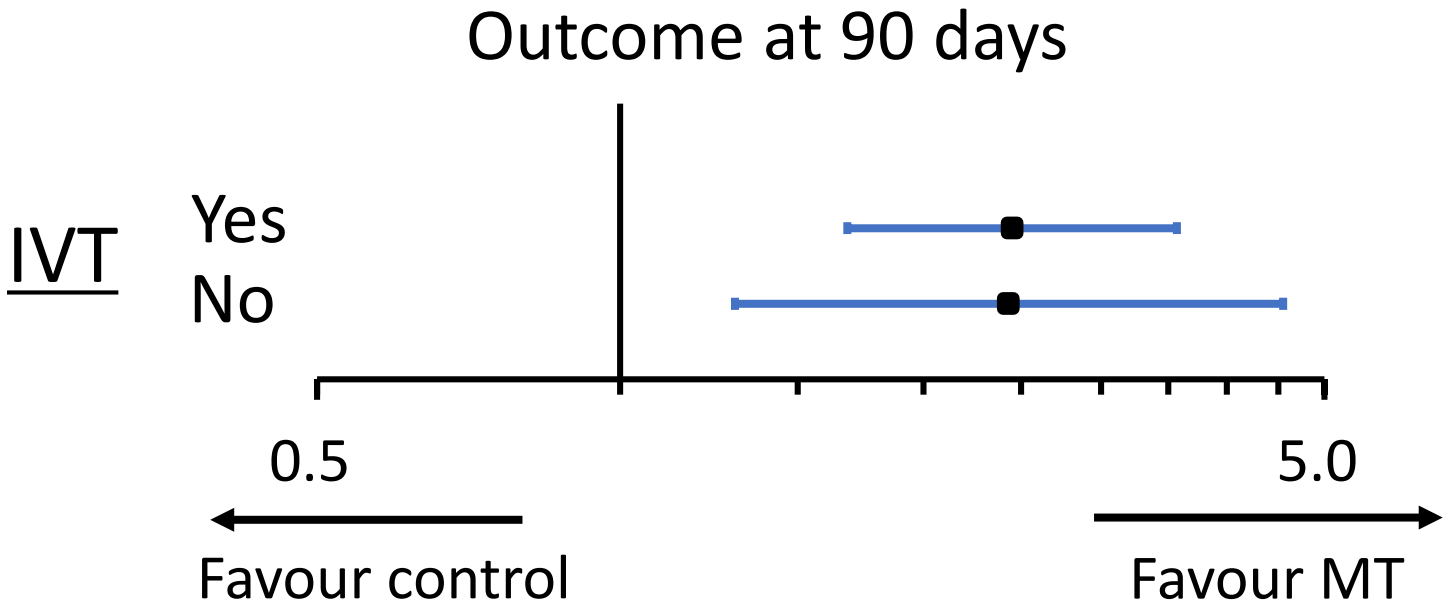
≒Bridging therapy



The rate of mRS 0-2: no difference

HERMES collaboration (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA) Mayank Goyal et al. LANCET 2016.

How was the subgroup analysis from HERMES?



No difference between With vs. Without IVT

HERMES collaboration (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA) Mayank Goyal et al. LANCET 2016.

Can we say Similar with or without IVT??

- No!

Most patients without IVT in HERMES collaboration included IVT ineligible patients.

We need a RCT in eligible IVT patients.

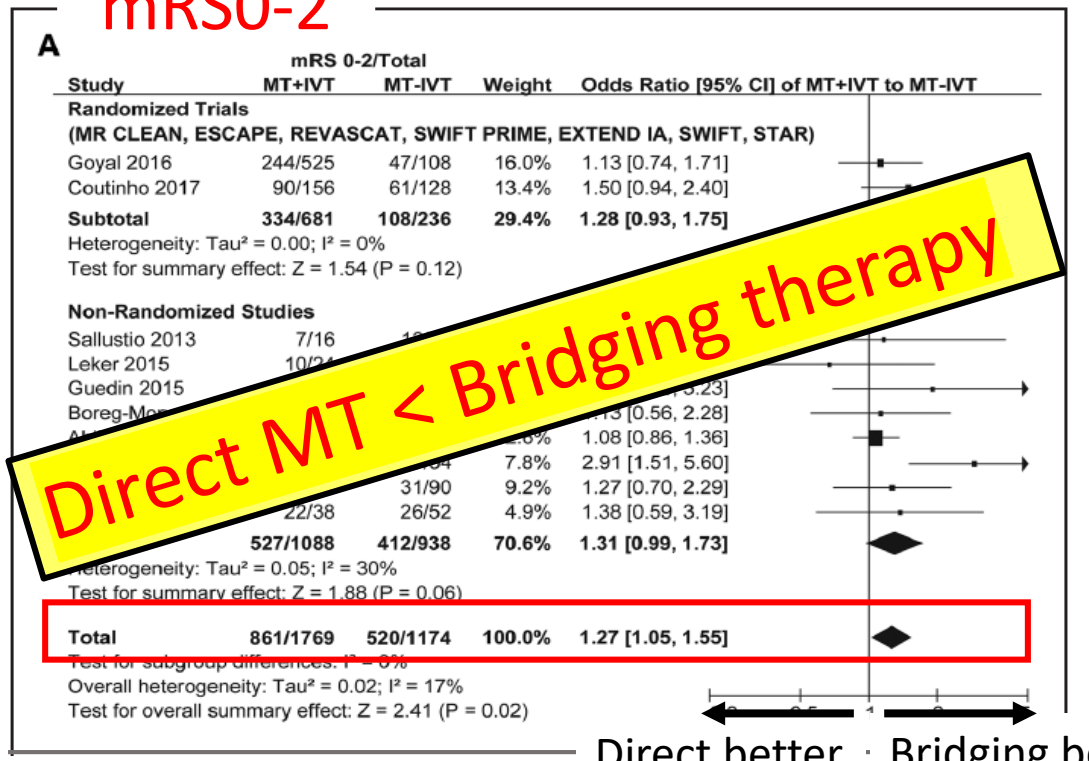
How were the cohort studies?

Mechanical Thrombectomy Outcomes With and Without Intravenous Thrombolysis in Stroke Patients

A Meta-Analysis

Eva A. Mistry, MD*; Akshitkumar M. Mistry, MD*; Mohammad Obadah Nakawah, MD; Rohan V. Chitale, MD; Robert F. James, MD; John J. Volpi, MD†; Matthew R. Fusco, MD†

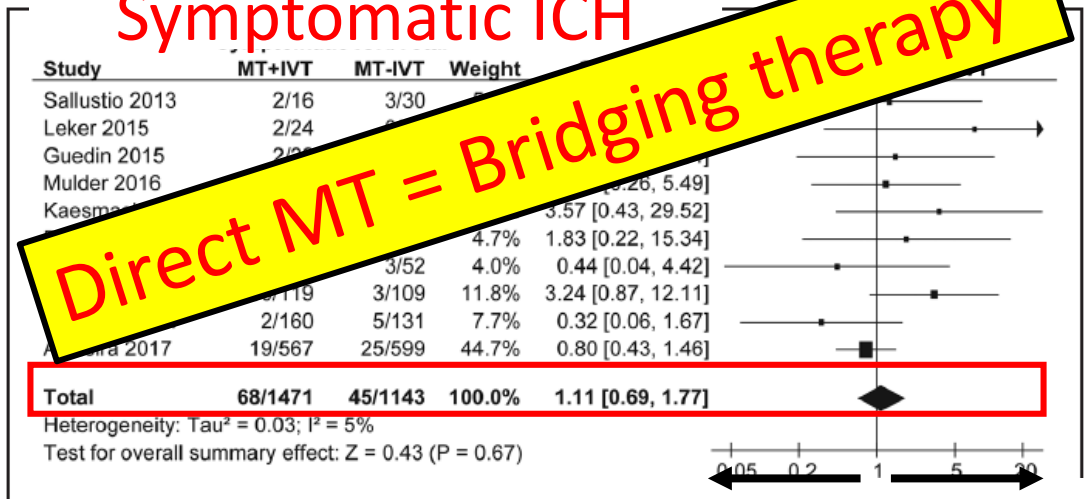
mRS0-2



Direct MT < Bridging therapy

Direct better · Bridging better

Symptomatic ICH



Direct MT = Bridging therapy

Direct better · Bridging better

Mistry EA et al. Stroke 2017.

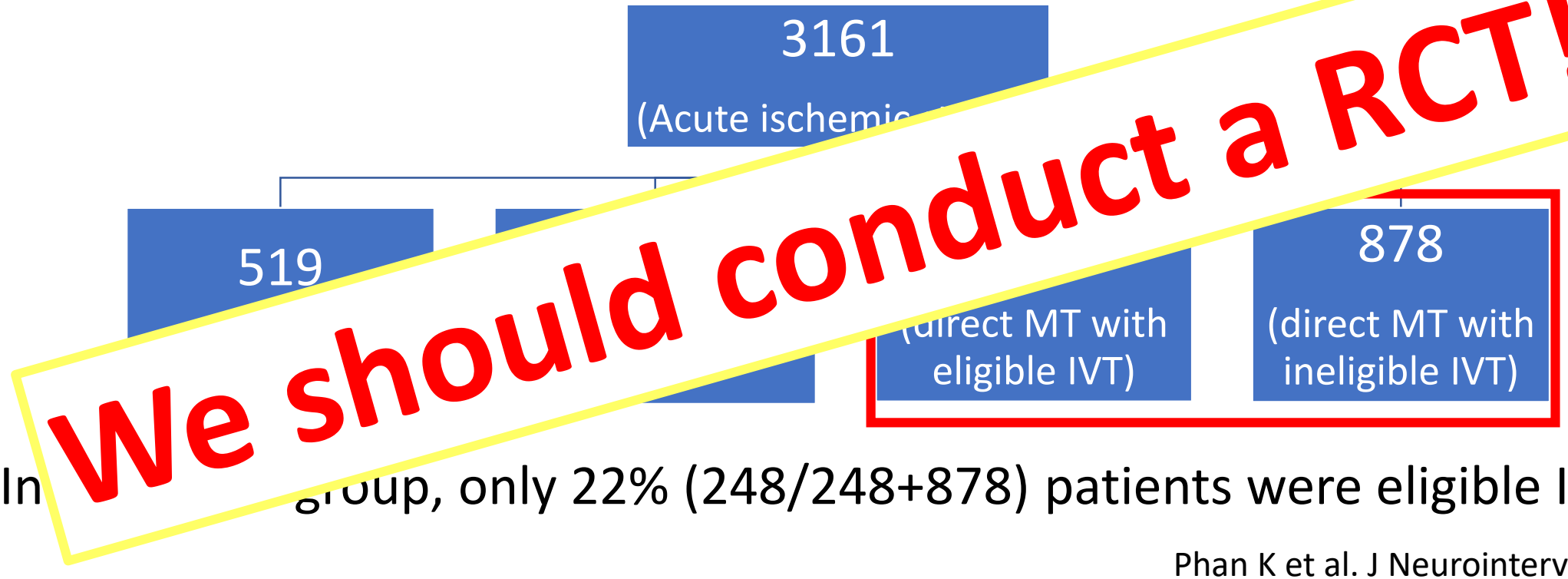
Can we say Bridging therapy is better??

- No!

Most patients without IVT in Cohort studies included IVT ineligible patients.

Can we say Bridging therapy is better??

Phan K et al analyzed 12 studies(5RCTs and 7 prospective cohorts).



We should conduct a RCT!!

In group, only 22% (248/248+878) patients were eligible IVT

Phan K et al. J Neurointervent Surg 2019.

We cannot say that IVT before MT is essential.

Purpose

✓We studied whether direct MT therapy in the patients with LVO has non-inferior efficacy and lower risk of any ICH compared to bridging therapy.

Trial Design

- ✓Multicenter, Randomized, Open-labeled trial
- ✓Registration period: Jan 2017 – July 2019
- ✓Trial registration: UMIN 000021488
- ✓Protocol

  Suzuki K, Kimura K, Matsumaru Y et al: Int J Stroke 2019

- ✓Registration: 23 sites, 200 cases

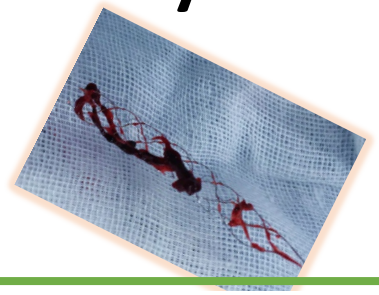
Inclusion criteria

- ✓ Age ≥18 or <86 years at the time of giving informed consent
- ✓ Clinical diagnosis of acute ischemic stroke with clinical symptom.
- ✓ Pre-mRS score ≤2
- ✓ ICA or M1 occlusion on MRA or CTA
- ✓ Initial NIHSS score ≥6
- ✓ Baseline ASPECTS ≥6 or DWI ASPECTS ≥5
- ✓ Puncture within 4 h from onset.
- ✓ Written informed consent by patient or relatives.

Exclusion criteria

- ✓ Contraindication of contrast agent or endovascular therapy
- ✓ Contraindication of IVT
- ✓ Presence of severe renal disorder (patients undergoing introduction of dialysis can be included)
- ✓ Pregnancy or possibility of pregnancy
- ✓ Unlikely to complete the study, such as due to progressive malignant tumor
- ✓ Judged as incompatible for the study by the investigators

Study Design



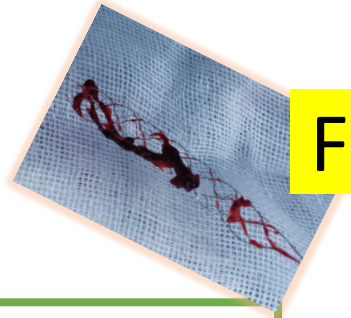
Subjects

- Acute ischemic stroke
- Within 4h from onset
- ICA/M1 occlusion
- CT-ASPECTS≥6, DWI-≥5

R

Direct MT group
(MT without tPA)

＋



F

Bridging group
(MT with tPA)

Clinical assessment

- Angiogram assessment
- CT within 36 h (ICH)
- CTA/MRA within 48 h
- NIHSS score
  at baseline, 24h and 72h
- mRS at 90 days

R; randomization, F; follow up

Efficacy outcomes

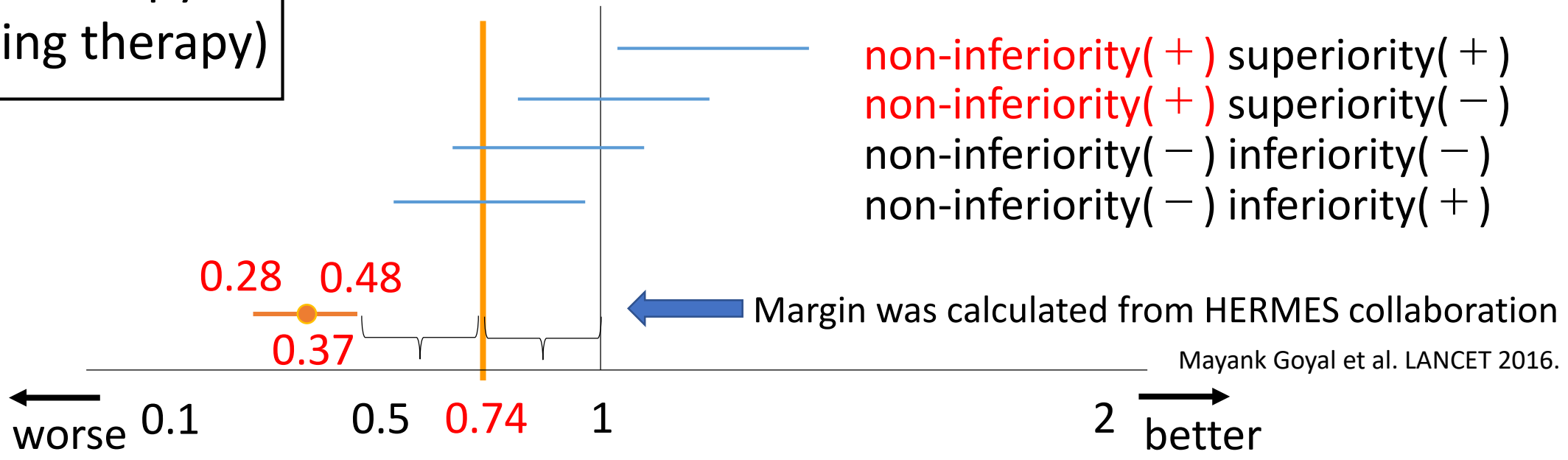
- ✓ Primary: mRS score 0-2 at 90 days
- ✓ Secondary:
    1. mRS score (Shift analysis)
    2. mRS score 0-2 (Per protocol analysis)
    3. Death at 90 days
    4. Reperfusion rate at MT (TICI grade≥2B)

Efficacy outcomes

- ✓ Primary: mRS score 0-2 at 90 days
- ✓ Secondary:
  1. mRS score (Shift analysis)
  2. mRS score 0-2 (Per protocol analysis)
  3. Death at 90 days
  4. Reperfusion rate at MT (TICI grade≥2B)

Non-inferiority margin

Direct MT therapy
(vs. Bridging therapy)



To satisfy the non-inferiority hypothesis, the lower bound of the one-sided 97.5% confidence interval for the odds ratio (OR) of the primary outcome (mRS 0-2 at 90 days) with Direct MT group as compared with Bridging group needed to exceed 0.74.

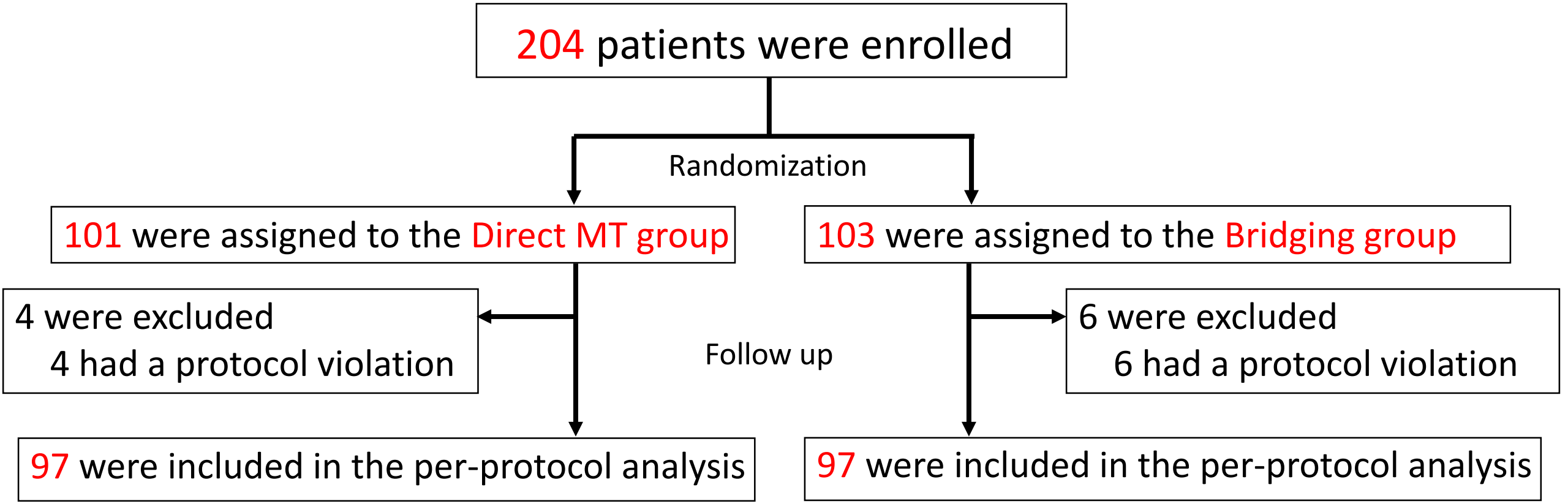
Safety outcomes

- ✓ Safety
  1. Any ICH within 36 h
  2. Symptomatic ICH within 36 h

     (NINDS criteria, SITS-MOST criteria)

RESULTS

The flowchart of Enrollment and Randomization



All patients were followed for 90 days.

Baseline Characteristics

	Direct MT group n=101	Bridging group n=103	P value
Age, y median (IQR)	74 [67-80]	76 [67-80]	0.79
Male gender, no. (%)	56(55)	72(70)	0.04
Weight, Kg median (IQR)	59 [52-66]	60 [53-68]	0.43
Medical history			
Hypertension, no. (%)	61(60)	61(59)	0.89
Dyslipidemia, no. (%)	30(30)	37(36)	0.37
Diabetes mellitus, no. (%)	16(16)	17(17)	1
Atrial fibrillation, no. (%)	57(56)	64(62)	0.48
Smoking, no. (%)	42(42)	54(52)	0.13
Past Stroke, no. (%)	12(12)	14(14)	0.83
Past CHD, no. (%)	7(7)	7(7)	1
Anti Platelet agent, no. (%)	16(16)	18(17)	0.85
Anti Coagulant agent, no. (%)	19(19)	17(17)	0.72
Blood sugar at admission, mg/dl	135 ± 48	135 ± 52	0.91

Baseline Characteristics

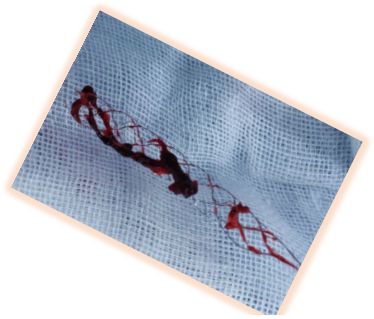
	Direct MT group n=101	Bridging group n=103	P value
TOAST Classification			0.48
Large artery (atherosclerosis) , no. (%)	21(21)	15(15)	
Cardioembolism, no. (%)	67(66)	72(70)	
Other / undetermined etiology, no. (%)	13(13)	16(16)	
SBP at admission, mmHg median (IQR)	158 [134-172]	150 [132-171]	0.64
DBP at admission, mmHg median (IQR)	83 [75-98]	86 [78-98]	0.47
NIHSS score at admission median (IQR)	19 [13-23]	17 [12-22]	0.46
Pre modified Rankin Scale score			0.77
0, no. (%)	84(83)	88(85)	
1, no. (%)	11(11)	6(6)	
2, no. (%)	6(6)	7(7)	
3, no. (%)	0	2(2)	
Onset to Door time (min)	92 ± 57	100 ± 55	0.34
Door to Randomization time (min)	36 ± 24	36 ± 19	0.88
Randomization to Puncture time (min)	22 ± 21	22 ± 16	0.61

Baseline Characteristics

	Direct MT group n=101	Bridging group n=103	P value
Examination at admission			0.13
MRI/MRA, no. (%)	86(85)	95(92)	
CT/CTA, no. (%)	15(15)	8(8)	
Occluded site by MRA/CTA			0.59
ICA, no. (%)	41(41)	36(35)	
M1 proximal, no. (%)	19(19)	18(17)	
M1 distal, no. (%)	41(41)	49(48)	
Occluded site by angiogram			0.41
None, no. (%)	1(1)	0	
ICA origin, no. (%)	13(13)	16(16)	
ICA C4-5, no. (%)	6(6)	6(6)	
ICA C1-3, no. (%)	17(17)	14(14)	
M1 proximal, no. (%)	10(10)	12(12)	
M1 distal, no. (%)	44(44)	35(34)	
M2, no. (%)	10(10)	20(19)	
ASPECTS	7 [6-9]	8 [6-9]	0.86

MAIN RESULT

mRS at 90 days



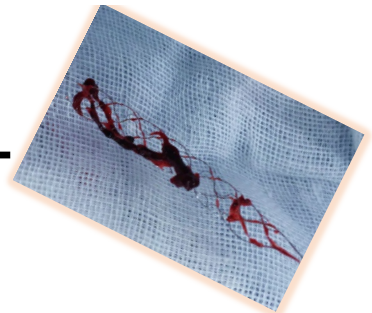
Direct MT group

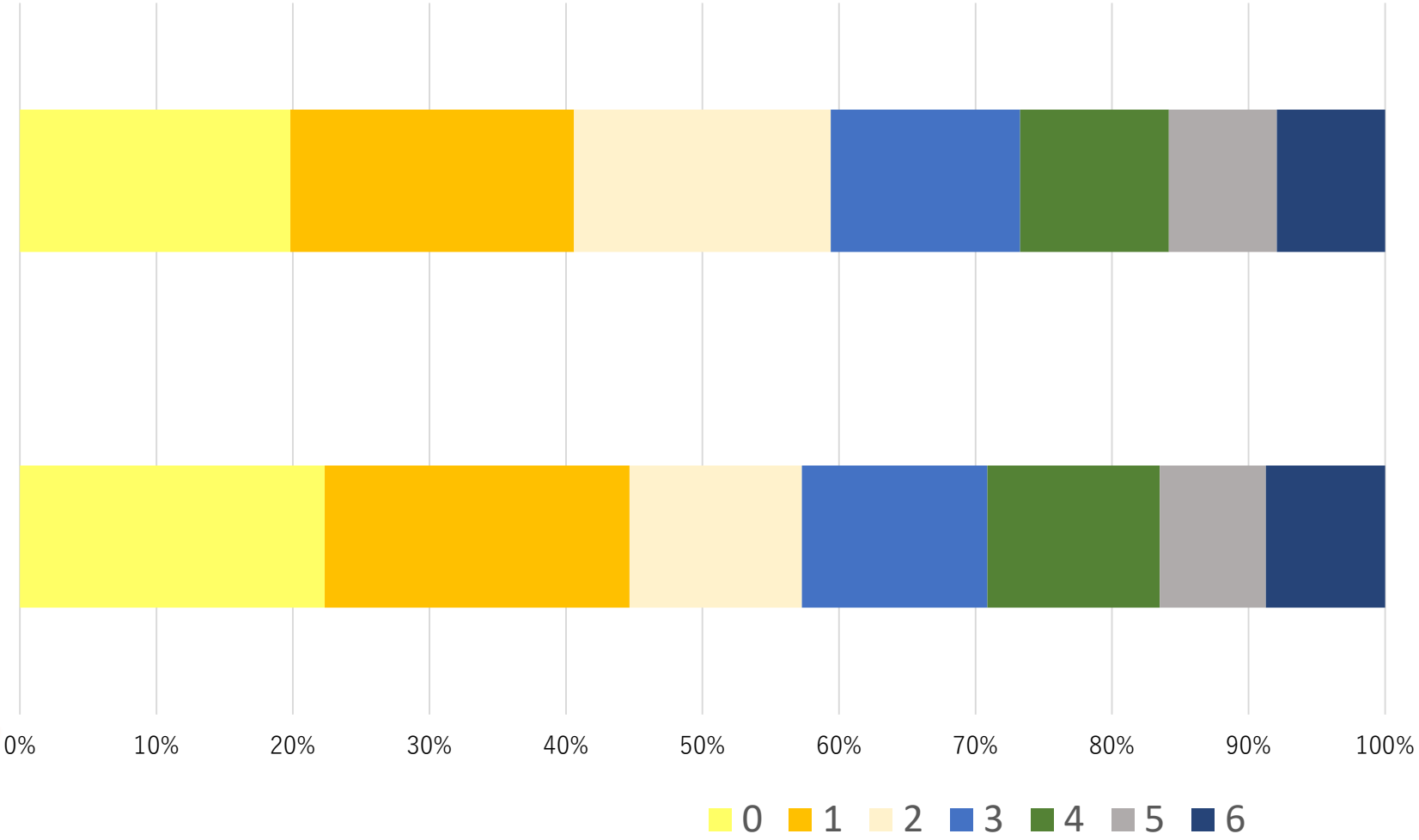
N=101

Bridging group

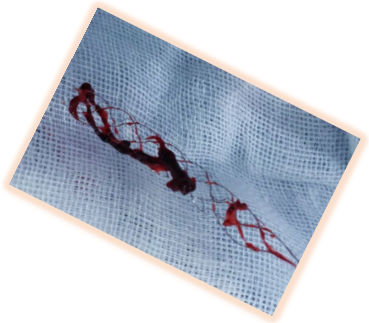
N=103

＋





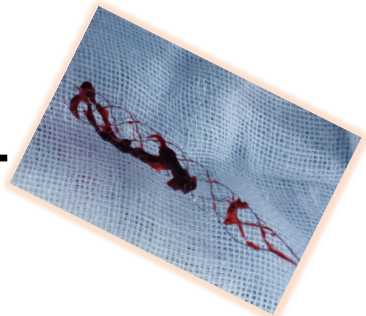
mRS at 90 days



Direct MT group

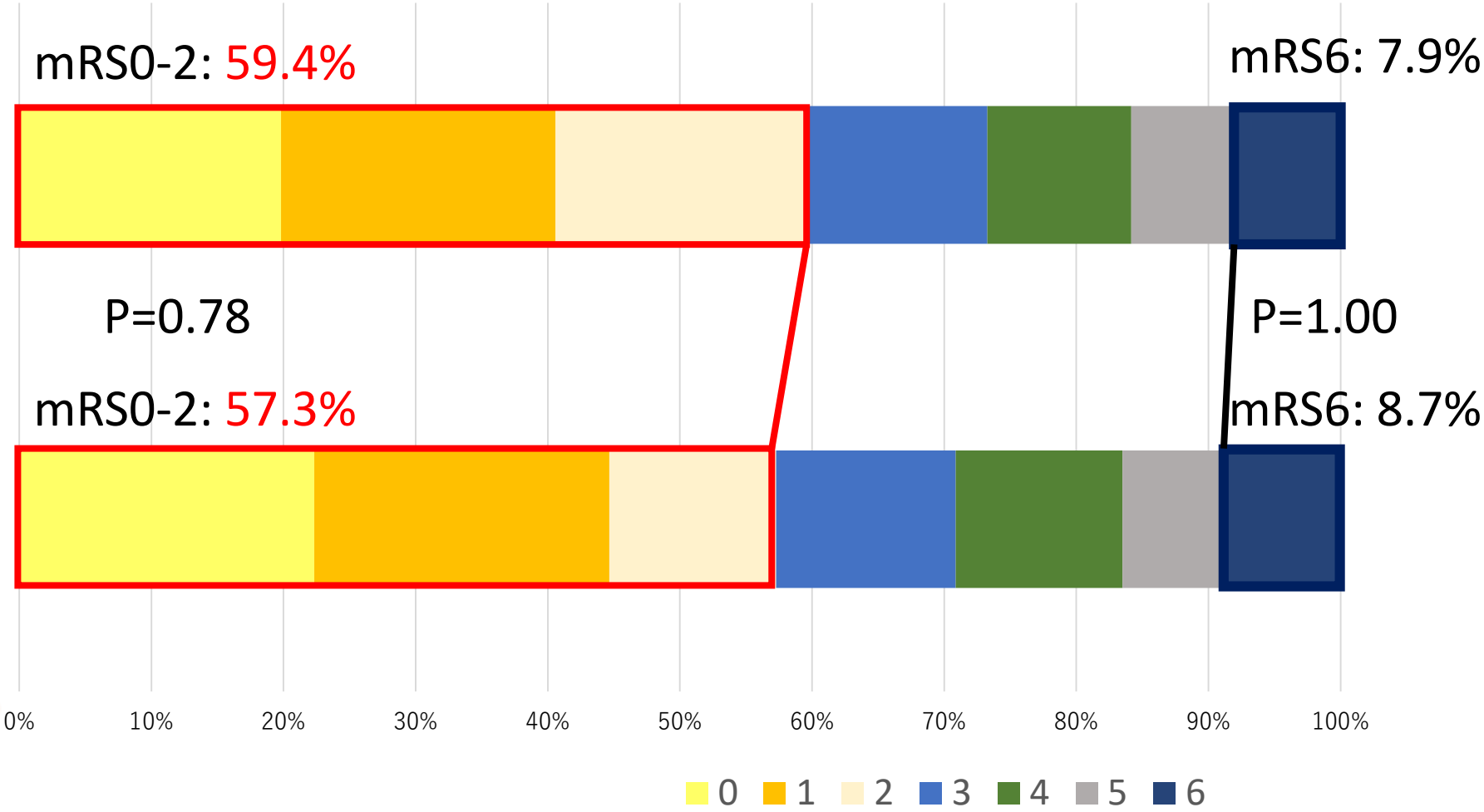
N=101

＋

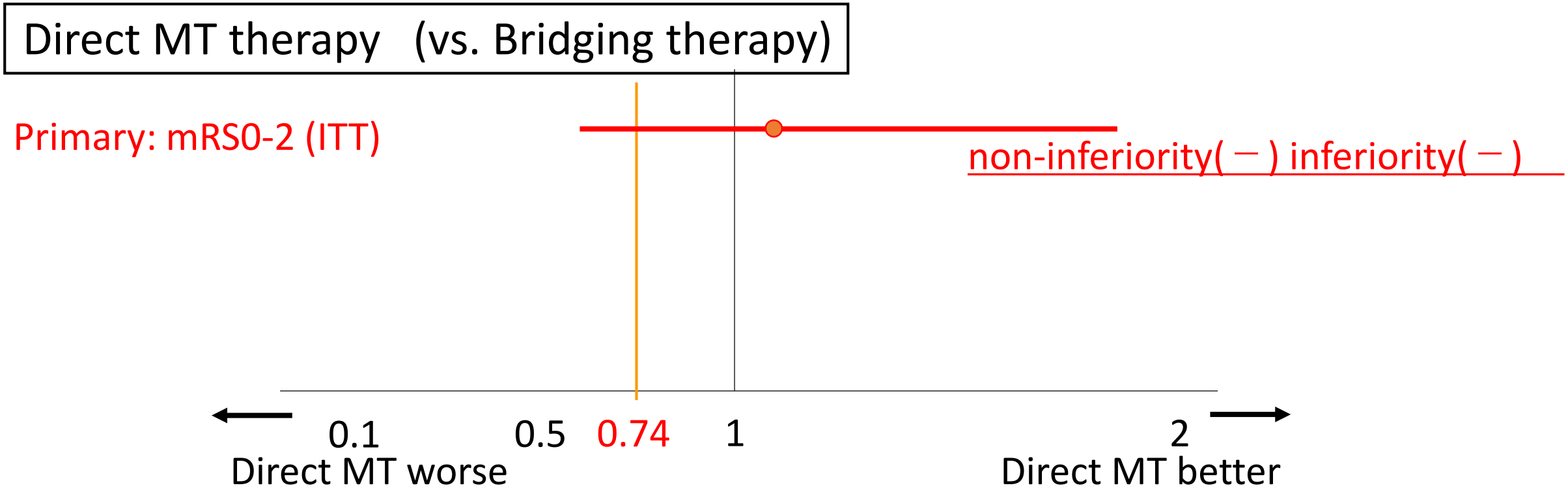


Bridging group

N=103



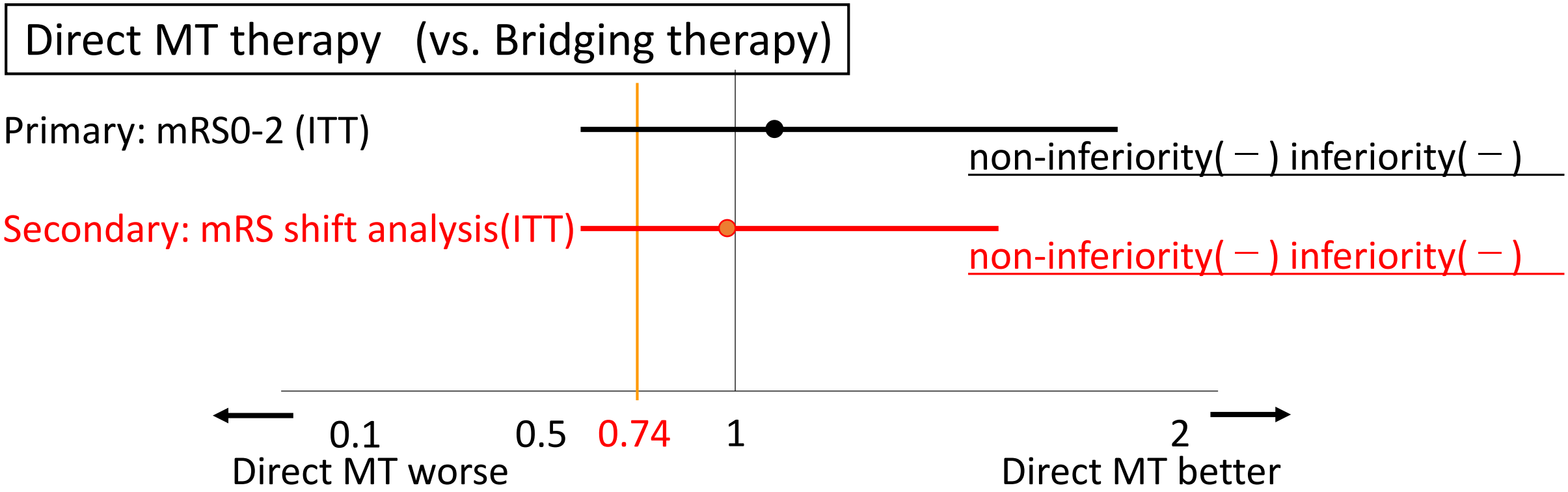
Primary efficacy outcome: mRS0-2



Primary outcome: unadjusted logistic regression model (ITT)

odds ratio 1.09, 95% CI 0.63 - 1.90, p=0.17 for noninferiority.

Secondary efficacy outcome: mRS



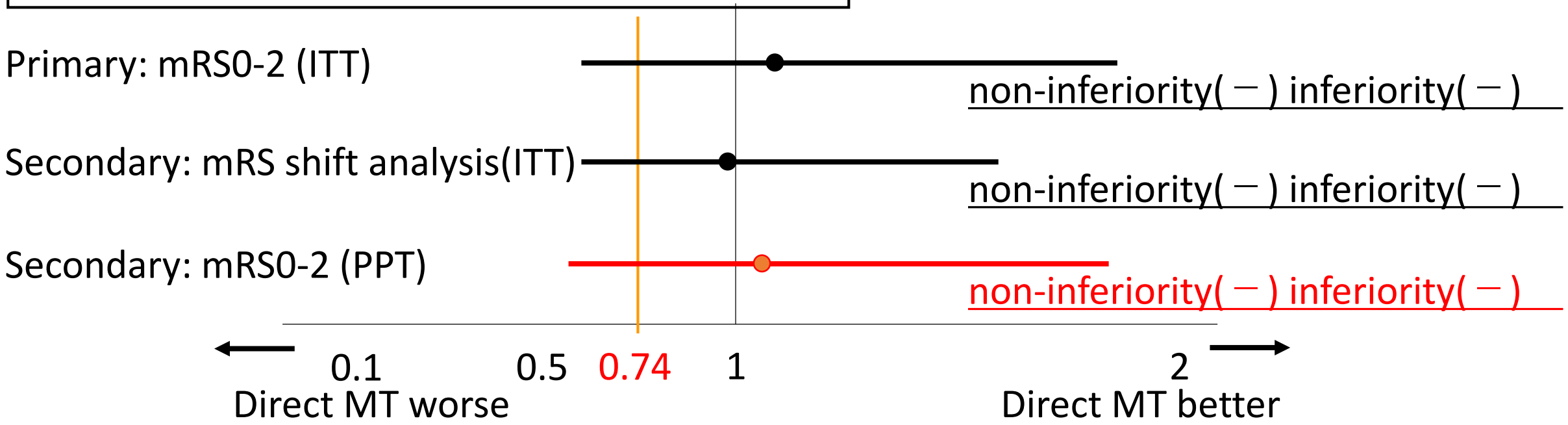
Primary outcome: odds ratio 1.09, 95% CI 0.63 - 1.90, p=0.17 for noninferiority.

Secondary outcome: Shift analysis(ITT)

odds ratio 0.97, 95% CI 0.60 - 1.56, p=0.27 for noninferiority.

Secondary efficacy outcome: mRS 0-2

Direct MT therapy (vs. Bridging therapy)



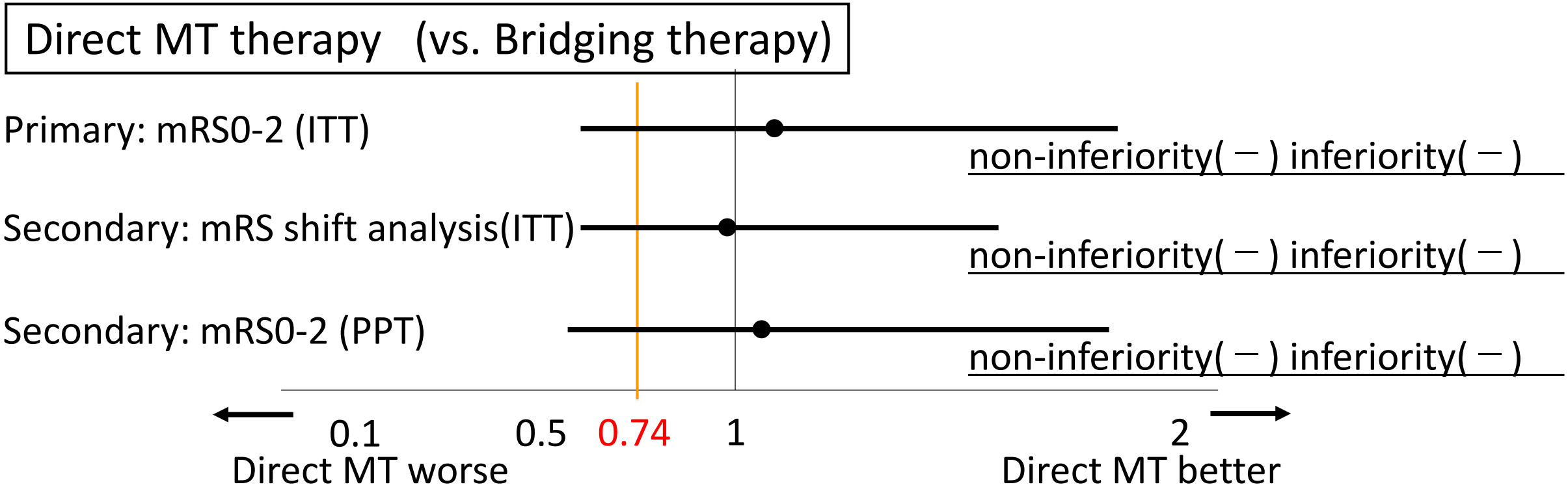
Primary outcome: odds ratio 1.09, 95% CI 0.63 - 1.90, p=0.17 for noninferiority.

Secondary outcome: odds ratio 0.97, 95% CI 0.60 - 1.56, p=0.27 for noninferiority.

Secondary outcome: unadjusted logistic regression model (PPT)

odds ratio 1.06, 95% CI 0.60 - 1.88, p=0.22 for noninferiority

Efficacy outcome



Primary outcome: odds ratio 1.09, 95% CI 0.63 - 1.90, p=0.17 for noninferiority.
Secondary outcome: odds ratio 0.97, 95% CI 0.60 - 1.56, p=0.27 for noninferiority.
Secondary outcome: odds ratio 1.06, 95% CI 0.60 - 1.88, p=0.22 for noninferiority

We could not prove non-inferiority of Direct MT to Bridging therapy

Secondary efficacy outcomes

	Direct MT group	Bridging group	HR(95%CI)	P value
	n=101	n=103		
Death at 90 days, no. (%)	8(8)	9(9)	0.90(0.33-2.43)	1.00
Puncture to Reperfusion time (min)	50 ± 37	42 ± 33		0.12
TICI grade ≥ 2B, no. (%)	91(90)	95(92)	0.89(0.51-1.55)	0.78

The recanalization rate were quite high (HERMES collaboration: 70.5%)

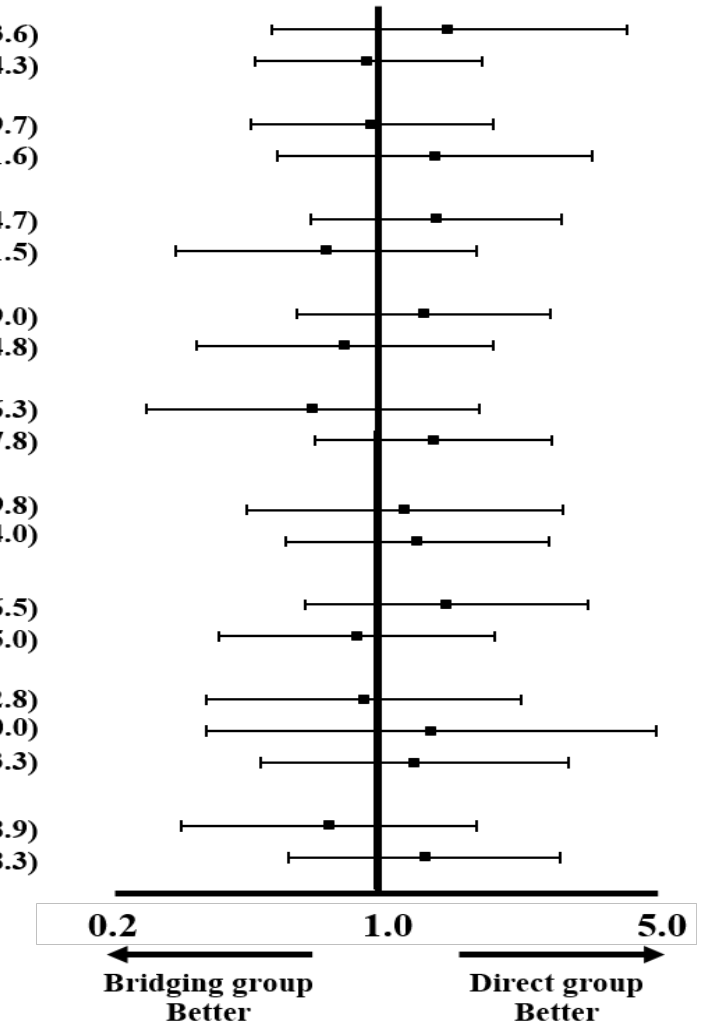
Safety outcomes

	Direct MT group	Bridging group	HR(95%CI)	P value
	n=101	n=103		
Any ICH at 36h	34(34)	52(50)	0.50(0.28-0.88)	0.02
Symptomatic ICH (NINDS criteria) at 36h	8(8)	12(12)	0.65(0.25-1.67)	0.48
Symptomatic ICH (SIT-MOST criteria) at 36h	6(6)	8(8)	0.75(0.25-2.24)	0.78

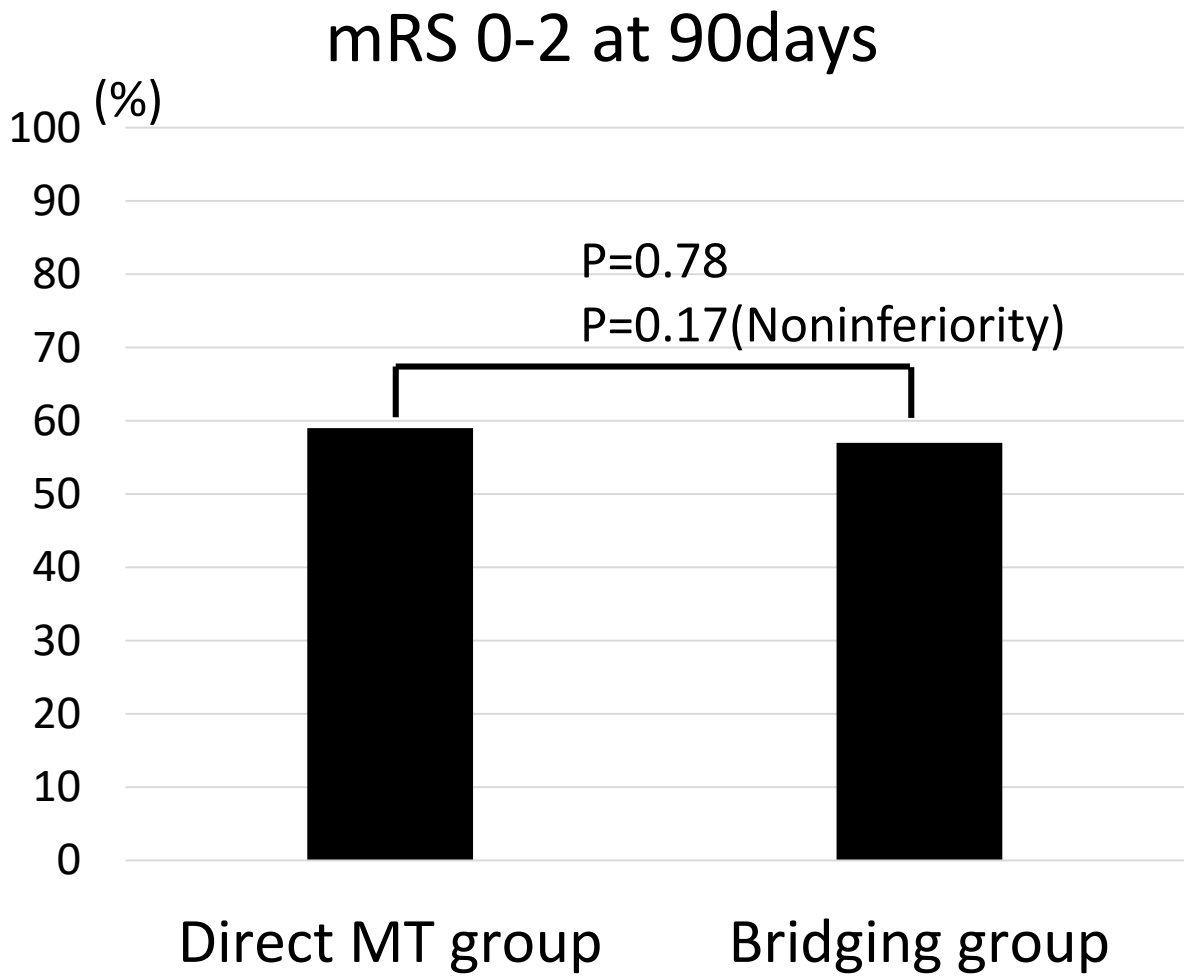
Any ICH was significantly lower in the Direct MT group

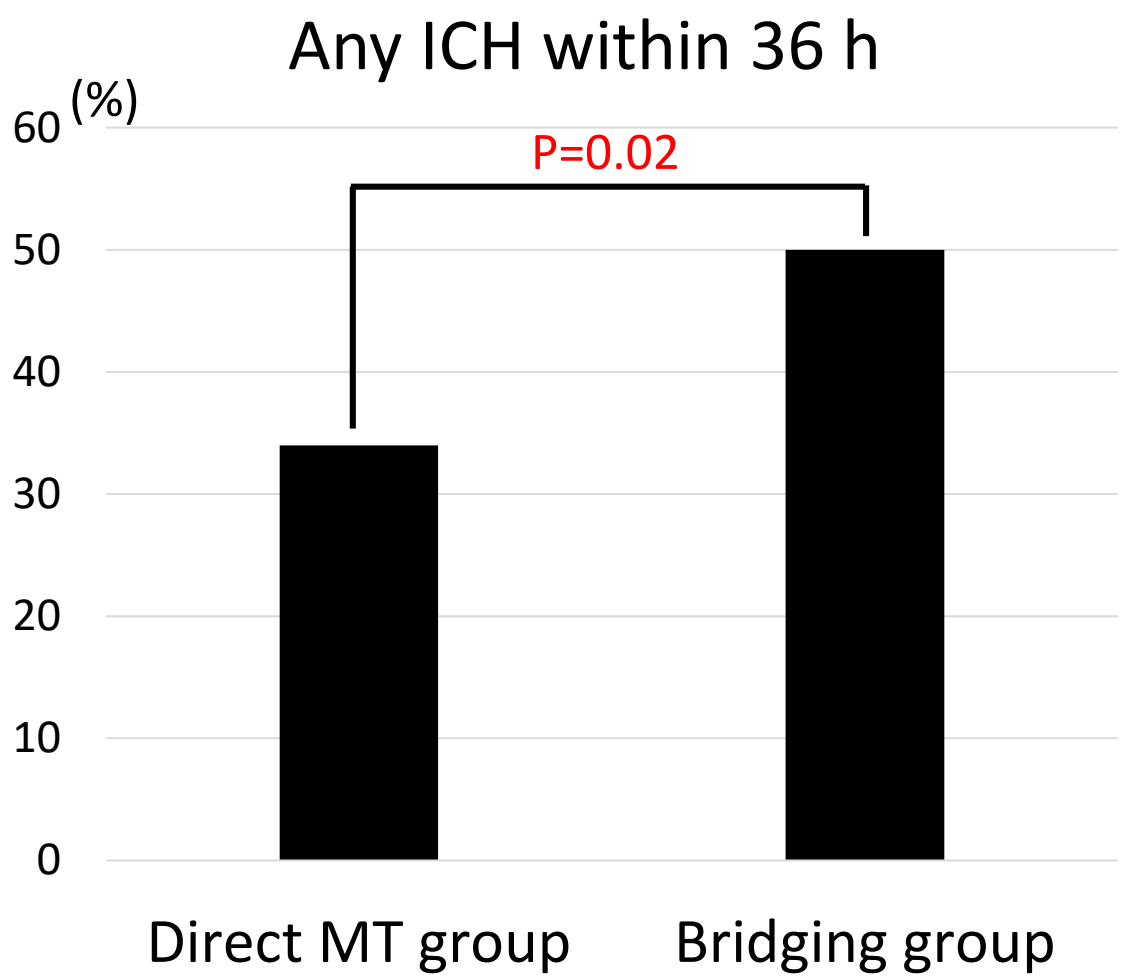
Primary efficacy outcome according to subgroups

	Direct group	Bridging group	Odds Ratio (95% CI)	P Value for Interaction
Age				0.45
<70 years	24(72.3)	21(63.6)	1.52(0.54-4.33)	
≥70 years	36(52.9)	38(54.3)	0.95(0.49-1.85)	
Sex				0.53
Male	33(58.9)	43(59.7)	0.97(0.48-1.97)	
Female	27(60.0)	16(51.6)	1.41(0.56-3.54)	
AF				0.27
YES	36(63.2)	35(54.7)	1.42(0.68-2.95)	
NO	24(54.6)	24(61.5)	0.75(0.31-1.80)	
Blood Sugar				0.42
<126 mg/dl	40(65.6)	36(59.0)	1.32(0.63-2.76)	
≥126 mg/dl	20(50.0)	23(54.8)	0.83(0.35-1.97)	
Use of antithrombotic agent				0.25
YES	16(47.1)	18(56.3)	0.69(0.26-1.82)	
NO	44(65.7)	41(57.8)	1.40(0.70-2.79)	
NIHSS score at admission				0.90
<18	30(73.2)	37(69.8)	1.18(0.48-2.92)	
≥18	30(50.0)	22(44.0)	1.27(0.60-2.70)	
ASPECTS				0.37
<8	30(56.6)	20(46.5)	1.50(0.67-3.37)	
≥8	30(62.5)	39(65.0)	0.90(0.41-1.98)	
Occluded artery				0.99
ICA	21(51.2)	19(52.8)	0.94(0.38-2.30)	
M1 proximal	11(57.9)	9(50.0)	1.38(0.38-5.03)	
M1 distal	28(68.3)	31(63.3)	1.25(0.52-3.01)	
Onset to Randmization				0.35
≤120 min	34(63.0)	31(68.9)	0.77(0.33-1.78)	
>120 min	26(55.3)	28(48.3)	1.33(0.61-2.87)	



Summary of Results





Limitations

1. Open labeled treatment
2. Limited to patients with ICA or M1 occlusion
3. Dosage of alteplase was only 0.6 mg/kg

We could not prove inferiority?

Frequency of favorable outcome due to high recanalization rate was higher than we expected, which could not statistically prove non-inferiority.

Conclusions

- ✓Frequency of favorable outcomes did not differ between Direct MT group and Bridging group, however, we could not prove non-inferiority of Direct MT therapy to Bridging therapy.

- ✓Any ICH was significantly less frequent in Direct MT group than in Bridging group.

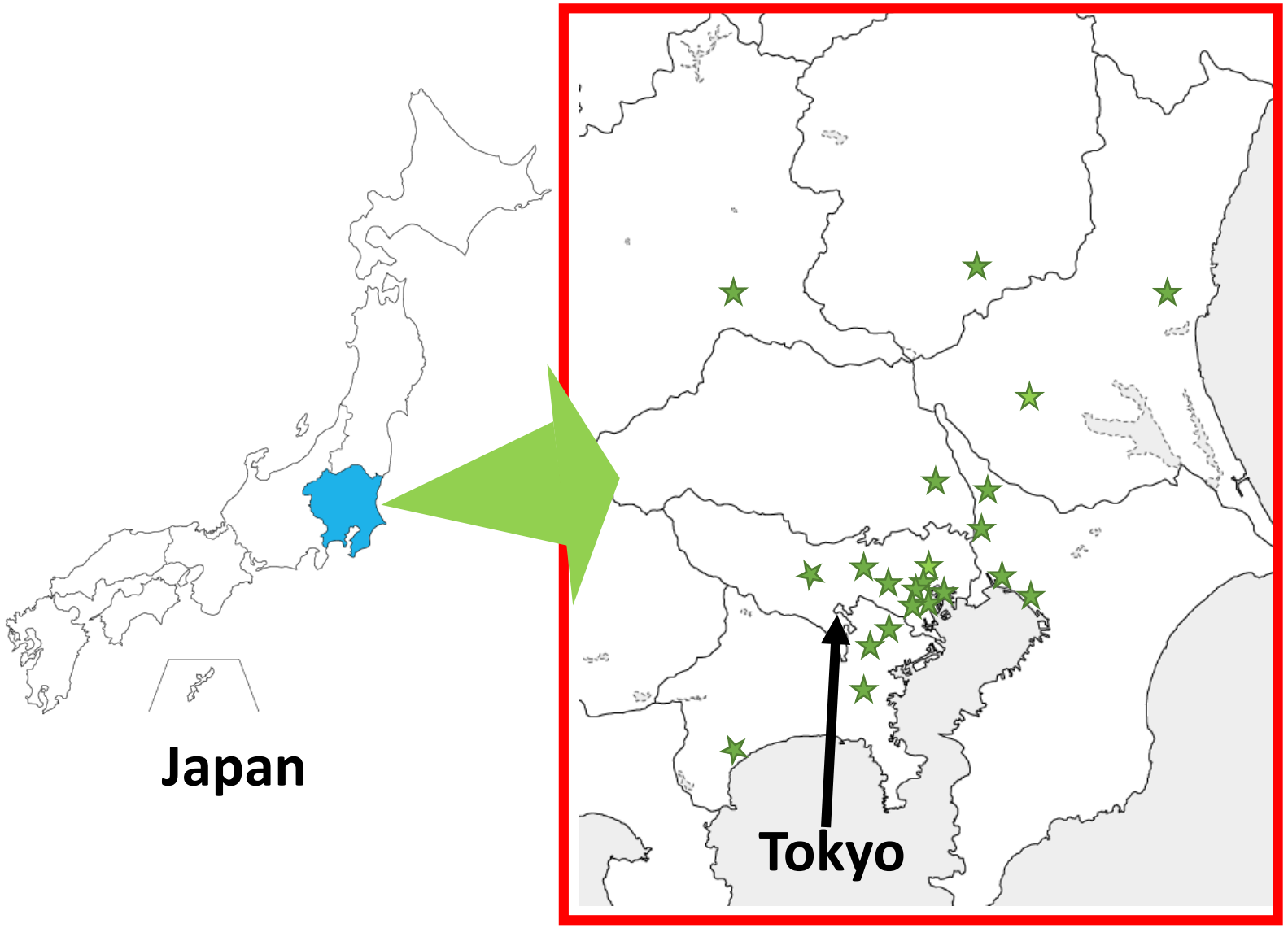
Committees

- **Principal Investigator**
  Kazumi Kimura
  Yuji Matsumaru
- **Protocol Authoring Committee**
  Kentaro Suzuki
- **Radiological Judging Committee**
  Teruyuki Hirano
  Shigeru Fujimoto

- **Steering Committee**
  Yasuyuki Iguchi
  Keigo Shigeta
  Seiji Okubo
  Masataka Takeuchi
  Masafumi Morimoto
  Ryuzaburo Kanazawa
  Yuki Kamiya
  Norihiro Ishii
  Yorio Koguchi
  Hiromichi Naito
  Masato Inoue
  Toshihiro Ueda
  Noriyuki Kato

- **Independent Data Monitoring Committee**
  Akio Morita
- **Event Evaluation Committee**
  Hiroyuki Yokota
- **Statistical Analysis Committee**
  Toshiaki Otsuka
  Kazumi Kimura
  Yasuhiro Nishiyama
  Kentaro Suzuki

Clinical Sites by Enrollment



Nippon Medical School Hospital
University of Tsukuba
Seishou Hospital
Yokohama Shintoshi Neurosurgery Hospital
Nagareyama Central Hospital
Akiyama Neurosurgical Hospital
Showa University Koto Toyosu Hospital
National Hospital Organization Disaster Medical Center
New Tokyo Hospital
Chiba Emergency Medical Center
NTT Medical Center Tokyo
National Center For Global Health and Medicine
Dokkyo Medical University Koshigaya Hospital
Metropolitan Tama Medical Center
Funabashi Municipal Medical Center
Mihara Memorial Hospital
Mito Medical Center
Kyorin University
St. Marianna University Toyoko Stroke Center
The Jikei University School of Medicine
Tokyo Medical And Dental University
Jichi Medical University Hospital
Toranomon Hospital


TOKYO 2020
See You at Tokyo Olympic
From Jan.24 – Aug.9.2020


Thank You
Grazie
شكرا
Terima kasih
Obrigado
TOKYO 2020
Gracias
Hvala ti
Teşekkür ederiz
Asante
ありがとう
Diolch Aitäh
E υ χ α ρ ι σ τ ο ύ μ ε
ขอบคุณ
Děkuju Tak
ধন্যবাদ
Salamat
Je vous
Danke
remercie
Je
vous remercie
متشكرم
Dank u
תודה