Oralisierung bei *S. aureus* Blutstrominfektionen

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Prof. Achim Kaasch
Institut für Medizinische Mikrobiologie und Krankenhaushygiene
Otto-von-Guericke-Universität Magdeburg

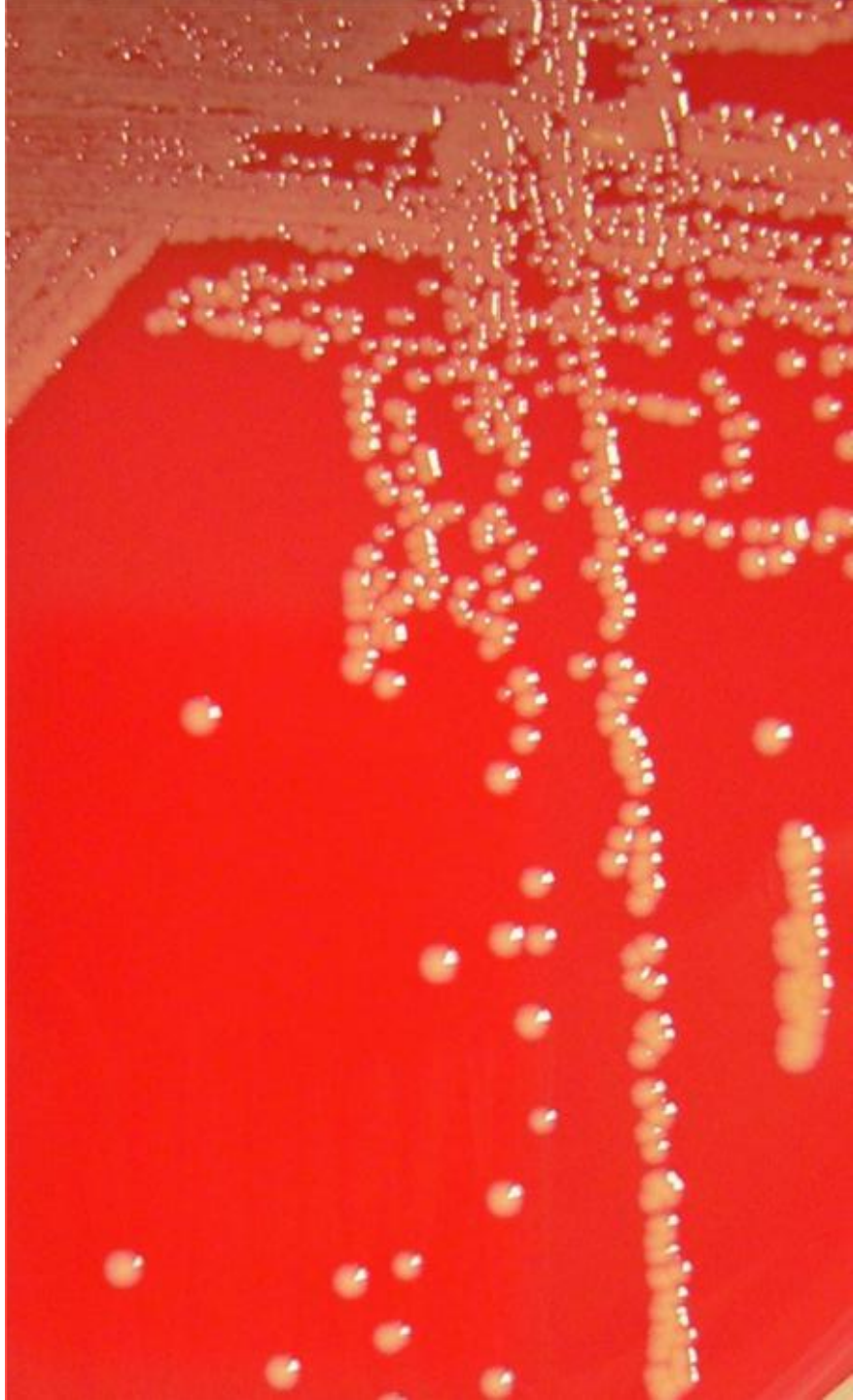
MEDIZINISCHE FAKULTÄT
UNIVERSITÄTSKLINIKUM MAGDEBURG A. ö. R.

Keine Interessenskonflikte

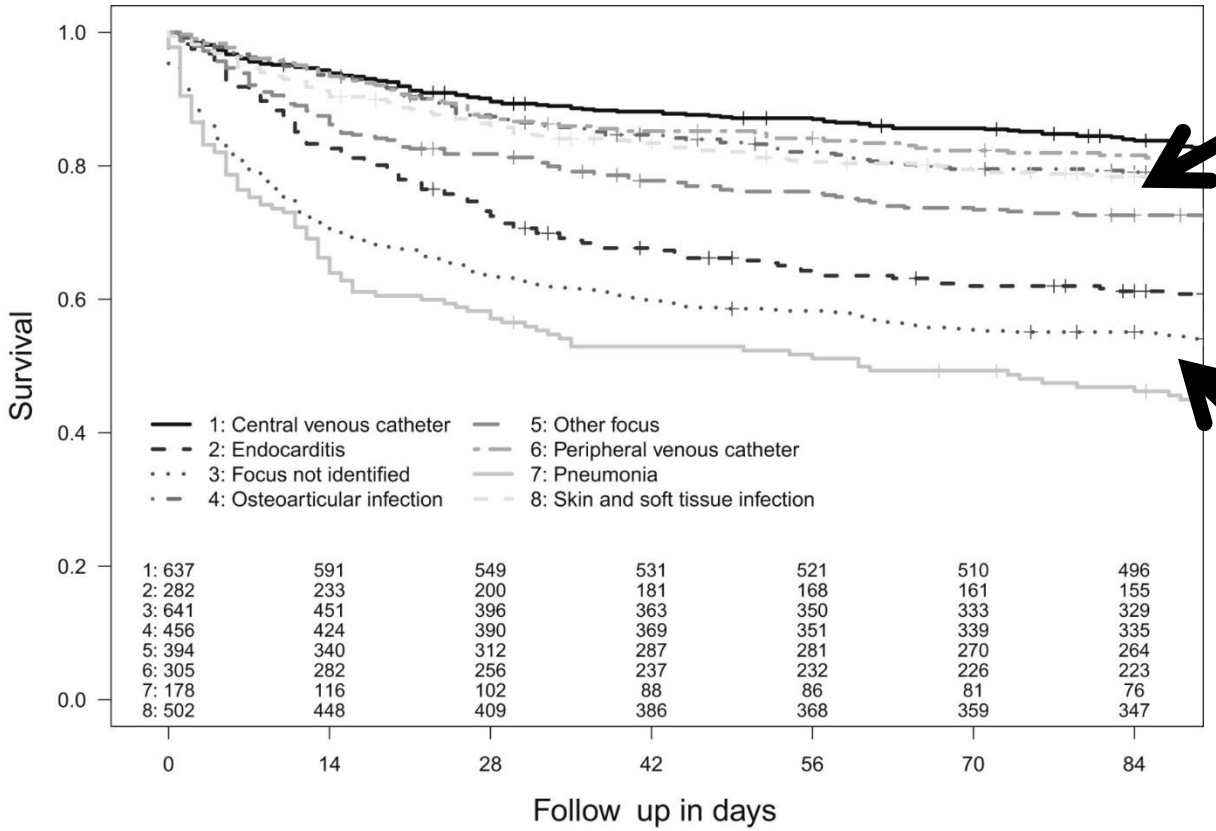
Staphylococcus aureus Blutstrominfektion

- Tiefer Fokus ist häufig
- Wiederkehrende Infektion
- (späte) Streuherde
- Therapiedauer mind. 14 Tage

Ist eine oral Therapie sicher und wirksam?



S. aureus bloodstream infection

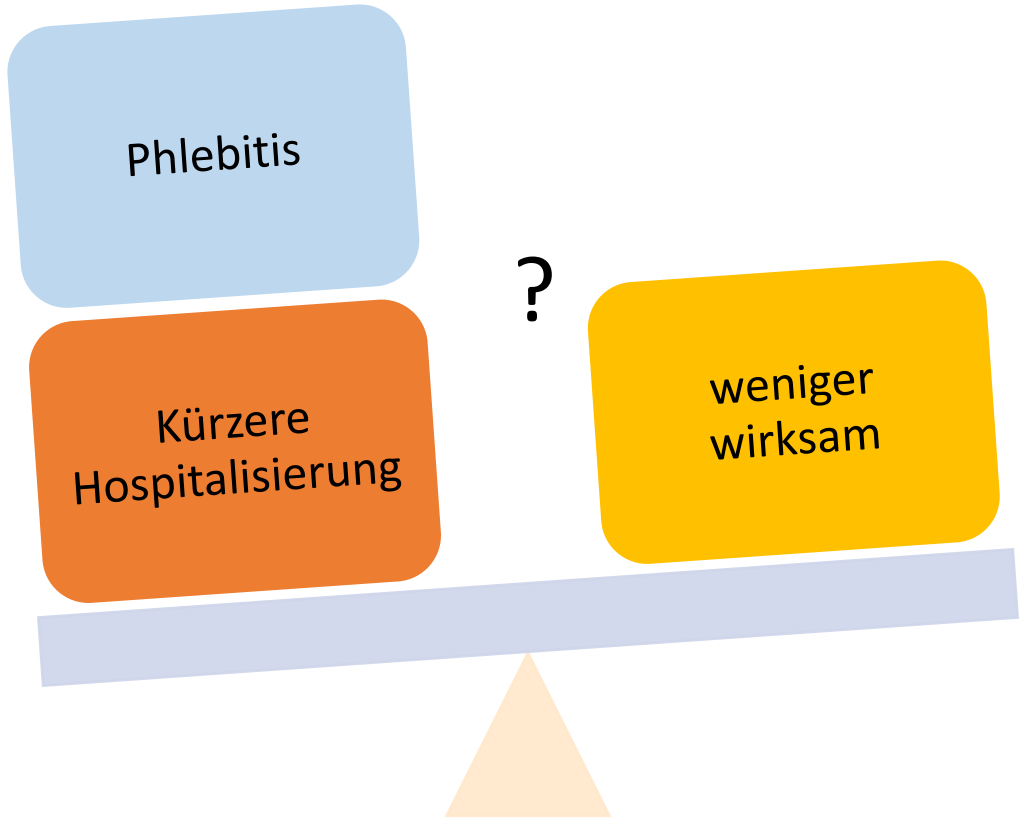


catheter-related, SSTI, osteoarticular infection

endocarditis, unknown focus, pneumonia

n=3395
Kaasch, *J Infect,* 2014

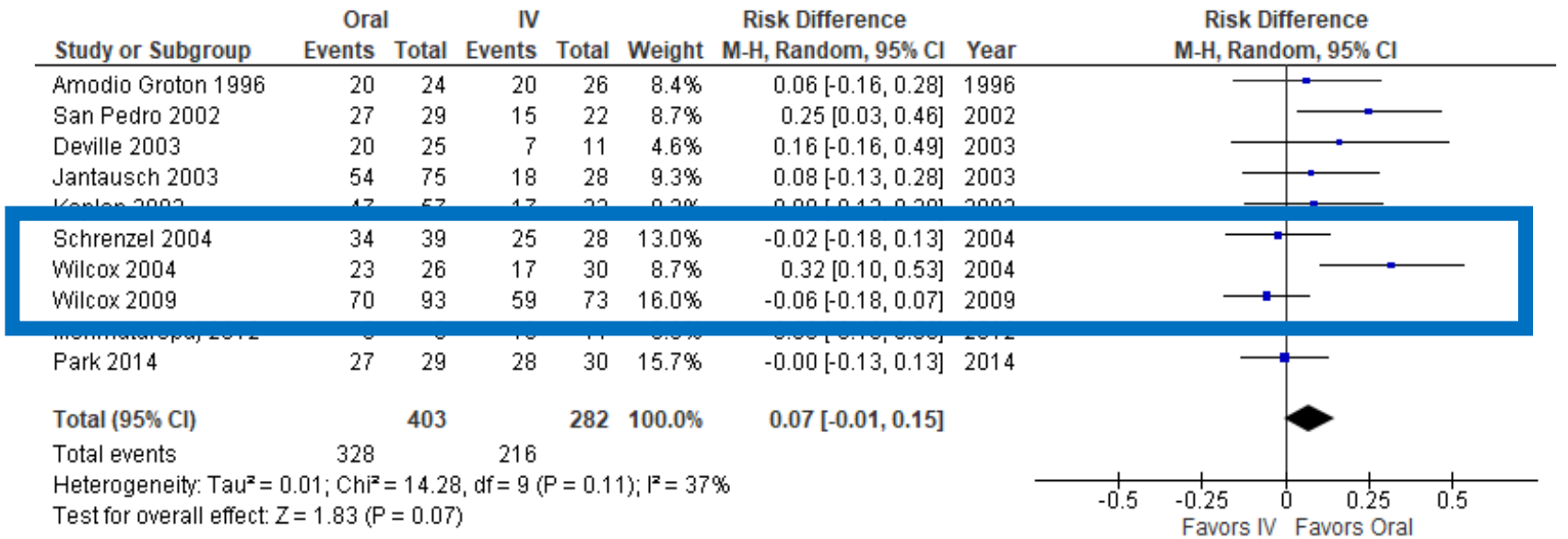
Oralisierung



Vorteile

Risiken

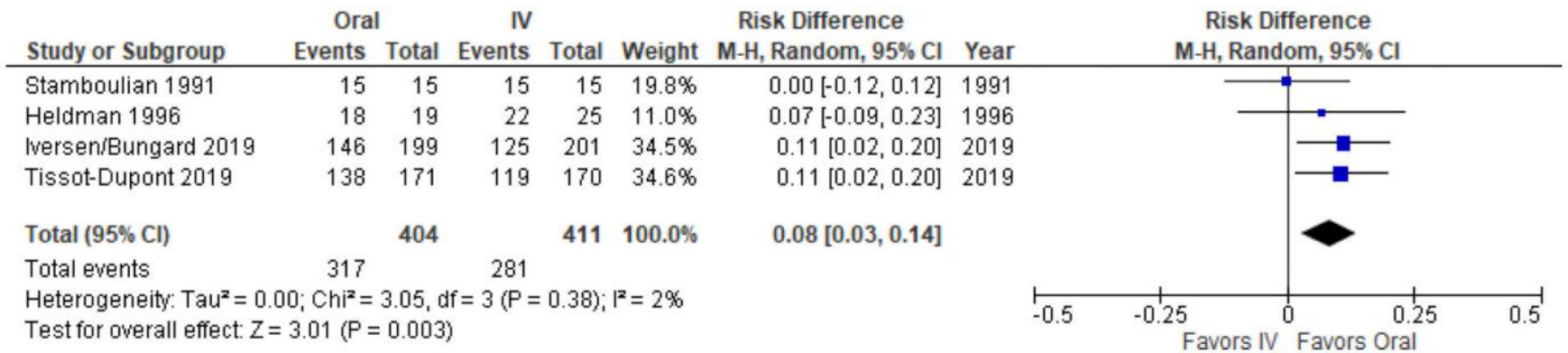
Meta-Analysis RCTs (not specific to *S. aureus*)



Study or Subgroup	Oral Events	Oral Total	IV Events	IV Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Amodio Groton 1996	20	24	20	26	8.4%	0.06 [-0.16, 0.28]	1996
San Pedro 2002	27	29	15	22	8.7%	0.25 [0.03, 0.46]	2002
Deville 2003	20	25	7	11	4.6%	0.16 [-0.16, 0.49]	2003
Jantausch 2003	54	75	18	28	9.3%	0.08 [-0.13, 0.28]	2003
Schrenzel 2004	34	39	25	28	13.0%	-0.02 [-0.18, 0.13]	2004
Wilcox 2004	23	26	17	30	8.7%	0.32 [0.10, 0.53]	2004
Wilcox 2009	70	93	59	73	16.0%	-0.06 [-0.18, 0.07]	2009
Park 2014	27	29	28	30	15.7%	-0.00 [-0.13, 0.13]	2014
Total (95% CI)		**403**		**282**	**100.0%**	**0.07 [-0.01, 0.15]**	
Total events	328		216				

Heterogeneity: Tau² = 0.01; Chi² = 14.28, df = 9 (P = 0.11); I² = 37%
Test for overall effect: Z = 1.83 (P = 0.07)

Adult Gram+ Bacteremia



Study or Subgroup	Oral Events	Oral Total	IV Events	IV Total	Weight	Risk Difference M-H, Random, 95% CI	Year
Stamboulian 1991	15	15	15	15	19.8%	0.00 [-0.12, 0.12]	1991
Heldman 1996	18	19	22	25	11.0%	0.07 [-0.09, 0.23]	1996
Iversen/Bungard 2019	146	199	125	201	34.5%	0.11 [0.02, 0.20]	2019
Tissot-Dupont 2019	138	171	119	170	34.6%	0.11 [0.02, 0.20]	2019
Total (95% CI)		**404**		**411**	**100.0%**	**0.08 [0.03, 0.14]**	
Total events	317		281				

Heterogeneity: Tau² = 0.00; Chi² = 3.05, df = 3 (P = 0.38); I² = 2%
Test for overall effect: Z = 3.01 (P = 0.003)

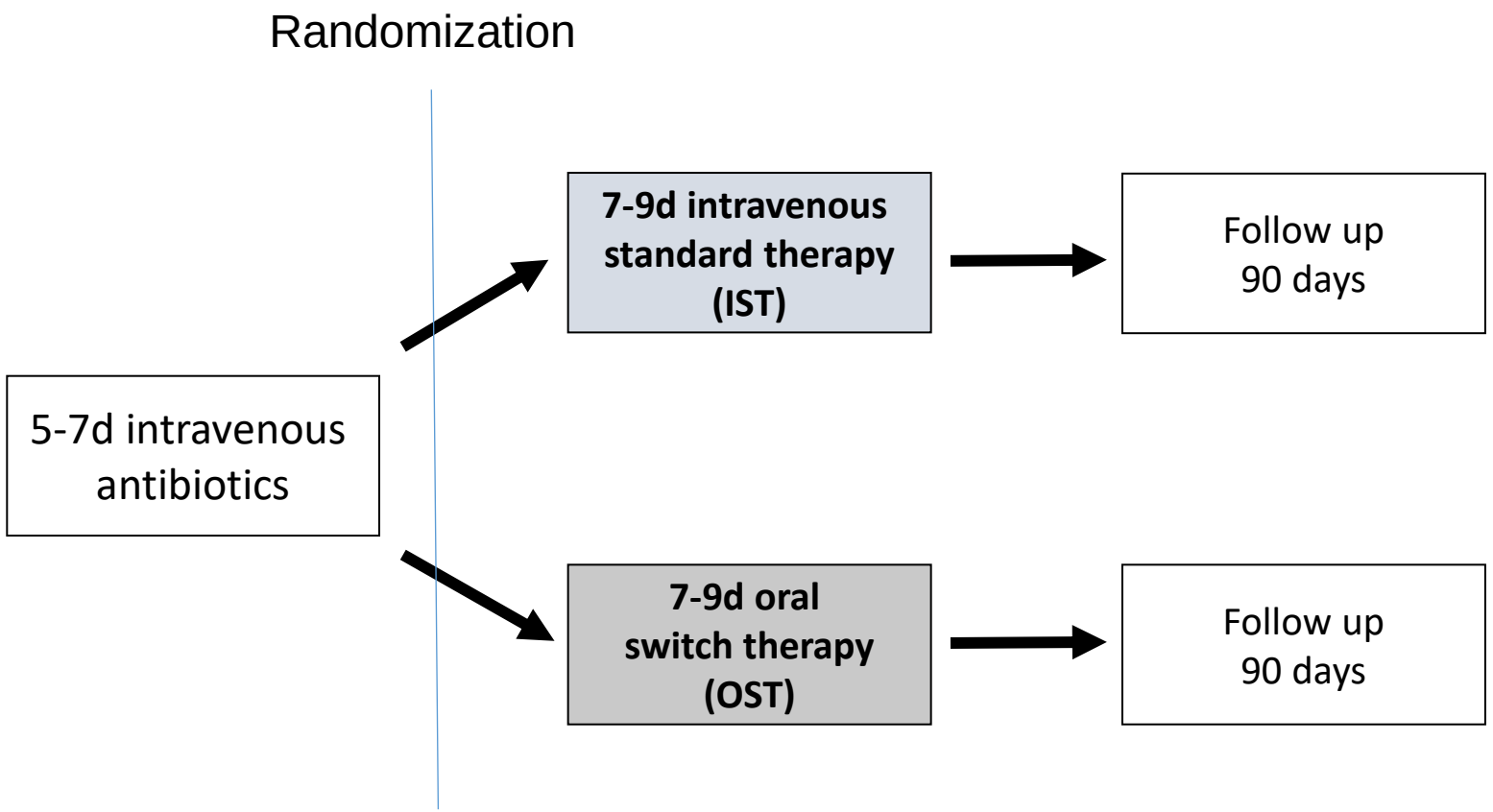
Endocarditis

Wald-Dickler *et al*, Am J Med 2021

Retrospektive Studien zur SAB

Author	Condition	N (oral/iv)	90-day mortality (oral vs. iv)	conclusion
Itoh N *et al*. PLOS One 2018	Uncomplicated MSSAB	32/28	11% vs. 53%	OST not associated with mortality
Willekens R *et al.* CID 2019	Uncomplicated SAB	45/107	2% vs. 16% (30-day)	Similar outcomes
Bupha-Intr O *et al.* AAC 2020	Uncomplicated SAB	84/16	2% vs. 6%	EOS possible
Mun SJ *et al.* J Chem 2022	Uncomplicated SAB	32/71	3% vs. 13% (incl. relapse)	may reduce the duration of hospitalization
Diego-Yagüe I *et al.* CMI 2023	Uncomplicated SAB	112/118	6% vs. 28%	OST is effective and safe
Jørgensen SCJ *et al.* JAC 2019	Complicated SAB (OOAT versus OPAT)	70/422	1% vs. 6%	at least equivalent clinical outcomes
Kouijzer IJE *et al.* CID 2021	Complicated SAB (no IE)	61/45	7% vs. 13%	IV-oral switch is effective and safe
Yeager SD *et al.* IJAA 2021	MRSA bacteremia (linezolid)	54/161	4% vs. 6%	similar clinical and safety outcomes
Pérez-Rodríguez MT *et al.* IJID 2021	Any SAB	125/76	7% vs. 16%	Safe option for properly selected patients

Study Design – „low risk“ SAB



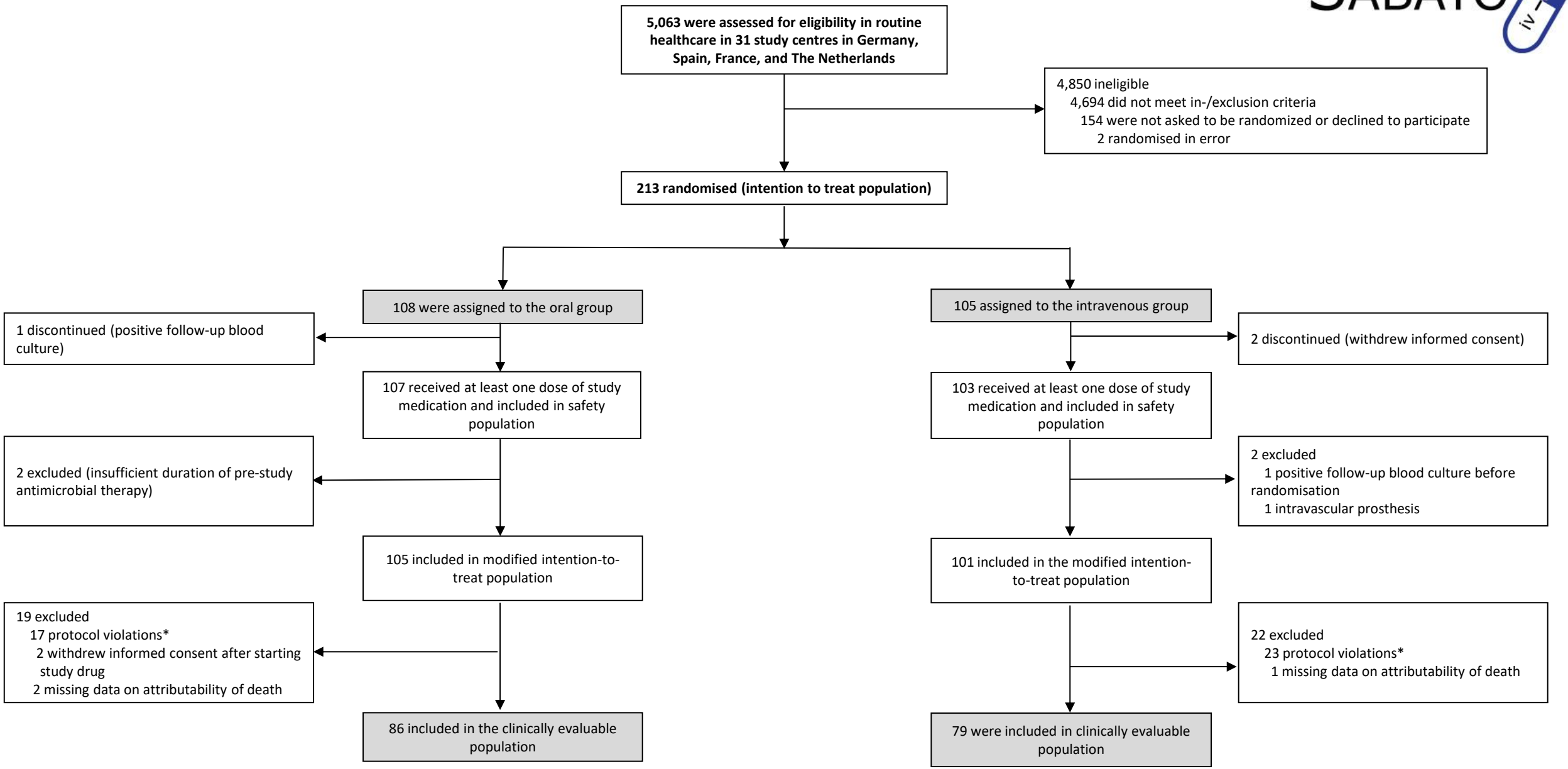
Primärer Endpunkt
„SAB related complication“
- Erneute Bakteriämie (Relapse)
- Tiefe Infektion
- attribuierbare Mortalität

Randomized, parallel-group, open-label, non-inferiority trial

Kaasch *et al.,* Trials 2015, Trials 2020, Lancet Inf Dis 2024

„Low-risk“ *S. aureus* Blutstrominfektion

- Definition
  - Negative Folgeblutkultur nach 24-96 Stunden
  - Keine Zeichen und Symptome von tiefem Fokus oder Streuherden
  - Intravaskuläre Katheter innerhalb von 4 Tagen entfernt
  - Keine Klappenprothese oder Gefäßprothese
  - Keine schwere Immunsuppression

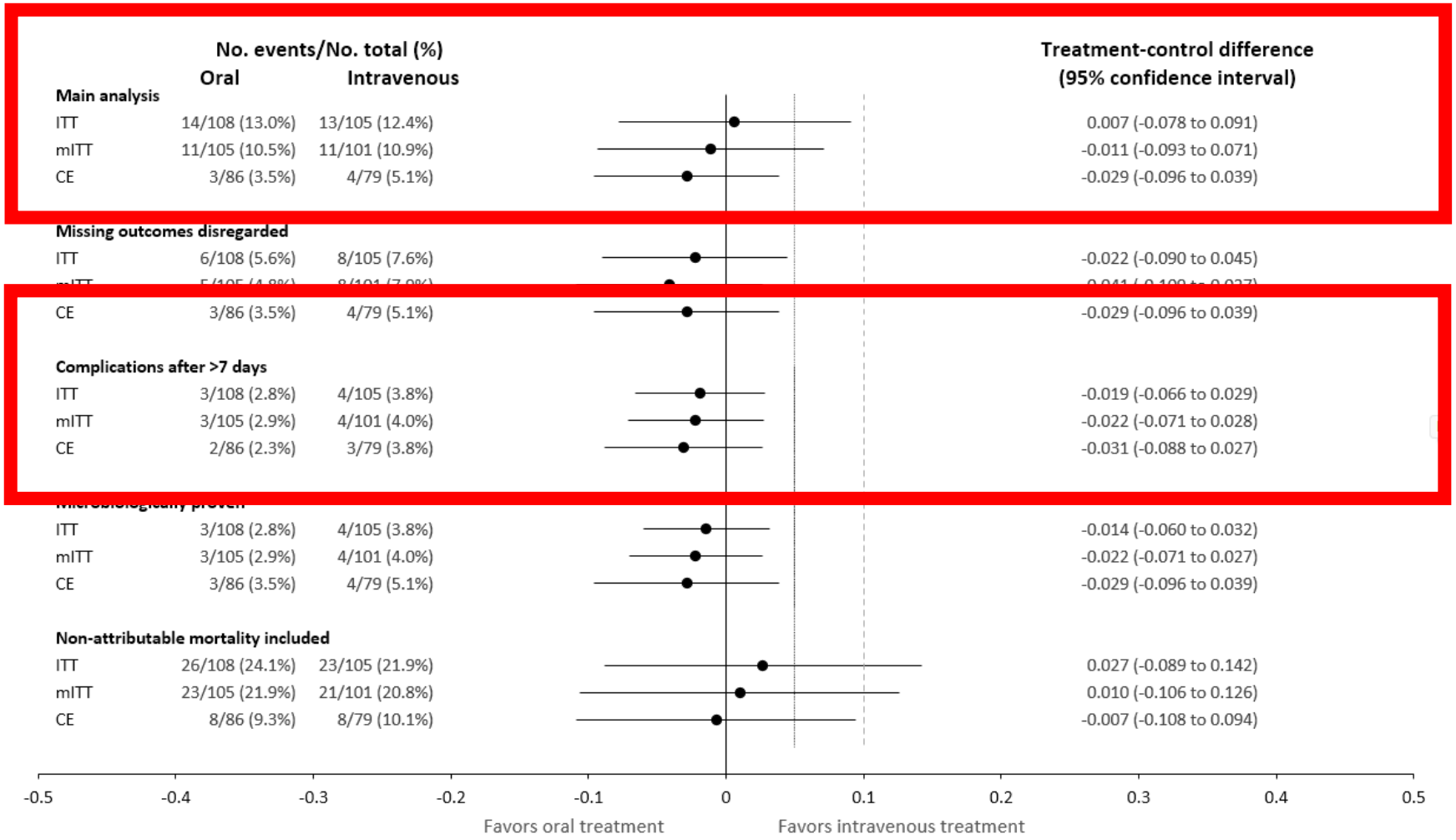


Trial profile: Four participants in the oral group and three in the intravenous group were lost to follow-up. *Some participants had more than one protocol violation

Baseline characteristics (ITT)

	Oral switch group (n=108)	Intravenous group (n=105)
Male sex – no. (%)	64.4 ±16.8	62.6 ±17.6
Age in years– mean ±SD	71 (65.7%)	77 (73.3%)
Body mass index – mean ±SD	27.6 ±6.7	25.6 ±5.4
Length of hospital stay – days (median, IQR)	10 (7-14)	11 (7-15)
Echocardiography (TTE and/or TEE) performed at randomization ±7 days – no. (%)	69 (63.9%)	60 (57.1%)
Charlson comorbidity index – median (IQR)	3 (1-5)	3 (1-4)
Methicillin-resistant Staphylococcus aureus – no. (%)	6 (5.6%)	10 (9.5%)
CRP in mg/L – median (IQR)	35 (13-70)	23 (10-59)
Main focus of infection		
Peripheral venous catheter	47 (43.5%)	46 (43.8%)
Central venous catheter	24 (22.2%)	25 (23.8%)
Skin and soft tissue infection	26 (24.1%)	22 (21.0%)
Other focus‡	5 (4.6%)	4 (3.8%)
Focus not identified	6 (5.6%)	8 (7.6%)

Primärer Endpunkt (Relapse, tiefer Fokus, attribuierbare Mortalität)



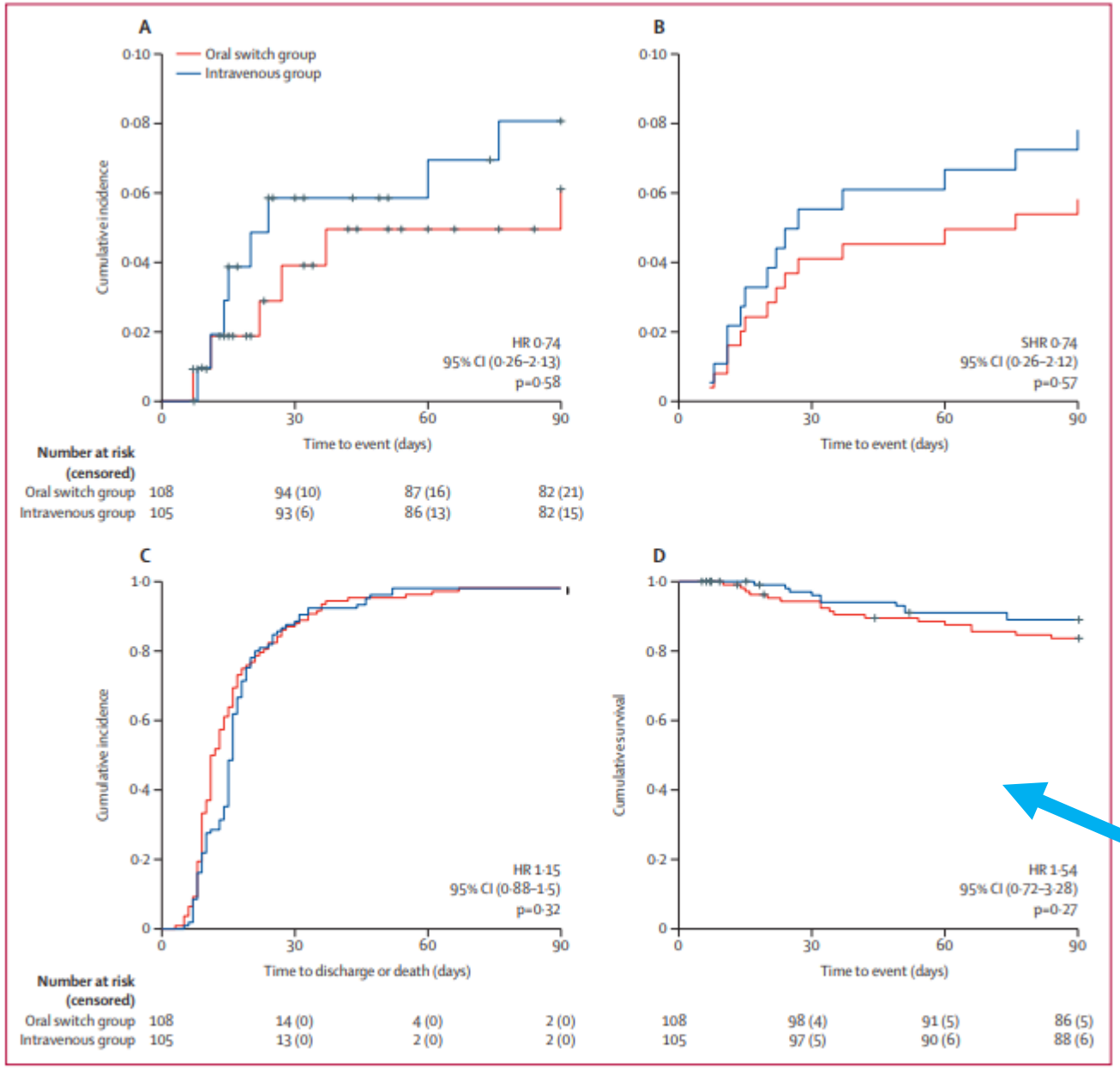


Figure 2: **Estimates of cumulative incidence from the date of the first positive blood culture for the intention-to-treat population**
(A) Cumulative incidence of the composite primary endpoint, complications related to *Staphylococcus aureus* bloodstream infection, with complications defined as relapsing *S aureus* infection, deep-seated *S aureus* infection, or death attributable to *S aureus* and participants with deaths not attributable to *S aureus* bloodstream infection censored (Kaplan-Meier method). (B) Cumulative incidence of the composite primary endpoint, with mortality not attributable to *S aureus* bloodstream infection considered a competing event (post-hoc sensitivity analysis, Fine and Gray model). (C) Cumulative incidence of hospital discharge or death. (D) Cumulative survival (all-cause mortality, Kaplan-Meier method) with HRs estimated from Cox regression. HR=hazard ratio. SHR=subdistribution hazard ratio.

SABATO iv → oral

Intention-to-treat

A: Cumulative incidence (primary endpoint)

B: Cumulative incidence with death as competing event

C: Length of hospital stay

D: Survival

„SAB-related complications“

- Orale vs. intravenöse Gruppe: 6 vs. 8 Ereignisse
- 7 Ereignisse in der ersten Woche (z.B. unerkannte Osteomyelitis)

Attribuierbare Mortalität (nur in der oralen Gruppe aufgetreten)

- disseminierte Infektion nach ZVK Infektion
  - 1 Patient: septische Arthritis und Aorten-Dissektion
  - 1 Patient: SAB Relapse und vermutete Dissemination, Wiederaufnahme abgelehnt

Und was ist mit „high-risk“ Patienten?

- POET trial - Endokarditis (S. aureus: OR 0.84; 95%-KI 0.15-4.78)

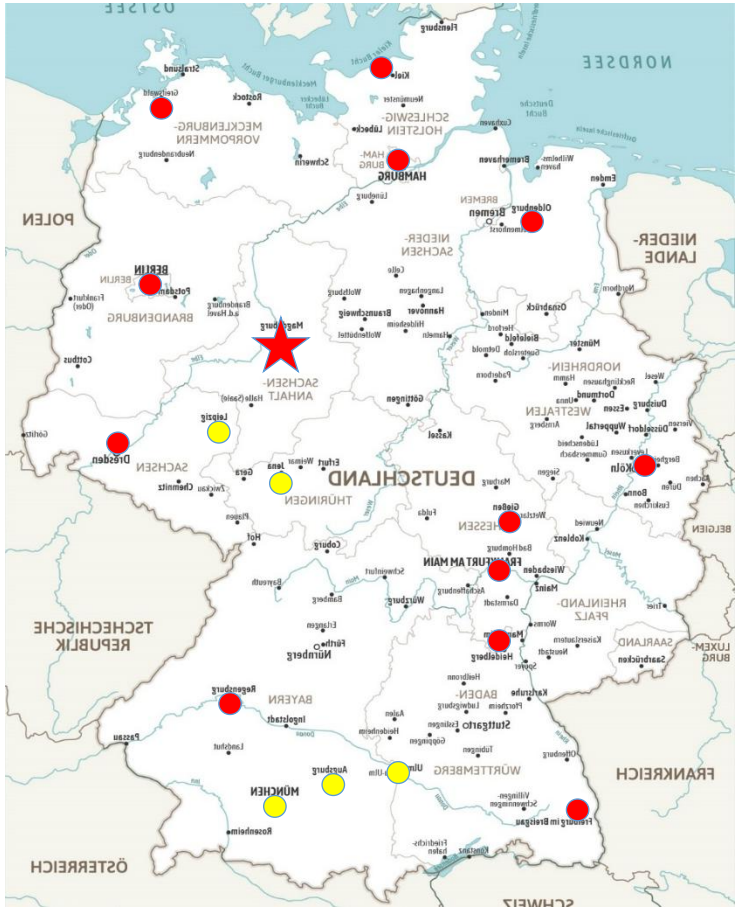
- OVIVA trial - Knochen- und Gelenkinfektionen (S. aureus: OR 0.89; 95%-KI 0.49-1.59, aber Bakteriämie ausgeschlossen)

→ Keine guten Daten für SAB

Iversen *et al.,* NEJM 2019
Li *et al.*, NEJM 2019

S. aureus adaptive platform trial

- Globale Plattformstudie
  - Oral switch d7, d14
  - Fluclox vs. Cefazolin
  - Adjunctive Clindamycin
- 131 Zentren: Australien, NZ, Canada, Israel, Singapur, UK, NL, D, Südafrika
- Lead
  - Joshua Davis, Stephen Tong
  - Europe: Marc Bonten
  - D: Achim Kaasch, Siegbert Rieg
- Akt. >4.240 Patienten randomisiert



SACHSEN-ANHALT

netzwerk universitäts medizin

Fazit

SABATO

- Early oral switch ist der Standardtherapie nicht unterlegen
- SNAP wird weitere Daten bringen

- Wichtig: Patienten **genau beurteilen** und **nachbeobachten** bei oraler Therapie

SABATO study group

Luis Eduard López-Cortés, Jesús Rodríguez-Baño, José Miguel Cisneros, M. Dolores Navajo, Valiente Adoración, María Macías, Jose A. Lepe, José Molina, María Nuñez, Elisa Moreno, Marina de Cueto, María J. Gómez-Gómez, Rocío Alvarez-Marín (Sevilla) Gerd Fätkenheuer, Norma Jung, Julia Fischer, Gregor Paul, Verena Weiss, Anne Adams, Martin Hellmich, Reinhild Prinz-Langenohl (Köln) Winfried Kern, Siegbert Rieg (Freiburg), Raphaël Lepeule, Laetitia Couttee, Sébastien Gallien, Vincent Fihman, Amina Moussafeur (Creteil), Louis Bernard, Adrien Lemaignen, Marion Lacasse, Francois Coustillieres (Tours), Katrin Kösters, Christian Becker (Krefeld), Colin MacKenzie, André Fuchs, Anna Rommerskirchen (Düsseldorf), Alex Soriano, Laura Morata (Barcelona), Stefan Hagel, Sebastian Weiss, Mathias Pletz, Stephanie Beier (Jena), Bruno Fantin, (Paris), Matthieu Laufaurie, Diane Ponscarme, Jean-Michel Molina, Marion Noret, Nathalie de Castro, Anne-Lise Munier (Paris), Jean-Philippe Talarmin, Lydie Khatchatourian, Nadia Saïdani, Florence Le Gall, Marie-Sarah Fangous (Quimper), Aurélien Dinh, Elisabeth Rouveix, Clara Duan (Garches), Thomas Guimard, Dominique Merrien, Hélène Pelerin, Marine Morrier, Edwige Migne (La Roche-sur-Yon), David Boutoille, Raphaël Lecomte, Anne-Sophie Lecompte (Nantes) Tobias Welte (Hannover), Stefan Reuter (Leverkusen), Jan Kluytmans, Jacobien Veenemans (Breda), Maria Luisa Martin, Helem H. Vilchez, Enrique Ruiz de Gopegui Bordes (Palma de Mallorca), Emmanuel Forestier (Chambéry), Hartmut Stocker (Berlin), Virginie Vitrat (Annecy), Christoph Stephan, Johanna Kessel (Frankfurt), Marc Bonten (Utrecht), Jan Rupp (Lübeck), Laurent Hocqueloux (Orléans), Pierre Tattevin, Enora Ouamara-Digue (Rennes), Frederic Lucht (Saint-Etienne), Jean-Paul Stahl (Grenoble), Anneloes Vlek (Utrecht)

Thank you

OTTO VON GUERICKE
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