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Leitlinienreport für die S3-Leitlinie DACH-Leitlinie: Nachsorge von Erwachsenen nach Lungentransplantation

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1 Informationen zum Leitlinienreport

1.1 Autor*innen des Leitlinienreports

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2 Methodisches Vorgehen

2.1 Formulierung der Schlüsselfragen und Priorisierung von Endpunkten

Die Schlüsselfragen wurden im PICO-Format von der Leitliniengruppe zusammengetragen und wichtige therapeutische Fragestellungen nach klinischer Relevanz priorisiert.

2.2 Systematische Recherche, Auswahl der Evidenz

Für die Beantwortung der Schlüsselfragen 1-5 führte eine erfahrene Informationsspezialistin eine systematische Recherche in verschiedenen relevanten Datenbanken durch. Zunächst wurde nach systematischen Übersichtsarbeiten und randomisiert-kontrollierten Studien recherchiert. Die Literaturrecherche, Flow Charts, Evidenztabellen und Bewertungen sind unter Überschrift 3 pro Schlüsselfrage zusammengefasst. Die Zielpopulation, Intervention, Vergleichsintervention sowie die vordefinierten Endpunkte sind jeweils pro Schlüsselfrage gelistet (ab Überschrift 3). Generell wurden nur auf Englisch oder Deutsch verfasste Publikationen eingeschlossen. Der Kontext wurde für die Schlüsselfragen dieser Leitlinie nicht eingeschränkt. Ausgeschlossen wurden irrelevante Studiendesigns wie narrative Übersichtsarbeiten, nicht-randomisierte Studien, und Fallserien. Auch die Publikationsformate Konferenzbeiträge, Preprints, und weitere Formate, die nicht in Peer-Review Journals publiziert wurden, wurden ausgeschlossen. Alle weiteren Ausschlüsse richten sich nach den individuellen Schlüsselfragen ab Überschrift 3.

Sofern keine aktuellen und qualitativ hochwertigen systematischen Übersichtsarbeiten identifiziert werden konnten, wurden nach Möglichkeit randomisiert-kontrollierte Studien herangezogen. Die Qualitätsbewertung der identifizierten systematischen Übersichtsarbeiten erfolgte mit dem Bewertungsinstrument AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews). Bei hoher methodischer Qualität und inhaltlicher Übereinstimmung der definierten Schlüsselfrage, wurden die eingeschlossenen Einzelstudien in Evidenztabellen extrahiert und die Datensynthese, sofern möglich, für die Erstellung eines Evidenzprofils herangezogen.

2.3 Datenextraktion und Bewertung des Verzerrungsrisikos

Die identifizierten Studien wurden systematisch in MS Excel Datenextraktionsformulare extrahiert. RCTs wurden mit dem Cochrane Risk of Bias 2 Tool bewertet. Meta-analysen wurden mit der Software RevMan erstellt.

2.4 Evidenzklassifikation nach GRADE

Die Bewertung der Studien erfolgte endpunktbezogen nach der GRADE (Grading of recommendations assessment, development and evaluation) Methodik. In die GRADE Bewertung gehen das Verzerrungsrisiko der einzelnen Studien (randomisierte Studien bewertet mit dem Cochrane Risk of Bias

Tool bzw. nichtrandomisierte Studien mit dem ROBINS I Tool) die Heterogenität der Effektschätzer, die Direktheit der untersuchten Patientenpopulation, Intervention, Vergleich bzw. Endpunkte, die Präzision der Effektschätzer und die Wahrscheinlichkeit eines Publikationsbias ein. Die Bewertung ist aus den Evidenztabellen (Summary of findings tables) im Evidenzbericht ersichtlich. Das Vertrauen in die Evidenz wird nach GRADE eingeteilt in hoch/Moderate/Low/Very low.

3 Resultate nach Schlüsselfrage

3.1 Schlüsselfrage 1: Tacrolimus vs. Cyclosporine (Empfehlung 2.2)

3.1.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants after lung transplantation

Intervention: Tacrolimus

Vergleichsintervention: Cyclosporine

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Cyclosporine	 Tacrolimus	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality[1] 1 to 3 years after transplantation	Relatives Risiko: 0.99 (CI 95% 0.75 - 1.3) Basierend auf Daten von 662 patienter und 4 Studien[2] Beobachtzungszeit 1 to 3 years after transplantation	**234** pro 1000	**232** pro 1000 Differenz: **2 weniger pro 1000** (CI 95% 58 weniger - 70 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[3]	We are uncertain whether tacrolimus increases or decreases mortality compared to cyclosporine
Graft loss - Retransplantation or death 3 years after transplantation					No studies were found that looked at graft loss - retransplantation or death
Retransplantation[4] 1 to 3 years after transplantation	Relatives Risiko: 0.22 (CI 95% 0.06 - 0.84) Basierend auf Daten von 323 patienter und 2 Studien[5] Beobachtzungszeit 1 to 3 years after transplantation	**68** pro 1000	**15** pro 1000 Differenz: **53 weniger pro 1000** (CI 95% 64 weniger - 11 weniger)	**Sehr niedrig** Due to serious imprecision, Due to very serious risk of bias[6]	We are uncertain whether tacrolimus increases or decreases the number of participants with retransplantation compared to cyclosprine
Chronic lung allograft dysfunction[7] 1 to 3 years after transplantation	Relatives Risiko: 0.4 (CI 95% 0.28 - 0.56) Basierend auf Daten von 662 patienter und 4 Studien[8] Beobachtzungszeit 1 to 3 years after transplantation	**288** pro 1000	**115** pro 1000 Differenz: **173 weniger pro 1000** (CI 95% 207 weniger - 127 weniger)	**Moderat** Due to serious risk of bias[9]	Tacrolimus probably decreases the number of participants with chronic lung allograft dysfunction compared to cyclosporine
Kidney dysfunction (creatinine over 2.0	Relatives Risiko: 1.29 (CI 95% 1.08 - 1.55)	**309** pro 1000	**399** pro 1000	**Moderat** Due to serious risk of bias[12]	Tacrolimus probably increases the number of

mg/dl, over 2.5 mg/dl, or persistent increase in creatinine over 2 mg/dL or dialysis dependency)[10] 1 to 3 years after transplantation	Basierend auf Daten von 662 patienter und 4 Studien[11] Beobachtzungszeit 1 to 3 years after transplantation	Differenz: **90 mehr pro 1000** (CI 95% 25 mehr - 170 mehr)		participants with kidney dysfunction compared to cyclosporine
Requirement for dialysis[13] 2.2 years after transplantation	Relatives Risiko: 1.57 (CI 95% 0.28 - 8.94) Basierend auf Daten von 90 patienter und 1 Studien[14] Beobachtzungszeit 2.2 years after transplantation	**43** pro 1000 **68** pro 1000 Differenz: **25 mehr pro 1000** (CI 95% 31 weniger - 341 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[15]	We are uncertain whether tacrolimus increases or decreases the number of participants with requirement for dialysis compared to cyclosporine
Serious adverse events 3 years after transplantation	Relatives Risiko: 0.97 (CI 95% 0.89 - 1.06) Basierend auf Daten von 249 patienter und 1 Studien[16] Beobachtzungszeit 3 years after transplantation	**896** pro 1000 **869** pro 1000 Differenz: **27 weniger pro 1000** (CI 95% 99 weniger - 54 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[17]	Tacrolimus may slightly decrease the number of participants with serious adverse events compared to cyclosporine
Adverse events - Cancer 1 to 3 years after transplantation	Relatives Risiko: 0.62 (CI 95% 0.34 - 1.12) Basierend auf Daten von 413 patienter und 3 Studien[18] Beobachtzungszeit 1 to 3 years after transplantation	**120** pro 1000 **74** pro 1000 Differenz: **46 weniger pro 1000** (CI 95% 79 weniger - 14 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[19]	Tacrolimus may decrease the number of participants with adverse events - cancer compared to cyclosporine
Treatment discontinuation 2.2 to 3 years after transplantation	Relatives Risiko: 0.27 (CI 95% 0.16 - 0.46) Basierend auf Daten von 413 patienter und 3 Studien[20] Beobachtzungszeit 2.2 to 3 years after transplantation	**260** pro 1000 **70** pro 1000 Differenz: **190 weniger pro 1000** (CI 95% 218 weniger - 140 weniger)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[21]	Tacrolimus may decrease the number of participants with treatment discontinuation compared to cyclosporine
Treated for one or more infection 3 years after transplantation	Relatives Risiko: 0.99 (CI 95% 0.91 - 1.08) Basierend auf Daten von 249 patienter und 1 Studien[22] Beobachtzungszeit 3 years after transplantation	**904** pro 1000 **895** pro 1000 Differenz: **9 weniger pro 1000** (CI 95% 81 weniger - 72 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[23]	Tacrolimus may have little or no difference on the number of participants treated for one or more infection compared to cyclosporine
Cytomegalovirus infection 3 years after transplantation				No studies were found that looked at cytomegalovirus infection
Loss of pulmonary function by at least 10% 1 year after transplantation				No studies were found that looked at loss of pulmonary function by at least 10%

Kidney function - Serum creatinine (mg/dl) 1.4 years after transplantation	Gemessen mit: Skala: - Niedriger ist besser Basierend auf Daten von 74 patienter und 1 Studien[25] Beobachtzungszeit 1.4 years after transplantation	**1.5** mg/dlMittelwert **1.6** mg/dlMittelwert Differenz: **MD 0.10 Größer** (CI 95% 0.16 kleiner - 0.36 Größer)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[26]	Tacrolimus may have little or no difference on serum creatinine compared to cyclosporine
Quality of life 3 years after transplantation				No studies were found that looked at quality of life

1. undefined
2. Systematic review . **Baseline/Vergleichsintervention** Systematic review . Referenzen [22]. [42].
3. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inkonsistenz: schwerwiegend.** The direction of the effect is not consistent between the included studies; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
4. undefined
5. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [42]. [26].
6. **Risiko für Bias: sehr schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, due to not accounted for competing risks; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
7. undefined
8. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [22]. [42].
9. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
10. creatinine over 2.0 mg/dl, over 2.5 mg/dl, or persistent increase in creatinine over 2 mg/dL or dialysis dependency
11. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [22]. [42].
12. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias;
13. undefined
14. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [22].
15. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Only data from one study, due to low number of events;
16. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [42].
17. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study;
18. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [42]. [22].
19. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
20. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [22].
21. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** due to low number of events;
22. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [42].
23. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study;
24. Keine Studien verfügbar . **Baseline/Vergleichsintervention** Keine Studien verfügbar . Referenzen [22].
25. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [22].
26. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study, Wide confidence intervals;

Referenzen

[21] Hachem RR, Yusen RD, Chakinala MM, Meyers BF, Lynch JP, Aloush AA, Patterson GA, Trulock EP : A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. Journal of Heart and Lung Transplantation 26(10):1012-8

[22] Penninga L., Penninga EI, Moller CH, Iversen M., Steinbruchel DA, Gluud C. : Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database of Systematic Reviews (5):CD008817

[24] Treede H., Glanville AR, Klepetko W., Aboyoun C., Vettorazzi E., Lama R., Bravo C., Knoop C., Aubert JD, Reichenspurner H., European, Australian Investigators in Lung T : Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. Journal of Heart and Lung Transplantation 31(8):797-804

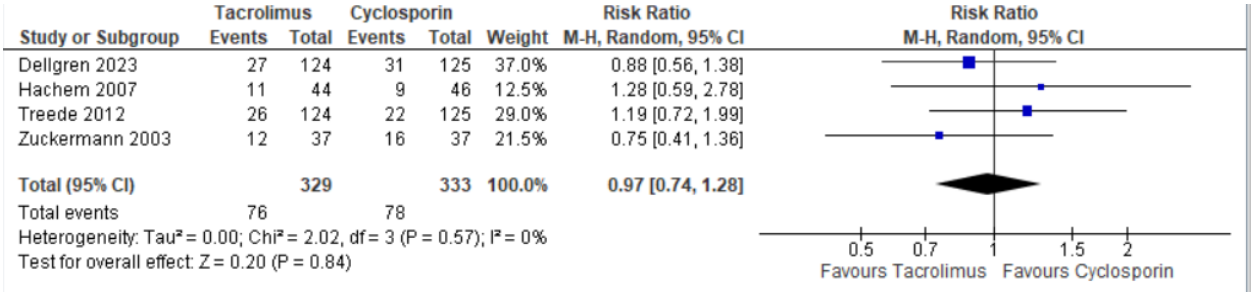
[25] Treede H., Klepetko W., Reichenspurner H., Zuckermann A., Meiser B., Birsan T., Wisser W., Reichert B., Munich, Vienna Lung Transplant G : Tacrolimus versus cyclosporine after lung transplantation: a prospective, open, randomized two-center trial comparing two different immunosuppressive protocols. Journal of Heart and Lung Transplantation 20(5):511-7

[26] Zuckermann A., Reichenspurner H., Birsan T., Treede H., Deviatko E., Reichart B., Klepetko W. : Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial. The Journal of Thoracic and Cardiovascular Surgery 125(4):891-900

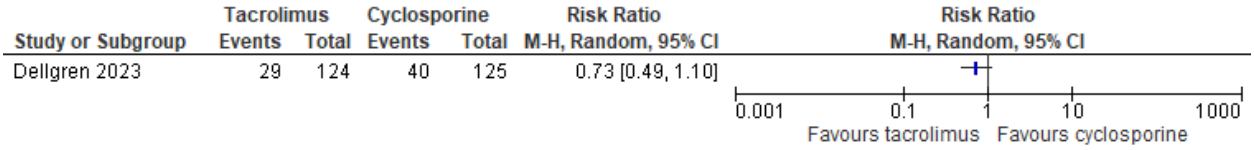
[42] Dellgren G, Lund TK, Raivio P, Leuckfeld I, Svahn J, Holmberg EC, Olsen PS, Halme M, Fiane A, Lindstedt S, Riise GC, Magnusson J : Effect of once-per-day tacrolimus versus twice-per-day ciclosporin on 3-year incidence of chronic lung allograft dysfunction after lung transplantation in Scandinavia (ScanCLAD): a multicentre randomised controlled trial. The Lancet Respiratory Medicine 2023.

3.1.2 Analysen / Forest Plots

Mortality, 1 to 3 years after transplantation



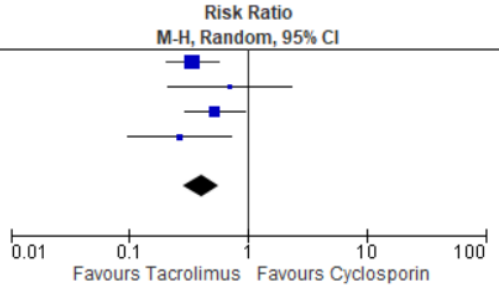
Graft loss – Retransplantation or death, 3 years after transplantation



Chronic lung allograft dysfunction, 1 to 3 years after transplantation

Study or Subgroup	Tacrolimus Events	Tacrolimus Total	Cyclosporin Events	Cyclosporin Total	Weight	Risk Ratio M-H, Random, 95% CI
Dellgren 2023	16	124	48	125	46.2%	0.34 [0.20, 0.56]
Hachem 2007	4	44	6	46	8.3%	0.70 [0.21, 2.30]
Treede 2012	14	124	27	125	33.6%	0.52 [0.29, 0.95]
Zuckermann 2003	4	37	15	37	11.8%	0.27 [0.10, 0.73]
Total (95% CI)		**329**		**333**	**100.0%**	**0.40 [0.29, 0.57]**
Total events	38		96			

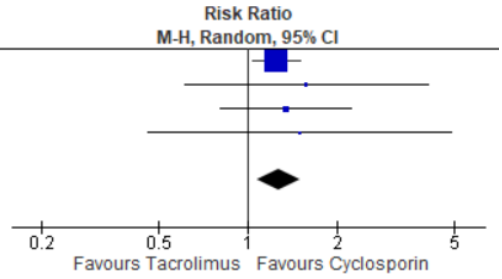
Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 5.15 (P < 0.00001)



Kidney dysfunction, 1 to 3 years after transplantation

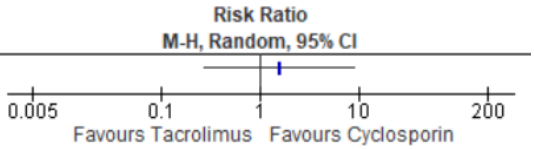
Study or Subgroup	Tacrolimus Events	Tacrolimus Total	Cyclosporin Events	Cyclosporin Total	Weight	Risk Ratio M-H, Random, 95% CI
Dellgren 2023	89	124	72	125	83.4%	1.25 [1.03, 1.50]
Hachem 2007	9	44	6	46	3.2%	1.57 [0.61, 4.04]
Treede 2012	28	124	21	125	11.2%	1.34 [0.81, 2.23]
Zuckermann 2003	6	37	4	37	2.1%	1.50 [0.46, 4.88]
Total (95% CI)		**329**		**333**	**100.0%**	**1.27 [1.07, 1.51]**
Total events	132		103			

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.76 (P = 0.006)



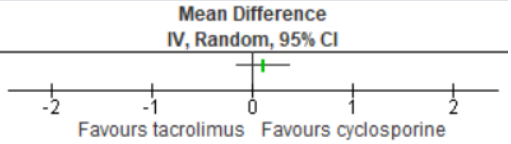
Requirement for dialysis, 2.2 years after transplantation

Study or Subgroup	Tacrolimus Events	Tacrolimus Total	Cyclosporin Events	Cyclosporin Total	Risk Ratio M-H, Random, 95% CI
Hachem 2007	3	44	2	46	1.57 [0.28, 8.94]



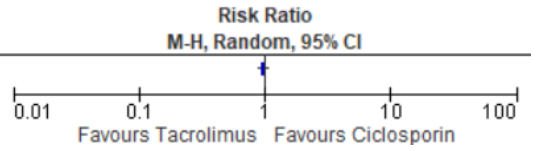
Kidney function - Serum creatinine (mg/dl), 1.4 years after transplantation

Study or Subgroup	Tacrolimus Mean	Tacrolimus SD	Tacrolimus Total	Cyclosporine Mean	Cyclosporine SD	Cyclosporine Total	Mean Difference IV, Random, 95% CI
Zuckermann 2003	1.6	0.7	37	1.5	0.4	37	0.10 [-0.16, 0.36]



Serious adverse events, 3 years after transplantation

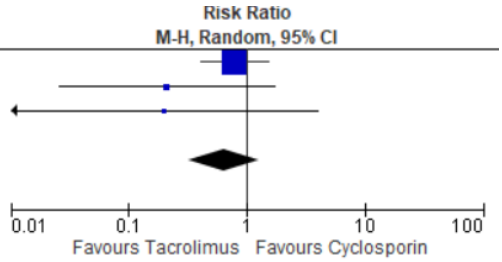
Study or Subgroup	Tacrolimus Events	Tacrolimus Total	Ciclosporin Events	Ciclosporin Total	Risk Ratio M-H, Random, 95% CI
Dellgren 2023	108	124	112	125	0.97 [0.89, 1.06]



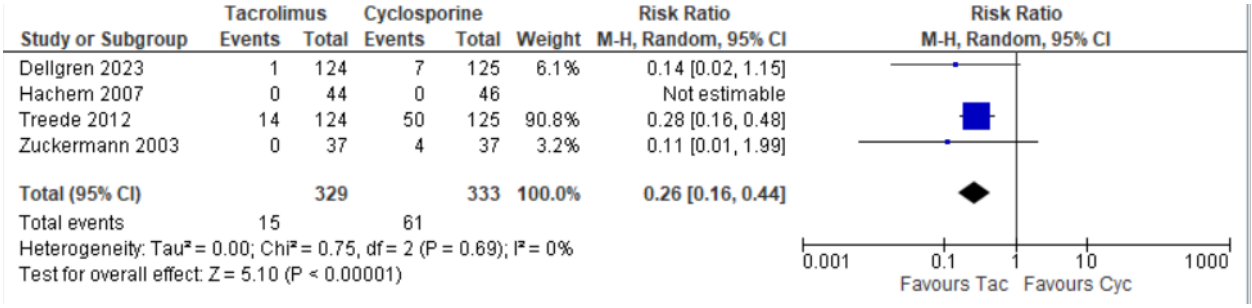
Adverse events – Cancer, 1 to 3 years after transplantation

Study or Subgroup	Tacrolimus Events	Tacrolimus Total	Cyclosporin Events	Cyclosporin Total	Weight	Risk Ratio M-H, Random, 95% CI
Dellgren 2023	14	124	18	125	84.7%	0.78 [0.41, 1.51]
Hachem 2007	1	44	5	46	10.2%	0.21 [0.03, 1.72]
Zuckermann 2003	0	37	2	37	5.1%	0.20 [0.01, 4.03]
Total (95% CI)		**205**		**208**	**100.0%**	**0.64 [0.32, 1.26]**
Total events	15		25			

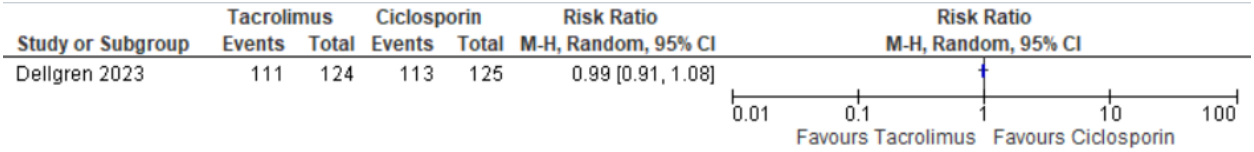
Heterogeneity: Tau² = 0.03; Chi² = 2.08, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 1.29 (P = 0.20)



Treatment discontinuation, 1 to 3 years after transplantation



Treated for one or more infection, 3 years after transplantation



3.1.3 Referenzen der eingeschlossenen Studien

- Dellgren G, Lund TK, Raivio P, Leuckfeld I, Svahn J, Holmberg EC, Olsen PS, Halme M, Fiane A, Lindstedt S, Riise GC, Magnusson J. Effect of once-per-day tacrolimus versus twice-per-day Cyclosporine on 3-year incidence of chronic lung allograft dysfunction after lung transplantation in Scandinavia (ScanCLAD): a multicentre randomised controlled trial. Lancet Respir Med. 2023 Sep 8:S2213-2600(23)00293-X. doi: 10.1016/S2213-2600(23)00293-X.
- Hachem RR, Yusen RD, Chakinala MM, Meyers BF, Lynch JP, Aloush AA, Patterson GA, Trulock EP. A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. J Heart Lung Transplant. 2007 Oct;26(10):1012-8. doi: 10.1016/j.healun.2007.07.027.
- Penninga L, Penninga EI, Møller CH, Iversen M, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database Syst Rev. 2013 May 31;(5):CD008817. doi: 10.1002/14651858.CD008817.pub2.
- Treede H, Klepetko W, Reichenspurner H, Zuckermann A, Meiser B, Birsan T, Wisser W, Reichert B; Munich and Vienna Lung Transplant Group. Tacrolimus versus cyclosporine after lung transplantation: a prospective, open, randomized two-center trial comparing two different immunosuppressive protocols. J Heart Lung Transplant. 2001 May;20(5):511-7. doi: 10.1016/s1053-2498(01)00244-3.
- Treede H, Glanville AR, Klepetko W, Aboyoun C, Vettorazzi E, Lama R, Bravo C, Knoop C, Aubert JD, Reichenspurner H; European and Australian Investigators in Lung Transplantation. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant. 2012 Aug;31(8):797-804. doi: 10.1016/j.healun.2012.03.008.
- Zuckermann A, Reichenspurner H, Birsan T, Treede H, Deviatko E, Reichart B, Klepetko W. Cyclosporine A versus tacrolimus in combination with mycophenolate mofetil and steroids as primary immunosuppression after lung transplantation: one-year results of a 2-center prospective randomized trial. J Thorac Cardiovasc Surg. 2003 Apr;125(4):891-900. doi: 10.1067/mtc.2003.71.

3.1.4 Charakteristika der eingeschlossenen Studien

3.1.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference / Study type	Study characteristics & inclusion criteria	Interventions	Study population	Results	Methodological Notes	Included publications
Penninga 2013 Systematic review with MA	**Search time frame** Cochrane Renal Group's Specialised Register to 10 April 2013 and online resources to 20 April 2013 **Sources** - Cochrane Renal Group's Specialised Register, including: ○ Quarterly searches of CENTRAL ○ Weekly searches of MEDLINE OVID SP ○ Handsearching of renal-related journals and the proceedings of major renal conferences ○ Searching of the current year of EMBASE OVID SP ○ Weekly current	**Intervention A** Tacrolimus **Intervention B** Cyclosporine	3 studies on 413 participants - Age: mean age 44 to 50 years - Single-centre and/or multi-centre trials: 1 single-centre trial and 2 multicentre trials - Transplantation type: Most recipients were reported to have undergone double lung transplantations (62%, 74% and 93%)	**<u>Comparison Tacrolimus vs. Cyclosporine:</u>** Number of studies: 3 Number of participants: 413 **Critical outcomes:** 1. Mortality (at 2.2 to 3 years): 226 per 1000 in comparison group, Difference: 14 fewer per 1000 (RR 1.06, CI 95% 0.75 to 1.49, N = 413 in 3 RCTs, I^2 = 0%, low certainty) 2. Acute rejection (at 3 years): 726 per 1000 in comparison group, Difference: 80 more per 1000 (RR 0.89, CI 95% 0.77 to 1.03, N = 323 in 2 RCTs, I^2 0%, low certainty) 3. BOS (at 2.2 to 3 years) 231 per 1000 in comparison group, Difference 125 more per 1000 (RR 0.46, CI 95% 0.29 to 0.74, N = 413 in 3 RCTs, I^2 0%, moderate certainty) 4. Infection (the number of overall infections per 100 patient days at 1.4 years): The mean infection in the intervention group was 0.15 lower (CI 95% -0.3 to 0, N = 74 in 1 RCT, low certainty)	**Methodological quality of included studies assessed using RoB 1 tool:** High risk of bias **Evidence synthesis:** • ITT • Random-effects and Fixed-effects model **GRADE:** 1. Mortality: low 2. Acute rejection: low 3. BOS: moderate 4. Infection: low 5. Treatment withdrawal: low 6. Arterial hypertension: low 7. Diabetes mellitus: low	Hachem 2007, *Journal of Heart & Lung Transplantation* Treede 2012, *Journal of Heart & Lung Transplantation* Zuckermann 2003, *Journal of Thoracic & Cardiovascular Surgery*

	awareness alerts for selected renal journals ○ Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov - Science Citation Index Expanded - Transplant Library **Eligibility criteria** **Study type:** - RCTs **Participants:** - Adult and paediatric patients after first-time single or double lung transplantation			**Additional outcomes:** 1. Quality of life: None of the included studies reported quality of life. 2. Any adverse event: RR 0.55, CI 95% 0.21 to 1.44, N = 249 in 1 RCT 3. Withdrawals (at 2.2 to 3 years): 260 per 1000 in comparison group, Difference 190 more per 1000 (RR 0.27, CI 95% 0.16 to 0.46, N = 413 in 3 RCTs, I^2 0%, low certainty) 4. Lymphocytic bronchitis: MD -0.60, CI 95% -1.04 to -0.16, N = 90 in 1 RCT 5. Pneumonia (viral, bacterial, and fungal): None of the included studies reported on pneumonia. 6. Cytomegalovirus infection: None of the included studies reported on cytomegalovirus infection. 7. Cancer: RR 0.21, CI 95% 0.04 to 1.16, N = 164 in 2 RCTs, I^2 0% 8. Neurotoxic reaction: RR 7.06, CI 95% 0.37 to 135.19, N = 249 in 1 RCT 9. a.) Kidney failure: RR 1.57, CI 95% 0.28 to 8.94, N = 90 in 1 RCT 9. b.) Kidney dysfunction (creatinine over 2.0 mg/dl, over 2.5 mg/dl, or persistent increase in creatinine over 2 mg/dL or dialysis dependency): RR 1.41, CI 95% 0.93 to 2.14, N = 413 in 3 RCTs, I^2 0% 10. Arterial hypertension (at 2.2 to 3 years)		

				614 per 1000 in comparison group, Difference 202 more per 1000 (RR 0.67, CI 95% 0.5 to 0.89, N = 164 in 2 RCTs, I^2 84.31%, low certainty) 11. Diabetes mellitus (at 2.2 to 3 years): 48 per 1000 in comparison group, Difference 156 more per 1000 (RR 4.24, CI 95% 1.58 to 11.4, N = 164 in 2 RCTs, I^2 41.24%, low certainty 12. Hyperlipidaemia: RR 0.60, CI 95% 0.30 to 1.20, N = 74 in 1 RCT 13. Hirsutism: None of the included studies reported on hirsutism. 14. Gingival hyperplasia: None of the included studies reported on gingival hyperplasia. 15. Serum creatinine: MD 0.10 mg/dl, CI 95% -0.16 to 0.36, N = 74 in 1 RCT 16. Total cholesterol: None of the included studies reported total cholesterol concentrations		

3.1.4.2 *Charakteristika der zusätzlich eingeschlossenen Studien*

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)

Dellgren 2023 ScanCLAD RCT, open-label	**Sample size:** N = 264* *249 included in mITT; correctly randomised, underwent double lung transplantation, and received first dose of study drug) **Enrolment period:** October 2016 to July 2019 Sweden, Norway, Finland, Denmark **Inclusion criteria:** • Patients aged 18–70 years who were planned to undergo a de novo double lung transplantation **Exclusion criteria:** • Cases of single lung transplantation or multiorgan transplantation, and those who had previously received any organ transplant (including lungs) • Hypersensitivity to or other contraindications for the immunosuppressive drugs used in the study	**Experimental:** - oral Tacrolimus (once per day) + mycophenolate mofetil + corticosteroids - the first dose of tacrolimus was given immediately before transplantation (day 0) (0.05 to 0.1 mg/kg) - from postoperative day 1, patients received tacrolimus 0.1 to 2 mg/kg once per day (in the early phase of the study, trough levels were difficult to manage with tacrolimus once per day and were more easily managed at twice per day for the first 1 to 2 weeks, which created some protocol violations; when patients were stable, and before discharge, they were switched to tacrolimus once per day) - N = 124 **Control:** - oral Cyclosporine (twice per day) + mycophenolate mofetil + corticosteroids - immediately before transplantation (day 0) (2 to 3 mg/kg) - from postoperative day 1, patients received Cyclosporine twice per day (total 3 mg/kg per day, administered morning and evening)	Mortality, 3 years after transplantation	RR 0.88 (CI 95% 0.56 to 1.38) Tacrolimus: 27/124 Cyclosporine: 31/125	1. Random sequence generation: low 2. Allocation concealment: low 3. Blinding of participants and personnel: high (open-label) 4. Blinding of outcome assessment: high (open-label) 5. Incomplete outcome data: low 6. Selective reporting: low 7. Other bias: low
			Retransplantation or death, 3 years after transplantation	Not reported	
			Retransplantation, 3 years after transplantation	RR 0.22 (CI 95% 0.05 to 1.02) Tacrolimus: 2/124 Cyclosporine: 9/125	
			Chronic lung allograft dysfunction, 3 years after transplantation	RR 0.34 (CI 95% 0.20 to 0.56) Tacrolimus: 16/124 Cyclosporine: 48/125	
			Kidney dysfunction (at least two consecutive values with calculated or measured GFR below 40 at least 3 days apart and also below 50% or more of baseline measured GFR), 3 years after transplantation	RR 1.25 (CI 95% 1.03 to 1.50) Tacrolimus: 89/124 Cyclosporine: 72/125	
			Treatment discontinuation	Not reported	

	• Previous treatment with anti-thymocyte globulin preparations • Platelet count less than 50 000 per µL on pre-transplantation assessment • History of malignancy (within 3 years for low-risk malignancy or 5 years for high-risk malignancy) or current malignancy (other than excised basal cell carcinoma) • And patient or donor positive for HIV, hepatitis B virus, or hepatitis C virus **Characteristics** **Age (median, IQR):** - Tacrolimus: 57.4 (50.5 to 62.2) - Cyclosporine: 58.3 (51.1 to 61.9) **Sex (% female):** • Tacrolimus: 45% • Cyclosporine: 44% **Ethnicity:** • White o Tacrolimus: 98% o Cyclosporine: 99% • East, southeast or south Asian	- N = 125	Treatment discontinuation due to AEs	Not reported	
			Serious adverse events, 3 years after transplantation	RR 0.97 (CI 95% 0.89 to 1.06) Tacrolimus: 108/124 Cyclosporine: 112/125	
			Adverse events – Cancer, 3 years after transplantation	RR 0.78 (CI 95% 0.41 to 1.51) Tacrolimus: 14/124 Cyclosporine: 18/125	
			Treated for one or more infection, 3 years after transplantation (pathogen detection not indicated)	RR 0.99 (CI 95% 0.91 to 1.08) Tacrolimus: 111/124 Cyclosporine: 113/125	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

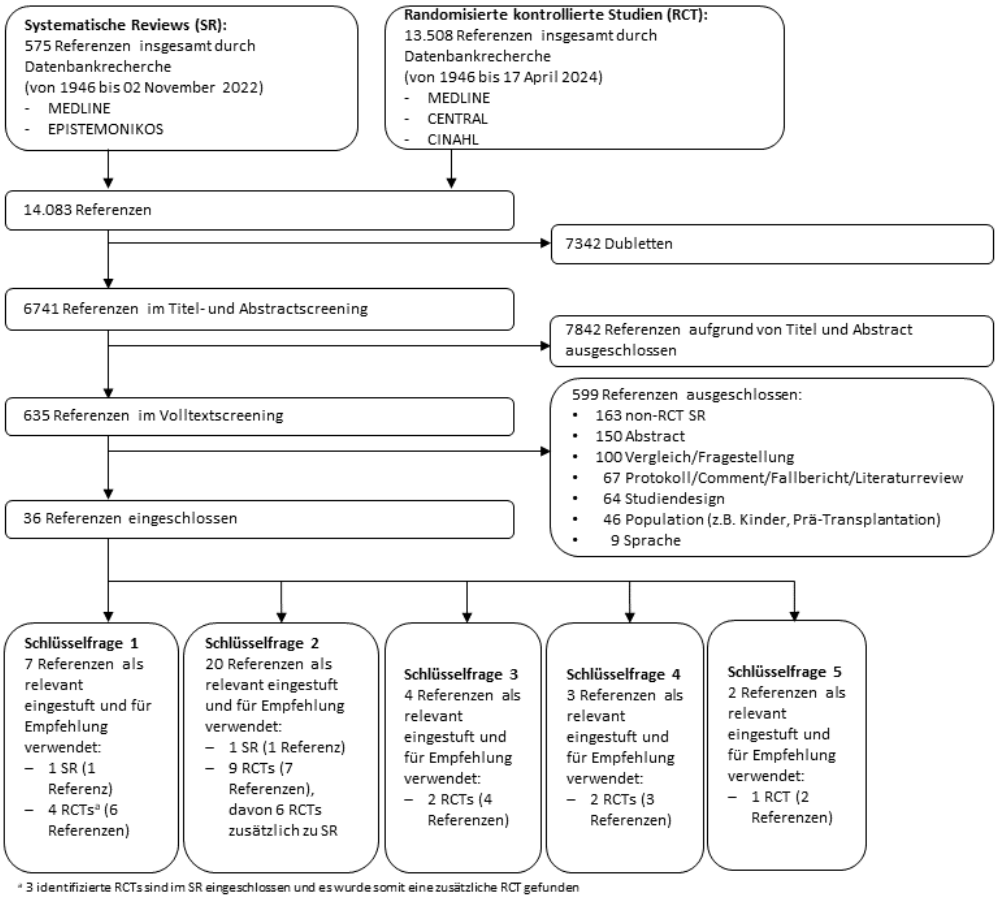
	○ Tacrolimus: 1% ○ Cyclosporine: 1% • Black ○ Tacrolimus: 1% ○ Cyclosporine: 0% • Pacific Islander ○ Tacrolimus: 1% ○ Cyclosporine: 0% **Type of transplantation:** • BLTx ○ Tacrolimus: 100% ○ Cyclosporine: 100% • SLTx ○ Tacrolimus: 0% ○ Cyclosporine: 0% • HLTx ○ Tacrolimus: 0% ○ Cyclosporine: 0% **Respiratory medical history:** • Emphysema (COPD) ○ Tacrolimus: 30% ○ Cyclosporine: 31% • Cystic fibrosis				

	○ Tacrolimus: 7% ○ Cyclosporine: 6% • Pulmonary hypertension ○ Tacrolimus: 7% ○ Cyclosporine: 6% • Pulmonary fibrosis ○ Tacrolimus: 28% ○ Cyclosporine: 34% • Scleroderma ○ Tacrolimus: 1% ○ Cyclosporine: 1% • Alpha1-antitrypsin deficiency ○ Tacrolimus: 12% ○ Cyclosporine: 13% • Sarcoidosis ○ Tacrolimus: 6% ○ Cyclosporine: 2% • Lymphangioleiomyomatosis ○ Tacrolimus: 0% ○ Cyclosporine: 2% • Other ○ Tacrolimus: 8% ○ Cyclosporine: 6%				

	Other medical history:
	• Neurological disease
	  ○ Tacrolimus: 6%
	  ○ Cyclosporine: 6%
	• Stroke or transient ischaemic attack
	  ○ Tacrolimus: 1%
	  ○ Cyclosporine: 4%
	• Renal disease or nephrosclerosis
	  ○ Tacrolimus: 2%
	  ○ Cyclosporine: 5%
	• Diabetes (insulin or tablet controlled)
	  ○ Tacrolimus: 8%
	  ○ Cyclosporine: 9%
	• Reflux or gastric ulcer
	  ○ Tacrolimus: 15%
	  ○ Cyclosporine: 21%
	• Cancer
	  ○ Tacrolimus: 1%
	  ○ Cyclosporine: 2%
	• Treatment of osteoporosis
	  ○ Tacrolimus:23%
	  ○ Cyclosporine: 24%				

	• Bacterial chronic infection
	  ○ Tacrolimus: 10%
	  ○ Cyclosporine: 10%
	• Systemic inflammatory disease
	  ○ Tacrolimus: 5%
	  ○ Cyclosporine: 10%
	• Psychiatric disease
	  ○ Tacrolimus:7 %
	  ○ Cyclosporine: 8%
	• Previous thoracotomy or thoracoscopy
	  ○ Tacrolimus: 8%
	  ○ Cyclosporine: 9%
	• Any other medical history
	  ○ Tacrolimus: 60%
	  ○ Cyclosporine: 56%				

3.1.5 Studienselektion: Flow Chart



3.1.6 Literaturrecherche

Systematic reviews

Datenbankauswahl:

MEDLINE
EPISTEMONIKOS

Suchdatum aller Datenbanken: 03.11.2022		
Datenbank	**Suche**	
MEDLINE	**374**	
Epistemonikos	**201**	
Total	**575**	
Total (after deduplication)	**417**	

Suchstrategien

MEDLINE (via OVID) 1946 to November 02, 2022
Search Strategy:

Searches

1 exp Lung Transplantation/

2 (lung* adj3 transplant*).ti.

3 or/1-2

4 Organ Transplantation/

5 Transplant Recipients/

6 solid organ transplant*.ti.

7 or/4-6

8 Lung/ or lung*.ab.

9 3 or (7 and 8)

10 cochrane database of systematic reviews.jn. or search*.tw. or meta analysis.pt. or medline.tw. or systematic review.tw. or systematic review.pt.

11 9 and 10

Note: line 11 *Wong 2006 – systematic reviews filter – high specificity, 90,2% sensitivity / 98,4% specificity*

WONG, S. S., WILCZYNSKI, N. L. & HAYNES, R. B. 2006. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc, 94, 451-5.

EPISTEMONIKOS

title:(organ transplant*) AND abstract:(lung*) OR title:("solid organ") AND title:(transplant*) AND abstract:(lung*) OR title:(lung*) AND title:(transplant*)

Publication type: systematic review

RCTS

Datenbank	**Suche 04.11.2022**	**Update 17.04.2024**
MEDLINE	**4597**	**4981**
CENTRAL	**1354**	**1474**
CINAHL	**538**	**564**
Total	**6489**	**7019**
Total (after deduplication)	**5813**	**517**

Suchstrategien

MEDLINE (via OVID) 1946 to November 03, 2022
Search Strategy:

#	Searches
1	exp Lung Transplantation/
2	(lung* adj3 (transplant* or retransplant*)).tw,kf.
3	or/1-2
4	Organ Transplantation/
5	Transplant Recipients/
6	organ transplant*.ti.
7	or/4-6
8	Lung/ or lung*.ab.
9	3 or (7 and 8)
10	randomized controlled trial.pt.
11	controlled clinical trial.pt.
12	randomi?ed.ab.
13	placebo.ab.
14	drug therapy.fs.
15	randomly.ab.
16	trial.ab.
17	groups.ab.
18	or/10-17
19	exp animals/ not humans/
20	18 not 19
21	clinical trial, phase iii/
22	("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
23	(21 or 22) not 19
24	20 or 23
25	9 and 24

Cochrane Central Register of Controlled Trials, CENTRAL (via Cochrane Library) 2024, Issue 04

ID	Search
#1	MeSH descriptor: [Lung Transplantation] explode all trees
#2	(lung* NEAR/3 (transplant* or retransplant*)):TI,AB,KW
#3	#1 OR #2
#4	MeSH descriptor: [Organ Transplantation] this term only
#5	organ transplant*:TI
#6	MeSH descriptor: [Transplant Recipients] this term only

#7	MeSH descriptor: [Lung] explode all trees
#8	lung*:AB
#9	(#4 OR #5 OR #6) AND (#7 OR #8)
#10	#3 OR #9

CINAHL (via EBSCO)

	Query
S30	S11 AND S29
S29	S28 NOT S27
S28	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
S27	S25 NOT S26
S26	MH human
S25	S23 OR S24
S24	TI animal model*
S23	MH animals+ OR MH animal studies
S22	AB cluster W3 RCT
S21	MH crossover design OR MH comparative studies
S20	AB control W5 group
S19	PT randomized controlled trial
S18	MH placebos
S17	MH sample size AND AB (assigned OR allocated OR control)
S16	TI trial
S15	AB random*
S14	TI randomised OR randomized
S13	MH randomized controlled trials OR MH double-blind studies OR MH single-blind studies OR MH random assignment OR MH pretest-posttest design OR MH cluster sample
S12	MH randomized controlled trials
S11	S1 OR S2 OR S10
S10	S6 AND S9
S9	S7 OR S8
S8	AB lung*
S7	(MM "Lung")
S6	S1 OR S2 OR S3
S5	TI organ transplant*
S4	(MM "Transplant Recipients")

S3 (MM "Organ Transplantation")

S2 (MH "Lung Transplantation+")

S1 TI ((lung* N3 (transplant* or retransplant*))) OR AB ((lung* N3 (transplant* or retransplant*)))

3.2 Schlüsselfrage 2a: mTOR Inhibitoren (Everolimus/Sirolimus) vs. Calcineurin inhibitoren (Cyclosporin/Tacrolimus) (Empfehlung 2.4)

3.2.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants after lung transplantation

Intervention: mTOR inhibitors (everolimus or sirolimus)

Vergleichsintervention: Calcineurin inhibitors (cyclosporine or tacrolimus)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Calcineurin inhibitors (cyclosporine or tacrolimus)	 mTOR inhibitors (everolimus or sirolimus)	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality 1 year after randomisation	Relatives Risiko: 3.95 (CI 95% 0.66 - 23.49) Basierend auf Daten von 428 patienter und 3 Studien[1] Beobachtzungszeit 1 year after randomisation	**5** pro 1000	**20** pro 1000 Differenz: **15 mehr pro 1000** (CI 95% 2 weniger - 112 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[2]	We are uncertain whether mTOR inhibitors (everolimus or sirolimus) increase or decrease mortality compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Graft loss - Retransplantation or death[3] 3 years after transplantation					No studies were found that looked at graft loss - retransplantation or death
Chronic lung allograft dysfunction[4] 1 year after randomisation	Relatives Risiko: 0.42 (CI 95% 0.14 - 1.29) Basierend auf Daten von 428 patienter und 3 Studien[5] Beobachtzungszeit 1 year after randomisation	**42** pro 1000	**18** pro 1000 Differenz: **24 weniger pro 1000** (CI 95% 36 weniger - 12 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[6]	There were too few who experienced chronic lung allograft dysfunction, to determine whether mTOR inhibitors (everolimus or sirolimus) made a difference compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Kidney function - Improved renal function 1 year after randomisation	Relatives Risiko: 16.14 (CI 95% 4.32 - 60.35) Basierend auf Daten von 227 patienter und 3 Studien[7] Beobachtzungszeit 1 year after randomisation	**18** pro 1000	**291** pro 1000 Differenz: **273 mehr pro 1000** (CI 95% 60 mehr - 1068 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[8]	mTOR inhibitors (everolimus or sirolimus) may increase the number of participants with improved renal function compared to calcineurin inhibitors (cyclosporine or tacrolimus)

Serious adverse events 1 year after randomisation	Relatives Risiko: 1.42 (CI 95% 1.11 - 1.82) Basierend auf Daten von 412 patienter und 2 Studien[9] Beobachtzungszeit 1 year after randomisation	**322** pro 1000 **457** pro 1000 Differenz: **135 mehr pro 1000** (CI 95% 35 mehr - 264 mehr)	**Moderat** Due to serious risk of bias[10]	mTOR inhibitors (everolimus or sirolimus) probably increase the number of participants with serious adverse events compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Adverse events - Cancer 1 year after randomisation	Relatives Risiko: 1.01 (CI 95% 0.39 - 2.63) Basierend auf Daten von 282 patienter und 1 Studien[11] Beobachtzungszeit 1 year after randomisation	**56** pro 1000 **57** pro 1000 Differenz: **1 mehr pro 1000** (CI 95% 34 weniger - 91 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[12]	We are uncertain whether mTOR inhibitors (everolimus or sirolimus) increase or decrease the number of participants with adverse events - cancer compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Treatment discontinuation 1 year after randomisation	Relatives Risiko: 5.29 (CI 95% 2.28 - 12.25) Basierend auf Daten von 412 patienter und 2 Studien[13] Beobachtzungszeit 1 year after randomisation	**29** pro 1000 **153** pro 1000 Differenz: **124 mehr pro 1000** (CI 95% 37 mehr - 326 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[14]	mTOR inhibitors (everolimus or sirolimus) may increase the number of participants with treatment discontinuation compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Infections 1 year after randomisation	Relatives Risiko: 1.71 (CI 95% 1.02 - 2.87) Basierend auf Daten von 282 patienter und 1 Studien[15] Beobachtzungszeit 1 year after randomisation	**134** pro 1000 **229** pro 1000 Differenz: **95 mehr pro 1000** (CI 95% 3 mehr - 251 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[16]	mTOR inhibitors (everolimus or sirolimus) may increase the number of participants with infections (pathogen detection not indicated) compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Cytomegalovirus infection 1 year after randomisation	Relatives Risiko: 0.67 (CI 95% 0.32 - 1.4) Basierend auf Daten von 130 patienter und 1 Studien[17] Beobachtzungszeit 1 year after randomisation	**222** pro 1000 **149** pro 1000 Differenz: **73 weniger pro 1000** (CI 95% 151 weniger - 89 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[18]	mTOR inhibitors (everolimus or sirolimus) may decrease the number of participants with cytomegalovirus infection compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Loss of pulmonary function by at least 10% - Decreased FEV1 1 year after randomisation	Relatives Risiko: 1.08 (CI 95% 0.56 - 2.1) Basierend auf Daten von 130 patienter und 1 Studien[19] Beobachtzungszeit 1 year after randomisation	**206** pro 1000 **222** pro 1000 Differenz: **16 mehr pro 1000** (CI 95% 91 weniger - 227 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[20]	mTOR inhibitors (everolimus or sirolimus) may have little or no difference on the number of participants with loss of pulmonary function by at least 10% compared to calcineurin inhibitors (cyclosporine or tacrolimus)
eGFR (ml/min per 1.73m²)[21] 1 year after randomisation	Gemessen mit: CKD-EPI formula Skala: - Höher ist besser	**54.6** adjusted mean (ml/min per 1.73m²)Mittelwert **64.5** adjusted mean (ml/min per 1.73m²)Mittelwert	**Niedrig** Due to serious imprecision, Due to serious risk of bias[23]	mTOR inhibitors (everolimus or sirolimus) may have little or no difference on eGFR

	Basierend auf Daten von 130 patienter und 1 Studien[22] Beobachtzungszeit 1 year after randomisation	Differenz: **MD 9.9 Größer** (CI 95% 2.82 Größer - 16.98 Größer)		(ml/min) compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Kidney function - Creatinine (µmol/l) 1 year after randomisation	Gemessen mit: Skala: - Niedriger ist besser Basierend auf Daten von 246 patienter und 1 Studien[24] Beobachtzungszeit 1 year after randomisation	**136.5** Mittelwert Differenz: **MD 11.0 kleiner** (CI 95% 23.78 kleiner - 1.78 Größer)	**125.5** Mittelwert	**Niedrig** Due to serious risk of bias, Due to serious imprecision[25]	mTOR inhibitors (everolimus or sirolimus) may have little or no difference on creatinine level (µmol/l) compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Quality of life - Physical component of SF-36 1 year after randomisation	Gemessen mit: SF-36 Skala: 1 - 100 Höher ist besser Basierend auf Daten von 130 patienter und 1 Studien[26] Beobachtzungszeit 1 year after randomisation	**47.7** Mittelwert Differenz: **MD 0.50 kleiner** (CI 95% 3.24 kleiner - 2.24 Größer)	**47.2** Mittelwert	**Niedrig** Due to serious risk of bias, Due to serious imprecision[27]	mTOR inhibitors (everolimus or sirolimus) may have little or no difference on quality of life - physical component of SF-36 compared to calcineurin inhibitors (cyclosporine or tacrolimus)
Quality of life - Mental component of SF-36 1 year after randomisation	Gemessen mit: SF-36 Skala: 1 - 100 Höher ist besser Basierend auf Daten von 130 patienter und 1 Studien[28] Beobachtzungszeit 1 year after randomisation	**53.8** Mittelwert Differenz: **MD 4.10 kleiner** (CI 95% 7.71 kleiner - 0.49 kleiner)	**49.7** Mittelwert	**Niedrig** Due to serious risk of bias, Due to serious imprecision[29]	mTOR inhibitors (everolimus or sirolimus) may have little or no difference on quality of life - mental component of SF-36 compared to calcineurin inhibitors (cyclosporine or tacrolimus)

27. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [4].
28. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: sehr schwerwiegend.** Very wide confidence intervals, due to few events;
29. undefined
30. undefined
31. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [4].
32. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, due to few events;
33. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [4].
34. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
35. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [9]. [7].
36. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
37. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [9].
38. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Only data from one study, due to few events;
39. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [7]. [9].
40. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
41. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [9].
42. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
43. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [7].
44. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
45. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [7].

46. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
47. undefined
48. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [7].
49. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study;
50. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [9].
51. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
52. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [7].
53. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
54. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [7].
55. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;

Referenzen

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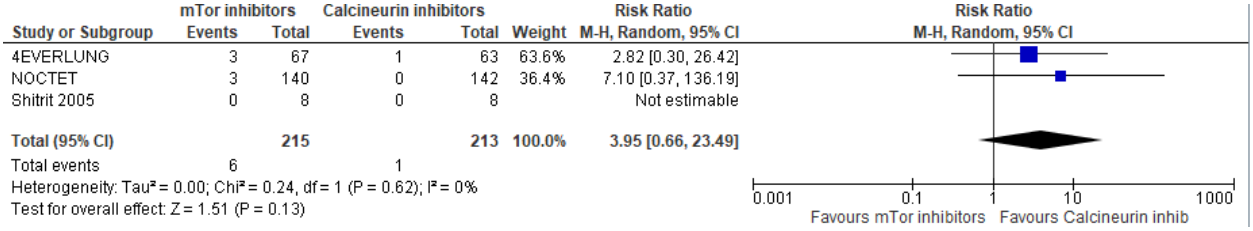
[7] Gottlieb J., Neurohr C., Muller-Quernheim J., Wirtz H., Sill B., Wilkens H., Bessa V., Knosalla C., Porstner M., Capusan C., Struber M. : A randomized trial of everolimus-based quadruple therapy vs standard triple therapy early after lung transplantation. American Journal of Transplantation 19(6):1759-1769

[9] Gullestad L., Iversen M., Mortensen SA, Eiskjaer H., Riise GC, Mared L., Bjortuft O., Ekmehag B., Jansson K., Simonsen S., Gude E., Rundqvist B., Fagertun HE, Solbu D., Bergh CH : Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: a multicenter, randomized trial. Transplantation 89(7):864-72

[16] Shitrit D., Rahamimov R., Gidon S., Bakal I., Bargil-Shitrit A., Milton S., Kramer MR : Use of sirolimus and low-dose calcineurin inhibitor in lung transplant recipients with renal impairment: results of a controlled pilot study. Kidney International 67(4):1471-5

3.2.2 Analysen / Forest Plots

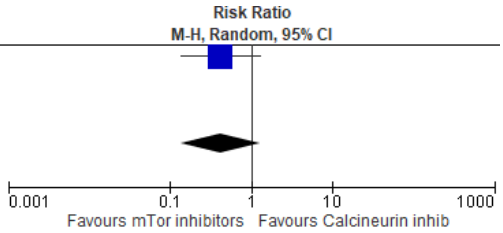
Mortality, 1 year after randomisation



Chronic lung allograft dysfunction, 1 year after randomisation

Study or Subgroup	mTor inhibitors Events	Total	Calcineurin inhibitors Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4EVERLUNG	4	67	9	63	100.0%	0.42 [0.14, 1.29]
NOCTET	0	140	0	142		Not estimable
Shitrit 2005	0	8	0	8		Not estimable
Total (95% CI)		**215**		**213**	**100.0%**	**0.42 [0.14, 1.29]**
Total events	4		9			

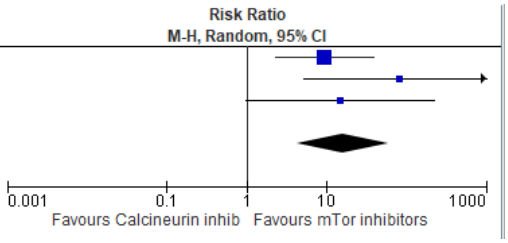
Heterogeneity: Not applicable
Test for overall effect: Z = 1.52 (P = 0.13)



Improved renal function, 1 year after randomisation

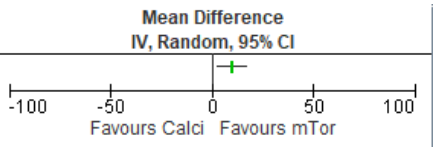
Study or Subgroup	mTor inhibitors Events	Total	Calcineurin inhibitors Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4EVERLUNG	20	67	2	63	58.7%	9.40 [2.29, 38.60]
NOCTET	40	40	0	41	20.3%	82.98 [5.28, 1305.08]
Shitrit 2005	7	8	0	8	20.9%	15.00 [1.00, 225.33]
Total (95% CI)		**115**		**112**	**100.0%**	**16.14 [4.32, 60.35]**
Total events	67		2			

Heterogeneity: Tau² = 0.25; Chi² = 2.38, df = 2 (P = 0.30); I² = 16%
Test for overall effect: Z = 4.13 (P < 0.0001)



eGFR (ml/min), 1 year after randomisation

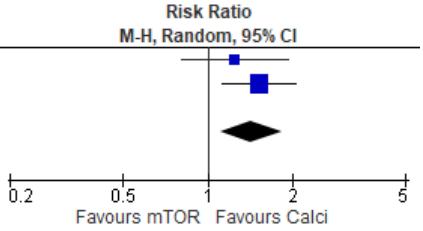
Study or Subgroup	mTor inhibitors Mean	SD	Total	Calcineurin inhibitors Mean	SD	Total	Mean Difference IV, Random, 95% CI
4EVERLUNG	64.5	20.9086	67	54.6	20.2504	63	9.90 [2.82, 16.98]



Serious adverse events, 1 year after randomisation

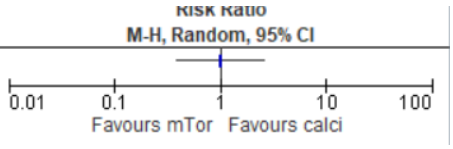
Study or Subgroup	mTor inhibitors Events	Total	Calcineurin inhibitors Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4EVERLUNG	29	67	22	63	32.5%	1.24 [0.80, 1.91]
NOCTET	66	140	44	142	67.5%	1.52 [1.13, 2.06]
Total (95% CI)		**207**		**205**	**100.0%**	**1.42 [1.11, 1.82]**
Total events	95		66			

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.79 (P = 0.005)



Adverse events – Cancer, 1 year after randomisation

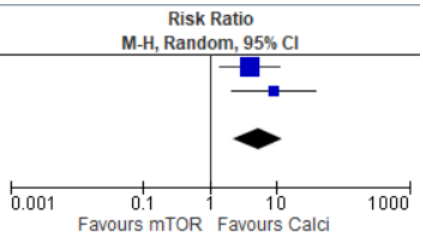
Study or Subgroup	mTor inhibitors Events	Total	Calcineurin inhibitors Events	Total	Risk Ratio M-H, Random, 95% CI
NOCTET	8	140	8	142	1.01 [0.39, 2.63]



Treatment discontinuation, 1 year after randomisation

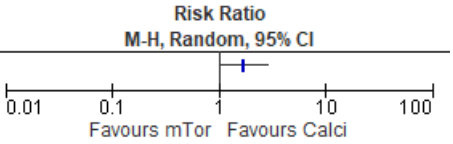
Study or Subgroup	mTor inhibitors Events	Total	Calcineurin inhibitors Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4EVERLUNG	17	67	4	63	66.1%	4.00 [1.42, 11.23]
NOCTET	18	140	2	142	33.9%	9.13 [2.16, 38.61]
Total (95% CI)		**207**		**205**	**100.0%**	**5.29 [2.28, 12.25]**
Total events	35		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 3.89 (P = 0.0001)



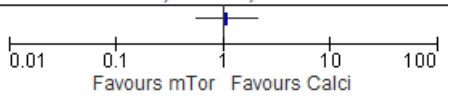
Infections (SAEs), 1 year after randomisation

Study or Subgroup	mTor inhibitors Events	Total	Calcineurin inhibitors Events	Total	Risk Ratio M-H, Random, 95% CI
NOCTET	32	140	19	142	1.71 [1.02, 2.87]



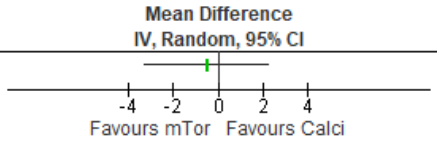
Loss of pulmonary function by at least 10%, 1 year after randomisation

Study or Subgroup	mTor inhibitors Events	Total	Calcineurin inhibitors Events	Total	Risk Ratio M-H, Random, 95% CI
4EVERLUNG	15	67	13	63	1.08 [0.56, 2.10]



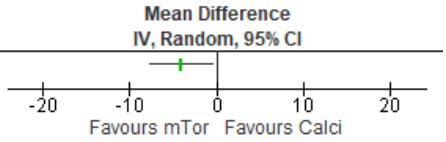
Quality of life - Physical component of SF-36, 1 year after randomisation

Study or Subgroup	mTor inhibitors Mean	SD	Total	Calcineurin inhibitors Mean	SD	Total	Mean Difference IV, Random, 95% CI
4EVERLUNG	47.2	8.8	67	47.7	7.1	63	-0.50 [-3.24, 2.24]



Quality of life - Mental component of SF-36, 1 year after randomisation

Study or Subgroup	mTor inhibitors Mean	SD	Total	Calcineurin inhibitors Mean	SD	Total	Mean Difference IV, Random, 95% CI
4EVERLUNG	49.7	11.8	67	53.8	9.1	63	-4.10 [-7.71, -0.49]



3.2.3 Referenzen der eingeschlossenen Studien

- Arora S, Gude E, Sigurdardottir V, Mortensen SA, Eiskjær H, Riise G, Mared L, Bjørtuft O, Ekmehag B, Jansson K, Simonsen S, Aukrust P, Solbu D, Iversen M, Gullestad L. Improvement in renal function after everolimus introduction and calcineurin inhibitor reduction in maintenance thoracic transplant recipients: the significance of baseline glomerular filtration rate. J Heart Lung Transplant. 2012 Mar;31(3):259-65. doi: 10.1016/j.healun.2011.12.010.
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- Gottlieb J, Neurohr C, Müller-Quernheim J, Wirtz H, Sill B, Wilkens H, Bessa V, Knosalla C, Porstner M, Capusan C, Strüber M. A randomized trial of everolimus-based quadruple therapy vs standard triple therapy early after lung transplantation. Am J Transplant. 2019 Jun;19(6):1759-1769. doi: 10.1111/ajt.15251.
- Gullestad L, Mortensen SA, Eiskjær H, Riise GC, Mared L, Bjørtuft O, Ekmehag B, Jansson K, Simonsen S, Gude E, Rundqvist B, Fagertun HE, Solbu D, Iversen M. Two-year outcomes in thoracic transplant recipients after conversion to everolimus with reduced calcineurin inhibitor within a multicenter, open-label, randomized trial. Transplantation. 2010 Dec 27;90(12):1581-9. doi: 10.1097/TP.0b013e3181fd01b7.
- Gullestad L, Iversen M, Mortensen SA, Eiskjaer H, Riise GC, Mared L, Bjørtuft O, Ekmehag B, Jansson K, Simonsen S, Gude E, Rundqvist B, Fagertun HE, Solbu D, Bergh CH. Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: a multicenter, randomized trial. Transplantation. 2010 Apr 15;89(7):864-72. doi: 10.1097/TP.0b013e3181cbac2d.

- Gullestad L, Eiskjaer H, Gustafsson F, Riise GC, Karason K, Dellgren G, Rådegran G, Hansson L, Gude E, Bjørtuft Ø, Jansson K, Schultz HH, Solbu D, Iversen M. Long-term outcomes of thoracic transplant recipients following conversion to everolimus with reduced calcineurin inhibitor in a multicenter, open-label, randomized trial. Transpl Int. 2016 Jul;29(7):819-29. doi: 10.1111/tri.12783.
- Kneidinger N, Valtin C, Hettich I, Frye BC, Wald A, Wilkens H, Bessa V, Gottlieb J. Five-year Outcome of an Early Everolimus-based Quadruple Immunosuppression in Lung Transplant Recipients: Follow-up of the 4EVERLUNG Study. Transplantation. 2022 Sep 1;106(9):1867-1874. doi: 10.1097/TP.0000000000004095.
- Shitrit D, Rahamimov R, Gidon S, Bakal I, Bargil-Shitrit A, Milton S, Kramer MR. Use of sirolimus and low-dose calcineurin inhibitor in lung transplant recipients with renal impairment: results of a controlled pilot study. Kidney Int. 2005 Apr;67(4):1471-5. doi: 10.1111/j.1523-1755.2005.00224.x.

3.2.4 Charakteristika der eingeschlossenen Studien

3.2.4.1 *Charakteristika des eingeschlossenen systematischen Reviews*

Reference / Study type	Study characteristics & inclusion criteria	Interventions	Study population	Results	Methodological Notes	Included publications
de Souza 2021 Systematic review with MA	**Search time frame** The strategy was carried out in March 2019 and updated in December 2019 **Sources** - MEDLINE (via PubMed) - Cochrane-CENTRAL - Embase - Web of Science - Scopus - LILACS - Clinical Trials - Brazilian Registry of Clinical Trials (ReBEC) - Gray Literature Report - Brazilian Library of Theses - Dissertations databases **Eligibility criteria** **Study type:** - RCTs **Participants:** - Patients undergoing unilateral or bilateral lung transplantation	**Intervention A** mTOR inhibitors **Intervention B** Calcineurin inhibitors	3 studies on 428 participants - Age: mean age 55.6 to 58.4 years - Single-centre and/or multi-centre trials: NR - Transplantation type: NR	**<u>Comparison mTOR inhibitors vs. Calcineurin inhibitors:</u>** Number of studies: 3 Number of participants: 428 **Critical outcomes:** 1. Mortality (1 year after randomisation): RR 3.95, CI 95% 0.66 to 23.49, N = 428 in 3 RCTs, I^2 = 0%) 2. New-onset chronic rejection development (1 year after randomisation): RR 0.42, CI 95% 0.14 to 1.29, N = 428 in 3 RCTs, I^2 = NA **Additional outcomes:** 1. Acute rejection (12 months after transplantation): RR 1.71, CI 95% 0.68 to 4.32, N = 428 in 3 RCTs, I^2 = 22% 2. Adverse events (12 months after transplantation): RR 1.11, CI 95% 1.03 to 1.20, N = 428 in 3 RCTs, I^2 = 0% 3. Improvement in renal function (12 months after transplantation): RR 22.21, CI 95% 7.23 to 68.20, N = 428 in 3 RCTs, I^2 = 18% 4. Quality of life: was only assessed by one RCT using the SF-36 scale, which was higher in the	**Methodological quality of included studies assessed using RoB 1 tool:** High risk of bias **Evidence synthesis:** • ITT • Random-effects and Fixed-effects model **GRADE:** The reliability analysis of the studies using the GRADE system indicated that all 3 showed high reliability of the reported results, considering the methodological design of the RCT (with a high level of evidence); few methodological limitations (low risk of bias); absence of	Shitrit 2005, *Kidney International* NOCTET: Gullestad 2010a, *Transplantation* Gullestad 2010b, *Transplantation* Arora 2012, *The Journal of Heart and Lung Transplantation* Gullestad 2016, *Transplant International* 4EVERLUNG: Gottlieb 2019, *American Journal of Transplantation*

	with chronic graft rejection			intervention group, especially in the mental component of the scale (P = 0.032)	inconsistency; absence of indirect evidence; little inaccuracy related to the heterogeneous sample numbers, which ranged from 16 to 38 or 130 patients, in addition to the variation in patient follow-up times (12, 18, and 24 months and 5 years); and absence of reporting bias.	

3.2.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.2.6 Literaturrecherche

Siehe 6.1.7

3.3 Schlüsselfrage 2b: Mycophenolate Mofetil vs. Azathioprine (Empfehlung 2.3)

3.3.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants after lung transplantation

Intervention: Mycophenolate Mofetil

Vergleichsintervention: Azathioprine

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Azathioprine	 Mycophenolate Mofetil	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality 6 months to 3 years after randomisation/transplantation	Relatives Risiko: 0.81 (CI 95% 0.58 - 1.13) Basierend auf Daten von 396 patienter und 2 Studien[1] Beobachtzungszeit 6 months to 3 years after randomisation/transplantation	**284** pro 1000	**230** pro 1000 Differenz: **54 weniger pro 1000** (CI 95% 119 weniger - 37 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[2]	Mycophenolate mofetil may decrease mortality compared to azathioprine
Retransplantation 3 years after randomisation	Relatives Risiko: 1.31 (CI 95% 0.3 - 5.75) Basierend auf Daten von 315 patienter und 1 Studien[3] Beobachtzungszeit 3 years after randomisation	**19** pro 1000	**25** pro 1000 Differenz: **6 mehr pro 1000** (CI 95% 13 weniger - 90 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[4]	There were too few who experienced the retransplantation, to determine whether mycophenolate mofetil made a difference compared to azathioprine
Freedom from BOS 3 years after randomisation	Relatives Risiko: 0.97 (CI 95% 0.85 - 1.11) Basierend auf Daten von 315 patienter und 1 Studien[5] Beobachtzungszeit 3 years after randomisation	**750** pro 1000	**728** pro 1000 Differenz: **22 weniger pro 1000** (CI 95% 112 weniger - 83 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[6]	Mycophenolate mofetil may slightly decrease the number of participants with freedom from BOS compared to azathioprine
Serious adverse events 3 years after transplantation					No studies were found that looked at serious adverse events
Abnormal kidney function 3 years after randomisation	Relatives Risiko: 0.67 (CI 95% 0.38 - 1.19) Basierend auf Daten von 320 patienter und 1 Studien[7]	**157** pro 1000	**105** pro 1000 Differenz: **52 weniger pro 1000** (CI 95% 97 weniger - 30 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[8]	Mycophenolate mofetil may decrease the number of participants with abnormal kidney function compared to azathioprine

	Beobachtzungszeit 3 years after randomisation			
Adverse events - Cancer 3 years after randomisation	Relatives Risiko: 0.94 (CI 95% 0.53 - 1.67) Basierend auf Daten von 320 patienter und 1 Studien[9] Beobachtzungszeit 3 years after randomisation	**132** pro 1000 **124** pro 1000 Differenz: **8 weniger pro 1000** (CI 95% 62 weniger - 88 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[10]	Mycophenolate mofetil may have little or no difference the number of participants with adverse events - cancer compared to azathioprine
Treatment discontinuation 3 years after randomisation	Relatives Risiko: 0.75 (CI 95% 0.6 - 0.95) Basierend auf Daten von 320 patienter und 1 Studien[11] Beobachtzungszeit 3 years after randomisation	**560** pro 1000 **420** pro 1000 Differenz: **140 weniger pro 1000** (CI 95% 224 weniger - 28 weniger)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[12]	Mycophenolate mofetil may decrease the number of participants with treatment discontinuation due to adverse events compared to azathioprine
Treatment discontinuation due to adverse events 6 months to 3 years after randomisation/transplantation	Relatives Risiko: 1.11 (CI 95% 0.44 - 2.79) Basierend auf Daten von 401 patienter und 2 Studien[13] Beobachtzungszeit 6 months to 3 years after randomisation/transplantation	**193** pro 1000 **214** pro 1000 Differenz: **21 mehr pro 1000** (CI 95% 108 weniger - 345 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency[14]	We are uncertain whether mycophenolate mofetil increases or decreases the number of participants with treatment discontinuation due to adverse events compared to azathioprine
Opportunistic infections 3 years after randomisation	Relatives Risiko: 0.9 (CI 95% 0.77 - 1.07) Basierend auf Daten von 320 patienter und 1 Studien[15] Beobachtzungszeit 3 years after randomisation	**673** pro 1000 **606** pro 1000 Differenz: **67 weniger pro 1000** (CI 95% 155 weniger - 47 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[16]	Mycophenolate mofetil may decrease the number of participants with opportunistic infections (no pathogen detection indicated) compared to azathioprine
Cytomegalovirus infection 6 months after transplantation	Relatives Risiko: 0.65 (CI 95% 0.34 - 1.23) Basierend auf Daten von 81 patienter und 1 Studien[17] Beobachtzungszeit 6 months after transplantation	**395** pro 1000 **257** pro 1000 Differenz: **138 weniger pro 1000** (CI 95% 261 weniger - 91 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[18]	We are uncertain whether mycophenolate mofetil increases or decreases the number of participants with cytomegalovirus infection (defined by positive histology results) compared to azathioprine
Loss of pulmonary function by at least 10% 1 year after transplantation				No studies were found that looked at loss of pulmonary function by at least 10%
Quality of life 3 years after transplantation				No studies were found that looked at quality of life

1. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13]. [14].

2. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
3. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
4. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: sehr schwerwiegend.** Very wide confidence intervals, Only data from one study, due to few events;
5. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
6. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study;
7. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
8. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study, Wide confidence intervals;
9. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
10. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
11. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
12. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study;
13. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [14]. [13].
14. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inkonsistenz: schwerwiegend.** The direction of the effect is not consistent between the included studies; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
15. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [13].
16. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
17. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [14].
18. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Only data from one study, Low number of patients;

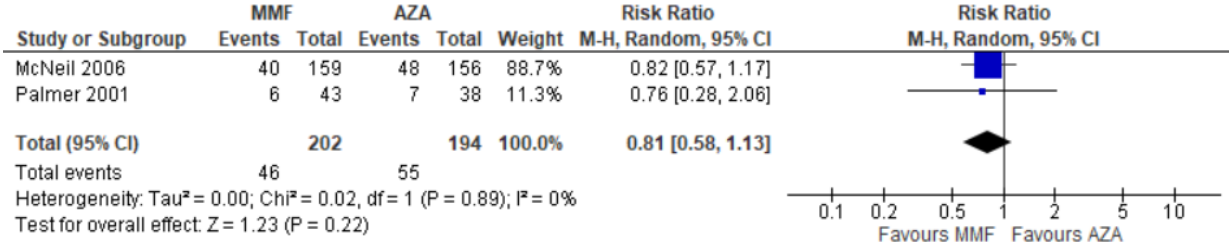
Referenzen

[13] McNeil K., Glanville AR, Wahlers T., Knoop C., Speich R., Mamelok RD, Maurer J., Ives J., Corris PA : Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients. Transplantation 2006;81(7):998-1003

[14] Palmer SM, Baz MA, Sanders L., Miralles AP, Lawrence CM, Rea JB, Zander DS, Edwards LJ, Staples ED, Tapson VF, Davis RD : Results of a randomized, prospective, multicenter trial of mycophenolate mofetil versus azathioprine in the prevention of acute lung allograft rejection. Transplantation 71(12):1772-6

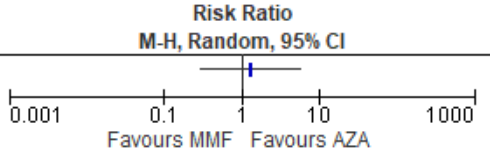
3.3.2 Analysen / Forest Plots

Mortality, 6 months to 3 years after randomisation/transplantation



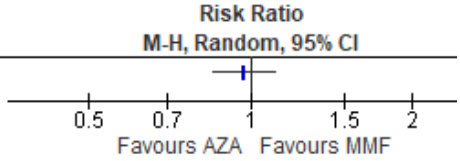
Retransplantation, 3 years after randomisation

Study or Subgroup	MMF Events	MMF Total	AZA Events	AZA Total	Risk Ratio M-H, Random, 95% CI
McNeil 2006	4	159	3	156	1.31 [0.30, 5.75]



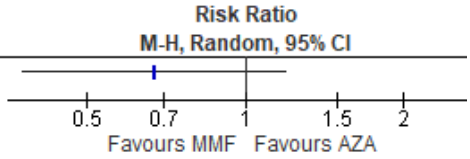
Freedom from BOS, 3 years after randomisation

Study or Subgroup	MMF Events	MMF Total	AZA Events	AZA Total	Risk Ratio M-H, Random, 95% CI
McNeil 2006	116	159	117	156	0.97 [0.85, 1.11]



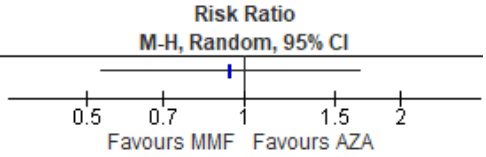
Abnormal kidney function, 3 years after randomisation

Study or Subgroup	MMF Events	MMF Total	AZA Events	AZA Total	Risk Ratio M-H, Random, 95% CI
McNeil 2006	17	161	25	159	0.67 [0.38, 1.19]



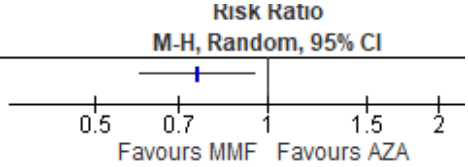
Adverse events – Cancer, 3 years after randomisation

Study or Subgroup	MMF Events	MMF Total	AZA Events	AZA Total	Risk Ratio M-H, Random, 95% CI
McNeil 2006	20	161	21	159	0.94 [0.53, 1.67]



Treatment discontinuation, 3 years after randomisation

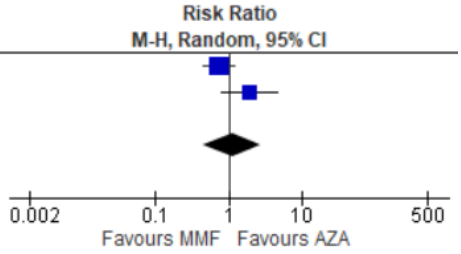
Study or Subgroup	MMF Events	MMF Total	AZA Events	AZA Total	Risk Ratio M-H, Random, 95% CI
McNeil 2006	68	161	89	159	0.75 [0.60, 0.95]



Treatment discontinuation due to AEs, 6 months to 3 years after randomisation/transplantation

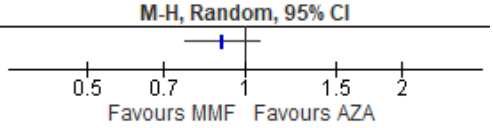
Study or Subgroup	MMF Events	MMF Total	AZA Events	AZA Total	Weight	Risk Ratio M-H, Random, 95% CI
McNeil 2006	24	161	32	159	57.4%	0.74 [0.46, 1.20]
Palmer 2001	13	43	6	38	42.6%	1.91 [0.81, 4.54]
Total (95% CI)		**204**		**197**	**100.0%**	**1.11 [0.44, 2.79]**
Total events	37		38			

Heterogeneity: Tau² = 0.32; Chi² = 3.55, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 0.22 (P = 0.82)

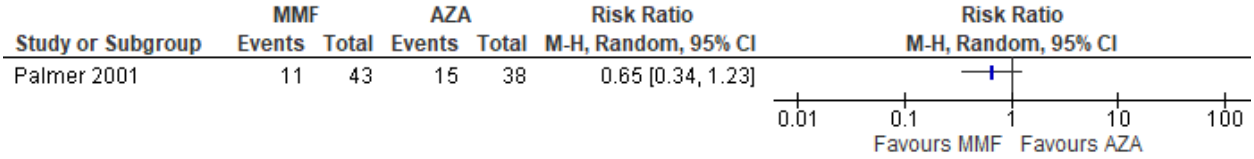


Opportunistic infections, 6 months after transplantation

Study or Subgroup	MMF Events	MMF Total	AZA Events	AZA Total	Risk Ratio M-H, Random, 95% CI
McNeil 2006	98	161	107	159	0.90 [0.77, 1.07]



Cytomegalovirus infection, 6 months after transplantation



3.3.3 Referenzen der eingeschlossenen Studien

- McNeil K, Glanville AR, Wahlers T, Knoop C, Speich R, Mamelok RD, Maurer J, Ives J, Corris PA. Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients. Transplantation. 2006 Apr 15;81(7):998-1003. doi: 10.1097/01.tp.0000202755.33883.61.
- Palmer SM, Baz MA, Sanders L, Miralles AP, Lawrence CM, Rea JB, Zander DS, Edwards LJ, Staples ED, Tapson VF, Davis RD. Results of a randomized, prospective, multicenter trial of mycophenolate mofetil versus azathioprine in the prevention of acute lung allograft rejection. Transplantation. 2001 Jun 27;71(12):1772-6. doi: 10.1097/00007890-200106270-00012.

3.3.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
McNeil 2006 RCT, open-label	**Sample size:** N = 320 **Enrolment period:** September 1997 to April 1999 Australia, Copenhagen, UK, France, Canada, Spain, Sweden, Norway, Germany, Netherlands, Belgium **Inclusion criteria:** • between the age of 18 and 65 years • receiving their first lung transplant (single, bilateral or heart-lung) • able to take MMF or AZA orally within 7 days of the procedure **Exclusion criteria:** Not reported **Characteristics** **Age (median, IQR):** - MMF: 46 (19 - 65) - AZA: 49 (17 - 63) **Sex (% female):**	**Experimental:** Oral mycophenolate Mofetil (MMF) - 1.5 g for the first 3 months, dropping to 1 g - 3 years duration of treatment - In conjunction with ATG induction, CsA and corticosteroids - N = 161 **Control:** Oral azathioprine (AZA) - 2 mg/kg/day, adjusted to maintain the white cell count > 4.5 x 109/L and/or platelets 75–100 x 109/L - 3 years duration of treatment - In conjunction with ATG induction, CsA and corticosteroids - N = 159	Mortality, 3 years after randomisation	RR 0.82 (CI 95% 0.57 to 1.17) MMF: 40/159 AZA: 48/156	1. Random sequence generation: low 2. Allocation concealment: low 3. Blinding of participants and personnel: high (open-label) 4. Blinding of outcome assessment: high (open-label) 5. Selective reporting: unclear (no protocol available) 6. Incomplete outcome data: low 7. Other bias: low
			Retransplantation or death, 3 years after randomisation	Not reported	
			Retransplantation, 3 years after randomisation	RR: 1.31 (CI 95% 0.30 to 5.74) MMF: 4/159 AZA: 3/156	
			Chronic lung allograft dysfunction, 3 years after randomisation	RR 1.08 (CI 95% 0.75 to 1.57) MMF: 43/159 AZA: 39/156	
			Abnormal kidney function, 3 years after randomisation	RR 0.67 (CI 95% 0.38 to 1.19) MMF: 17/161 AZA: 25/159	

	• MMF: 50%
	• AZA: 40%
	Ethnicity:
	Not reported
	Type of transplantation:
	• DLTx
	  ○ MMF: 55%
	  ○ AZA: 56%
	• SLTx
	  ○ MMF: 34%
	  ○ AZA: 33%
	• HLTx
	  ○ MMF: 11%
	  ○ AZA: 11%
	Respiratory medical history:
	• Emphysema (COPD)
	  ○ MMF: 36%
	  ○ AZA: 42%
	• Cystic fibrosis
	  ○ MMF: 20%
	  ○ AZA: 18%
	• Pulmonary hypertension
	  ○ MMF: 7%
	  ○ AZA: 6%
	• Other
	  ○ MMF: 37%
	  ○ AZA: 34%
	Other medical history:
	Not reported
			Treatment discontinuation	RR 0.75 (CI 95% 0.60 to 0.95)
				MMF: 68/161
				AZA: 89/159	

			Treatment discontinuation due to AEs	RR 0.74 (CI 95% 0.46 to 1.20) MMF: 24/161 AZA: 32/159	
			Serious adverse events, 3 years after randomisation	RR 0.97 (CI 95% 0.89 to 1.06) Tacrolimus: 108/124 Cyclosporine: 112/125	
			Adverse events – Cancer, 3 years after randomisation	RR 0.94 (CI 95% 0.53 to 1.67) MMF: 20/161 AZA: 21/159	
			Opportunistic infections (no pathogen detection indicated), 6 months after transplantation	RR 0.90 (CI 95% 0.77 to 1.07) MMF: 98/161 AZA:107/159	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Palmer 2001 RCT, open-label	**Sample size:** N = 81 **Enrolment period:** March 1997 to January 1999 USA **Inclusion criteria:** • All adult (18 years of age or older) lung transplant recipients **Exclusion criteria:** Not reported **Characteristics** **Age (mean, SD):** - MMF: 46 (14) - AZA: 50 (12) **Sex (% female):** • MMF: 49% • AZA: 58% **Ethnicity:** Not reported **Type of transplantation:** • DLTx o MMF: 30%	**Experimental:** Mycophenolate Mofetil (MMF) - 1 g twice daily (dose was routinely held or reduced if the white blood cell count decreased below 4000 cells/mm³) - by nasogastric tube until oral medications were tolerated - Triple immunosuppressive therapy with cyclosporine, corticosteroids, and MMF - N = 43 **Control:** Azathioprine (AZA) - 2 mg/kg (dose was routinely held or reduced if the white blood cell count decreased below 4000 cells/mm³) - by nasogastric tube until oral medications were tolerated - Triple immunosuppressive therapy with cyclosporine, corticosteroids, and MMF - N = 38	Mortality, 6 months after transplantation	RR 0.76 (CI 95% 0.28 to 2.06) MMF: 6/43 AZA: 7/39	1. Random sequence generation: unclear (no information on randomisatin process) 2. Allocation concealment: unclear 3. Blinding of participants and personnel: high (open-label) 4. Blinding of outcome assessment: high (open-label) 5. Incomplete outcome data: low 6. Selective reporting: unclear (no protocol available) 7. Other bias: low
			Retransplantation or death, 3 years after randomisation	Not reported	
			Retransplantation	Not reported	
			Chronic lung allograft dysfunction, 3 years after randomisation	Not reported	
			Abnormal kidney function, 3 years after randomisation	Not reported	
			Treatment discontinuation, 6 months after transplantation	Not reported	

	○ AZA: 37% • SLTx ○ MMF: 63% ○ AZA: 63% • HLTx ○ MMF: 3% ○ AZA: 0% **Respiratory medical history:** • Pulmonary fibrosis ○ MMF: 5% ○ AZA: 10% • Cystic fibrosis ○ MMF: 21% ○ AZA: 18% • Other ○ MMF: 19% ○ AZA: 18% **Other medical history:** Not reported		Treatment discontinuation due to AEs	RR 1.91 (CI 95% 0.81 to 4.54) MMF: 13/43 AZA: 6/38	
			Serious adverse events, 3 years after randomisation	Not reported	
			Adverse events – Cancer, 3 years after randomisation	Not reported	
			Cytomegalovirus infection, 6 months after transplantation	RR 0.65 (CI 95% 0.34 to 1.23) MMF: 11/43 AZA: 15/38	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

3.3.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.3.6 Literaturrecherche

Siehe 6.1.7

3.4 Schlüsselfrage 2c: Mycophenolate Mofetil vs. Everolimus (Empfehlung 2.3)

3.4.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants after lung transplantation

Intervention: Mycophenolate Mofetil

Vergleichsintervention: Everolimus

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Everolimus	 Mycophenolate Mofetil	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality[1] 2 to 3 years after transplantation	Relatives Risiko: 0.84 (CI 95% 0.46 - 1.52) Basierend auf Daten von 354 patienter und 2 Studien[2] Beobachtzungszeit 2 to 3 years after transplantation	**173** pro 1000	**145** pro 1000 Differenz: **28 weniger pro 1000** (CI 95% 93 weniger - 90 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency[3]	We are uncertain whether mycophenolate mofetil increases or decreases mortality compared to everolimus
Graft loss - Retransplantation or death 3 years after transplantation					No studies were found that looked at graft loss - retransplantation or death
Chronic lung allograft dysfunction 2 to 3 years after transplantation	Relatives Risiko: 1.2 (CI 95% 0.82 - 1.76) Basierend auf Daten von 354 patienter und 2 Studien[4] Beobachtzungszeit 2 to 3 years after transplantation	**211** pro 1000	**253** pro 1000 Differenz: **42 mehr pro 1000** (CI 95% 38 weniger - 160 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[5]	Mycophenolate mofetil may increase the number of participants with chronic lung allograft dysfunction compared to everolimus
Kidney function - GFR < 30 2 to 3 years after transplantation	Relatives Risiko: 0.57 (CI 95% 0.17 - 1.89) Basierend auf Daten von 190 patienter und 1 Studien[6] Beobachtzungszeit 2 years after transplantation	**74** pro 1000	**42** pro 1000 Differenz: **32 weniger pro 1000** (CI 95% 61 weniger - 66 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[7]	Mycophenolate mofetil may decrease the number of participants with GFR < 30 compared to everolimus
Kidney function - Creatinine > 265 µmol/l 2 years after transplantation	Relatives Risiko: 0.33 (CI 95% 0.07 - 1.61) Basierend auf Daten von 190 patienter und 1 Studien[8] Beobachtzungszeit 2 years after transplantation	**63** pro 1000	**21** pro 1000 Differenz: **42 weniger pro 1000** (CI 95% 59 weniger - 38 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[9]	Mycophenolate mofetil may decrease the number of participants with creatinine > 265 µmol/l compared to everolimus

Acute kidney injury with increased creatinine levels 2 years after transplantation	Relatives Risiko: 1.0 (CI 95% 0.98 - 1.02) Basierend auf Daten von 190 patienter und 1 Studien[10] Beobachtzungszeit 2 years after transplantation	**1000** pro 1000 **1000** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 20 weniger - 20 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[11]	Mycophenolate mofetil may have little or no difference on the number of participants with acute kidney injury with increased creatinine levels compared to everolimus
Serious adverse events 2 to 3 years after transplantation	Relatives Risiko: 0.86 (CI 95% 0.63 - 1.18) Basierend auf Daten von 354 patienter und 2 Studien[12] Beobachtzungszeit 2 to 3 years after transplantation	**693** pro 1000 **596** pro 1000 Differenz: **97 weniger pro 1000** (CI 95% 256 weniger - 125 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency[13]	We are uncertain whether mycophenolate mofetil increases or decreases the number of participants with serious adverse events compared to everolimus
Adverse events - Cancer 3 years after transplantation				No studies were found that looked at adverse events - cancer
Treatment discontinuation 2 to 3 years after transplantation	Relatives Risiko: 0.62 (CI 95% 0.35 - 1.1) Basierend auf Daten von 355 patienter und 2 Studien[14] Beobachtzungszeit 2 to 3 years after transplantation	**464** pro 1000 **288** pro 1000 Differenz: **176 weniger pro 1000** (CI 95% 302 weniger - 46 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious inconsistency[15]	We are uncertain whether mycophenolate mofetil increases or decreases the number of participants with treatment discontinuation compared to everolimus
Infection 3 years after transplantation	Relatives Risiko: 1.04 (CI 95% 0.92 - 1.16) Basierend auf Daten von 164 patienter und 1 Studien[16] Beobachtzungszeit 3 years after transplantation	**857** pro 1000 **891** pro 1000 Differenz: **34 mehr pro 1000** (CI 95% 69 weniger - 137 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[17]	Mycophenolate mofetil may increase the number of participants with infections (no pathogen detection indicated) slightly compared to everolimus
Cytomegalovirus infection 2 to 3 years after transplantation	Relatives Risiko: 3.78 (CI 95% 1.69 - 8.49) Basierend auf Daten von 354 patienter und 2 Studien[18] Beobachtzungszeit 2 to 3 years after transplantation	**39** pro 1000 **147** pro 1000 Differenz: **108 mehr pro 1000** (CI 95% 27 mehr - 292 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[19]	Mycophenolate mofetil may increase the number of participants with cytomegalovirus infection (pathogen detection indicated) compared to everolimus
Loss of pulmonary function by at least 10% 1 year after transplantation				No studies were found that looked at loss of pulmonary function by at least 10%
Kidney function - Creatinine µmol/l 3 years after transplantation	Gemessen mit: Skala: - Niedriger ist besser Basierend auf Daten von 164 patienter und 1 Studien[20]	**152** ymol/lMittelwert **160** ymol/lMittelwert Differenz: **MD 8.00 Größer** (CI 95% 24.27 kleiner - 40.27 Größer)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[21]	Mycophenolate mofetil may have little or no difference on creatinine level (µmol/l) compared to everolismus

	Beobachtzungszeit 3 years after transplantation			
Quality of life 3 years after transplantation				No studies were found that looked at quality of life

1. undefined
2. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [20]. [6].
3. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inkonsistenz: schwerwiegend.** The direction of the effect is not consistent between the included studies; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
4. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [6]. [20].
5. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
6. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [20].
7. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
8. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [20].
9. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
10. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [20].
11. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Only data from one study;
12. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [20]. [6].
13. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inkonsistenz: schwerwiegend.** The magnitude of statistical heterogeneity was high, with I^2: 74%., The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
14. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [6]. [20].
15. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inkonsistenz: sehr schwerwiegend.** The magnitude of statistical heterogeneity was high, with I^2: 72%.;
16. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [6].
17. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
18. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [20]. [6].
19. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
20. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [6].
21. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;

Referenzen

[6] Glanville AR, Aboyoun C., Klepetko W., Reichenspurner H., Treede H., Verschuuren EA, Boehler A., Benden C., Hopkins P., Corris PA, European, Australian Investigators in Lung T : Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. Journal of Heart and Lung Transplantation 34(1):16-25

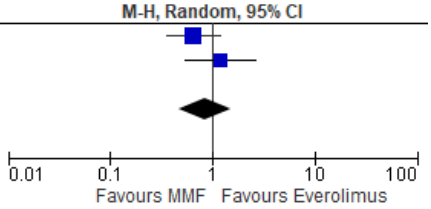
[20] Strueber M., Warnecke G., Fuge J., Simon AR, Zhang R., Welte T., Haverich A., Gottlieb J. : Everolimus versus mycophenolate mofetil de novo after lung transplantation: a prospective, randomized, open-Label trial. American Journal of Transplantation 16(11):3171-3180

3.4.2 Analysen / Forest Plots

Mortality, 2 to 3 years after transplantation

Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolimus Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Glanville 2015	13	80	21	84	58.3%	0.65 [0.35, 1.21]
Strueber 2016	12	95	10	95	41.7%	1.20 [0.54, 2.64]
Total (95% CI)		**175**		**179**	**100.0%**	**0.84 [0.46, 1.52]**
Total events	25		31			

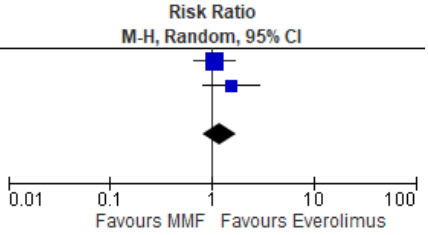
Heterogeneity: Tau² = 0.06; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 0.58 (P = 0.56)



Chronic lung allograft dysfunction, 2 to 3 years after transplantation

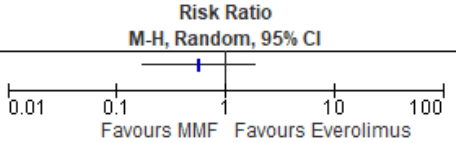
Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolimus Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Glanville 2015	24	80	24	84	64.2%	1.05 [0.65, 1.69]
Strueber 2016	20	95	13	95	35.8%	1.54 [0.81, 2.91]
Total (95% CI)		**175**		**179**	**100.0%**	**1.20 [0.82, 1.76]**
Total events	44		37			

Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)



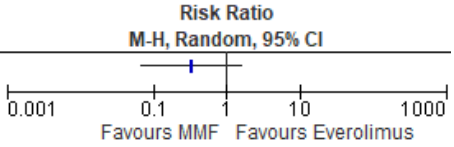
Kidney function – GFR < 30, 2 to 3 years after transplantation

Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolimus Events	Total	Risk Ratio M-H, Random, 95% CI
Strueber 2016	4	95	7	95	0.57 [0.17, 1.89]



Kidney function - Creatinine > 265 µmol/l, 2 years after transplantation

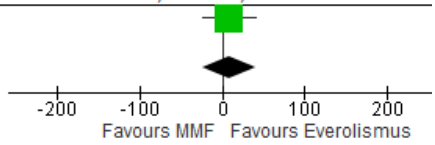
Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolimus Events	Total	Risk Ratio M-H, Random, 95% CI
Strueber 2016	2	95	6	95	0.33 [0.07, 1.61]



Kidney function – Creatinine in µmol/l, 3 years after transplantation

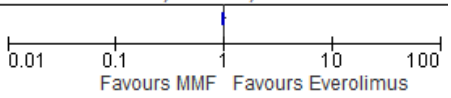
Study or Subgroup	MMF Mean	SD	Total	Everolismus Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Glanville 2015	160	112	80	152	98	84	100.0%	8.00 [-24.27, 40.27]
Total (95% CI)			**80**			**84**	**100.0%**	**8.00 [-24.27, 40.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.63)



Acute kidney injury with increased creatinine levels, 2 years after transplantation

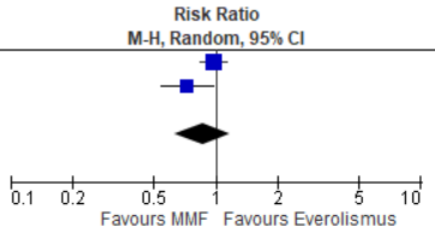
Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolimus Events	Total	Risk Ratio M-H, Random, 95% CI
Strueber 2016	95	95	95	95	1.00 [0.98, 1.02]



Serious adverse events, 2 to 3 years after transplantation

Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolismus Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Glanville 2015	64	80	69	84	57.6%	0.97 [0.84, 1.13]
Strueber 2016	40	95	55	95	42.4%	0.73 [0.54, 0.97]
Total (95% CI)		**175**		**179**	**100.0%**	**0.86 [0.63, 1.18]**
Total events	104		124			

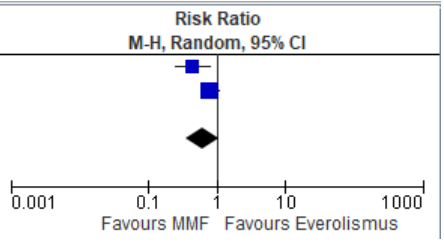
Heterogeneity: Tau² = 0.04; Chi² = 3.88, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.92 (P = 0.36)



Treatment discontinuation, 2 to 3 years after transplantation

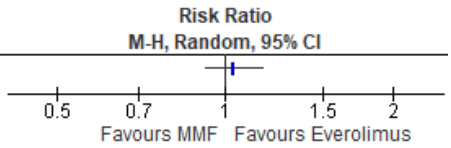
Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolismus Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Glanville 2015	13	80	31	84	41.3%	0.44 [0.25, 0.78]
Strueber 2016	41	95	52	95	58.7%	0.79 [0.59, 1.06]
Total (95% CI)		**175**		**179**	**100.0%**	**0.62 [0.35, 1.10]**
Total events	54		83			

Heterogeneity: Tau² = 0.13; Chi² = 3.33, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 1.62 (P = 0.10)



Infections, 3 years after transplantation

Study or Subgroup	Mycophenolate Mofetil Events	Total	Everolimus Events	Total	Risk Ratio M-H, Random, 95% CI
Glanville 2015	71	80	72	84	1.04 [0.92, 1.16]



3.4.3 Referenzen der eingeschlossenen Studien

- Glanville AR, Aboyoun C, Klepetko W, Reichenspurner H, Treede H, Verschuuren EA, Boehler A, Benden C, Hopkins P, Corris PA; European and Australian Investigators in Lung Transplantation. Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. J Heart Lung Transplant. 2015 Jan;34(1):16-25. doi: 10.1016/j.healun.2014.06.001.
- Strueber M, Warnecke G, Fuge J, Simon AR, Zhang R, Welte T, Haverich A, Gottlieb J. Everolimus Versus Mycophenolate Mofetil De Novo After Lung Transplantation: A Prospective, Randomized, Open-Label Trial. Am J Transplant. 2016 Nov;16(11):3171-3180. doi: 10.1111/ajt.13835.

3.4.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Glanville 2015 ACTRN12605000141640 RCT, open-label	**Sample size:** N = 165 **Enrolment period:** August 2005 to December 2008 Australia, Germany, Austria, Switzerland Netherlands, UK **Inclusion criteria:** • Recipients of a first heart-lung, bilateral lung or single lung allograft who are suitable to receive everolimus or mycophenolate sodium plus cyclosporin and corticosteroid triple therapy • Patients capable of understanding the purposes and risks of the study and who have given informed written consent • Male and female patients of childbearing	**Experimental:** Enteric-coated mycophenolatesodium (MPS) • by nasogastric tube and switched to oral administration after extubation • Before randomization all patients received immunosuppression with CsA, MPS, and corticosteroids (MPS therapy was started immediately after surgery with fixed doses of 1,080 mg twice- daily by nasogastric tube for 2 to 3 days) • N = 81 **Control:** Everolimus (RAD) • target therapeutic range was 3 to 8 ng/ml commencing 4 to 12 weeks after transplantation • Before randomization all patients received immunosuppression with	Mortality, 3 years after transplantation	RR 0.65 (CI 95% 0.35 to 1.21) MPS: 13/80 Everolimus: 21/84	1. Random sequence generation: low 2. Allocation concealment: low 3. Blinding of participants and personnel: high (open-label) 4. Blinding of outcome assessment: high (open-label) 5. Incomplete outcome data: low 6. Selective reporting: unclear (no protocol available) 7. Other bias: low
			Retransplantation or death, 3 years after randomisation	Not reported	
			Retransplantation	Not reported	
			Chronic lung allograft dysfunction, 3 years after transplantation	RR 1.05 (CI 95% 0.65 to 1.69) MPS: 24/80 Everolimus: 24/84	
			Creatinine (µmol/l), 3 years after transplantation	MD 8.00 (CI 95% -24.27 to 40.27) MPS: 160 µmol/l (SD 112)	

	age agree to maintain effective birth control practice during the study and from 3 months after cessation **Exclusion criteria:** • Patients who require immunosuppressive therapy other than study medication • Patients receiving a lobar lung transplant from a living donor • Patients who have received a prior ling or other organ transplant • Pregnant women and nursing mothers • Women unwilling to use adequate contraception during and for 3 months following the conclusion of treatment with study drug • Patients or their donors with serologic evidence of HIV, HbsAg or HCV antibodies • Patients with maligancies or history of malignancy with a recurrence free interval of < 5 years except non metastatic basal or squameous cell carcinoma of the skin that has bee treated successfully	CsA, MPS, and corticosteroids (MPS therapy was started immediately after surgery with fixed doses of 1,080 mg twice- daily by nasogastric tube for 2 to 3 days) • N = 84		Everolimus: 152 µmol/l (SD 98)	
			Treatment discontinuation, 3 years after transplantation	RR 0.44 (CI 95% 0.25 to 0.78) MPS: 13/80 Everolimus: 31/84	
			Treatment discontinuation due to AEs	Not reported	
			Serious adverse events, 3 years after transplantation	RR 0.97 (CI 95% 0.84 to 1.13) MPS: 64/80 Everolimus: 69/84	
			Adverse events – Cancer, 3 years after randomisation	Not reported	
			Infections, 3 years after transplantation (no pathogen detection indicated)	RR 1.04 (CI 95% 0.92 to 1.16) MPS: 71/80 Everolimus: 72/84	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

	• Patients with systemic infections requiring therapy at the time of entry into the study. (A systemic infection is defined as a body temperature of 38 degrees C or above on 2 occasions, or 39 degrees C accompanied by a culture of body fluid regarded as significant by the local laboratory and requiring antibiotic therapy) • Patients with panresistant infections with Burkholderia cepacia or mycobacteria in the last year.10 • Patients with renal insufficiency (creatinine clearance < 50ml/min) • Patients with severe uncontrolled hypercholesterolaemia (greater than or equal too 350mg/dL, 9.1 mmol/L) or hypertriglyceridaemia (greater than or equal too 750mg/dL, 8.5 mmol/L) • Patients with a white blood cell count of <2,500/mm3 or platlet count < 50,000/mm3 • Presence of any severe allergy requiring acute				

	or chronic treatment, or hypersensitivity to drugs similar to RAD (eg. erythromycin or other macrolide antibiotics) or to Myfortic • Patients on invasive ventilator devices or extracorporeal membrane oxygenators (ECMO) **Characteristics** **Age (median, SD):** - MPS: 48.9 (11.3) - Everolimus: 49.7 (13.6) **Sex (% female):** • MPS: 48.8% • Everolimus: 50% **Ethnicity:** • Causasian o MPS: 97.5% o Everolimus: 97.6% • Asian o MPS: 2.5% o Everolimus: 1.2% • Other o MPS: 0% o Everolimus: 1.2% **Type of transplantation:** • DLTx				

	○ MPS: 85% ○ Everolimus: 81% • SLTx ○ MPS: 12% ○ Everolimus: 17% • HLTx ○ MPS: 3% ○ Everolimus: 2% **Respiratory medical history:** • Emphysema (COPD) ○ MPS: 31% ○ Everolimus: 31% • Pulmonary fibrosis ○ MPS: 11% ○ Everolimus: 18% • Cystic fibrosis ○ MPS: 16% ○ Everolimus: 17% • a1-Antitrypsin deficiency ○ MPS: 13% ○ Everolimus: 4% • Pulmonary arterial hypertension ○ MPS: 4% ○ Everolimus: 4% • Other ○ MPS: 25%				

	○ Everolimus: 27% **Other medical history:** Not reported				

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Strueber 2016 NCT00402532 RCT, open-label	**Sample size:** N = 190 **Enrolment period:** March 2005 to November 2011 Germany **Inclusion criteria:** • Adult (18–65 years) • male or nonpregnant female patients following de novo single- or double-lung transplantation **Exclusion criteria:** • Maintenance immunosuppressive therapy before the transplantation, induction therapy or prior treatment with	**Experimental:** Mycophenolate Mofetil (MMF) • 500 mg twice a day and increased to a daily dose of 2 g • Combined with cyclosporine A and steroids • Before randomization all patients received immunosuppression with MMF, cyclosporine A and steroids • After randomization immunosuppressive • regimen was maintained unchanged • N = 95 **Control:** Everolimus (RAD) • 0.75 mg twice daily • the blood level of was examined on days 4 and 7, followed by weekly analysis and adapted to a blood level of 6–8 ng/mL	Mortality, 2 years after transplantation	RR 1.20 (CI 95% 0.54 to 2.64) MMF: 12/95 Everolimus: 10/95	1. Random sequence generation: low 2. Allocation concealment: unclear 3. Blinding of participants and personnel: high (open-label) 4. Blinding of outcome assessment: high (open-label) 5. Incomplete outcome data: low 6. Selective reporting: unclear (no protocol available) 7. Other bias: low
			Retransplantation or death, 3 years after randomisation	Not reported	
			Retransplantation	Not reported	
			Chronic lung allograft dysfunction, 2 years after transplantation	RR 1.54 (CI 95% 0.81 to 2.91) MMF: 20/95 Everolimus: 13/95	

	an experimental drug within 30 days • leukopenia with <4/nL leukocytes, thrombocytopenia with platelet count <60/nL, any platelet transfusions or use of granulocyte colony-stimulating factor and uncontrolled infection before study entry • Patients with multiorgan transplantation, systemic infections, wound healing failure of bronchial anastomosis, need for invasive or noninvasive mechanical ventilation support upon time of randomization and patients after retransplantation **Characteristics** **Age (median, IQR):** - MMF: 60 (47 - 64) - Everolimus: 56 (45 - 62) **Sex (% female):** • MMF: 41.1% • Everolimus: 44.2% **Ethnicity:** Not reported **Type of transplantation:** • DLTx o MMF: 91%	• Before randomization all patients received immunosuppression with MMF, cyclosporine A and steroids • After randomization MMF was replaced by Everolimus, and the CsA dose was lowered • N = 84	Kidney function - GFR < 30	RR 0.57 (CI 95% 0.17 to 1.89) MMF: 4/95 Everolimus: 7/95	
			Kidney function - Creatinine > 265 µmol/l	RR 0.33 (CI 95% 0.07 to 1.61) MMF: 2/95 Everolimus: 6/65	
			Acute kidney injury with increased creatinine levels by 59 to 94 µmol/lRR	RR 1.0 (0.98 to 1.02) MMF: 95/95 Everolimus: 95/95	
			Treatment discontinuation, 2 years after transplantation	RR 0.79 (CI 95% 0.59 to 1.06) MMF: 41/95 Everolimus: 52/95	
			Treatment discontinuation due to AEs	Not reported	
			Serious adverse events, 2 years after transplantation	RR 0.73 (CI 95% 0.54 to 0.97) MMF: 40/95 Everolimus: 55/95	
			Adverse events – Cancer, 3 years after randomisation	Not reported	
			Infections, 3 years after transplantation	Not reported	
			Loss of pulmonary function by at least	Not reported	

	○ Everolimus: 84% • SLTx ○ MMF: 10% ○ Everolimus: 16% • HLTx ○ MMF: 0% ○ Everolimus: 0% **Respiratory medical history:** • Emphysema (COPD) ○ MMF: 41% ○ Everolimus: 39% • Pulmonary fibrosis ○ MMF: 21% ○ Everolimus: 26% • Cystic fibrosis ○ MMF: 25% ○ Everolimus: 25% • Pulmonary arterial hypertension ○ MMF: 2% ○ Everolimus: 0% • Other ○ MMF: 11% ○ Everolimus: 10% **Other medical history:** Not reported		10% (1 year after transplantation)		
			Quality of life	Not reported	

3.4.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.4.6 Literaturrecherche

Siehe 6.1.7

3.5 Schlüsselfrage 2d: Everolimus/Sirolimus vs. Azathioprine (Empfehlung 2.3)

3.5.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants after lung transplantation

Intervention: mTOR inhibitors (everolimus or sirolimus)

Vergleichsintervention: Azathioprine

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Azathioprine	 mTOR inhibitors (everolimus or sirolimus)	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality 2 to 3 years after randomisation/transplantation	Relatives Risiko: 0.87 (CI 95% 0.52 - 1.45) Basierend auf Daten von 394 patienter und 2 Studien[1] Beobachtzungszeit 2 to 3 years after randomisation/transplantation	**141** pro 1000	**123** pro 1000 Differenz: **18 weniger pro 1000** (CI 95% 68 weniger - 63 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[2]	mTOR inhibitors (everolimus or sirolimus) may slightly decrease mortality compared to azathioprine
Retransplantation 3 years after transplantation	Relatives Risiko: 1.08 (CI 95% 0.22 - 5.21) Basierend auf Daten von 181 patienter und 1 Studien[3] Beobachtzungszeit 3 years after transplantation	**32** pro 1000	**35** pro 1000 Differenz: **3 mehr pro 1000** (CI 95% 25 weniger - 135 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to very serious imprecision[4]	There were too few who experienced retransplantation, to determine whether mTOR inhibitors (everolimus or sirolimus) made a difference compared to azathioprine
Chronic lung allograft dysfunction 3 years after transplantation	Relatives Risiko: 1.05 (CI 95% 0.71 - 1.57) Basierend auf Daten von 394 patienter und 2 Studien[5] Beobachtzungszeit 2 to 3 years after randomisation/transplantation	**296** pro 1000	**311** pro 1000 Differenz: **15 mehr pro 1000** (CI 95% 86 weniger - 169 mehr)	**Sehr niedrig** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[6]	We are uncertain whether mTOR inhibitors (everolimus or sirolimus) increase or decrease the number of participants with chronic lung allograft dysfunction compared to azathioprine
Increased creatinine (>30% higher than baseline) 1 year after randomisation	Relatives Risiko: 1.72 (CI 95% 1.34 - 2.21) Basierend auf Daten von 222 patienter und 1 Studien[7] Beobachtzungszeit 1 year after randomisation	**414** pro 1000	**712** pro 1000 Differenz: **298 mehr pro 1000** (CI 95% 141 mehr - 501 mehr)	**Moderat** Due to serious imprecision[8]	mTOR inhibitors (everolimus or sirolimus) probably increase the number of participants with increased creatinine (>30% higher than baseline) compared to azathioprine

Renal insuffiency or increased creatinine 3 years after transplantation	Relatives Risiko: 1.11 (CI 95% 0.76 - 1.63) Basierend auf Daten von 181 patienter und 1 Studien[9] Beobachtzungszeit 3 years after transplantation	**351** pro 1000 **390** pro 1000 Differenz: **39 mehr pro 1000** (CI 95% 84 weniger - 221 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[10]	mTOR inhibitors (everolimus or sirolimus) may slightly increase the number of participants with renal insuffiency or increased creatinine compared to azathioprine
Non-fatal serious adverse events 1 year after randomisation	Relatives Risiko: 1.46 (CI 95% 1.13 - 1.88) Basierend auf Daten von 222 patienter und 1 Studien[11] Beobachtzungszeit 1 year after randomisation	**432** pro 1000 **631** pro 1000 Differenz: **199 mehr pro 1000** (CI 95% 56 mehr - 380 mehr)	**Moderat** Due to serious imprecision[12]	mTOR inhibitors (everolimus or sirolimus) probably increase the number of participants with non-fatal serious adverse events compared to azathioprine
Treatment discontinuation 2 to 3 years after randomisation/transplantation	Relatives Risiko: 1.32 (CI 95% 1.1 - 1.58) Basierend auf Daten von 394 patienter und 2 Studien[13] Beobachtzungszeit 2 to 3 years after randomisation/transplantation	**476** pro 1000 **628** pro 1000 Differenz: **152 mehr pro 1000** (CI 95% 48 mehr - 276 mehr)	**Moderat** Due to serious risk of bias[14]	mTOR inhibitors (everolimus or sirolimus) probably increase the number of participants with treatment discontinuation compared to azathioprine
Treatment discontinuation due to adverse events 2 years after randomisation	Relatives Risiko: 3.5 (CI 95% 1.19 - 10.3) Basierend auf Daten von 222 patienter und 1 Studien[15] Beobachtzungszeit 2 years after randomisation	**36** pro 1000 **126** pro 1000 Differenz: **90 mehr pro 1000** (CI 95% 7 mehr - 335 mehr)	**Niedrig** Due to very serious imprecision[16]	mTOR inhibitors (everolimus or sirolimus) may increase the number of participants with treatment discontinuation due to adverse events compared to azathioprine
Adverse events - Cancer 2 to 3 years after randomisation/transplantation	Relatives Risiko: 1.58 (CI 95% 0.81 - 3.09) Basierend auf Daten von 403 patienter und 2 Studien[17] Beobachtzungszeit 2 to 3 years after randomisation/transplantation	**63** pro 1000 **100** pro 1000 Differenz: **37 mehr pro 1000** (CI 95% 12 weniger - 132 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[18]	mTOR inhibitors (everolimus or sirolimus) may increase the number of participants with adverse events - cancer compared to azathioprine
Serious infections 1 year after randomisation	Relatives Risiko: 1.8 (CI 95% 1.19 - 2.72) Basierend auf Daten von 222 patienter und 1 Studien[19] Beobachtzungszeit 1 year after randomisation	**225** pro 1000 **405** pro 1000 Differenz: **180 mehr pro 1000** (CI 95% 43 mehr - 387 mehr)	**Niedrig** Due to very serious imprecision[20]	mTOR inhibitors (everolimus or sirolimus) may increase the number of participants with serious infections (pathogen detection not indicated) compared to azathioprine
One or more infections[21] 1 to 3 years after transplantation	Relatives Risiko: 1.06 (CI 95% 0.95 - 1.18) Basierend auf Daten von 403 patienter und 2 Studien[22] Beobachtzungszeit 1 to 3 years after transplantation	**712** pro 1000 **755** pro 1000 Differenz: **43 mehr pro 1000** (CI 95% 36 weniger - 128 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[23]	mTOR inhibitors (everolimus or sirolimus) may increase the number of participants with one or more infection (pathogen detection indicated) compared to azathioprine

Cytomagelovirus infection 1 to 3 years after randomisation/transplantation	Relatives Risiko: 0.77 (CI 95% 0.49 - 1.21) Basierend auf Daten von 403 patienter und 2 Studien[24] Beobachtzungszeit 1 to 3 years after randomisation/transplantation	**176** pro 1000 **136** pro 1000 Differenz: **40 weniger pro 1000** (CI 95% 90 weniger - 37 mehr)	**Niedrig** Due to serious risk of bias, Due to serious imprecision[25]	mTOR inhibitors (everolimus or sirolimus) may slightly decrease the number of participants with cytomegalovirus infection (pathogen detection not indicated) compared to azathioprine
Loss of pulmonary function by at least 10% - Decline in FEV1 > 15% 1 year after randomisation	Relatives Risiko: 0.57 (CI 95% 0.33 - 0.98) Basierend auf Daten von 213 patienter und 1 Studien[26] Beobachtzungszeit 1 year after randomisation	**277** pro 1000 **158** pro 1000 Differenz: **119 weniger pro 1000** (CI 95% 186 weniger - 6 weniger)	**Moderat** Due to serious imprecision[27]	mTOR inhibitors (everolimus or sirolimus) probably decrease the number of pariticpants with decline in FEV1 > 15% compared to azathioprine
Quality of life 3 years after transplantation	Gemessen mit: Skala: -	Differenz: **null kleiner**		No studies were found that looked at quality of life

1. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3]. [19].
2. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
3. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3].
4. **Risiko für Bias: schwerwiegend.** Missing intention-to-treat analysis, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Only data from one study, due to few events;
5. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3]. [19].
6. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inkonsistenz: schwerwiegend.** The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I^2: 40%.; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
7. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [19].
8. **Unzureichende Präzision: schwerwiegend.** Only data from one study, Wide confidence intervals;
9. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3].
10. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
11. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [19].
12. **Unzureichende Präzision: schwerwiegend.** Only data from one study;
13. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3]. [19].
14. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
15. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [19].
16. **Unzureichende Präzision: sehr schwerwiegend.** Very wide confidence intervals, Only data from one study;
17. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3]. [19].
18. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
19. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [19].
20. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Only data from one study;
21. undefined
22. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [3]. [19].
23. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
24. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [19].

25. **Risiko für Bias: schwerwiegend.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
26. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [19].
27. **Unzureichende Präzision: schwerwiegend.** Only data from one study;

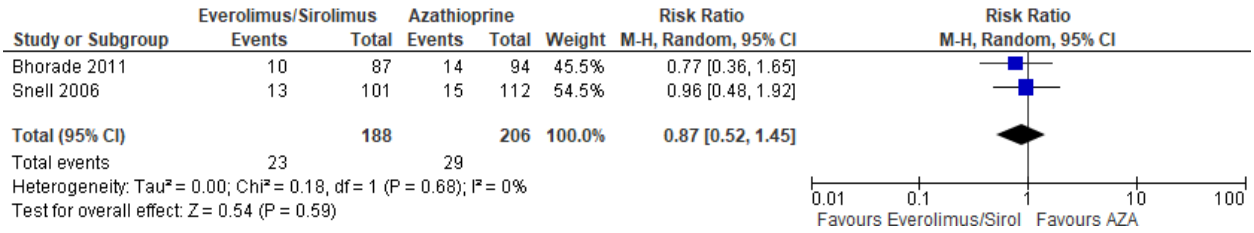
Referenzen

[3] Bhorade S., Ahya VN, Baz MA, Valentine VG, Arcasoy SM, Love RB, Seethamraju H., Alex CG, Bag R., Deoliveira NC, Husain A., Vigneswaran WT, Charbeneau J., Krishnan JA, Durazo-Arvizu R., Norwick L., Garrity E. : Comparison of sirolimus with azathioprine in a tacrolimus-based immunosuppressive regimen in lung transplantation. American Journal of Respiratory and Critical Care Medicine 183(3):379-87

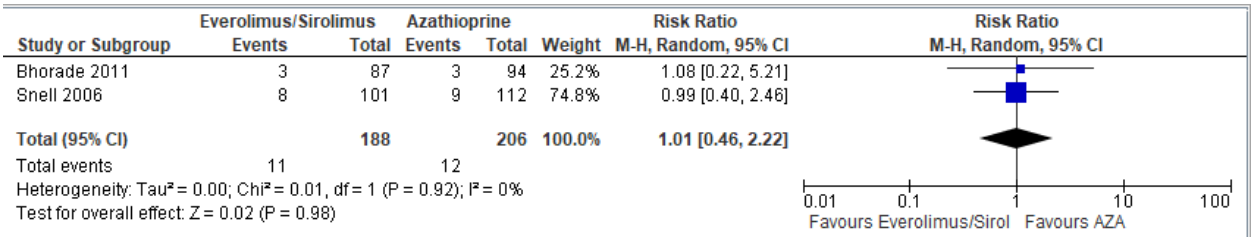
[19] Snell GI, Valentine VG, Vitulo P., Glanville AR, McGiffin DC, Loyd JE, Roman A., Aris R., Sole A., Hmissi A., Pirron U., Group RBS : Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. American Journal of Transplantation 6(1):169-77

3.5.2 Analysen / Forest Plots

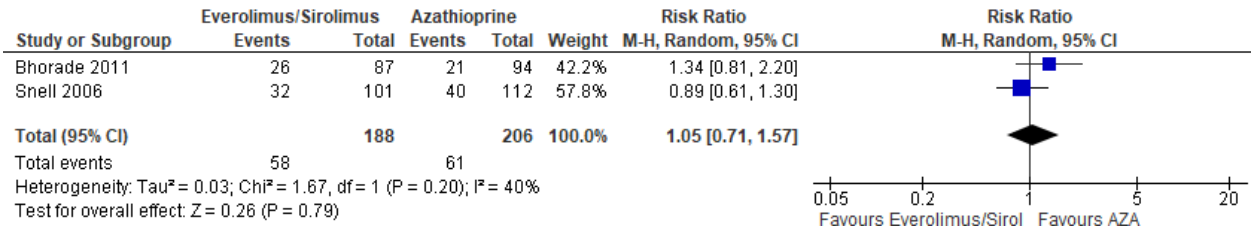
Mortality, 2 to 3 years after randomisation/transplantation



Retransplantation, 2 to 3 years after transplantation



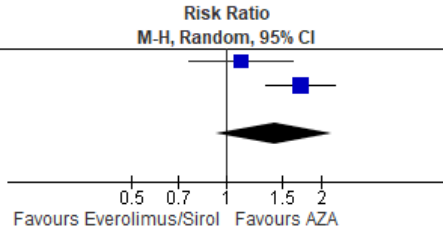
Chronic lung allograft dysfunction, 3 years after transplantation



Renal insuffiency or increased creatinine, 1 year to 3 years after transplantation/randomisation

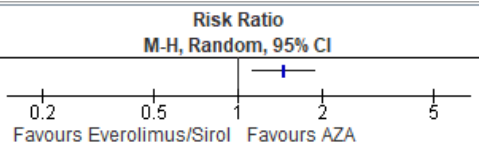
Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhorade 2011	34	87	33	94	44.4%	1.11 [0.76, 1.63]
Snell 2006	79	111	46	111	55.6%	1.72 [1.34, 2.21]
Total (95% CI)		**198**		**205**	**100.0%**	**1.42 [0.93, 2.17]**
Total events	113		79			

Heterogeneity: Tau² = 0.07; Chi² = 3.53, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.60 (P = 0.11)



Non-fatal serious adverse events, 1 year after randomisation

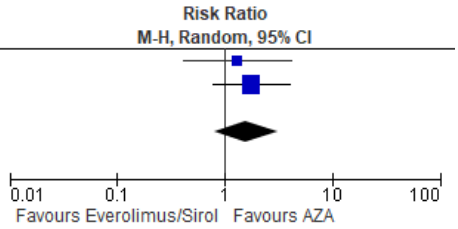
Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Risk Ratio M-H, Random, 95% CI
Snell 2006	70	111	48	111	1.46 [1.13, 1.88]



Adverse events – Cancer, 2 to 3 years after transplantation/randomisation

Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhorade 2011	6	87	5	94	34.1%	1.30 [0.41, 4.10]
Snell 2006	14	111	8	111	65.9%	1.75 [0.76, 4.00]
Total (95% CI)		**198**		**205**	**100.0%**	**1.58 [0.81, 3.09]**
Total events	20		13			

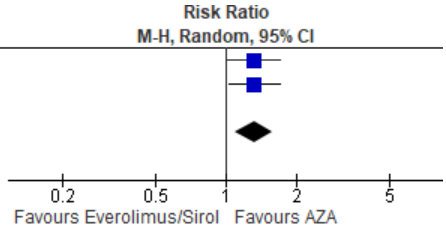
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



Treatment discontinuation, 2 to 3 years after randomisation/transplantation

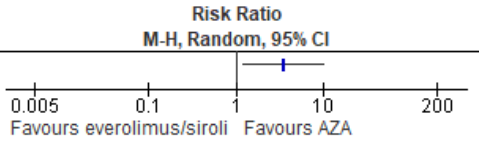
Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhorade 2011	56	87	46	94	48.6%	1.32 [1.02, 1.70]
Snell 2006	62	101	52	112	51.4%	1.32 [1.03, 1.70]
Total (95% CI)		**188**		**206**	**100.0%**	**1.32 [1.10, 1.58]**
Total events	118		98			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)



Treatment discontinuation due to AEs, 2 years after randomisation

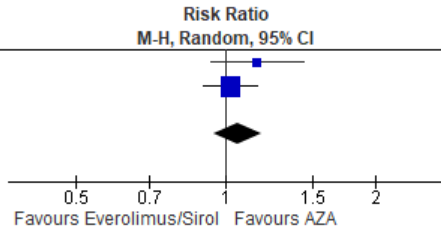
Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Risk Ratio M-H, Random, 95% CI
Snell 2006	14	111	4	111	3.50 [1.19, 10.30]



One or more infections, 1 to 3 years after transplantation

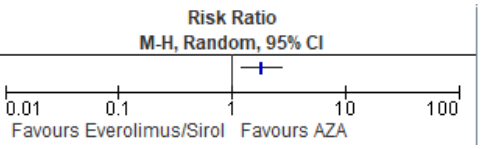
Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhorade 2011	61	87	57	94	27.0%	1.16 [0.93, 1.43]
Snell 2006	91	111	89	111	73.0%	1.02 [0.90, 1.16]
Total (95% CI)		**198**		**205**	**100.0%**	**1.06 [0.95, 1.18]**
Total events	152		146			

Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 0.97 (P = 0.33)



Serious infections, 1 year after randomisation

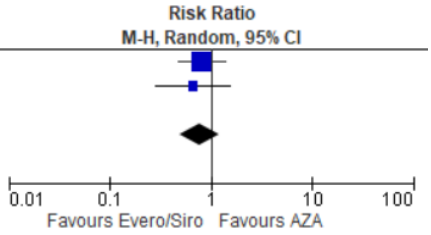
Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Risk Ratio M-H, Random, 95% CI
Snell 2006	45	111	25	111	1.80 [1.19, 2.72]



Cytomegalovirus infection, 1 to 3 years after transplantation/randomisation

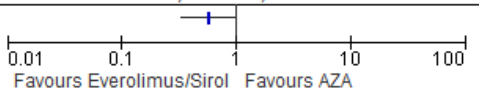
Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhorade 2011	18	87	24	94	71.7%	0.81 [0.47, 1.39]
Snell 2006	8	111	12	111	28.3%	0.67 [0.28, 1.57]
Total (95% CI)		**198**		**205**	**100.0%**	**0.77 [0.49, 1.21]**
Total events	26		36			

Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.25)



Loss of pulmonary function by at least 10%, 1 year after randomisation

Study or Subgroup	Everolimus/Sirolimus Events	Total	Azathioprine Events	Total	Risk Ratio M-H, Random, 95% CI
Snell 2006	16	101	31	112	0.57 [0.33, 0.98]



3.5.3 Referenzen der eingeschlossenen Studien

- Ahya VN, McShane PJ, Baz MA, Valentine VG, Arcasoy SM, Love RB, Seethamraju H, Garrity E, Alex CG, Bag R, DeOliveira NC, Vigneswaran WT, Charbeneau J, Krishnan JA, Durazo-Arvizu R, Norwick L, Bhorade S. Increased risk of venous thromboembolism with a sirolimus-based immunosuppression regimen in lung transplantation. J Heart Lung Transplant. 2011 Feb;30(2):175-81. doi: 10.1016/j.healun.2010.08.010.
- Bhorade S, Ahya VN, Baz MA, Valentine VG, Arcasoy SM, Love RB, Seethamraju H, Alex CG, Bag R, Deoliveira NC, Husain A, Vigneswaran WT, Charbeneau J, Krishnan JA, Durazo-Arvizu R, Norwick L, Garrity E. Comparison of sirolimus with azathioprine in a tacrolimus-based immunosuppressive regimen in lung transplantation. Am J Respir Crit Care Med. 2011 Feb 1;183(3):379-87. doi: 10.1164/rccm.201005-0775OC.
- Ghassemieh B, Ahya VN, Baz MA, Valentine VG, Arcasoy SM, Love RB, Seethamraju H, Alex CG, Bag R, DeOliveira NC, Vigneswaran WT, Charbeneau J, Garrity ER, Bhorade SM. Decreased incidence of cytomegalovirus infection with sirolimus in a post hoc randomized, multicenter study in lung transplantation. J Heart Lung Transplant. 2013 Jul;32(7):701-6. doi: 10.1016/j.healun.2013.04.010.
- Kovarik JM, Snell GI, Valentine V, Aris R, Chan CK, Schmidli H, Pirron U. Everolimus in pulmonary transplantation: pharmacokinetics and exposure-response relationships. J Heart Lung Transplant. 2006 Apr;25(4):440-6. doi: 10.1016/j.healun.2005.12.001.
- Snell GI, Levvey BJ, Zheng L, Bailey M, Orsida B, Law L, Whitford HM, Kotsimbos TC, Williams TJ. Everolimus alters the bronchoalveolar lavage and endobronchial biopsy immunologic profile post-human lung transplantation. Am J Transplant. 2005 Jun;5(6):1446-51. doi: 10.1111/j.1600-6143.2005.00863.x.
- Snell GI, Levvey BJ, Zheng L, Bailey M, Orsida B, Williams TJ, Kotsimbos TC. Interleukin-17 and airway inflammation: a longitudinal airway biopsy study after lung transplantation. J Heart Lung Transplant. 2007 Jul;26(7):669-74. doi: 10.1016/j.healun.2007.05.004.
- Snell GI, Valentine VG, Vitulo P, Glanville AR, McGiffin DC, Loyd JE, Roman A, Aris R, Sole A, Hmissi A, Pirron U; RAD B159 Study Group. Everolimus versus azathioprine in

maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. Am J Transplant. 2006 Jan;6(1):169-77. doi: 10.1111/j.1600-6143.2005.01134.x.

3.5.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Bhorade 2011 Ahya 2011; Ghassemieh 2013 NCT00321906 RCT, open-label	**Sample size:** N = 181 **Enrolment period:** April 2002 to June 2006 USA **Inclusion criteria:** • All lung transplant recipients between the ages of 18 and 65 **Exclusion criteria:** • prior organ transplant • prior treatment with an experimental drug within 30 days • leukopenia, thrombocytopenia, severe hypercholesterolemia, or uncontrolled infection • use of maintenance immunosuppression other than IL-2 receptor antagonist, tacrolimus, azathioprine, and	**Experimental:** Sirolimus • 2 mg/day with target trough levels between 5 and 15 ng/ml • 3 years duration of treatment • All patients received IL-2 receptor antagonist induction therapy, tacrolimus, azathioprine, and corticosteroids until 90 days after transplantation. At 90 days after transplantation, patients were randomized • N = 87 **Control:** Azathioprine (AZA) • 3 years duration of treatment • All patients received IL-2 receptor antagonist induction therapy, tacrolimus, azathioprine, and corticosteroids until 90 days after transplantation. At 90 days after transplantation, patients were randomized • N = 94	Mortality, 3 years after transplantation	RR 0.77 (CI 95% 0.36 to 1.65) Sirolimus: 10/87 AZA:14/94	1. Random sequence generation: low 2. Allocation concealment: unclear 3. Blinding of participants and personnel: high (open-label) 4. Blinding of outcome assessment: high (open-label) 5. Incomplete outcome data: low 6. Selective reporting: unclear (no protocol available) 7. Other bias: low
			Retransplantation or death, 3 years after randomisation	Not reported	
			Retransplantation	RR 1.08 (CI 95% 0.22 to 5.21) Sirolimus: 3/87 AZA:3/94	
			Chronic lung allograft dysfunction, 3 years after transplantation	RR 1.34 (CI 95% 0.81 to 2.20) Sirolimus: 26/87 AZA: 21/94	
			Renal insufficiency or increased creatinine level	RR 1.11 (CI 95% 0.76 to 1.63) Sirolimus: 34/87 AZA: 33/94	

	prednisone before randomization • the use of an extracorporeal membrane oxygenator; mechanical ventilation for more than 7 days • the presence of airway dehiscence or necrosis; or declining pulmonary function within the first 3 months after transplantation **Characteristics** **Age (median, Q1, Q3):** • Sirolimus: 57 (48, 60) • AZA: 58 (52, 62) **Sex (% female):** • Sirolimus: 50% • AZA: 40% **Ethnicity:** Not reported **Type of transplantation:** • DLTx o Sirolimus: 54% o AZA: 52% • SLTx o Sirolimus: NR o AZA: NR • HLTx o Sirolimus: NR o AZA: NR **Respiratory medical history:** • Emphysema (COPD) o Sirolimus: 34% o AZA: 50%		Treatment discontinuation, 3 years after transplantation	RR 1.32 (CI 95% 1.02 to 1.70) Sirolimus: 56/87 AZA: 46/94	
			Treatment discontinuation due to AEs	Not reported	
			Serious adverse events, 3 years after transplantation	Not reported	
			Adverse events – Cancer, 3 years after transplantation	RR 1.30 (0.41 to 4.10) Sirolimus: 6/87 AZA: 5/94	
			One or more infections, 3 years after transplantation	RR 1.16 (CI 95% 0.93 to 1.43) Sirolimus: 61/87 AZA: 57/94	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

	• Cystic fibrosis
	  ○ Sirolimus: 9%
	  ○ AZA: 16%
	• Pulmonary fibrosis
	  ○ Sirolimus: 37%
	  ○ AZA: 27%
	• Pulmonary hypertension
	  ○ Sirolimus: 2%
	  ○ AZA: 4%
	• Other
	  ○ Sirolimus: 10%
	  ○ AZA: 11%
	Other medical history:
	Not reported				

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Snell 2006; Snell 2005; Snell 2007; Kovarik 2006 RCT, double-blind	**Sample size:** N = 213 **Enrolment period:** Not reported USA, Australia, Canada, Germany, France, Italy, Sweden, UK **Inclusion criteria:**	**Experimental:** Oral everolimus • 3 mg/day (1.5 mg twice daily) • All patients received cyclosporine and corticosteroids • The treatment arm with everolimus • 1.5 mg/day, originally included in the protocol, had been discontinued • N = 101	Mortality, 2 years after randomisation	RR 0.96 (CI 95% 0.48 to 1.92) Everolimus: 13/101 AZA:15/112	1. Random sequence generation: low 2. Allocation concealment: unclear 3. Blinding of participants and personnel: low 4. Blinding of outcome assessment: low
			Retransplantation or death, 3 years after randomisation	Not reported	

	• Stable lung or heart/lung transplant recipients
	• 14–70 years old
	• enrolled 3 - 36 months post-transplantation if they were free from BOS
	
	Exclusion criteria:
	• Patients with histological evidence of OB
	Characteristics
	Age (mean, SD):
	• Everolimus: 41.6 (SD 13.4)
	• AZA: 47.7 (SD 12.9)
	Sex (% female):
	• Everolimus: 40.6%
	• AZA: 39.3%
	Ethnicity:
	• Caucasian
	  ○ Everolimus: 97%
	  ○ AZA: 94.6%
	• African-American
	  ○ Everolimus: 3%
	  ○ AZA: 2.7%
	• Other
	  ○ Everolimus: 0
	  ○ AZA: 2.7%
	Type of transplantation:
	• DLTx
		Control:
		Oral azathioprine (AZA)
		• 1-3 mg/kg/day
		• All patients received cyclosporine and corticosteroids
		• N = 112
			Retransplantation	Not reported	5. Incomplete outcome data: low
					
					6. Selective reporting: unclear (no protocol available)
					
					7. Other bias: low

			Chronic lung allograft dysfunction, 2 years after randomisation	RR 0.89 (CI 95% 0.61 to 1.30) Everolimus: 32/101 AZA: 40/112	
			Incidence of elevated creatinine (>30% higher than baseline), 1 year after transplantation	RR 1.72 (CI 95% 1.34 to 2.21) Everolimus: 79/111 AZA: 46/111	
			Treatment discontinuation, 2 years after randomisation	RR 1.32 (CI 95% 1.03 to 1.70) Everolimus: 62/101 AZA: 52/112	
			Treatment discontinuation due to AEs, 2 years after randomisation	RR 3.50 (CI 95% 1.19 to 10.30) Everolimus: 14/111 AZA: 4/111	
			Non-fatal serious adverse events, 1 year after randomisation	RR 1.46 (CI 95% 1.13 to 1.88) Everolimus: 70/111 AZA: 48/111	
			Adverse events – Cancer, 2 years after randomisation	RR 1.75 (CI 95% 0.76 to 4.00)5	

	○ Everolimus: 54% ○ AZA: 47% • SLTx ○ Everolimus: NR ○ AZA: NR • HLTx ○ Everolimus: NR ○ AZA: NR **Respiratory medical history:** • Emphysema (COPD) ○ Everolimus: 42% ○ AZA: 49% • Cystic fibrosis ○ Everolimus: 21.8% ○ AZA: 17.9% • a1-Antitrypsin deficiency ○ Everolimus: 7.9% ○ AZA: 10.7% • Pulmonary fibrosis ○ Everolimus: 20.8% ○ AZA: 19.6% • Pulmonary hypertension ○ Everolimus: 5% ○ AZA: 2.7% • Other ○ Everolimus: 13.9%			Everolimus: 14/111 AZA: 8/111	
			One or more infections, 1 year after randomisation	RR 1.02 (CI 95% 0.90 to 1.16) Everolimus: 91/111 AZA: 89/111	
			Serious infections, 1 year after randomisation (no pathogen detection indicated)	RR 1.80 (CI 95% 1.19 to 2.72) Everolimus: 45/111 AZA: 25/111	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	RR 0.57 (CI 95% 0.33 to 0.98) Everolimus: 16/101 AZA: 31/112	
			Quality of life	Not reported	

	○ AZA: 16.1% **Other medical history:** Not reported				

3.5.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.5.6 Literaturrecherche

Siehe 6.1.7

3.6 Schlüsselfrage 3: Azithromycin vs. Placebo (Empfehlung 4.1)

3.6.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants with after lung transplantation

Intervention: Azithromycin

Vergleichsintervention: Placebo

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo	 Azithromycin	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality 2 years after transplantation	Relatives Risiko: 0.75 (CI 95% 0.35 - 1.57) Basierend auf Daten von 151 patienter und 2 Studien[1] Beobachtungszeit 2 years after transplantation	**182** pro 1000	**137** pro 1000 Differenz: **45 weniger pro 1000** (CI 95% 118 weniger - 104 mehr)	**Moderat** Due to serious imprecision[2]	Azithromycin probably decreases mortality compared to placebo
Retransplantation 2 years after transplantation	Relatives Risiko: 0.54 (CI 95% 0.05 - 5.7) Basierend auf Daten von 83 patienter und 1 Studien[3] Beobachtungszeit 2 years after transplantation	**47** pro 1000	**25** pro 1000 Differenz: **22 weniger pro 1000** (CI 95% 45 weniger - 221 mehr)	**Niedrig** Due to very serious imprecision[4]	Azithromycin may decrease the number of participants with retransplantation compared to placebo
Chronic lung allograft dysfunction 2 years after transplantation	Relatives Risiko: 0.56 (CI 95% 0.14 - 2.32) Basierend auf Daten von 151 patienter und 2 Studien[5] Beobachtungszeit 2 years after transplantation	**312** pro 1000	**175** pro 1000 Differenz: **137 weniger pro 1000** (CI 95% 268 weniger - 412 mehr)	**Sehr niedrig** Due to very serious inconsistency, Due to serious imprecision[6]	We are uncertain whether azithromycin increases or decreases the number of participants with chronic lung allograft dysfunction compared to placebo
Kidney function 3 years after transplantation					No studies were found that looked at kidney function
Serious adverse events 2 years after transplantation	Relatives Risiko (CI 95% -) Basierend auf Daten von 83 patienter und 1 Studien[7] Beobachtungszeit 2 years after transplantation	**0** pro 1000	**0** pro 1000 Differenz: **weniger pro 1000** (CI 95% 0 weniger - 0 weniger)	**Niedrig** Due to very serious imprecision[8]	There were too few who experienced serious adverse events, to determine whether azithromycin made a difference compared to placebo

Adverse events - Cancer 3 years after transplantation				No studies were found that looked at adverse events - cancer
Treatment discontinuation 2 years after transplantation	Relatives Risiko: 1.79 (CI 95% 0.46 - 7.02) Basierend auf Daten von 83 patienter und 1 Studien[9] Beobachtzungszeit 2 years after transplantation	**70** pro 1000 **125** pro 1000 Differenz: **55 mehr pro 1000** (CI 95% 38 weniger - 421 mehr)	**Niedrig** Due to very serious imprecision[10]	Azithromycin may increase the number of participants with treatment discontinuation
Infection - respiratory infections (no pathogen detection indicated) < 6 months after transplantation	Relatives Risiko: 1.29 (CI 95% 0.54 - 3.06) Basierend auf Daten von 68 patienter und 1 Studien[11] Beobachtzungszeit < 6 months after transplantation	**206** pro 1000 **266** pro 1000 Differenz: **60 mehr pro 1000** (CI 95% 95 weniger - 424 mehr)	**Niedrig** Due to serious imprecision, Due to serious indirectness[12]	Azithromycin may increase the number of participants with respiratory infections (pathogen detection not indicated) compared to placebo
Infection - Respiratory culture positive < 6 months after transplantation	Relatives Risiko: 0.54 (CI 95% 0.25 - 1.18) Basierend auf Daten von 68 patienter und 1 Studien[13] Beobachtzungszeit < 6 months after transplantation	**382** pro 1000 **206** pro 1000 Differenz: **176 weniger pro 1000** (CI 95% 286 weniger - 69 mehr)	**Niedrig** Due to serious indirectness, Due to serious imprecision[14]	Azithromycin may decrease the number of participants with respiratory culture positive
Loss of pulmonary function by at least 10% 1 year after transplantation				No studies were found that looked at loss of pulmonary function by at least 10%
Quality of life 3 years after transplantation				No studies were found that looked at quality of life

1. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [31]. [32].
2. **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
3. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [32].
4. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Only data from one study, due to few events;
5. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [31]. [32].
6. **Inkonsistenz: sehr schwerwiegend.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I^2:... %.; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals;
7. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [32].
8. **Unzureichende Präzision: sehr schwerwiegend.** due to no events observed, effect not estimable, Only data from one study;
9. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [32].
10. **Unzureichende Präzision: sehr schwerwiegend.** Very wide confidence intervals, Only data from one study;
11. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [31].
12. **Indirektheit: schwerwiegend.** The outcome time frame in studies were insufficient; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
13. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [31].
14. **Indirektheit: schwerwiegend.** The outcome time frame in studies were insufficient; **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;

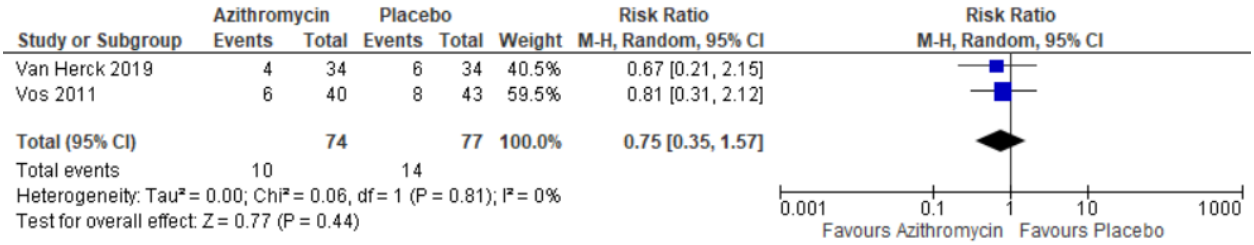
Referenzen

[31] Van Herck A., Frick AE, Schaevers V., Vranckx A., Verbeken EK, Vanaudenaerde BM, Sacreas A., Heigl T., Neyrinck AP, Van Raemdonck D., Dupont LJ, Yserbyt J., Verleden SE, Verleden GM, Vos R. : Azithromycin and early allograft function after lung transplantation: A randomized, controlled trial. Journal of Heart and Lung Transplantation 38(3):252-259

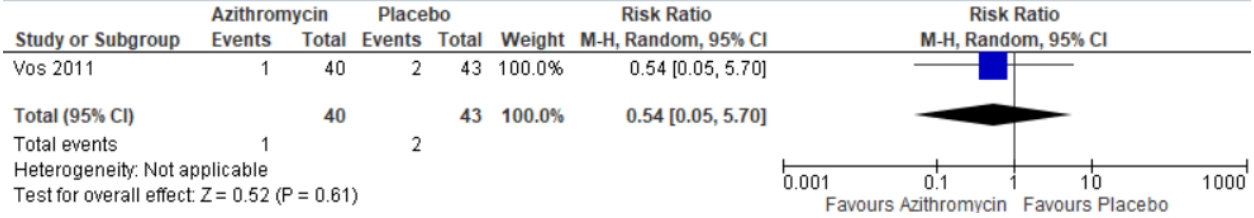
[32] Vos R., Vanaudenaerde BM, Verleden SE, De Vleeschauwer SI, Willems-Widyastuti A., Van Raemdonck DE, Schoonis A., Nawrot TS, Dupont LJ, Verleden GM : A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. European Respiratory Journal 37(1):164-72

3.6.2 Analysen / Forest Plots

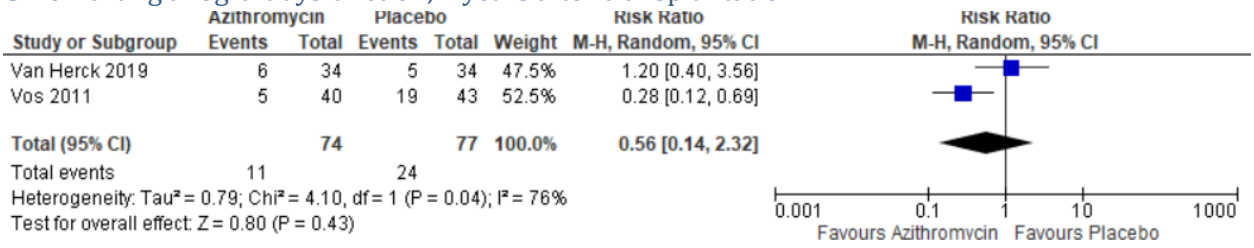
Mortality 2 years after transplantation



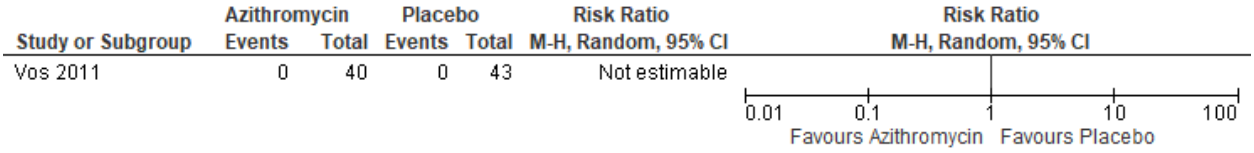
Retransplantation, 2 years after transplantation



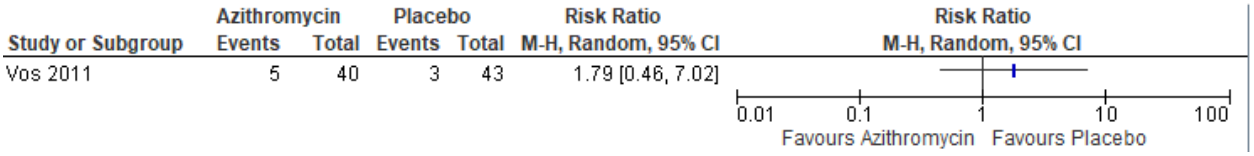
Chronic lung allograft dysfunction, 2 years after transplantation



Serious adverse events, 2 years after transplantation

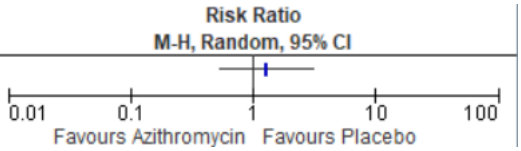


Treatment discontinuation, 2 years after transplantation



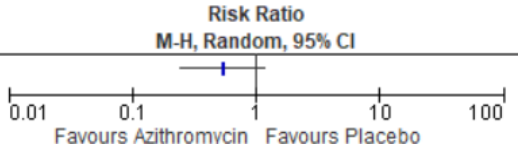
Respiratory infections, < 6 months after transplantation

Study or Subgroup	Azithromycin Events	Azithromycin Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Van Herck 2019	9	34	7	34	1.29 [0.54, 3.06]



Respiratory culture positive, < 6 months after transplantation

Study or Subgroup	Azithromycin Events	Azithromycin Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Van Herck 2019	7	34	13	34	0.54 [0.25, 1.18]



3.6.3 Referenzen der eingeschlossenen Studien

- Van Herck A, Frick AE, Schaevers V, Vranckx A, Verbeken EK, Vanaudenaerde BM, Sacreas A, Heigl T, Neyrinck AP, Van Raemdonck D, Dupont LJ, Yserbyt J, Verleden SE, Verleden GM, Vos R. Azithromycin and early allograft function after lung transplantation: A randomized, controlled trial. J Heart Lung Transplant. 2019 Mar;38(3):252-259. doi: 10.1016/j.healun.2018.12.006.
- Ruttens D, Verleden SE, Vandermeulen E, Bellon H, Vanaudenaerde BM, Somers J, Schoonis A, Schaevers V, Van Raemdonck DE, Neyrinck A, Dupont LJ, Yserbyt J, Verleden GM, Vos R. Prophylactic Azithromycin Therapy After Lung Transplantation: Post hoc Analysis of a Randomized Controlled Trial. Am J Transplant. 2016 Jan;16(1):254-61. doi: 10.1111/ajt.13417.
- Spence CD, Vanaudenaerde B, Einarsson GG, Mcdonough J, Lee AJ, Johnston E, Verleden GM, Elborn JS, Dupont LJ, Van Herck A, Gilpin DF, Vos R, Tunney MM, Verleden SE. Influence of azithromycin and allograft rejection on the post-lung transplant microbiota. J Heart Lung Transplant. 2020 Feb;39(2):176-183. doi: 10.1016/j.healun.2019.11.007.
- Vos R, Vanaudenaerde BM, Verleden SE, De Vleeschauwer SI, Willems-Widyastuti A, Van Raemdonck DE, Schoonis A, Nawrot TS, Dupont LJ, Verleden GM. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. Eur Respir J. 2011 Jan;37(1):164-72. doi: 10.1183/09031936.00068310.

3.6.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Van Herck 2019 NCT01915082 RCT, double-blind	**Sample size:** N = 72 **Enrolment period:** October 2013 to October 2015 Belgium **Inclusion criteria:** • Patients undergoing double LTx **Exclusion criteria:** • did not consent before LTx • included in another trial • underwent retransplantation or multi-organ transplant • <18 years old • azithromycin allergy **Characteristics** **Age (median, IQR):** • Azithromycin: 59 (56-62) • Placebo: 58 (47-63)	**Experimental:** Oral azithromycin in addition to standard of care for 31 days: • Zithromax, oral suspension 200 mg/5 ml) • N = 34 **Control:** Placebo in addition to standard of care for 31 days: • Ora-plus (97% purified water, <1% sodium phosphate monobasic, <1% sodium carboxymethylcellulose, <1% microcrystalline cellulose, <1% xanthan gum, <1% carrageenan) • N = 34	Mortality, 2 years after transplantation	Mortalität RR 0.67 (CI 95% 0.21 to 2.15) Azithromycin: 4/34 Placebo: 6/34	1. Random sequence generation: unclear (no information regarding the randomisation process) 2. Allocation concealment: unclear 3. Blinding of participants and personnel: low 4. Blinding of outcome assessment: low 5. Incomplete outcome data: low 6. Selective reporting: low 7. Other bias: low
			Retransplantation or death, 3 years after randomisation	Not reported	
			Retransplantation	Not reported	
			Chronic lung allograft dysfunction, 2 years after transplantation	RR 1.20 (CI 95% 0.40 to 3.56) Azithromycin: 6/34 Placebo: 5/34	
			Kidney function	Not reported	
			Treatment discontinuation	Not reported	

	Sex (% female):
	• Azithromycin: 48%
	• Placebo: 52%
	Ethnicity:
	Not reported
	
	Type of transplantation:
	• SSLTx
	  ○ Azithromycin: 100%
	  ○ Placebo: 100%
	• SLTx
	  ○ Azithromycin: 0%
	  ○ Placebo: 0%
	• HLTx
	  ○ Azithromycin: 0%
	  ○ Placebo: 0%
	Respiratory medical history:
	• Emphysem (COPD)
	  ○ Azithromycin: 68%
	  ○ Placebo: 65%
	• Pulmonary fibrosis
	  ○ Azithromycin: 24%
	  ○ Placebo: 15%
	• Cystic fibrosis
	  ○ Azithromycin: 3%
	  ○ Placebo: 9%
	• Pulmonary arterial hypertension
	  ○ Azithromycin: 0%
	  ○ Placebo: 6%
			Treatment discontinuation due to AEs	Not reported	

			Serious adverse events	Not reported	
			Adverse events – Cancer	Not reported	
			Respiratory infections, < 6 months after transplantation (no pathogen detection indicated)	RR 1.29 (CI 95% 0.54 to 3.06) Azithromycin: 9/34 Placebo: 7/34	
			Respiratory culture positive, < 6 months after transplantation)	RR 0.54 (CI 95% 0.25 to 1.18) Azithromycin: 7/34 Placebo: 13/34	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

	• Other
	  ○ Azithromycin: 6%
	  ○ Placebo: 6%
	Other medical history:
	Not reported				

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Vos 2011; Ruttens 2016; Spence 2020 NCT01009619; ISRCTN36220396 RCT, double-blind	**Sample size:** N = 83 **Enrolment period:** September 2005 to December 2007 Belgium **Inclusion criteria:** • Single-lung, bilateral lung or heart–lung transplant recipients • ≥ 18 yrs of age **Exclusion criteria:** • Intensive care unit stay of > 30 days or had died < 30 days post-transplantation • had an important bronchial stenosis	**Experimental:** Oral azithromycin in addition to conventional immunosuppression for 2 years: Zithromax, azithromycin dihydrate, 250 mg hard gelatine capsule formulation) • Initiated at one dose a day for five consecutive days, followed by one dose three times a week on Mondays, Wednesdays and Fridays • N = 40 **Control:** Placebo in addition to conventional immunosuppression for 2 years: • Lactose monohydricum compounded into 300 mg hard gelatine	Mortality, 2 years after transplantation	RR 0.81 (CI 95% 0.31 to 2.12) Azithromycin: 6/40 Placebo: 8/43	1. Random sequence generation: low 2. Allocation concealment: low 3. Blinding of participants and personnel: low 4. Blinding of outcome assessment: low 5. Incomplete outcome data: low 6. Selective reporting: low 7. Other bias: low
			Retransplantation or death, 2 years after transplantation	Not reported	
			Retransplantation, 2 years after transplantation	RR 0.54 (CI 95% 0.05 to 5.70) Azithromycin: 1/40 Placebo: 2/43	
			Chronic lung allograft dysfunction, 2 years after transplantation	RR 0.28 (CI 95% 0.12 to 0.69) Azithromycin: 5/40	

	• underwent retransplantation or multiorgan transplantation (lung plus a solid organ)
	• had undergone solid-organ or bone marrow transplantation in the past
	
	Characteristics
	Age (median, IQR):
	• Azithromycin: 56.1 (47.7 – 61.2)
	• Placebo: 55.1 (44.2 – 59.4)
	Sex (% female):
	• Azithromycin: 57.5%
	• Placebo: 53.5%
	Ethnicity:
	Not reported
	
	Type of transplantation:
	• SSLTx
	  ○ Azithromycin: 65%
	  ○ Placebo: 76.7%
	• SLTx
	  ○ Azithromycin: 30%
	  ○ Placebo: 23.3%
	• HLTx
	  ○ Azithromycin: 5%
	  ○ Placebo: 0%
	Respiratory medical history:
	• Emphysem (COPD)
		• Initiated at one dose a day for five consecutive days, followed by one dose three times a week on Mondays, Wednesdays and Fridays
		• N = 43
				Placebo: 19/43	

			Kidney function	Not reported	
			Treatment discontinuation	RR 1.79 (CI 95% 0.46 to 7.02) Azithromycin: 5/40 Placebo: 3/43	
			Treatment discontinuation due to AEs	Not reported	
			Serious adverse events	RR not estimable Azithromycin: 0/40 Placebo: 0/43	
			Adverse events – Cancer	Not reported	
			Infections	Not reported	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

	○ Azithromycin: 42.5% ○ Placebo: 55.8% • Pulmonary fibrosis ○ Azithromycin: 22.5% ○ Placebo: 23.3% • Cystic fibrosis ○ Azithromycin: 20% ○ Placebo: 13.9% • a1-Antitrypsin deficiency ○ Azithromycin: 2.5% ○ Placebo: 4.7% • Pulmonary arterial hypertension ○ Azithromycin: 5% ○ Placebo: 0% • Asthma ○ Azithromycin: 2.5% ○ Placebo: 2.3% • Brochiectasis ○ Azithromycin: 2.5% ○ Placebo: 0% • Lymphangioleiomyomatosis ○ Azithromycin: 2.5% ○ Placebo: 0% **Other medical history:** Not reported				

3.6.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.6.6 Literaturrecherche

Siehe 6.1.7

3.7 Schlüsselfrage 4a: Montelukast vs. Placebo (Empfehlung 4.2)

3.7.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants with chronic lung allograft dysfunction (CLAD) after lung transplantation

Intervention: Montelukast + SoC (azithromycin)

Vergleichsintervention: Placebo + SoC (azithromycin)

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo + SoC (azithromycin)	 Montelukast + SoC (azithromycin)	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality 2 years after randomisation	Relatives Risiko: 0.4 (CI 95% 0.09 - 1.75) Basierend auf Daten von 30 patienter und 1 Studien[1] Beobachtzungszeit 2 years after randomisation	**333** pro 1000	**133** pro 1000 Differenz: **200 weniger pro 1000** (CI 95% 303 weniger - 250 mehr)	**Niedrig** Due to very serious imprecision[2]	Montelukast may decrease mortality compared to placebo
Graft loss - Retransplantation or death 2 years after randomisation	Relatives Risiko: 0.4 (CI 95% 0.09 - 1.75) Basierend auf Daten von 30 patienter und 1 Studien[3] Beobachtzungszeit 2 years after randomisation	**333** pro 1000	**133** pro 1000 Differenz: **200 weniger pro 1000** (CI 95% 303 weniger - 250 mehr)	**Niedrig** Due to very serious imprecision[4]	Montelukast may decrease the number of participants with graft loss compared to placebo
Lung function evolution: improvement (> 110% compared to the time of BOS diagnosis) 1 year after randomisation	Relatives Risiko: 1.0 (CI 95% 0.07 - 14.55) Basierend auf Daten von 30 patienter und 1 Studien[5] Beobachtzungszeit 1 year after randomisation	**67** pro 1000	**67** pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 62 weniger - 908 mehr)	**Niedrig** Due to very serious imprecision[6]	There were too few who experienced lung function improvement (> 110%), to determine whether montelukast made a difference compared to placebo
Lung function evolution: stabilization (110%-90% compared to the time of BOS diagnosis) 1 year after randomisation	Relatives Risiko: 1.17 (CI 95% 0.51 - 2.66) Basierend auf Daten von 30 patienter und 1 Studien[7] Beobachtzungszeit 1 year after randomisation	**400** pro 1000	**468** pro 1000 Differenz: **68 mehr pro 1000** (CI 95% 196 weniger - 664 mehr)	**Niedrig** Due to very serious imprecision[8]	Montelukast may increase the number of participants with lung function stabilization (110% to 90%) compared to placebo
Kidney function 3 years after transplantation					No studies were found that looked at kidney function

Serious adverse events 1 year after randomisation	Relatives Risiko (CI 95% -) Basierend auf Daten von 30 patienter und 1 Studien[9] Beobachtzungszeit 1 year after randomisation	**0** pro 1000 **0** pro 1000 Differenz: **weniger pro 1000** (CI 95% 0 weniger - 0 weniger)	**Niedrig** Due to very serious imprecision[10]	There were too few who experienced serious adverse events, to determine whether montelukast made a difference compared to placebo
Adverse events - Cancer 3 years after transplantation				No studies were found that looked at adverse events - cancer
Treatment discontinuation 1 year after randomisation	Relatives Risiko: 0.33 (CI 95% 0.04 - 2.85) Basierend auf Daten von 30 patienter und 1 Studien[11] Beobachtzungszeit 1 year after randomisation	**200** pro 1000 **66** pro 1000 Differenz: **134 weniger pro 1000** (CI 95% 192 weniger - 370 mehr)	**Niedrig** Due to very serious imprecision[12]	There were too few who experienced treatment discontinuation, to determine whether montelukast made a difference compared to placebo
Symptomatic infection - one or more respiratory infections 1 year after randomisation	Relatives Risiko: 0.42 (CI 95% 0.06 - 2.77) Basierend auf Daten von 30 patienter und 1 Studien[13] Beobachtzungszeit 1 year after randomisation	**267** pro 1000 **112** pro 1000 Differenz: **155 weniger pro 1000** (CI 95% 251 weniger - 473 mehr)	**Niedrig** Due to very serious imprecision[14]	Montelukast may decrease the number of participants with one or more respiratory infections (pathogen detection indicated) compared to placebo
Loss of pulmonary function by at least 10% 1 year after randomisation	Relatives Risiko: 0.67 (CI 95% 0.23 - 1.89) Basierend auf Daten von 30 patienter und 1 Studien[15] Beobachtzungszeit 1 year after randomisation	**400** pro 1000 **268** pro 1000 Differenz: **132 weniger pro 1000** (CI 95% 308 weniger - 356 mehr)	**Niedrig** Due to very serious imprecision[16]	Montelukast may decrease the number of participants with loss of pulmonary function by at least 10% compared to placebo
Quality of life 3 years after transplantation				No studies were found that looked at quality of life

1. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
2. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study;
3. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
4. **Unzureichende Präzision: sehr schwerwiegend.** Low number of patients, Only data from one study, due to no events observed, effect not estimable;
5. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
6. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events;
7. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
8. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study;
9. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
10. **Unzureichende Präzision: sehr schwerwiegend.** Low number of patients, Only data from one study, due to no events observed, effect not estimable;
11. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
12. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events;
13. Systematic review . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
14. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study;
15. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [35].
16. **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study;

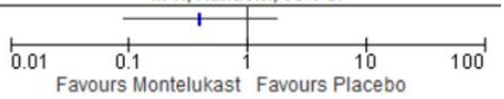
Referenzen

[35] Ruttens D., Verleden SE, Demeyer H., Van Raemdonck DE, Yserbyt J., Dupont LJ, Vanaudenaerde BM, Vos R., Verleden GM : Montelukast for bronchiolitis obliterans syndrome after lung transplantation: A randomized controlled trial. PLoS ONE 13(4):e0193564

3.7.2 Analysen / Forest Plots

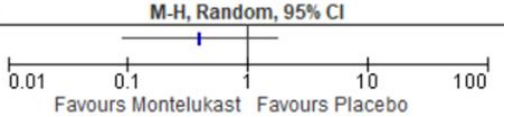
Mortality, 2 years after randomisation

Study or Subgroup	Montelukast Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Ruttens 2018	2	15	5	15	0.40 [0.09, 1.75]



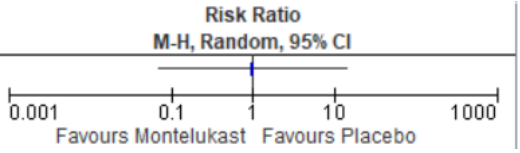
Graft loss – Retransplantation or death, 2 years after randomisation

Study or Subgroup	Montelukast Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Ruttens 2018	2	15	5	15	0.40 [0.09, 1.75]



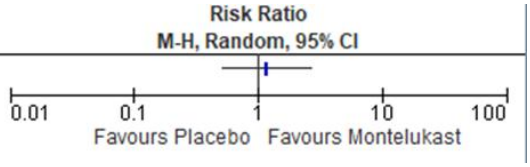
Lung function evolution: improvement, > 110% compared to the time of BOS diagnosis) (1 year after randomisation

Study or Subgroup	Montelukast Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Ruttens 2018	1	15	1	15	1.00 [0.07, 14.55]



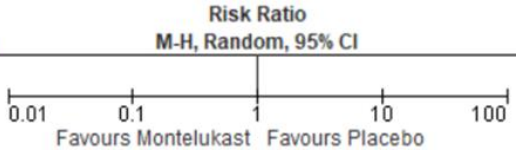
Lung function evolution: stabilization, 110%-90% compared to the time of BOS diagnosis) (1 year after randomisation

Study or Subgroup	Montelukast Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Ruttens 2018	7	15	6	15	1.17 [0.51, 2.66]



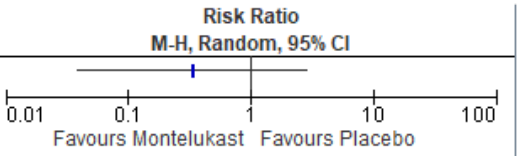
Serious adverse events, 1 year after randomisation

Study or Subgroup	Montelukast Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Ruttens 2018	0	15	0	15	Not estimable

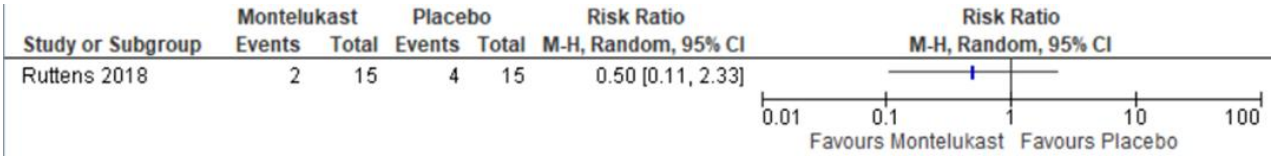


Treatment discontinuation, 1 year after randomisation

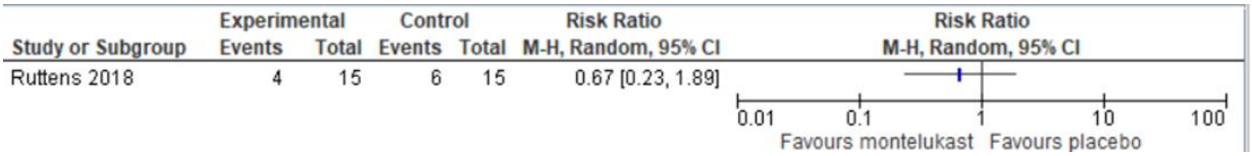
Study or Subgroup	Montelukast Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Ruttens 2018	1	15	3	15	0.33 [0.04, 2.85]



One or more respiratory infections, 1 year after randomisation



Loss of pulmonary function by at least 10%, 1 year after transplantation



3.7.3 Referenzen der eingeschlossenen Studien

- Ruttens D, Verleden SE, Demeyer H, Van Raemdonck DE, Yserbyt J, Dupont LJ, Vanaudenaerde BM, Vos R, Verleden GM. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: A randomized controlled trial. PLoS One. 2018 Apr 6;13(4):e0193564. doi: 10.1371/journal.pone.0193564.

3.7.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Ruttens 2018 NCT01211509 RCT, double-blind	**Sample size:** N = 30 **Enrolment period:** November 2010 to July 2014 Belgium **Inclusion criteria:** • Adult (18 years) lung transplant recipients • diagnosed with chronic rejection (BOS grade 1 and non-responsive to azithromycin (no increase in FEV1 to at least 80% compared to the 2 best post operative values) after at least 3 months of therapy, excluding azithromycin • responsive allograft dysfunction (ARAD) (increase in FEV1 to at least 80% compared to the 2 best post operative values) • ability to take oral medication	**Experimental:** Oral montelukast in 10 mg hard gelatine capsule formulation) Daily • 'Standard of care' treatment of BOS including azithromycin, 250 mg three times a week • N = 15 **Control:** Oral placebo • 10 mg lactose monohydricum Ph. Eur. • Daily • 'Standard of care' treatment of BOS including azithromycin, 250 mg three times a week • N = 15	Mortality, 2 years after randomisation	R 0.40 (CI 95% 0.09 to 1.75) Montelukast: 2/15 Placebo: 5/15	1. Random sequence generation: low 2. Allocation concealment: low 3. Blinding of participants and personnel: low 4. Blinding of outcome assessment: low 5. Incomplete outcome data: low 6. Selective reporting: low 7. Other bias: low
			Retransplantation or death, 2 years after transplantation	Not reported	
			Retransplantation, 2 years after randomisation	RR not estimable Montelukast: 0/15 Placebo: 0/15	
			Lung function evolution: improvement (> 110% compared to the time of BOS diagnosis), 1 year after randomisation	RR 1.00 (CI 95% 0.07 to 14.55) Montelukast: 1/15 Placebo: 1/15	
			Lung function evolution: stabilization (110%-90% compared to the time of BOS	RR 1.17 (CI 95% 0.51 to 2.66) Montelukast: 7/15	

	Exclusion criteria: • Retransplantation (lung) • previous transplantation (solid organ) • rapid decliner (decline in FEV1 of >150 ml/ month during 3 months before inclusion) • early onset of BOS (first 2 years after LTx) • multi-organ transplantation (lung + other solid organ) **Characteristics** **Age (median, SD):** • Montelukast: 61 (1.7) • Placebo: 60 (1.7) **Sex (% female):** • Montelukast: 60% • Placebo: 60% **Ethnicity:** Not reported **BOS stadium at inclusion:** • BOS 1 o Montelukast: 53% o Placebo: 73% • BOS 2 o Montelukast: 40% o Placebo: 20% • BOS 3 o Montelukast: 7%		diagnosis), 1 year after randomisation	Placebo: 6/15	
			Kidney function	Not reported	
			Treatment discontinuation, 1 year after randomisation	RR 0.33 (CI 95% 0.04 to 2.85) Montelukast: 1/15 Placebo: 3/15	
			Treatment discontinuation due to AEs	Not reported	
			Serious adverse events	RR not estimable Montelukast: 0/15 Placebo: 0/15	
			Adverse events – Cancer	Not reported	
			One or more respiratory infections (pathogen detection not indicated), 1 year after randomisation	RR 0.42 (CI 95% 0.06 to 2.77) Montelukast: 2/15 Placebo: 4/15	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	RR 0.67 (CI 95% 0.23 to 1.89) Montelukast: 4/15 Placebo: 6/15	
			Quality of life	Not reported	

	○ Placebo: 7% **Type of transplantation:** • SSLTx ○ Montelukast: 73% ○ Placebo: 73% • SLTx ○ Montelukast: 27% ○ Placebo: 20% • HLTx ○ Montelukast: 0% ○ Placebo: 0% **Respiratory medical history:** • Emphysema (COPD) ○ Montelukast: 73% ○ Placebo: 73% • Pulmonary fibrosis ○ Montelukast: 13% ○ Placebo: 13% • Cystic fibrosis ○ Montelukast: 7% ○ Placebo: 0% • a1-Antitrypsin deficiency ○ Montelukast: 0% ○ Placebo: 0% • Pulmonary arterial hypertension ○ Montelukast: 7% ○ Placebo: 13% • Asthma				

	○ Montelukast: 0% ○ Placebo: 0% • Brochiectasis ○ Montelukast: 0% ○ Placebo: 0% • Lymphangioleiomyomatosis ○ Montelukast: 0% ○ Placebo: 0% **Other medical history:** • BMI (kg/m²) ○ Montelukast: 25.5 (SD 1.4) ○ Placebo: 25.2 (SD 1.2)				

3.7.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.7.6 Literaturrecherche

Siehe 6.1.7

3.8 Schlüsselfrage 4b: Azithromycin vs. Placebo (Empfehlung 4.2)

3.8.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants with chronic lung allograft dysfunction (CLAD) after lung transplantation

Intervention: Azithromycin

Vergleichsintervention: Placebo

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** Placebo Azithromycin	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality 12 weeks after randomisation	Relatives Risiko (CI 95% -) Basierend auf Daten von 46 patienter und 1 Studien[1] Beobachtzungszeit 12 weeks after randomisation	pro 1000 pro 1000 Differenz: **weniger pro 1000**	**Sehr niedrig** Due to very serious imprecision, Due to serious indirectness[2]	There were too few who experienced mortality, to determine whether azithromycin made a difference compared to placebo
Graft loss - Retransplantation or death 12 weeks after randomisation	Relatives Risiko (CI 95% -) Basierend auf Daten von 46 patienter und 1 Studien[3] Beobachtzungszeit 12 weeks after randomisation	pro 1000 pro 1000 Differenz: **weniger pro 1000**	**Sehr niedrig** Due to very serious imprecision, Due to serious indirectness[4]	There were too few who experienced graft loss, to determine whether azithromycin made a difference compared to placebo
Lung function evolution: improvement (> 10% gain in FEV1 from baseline) 12 weeks after randomisation	Relatives Risiko: 19.0 (CI 95% 1.17 - 308.4) Basierend auf Daten von 46 patienter und 1 Studien[5] Beobachtzungszeit 12 weeks after randomisation	**0** **0** pro 1000 pro 1000 Differenz: **0 weniger pro 1000** (CI 95% 0 weniger - 0 weniger)	**Sehr niedrig** Due to very serious imprecision, Due to serious indirectness[6]	There were too few who experienced the lung function improvement (> 10% gain in FEV1 from baseline), to determine whether azithromycin made a difference compared to placebo
Serious adverse events 12 weeks after randomisation	Relatives Risiko: 0.75 (CI 95% 0.19 - 2.98) Basierend auf Daten von 46 patienter und 1 Studien[7] Beobachtzungszeit 12 weeks after randomisation	**174** **131** pro 1000 pro 1000 Differenz: **43 weniger pro 1000** (CI 95% 141 weniger - 345 mehr)	**Sehr niedrig** Due to serious indirectness, Due to very serious imprecision[8]	We are uncertain whether azithromycin increases or decreases the number of participants with serious adverse events compared to placebo
Kidney function 3 years after transplantation				No studies were found that looked at kidney function
Adverse events - Cancer				

3 years after transplantation				No studies were found that looked at adverse events - cancer
Treatment discontinuation 1 year after randomisation	Relatives Risiko: 1.17 (CI 95% 0.46 - 2.94) Basierend auf Daten von 43 patienter und 1 Studien[9] Beobachtzungszeit 1 year after randomisation	**261** pro 1000 **305** pro 1000 Differenz: **44 mehr pro 1000** (CI 95% 141 weniger - 506 mehr)	**Sehr niedrig** Due to very serious imprecision, Due to serious indirectness[10]	Azithromycin may increase the number of participants with treatment discontinuation compared to placebo
Symptomatic infection 3 years after transplantation				No studies were found that looked at symptomatic infection
Loss of pulmonary function by at least 10% 1 year after transplantation				No studies were found that looked at loss of pulmonary function by at least 10%
Quality of life 3 years after transplantation				No studies were found that looked at quality of life

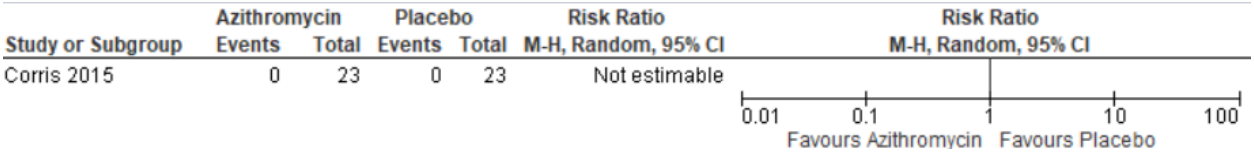
1. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [33].
2. **Indirektheit: schwerwiegend.** The outcome time frame in studies were insufficient; **Unzureichende Präzision: sehr schwerwiegend.** Low number of patients, Only data from one study, due to no events observed;
3. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [33].
4. **Indirektheit: schwerwiegend.** The outcome time frame in studies were insufficient; **Unzureichende Präzision: sehr schwerwiegend.** Low number of patients, Only data from one study, due to no events observed;
5. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [33].
6. **Indirektheit: schwerwiegend.** The outcome time frame in studies were insufficient.; **Unzureichende Präzision: sehr schwerwiegend.** Very wide confidence intervals, Low number of patients, Only data from one study, due to few events;
7. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [33].
8. **Indirektheit: schwerwiegend.** The outcome time frame in studies were insufficient; **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study;
9. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [33].
10. **Indirektheit: schwerwiegend.** The outcome time frame in studies were insufficient; **Unzureichende Präzision: sehr schwerwiegend.** Wide confidence intervals, Low number of patients, Only data from one study;

Referenzen

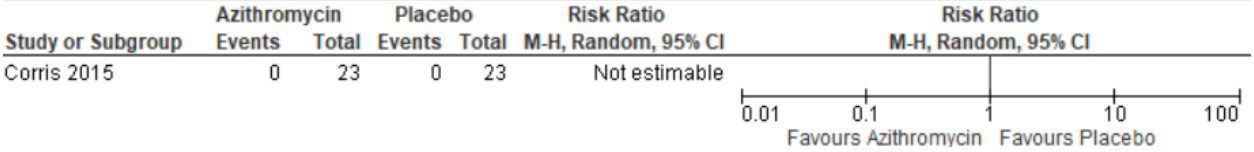
[33] Corris PA, Ryan VA, Small T., Lordan J., Fisher AJ, Meachery G., Johnson G., Ward C. : A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. Thorax 70(5):442-50

3.8.2 Analysen / Forest Plots

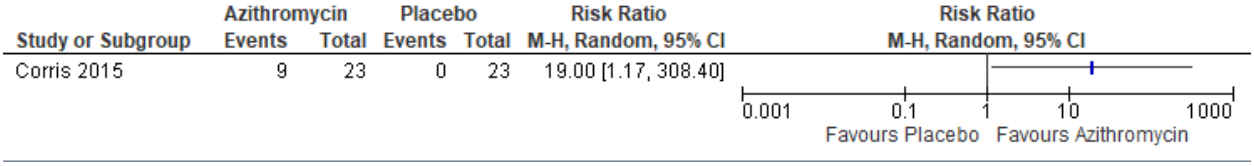
Mortality, 12 weeks after randomisation



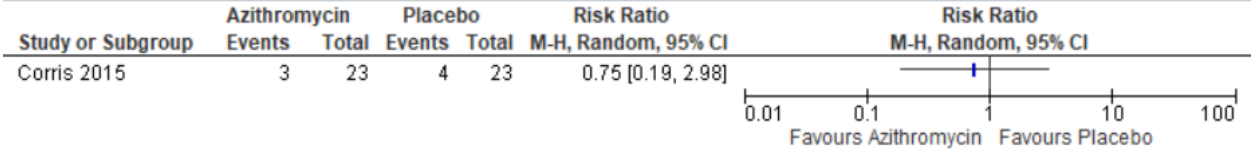
Graft loss – Retransplantation or death, 12 weeks after randomisation



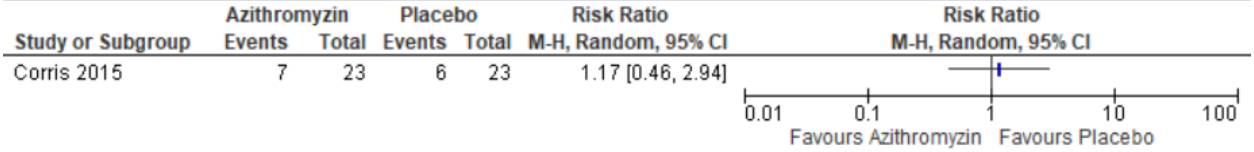
Lung function evolution: improvement (> 10% gain in FEV1 from baseline), 12 weeks after randomisation



Serious adverse events, 12 weeks after randomisation



Treatment discontinuation, 1 year after randomisation



3.8.3 Referenzen der eingeschlossenen Studien

- Corris PA, Ryan VA, Small T, Lordan J, Fisher AJ, Meachery G, Johnson G, Ward C. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. Thorax. 2015 May;70(5):442-50. doi: 10.1136/thoraxjnl-2014-205998.
- Gan CT, Ward C, Meachery G, Lordan JL, Fisher AJ, Corris PA. Long-term effect of azithromycin in bronchiolitis obliterans syndrome. BMJ Open Respir Res. 2019 Oct 15;6(1):e000465. doi: 10.1136/bmjresp-2019-000465.

3.8.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Corris 2015; Gan 2019 EU-CTR-2006-000485-36/GB RCT, double-blind	**Sample size:** N = 48 **Enrolment period:** November 2006 to December 2010 UK **Inclusion criteria:** • Lung transplant recipient • Male or Female • Age 16 years or over • Airflow limitation – FEV1 < 80% maximum recorded post transplant **Exclusion criteria:** • Airflow limitation caused by other clinical problems (e.g clinical infection) • Known hypersensitivity to Azithromycin or any of the macrolide antibiotics • Participation in another drug related trial within 90 days • Severe renal or hepatic impairment	**Experimental:** Oral azithromycin in addition to standard immunosuppressant comprising cyclosporine, prednisolone and azathioprine: • 250 mg on alternate days over 12 weeks • N = 25 **Control:** Oral placebo in addition to immunosuppressant comprising cyclosporine, prednisolone and azathioprine: • on alternate days over 12 weeks • N = 23	Mortality, 12 weeks after randomisation	RR not estimable Azithromycin: 0/23 Placebo: 0/23	1. Random sequence generation: low 2. Allocation concealment: unclear 3. Blinding of participants and personnel: low 4. Blinding of outcome assessment: low 5. Incomplete outcome data: low 6. Selective reporting: unclear (no protocol available) 7. Other bias: low
			Retransplantation or death, 12 weeks after randomisation	RR not estimable Azithromycin: 0/23 Placebo: 0/23	
			Retransplantation, 12 weeks after randomisation	RR not estimable Azithromycin: 0/23 Placebo: 0/23	
			Lung function evolution: improvement (> 10% gain in FEV1 from baseline, 12 weeks after randomisation	RR 19.00 (CI 95% 1.17 to 308.40) Montelukast: 1/15 Placebo: 1/15	
			Kidney function	Not reported	
			Treatment discontinuation, 1 year after randomisation	RR 1.17 (CI 95% 0.46 to 2.94)	

	• Use of concomitant medication that would interact with azithromycin
	
	Characteristics
	Age (median, IQR):
	• Azithromycin: 51.0 (35-56)
	• Placebo: 51.0 (44-59)
	Sex (% female):
	• Azithromycin: 52%
	• Placebo: 35%
	
	Ethnicity:
	Not reported
	
	BOS stadium at inclusion:
	• BOS 1
	  ○ Azithromycin: 57%
	  ○ Placebo: 74%
	• BOS 2
	  ○ Azithromycin: 35%
	  ○ Placebo: 17%
	• BOS 3
	  ○ Azithromycin: 9%
	  ○ Placebo: 9%
	
	Type of transplantation:
	• SSLTx
	  ○ Azithromycin: 61%
	  ○ Placebo: 57%
	• SLTx
	  ○ Azithromycin: 39%
	  ○ Placebo: 39%
	• HLTx
				Azithromycin: 7/23
				Placebo: 6/23	

			Treatment discontinuation due to AEs	Not reported	
			Serious adverse events, 12 weeks after randomisation	RR 0.75 (CI 95% 0.19 to 2.98) Azithromycin: 3/23 Placebo: 4/23	
			Adverse events – Cancer	Not reported	
			Symptomatic infections	Not reported	
			Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

	○ Azithromycin: 0% ○ Placebo: 4% **Respiratory medical history:** • Emphysema (COPD) ○ Azithromycin: 48% ○ Placebo: 35% • Pulmonary fibrosis ○ Azithromycin: 9% ○ Placebo: 17% • Cystic fibrosis ○ Azithromycin: 30% ○ Placebo: 26% • Other ○ Azithromycin: 13% ○ Placebo: 22% **Other medical history:** Not reported				

3.8.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.8.6 Literaturrecherche

Siehe 6.1.7

3.9 Schlüsselfrage 5: 12 Monate Valganciclovir vs. 3 Monate Valganciclovir (Empfehlung 3.2)

3.9.1 Evidenzprofile / Summary of Findings (MAGICapp)

Population: Adult participants after lung transplantation

Intervention: 12 months valganciclovir

Vergleichsintervention: 3 months valganciclovir

Endpunkt Zeitrahmen	**Ergebnisse und Messwerte**	**Absolute Effektschätzer** 3 months valganciclovir	 12 months valganciclovir	**Vertrauenswürdigkeit der Evidenz** (Vertrauenswürdigkeit der Evidenz)	**Zusammenfassung**
Mortality 13 months after transplantation	Relatives Risiko: 1.26 (CI 95% 0.29 - 5.41) Basierend auf Daten von 136 patienter und 1 Studien[1] Beobachtzungszeit 13 months after transplantation	**45** pro 1000	**57** pro 1000 Differenz: **12 mehr pro 1000** (CI 95% 32 weniger - 198 mehr)	**Niedrig** Due to very serious imprecision[2]	12 months valganciclovir may have little or no difference on mortality compared to 3 months valganciclovir
Graft loss - Retransplantation or death[3] 3 years after transplantation					No studies were found that looked at graft loss - retransplantation or death
Chronic lung allograft dysfunction 3 years after transplantation					No studies were found that looked at chronic lung allograft dysfunction
Kidney function - more than one laboratory abnormality of creatinine 13 months after transplantation	Relatives Risiko: 0.82 (CI 95% 0.32 - 2.15) Basierend auf Daten von 136 patienter und 1 Studien[4] Beobachtzungszeit 13 months after transplantation	**121** pro 1000	**99** pro 1000 Differenz: **22 weniger pro 1000** (CI 95% 82 weniger - 139 mehr)	**Niedrig** Due to very serious imprecision[5]	12 months valganciclovir may decrease the number of participants with more than one laboratory abnormality of creatinine slightly compared to 3 months valganciclovir
Serious adverse events 13 months after transplantation	Relatives Risiko: 1.02 (CI 95% 0.75 - 1.4) Basierend auf Daten von 136 patienter und 1 Studien[6]	**530** pro 1000	**541** pro 1000 Differenz: **11 mehr pro 1000** (CI 95% 132 weniger - 212 mehr)	**Moderat** Due to serious imprecision[7]	12 months valganciclovir probably has little or no difference on serious adverse events compared to 3 months valganciclovir

	Beobachtzungszeit 13 months after transplantation			
Adverse events - Cancer 3 years after transplantation				No studies were found that looked at adverse events - cancer
Treatment discontinuation 13 months after transplantation	Relatives Risiko: 1.08 (CI 95% 0.67 - 1.74) Basierend auf Daten von 136 patienter und 1 Studien[8] Beobachtzungszeit 13 months after transplantation	**318** pro 1000 **343** pro 1000 Differenz: **25 mehr pro 1000** (CI 95% 105 weniger - 235 mehr)	**Moderat** Due to serious imprecision[9]	12 months valganciclovir probably increases the number of participants with treatment discontinuation slightly compared to 3 months valganciclovir
Treatment discontinuation due to adverse events 13 months after transplantation	Relatives Risiko: 1.73 (CI 95% 0.68 - 4.41) Basierend auf Daten von 136 patienter und 1 Studien[10] Beobachtzungszeit 13 months after transplantation	**91** pro 1000 **157** pro 1000 Differenz: **66 mehr pro 1000** (CI 95% 29 weniger - 310 mehr)	**Niedrig** Due to very serious imprecision[11]	12 months valganciclovir may increase the number of participants with treatment discontinuation due to adverse events compared to 3 months valganciclovir
Infection - Cytomegalovirus syndrome or disease 13 months after transplantation	Relatives Risiko: 0.13 (CI 95% 0.04 - 0.43) Basierend auf Daten von 136 patienter und 1 Studien[12] Beobachtzungszeit 13 months after transplantation	**318** pro 1000 **41** pro 1000 Differenz: **277 weniger pro 1000** (CI 95% 305 weniger - 181 weniger)	**Moderat** Due to serious imprecision[13]	12 months valganciclovir probably decreases the number of participants with cytomegalovirus syndrome or disease (pathogen detection indicated) compared to 3 months valganciclovir
Infection - Non-cytomegalovirus infection 13 months after transplantation	Relatives Risiko: 1.05 (CI 95% 0.77 - 1.43) Basierend auf Daten von 136 patienter und 1 Studien[14] Beobachtzungszeit 13 months after transplantation	**530** pro 1000 **557** pro 1000 Differenz: **27 mehr pro 1000** (CI 95% 122 weniger - 228 mehr)	**Moderat** Due to serious imprecision[15]	12 months valganciclovir probably increases the number of participants with non-cytomegalovirus infection slightly compared to 3 months valganciclovir
Symptomatic infection - Cytomegalovirus invasive disease (pathogen detection indicated) 13 months after transplantation	Relatives Risiko: 0.07 (CI 95% 0.01 - 0.5) Basierend auf Daten von 136 patienter und 1 Studien[16] Beobachtzungszeit 13 months after transplantation	**212** pro 1000 **15** pro 1000 Differenz: **197 weniger pro 1000** (CI 95% 210 weniger - 106 weniger)	**Moderat** Due to serious imprecision[17]	12 months valganciclovir probably decreases symptomatic infection - cytomegalovirus invasive disease (pathogen detection indicated) compared to 3 months valganciclovir
Symptomatic infection -	Relatives Risiko: 0.22 (CI 95% 0.06 - 0.73)	**197** pro 1000 **43** pro 1000	**Moderat**	12 months valganciclovir probably decreases the

Cytomegalovirus syndrome 13 months after transplantation	Basierend auf Daten von 136 patienter und 1 Studien[18] Beobachtzungszeit 13 months after transplantation	Differenz: **154 weniger pro 1000** (CI 95% 185 weniger - 53 weniger)	Due to serious imprecision[19]	number of participants with cytomegalovirus syndrome (pathogen detection indicated) compared to 3 months valganciclovir
Loss of pulmonary function by at least 10% 1 year after randomisation				No studies were found that looked at loss of pulmonary function by at least 10%
Quality of life 3 years after transplantation				No studies were found that looked at quality of life

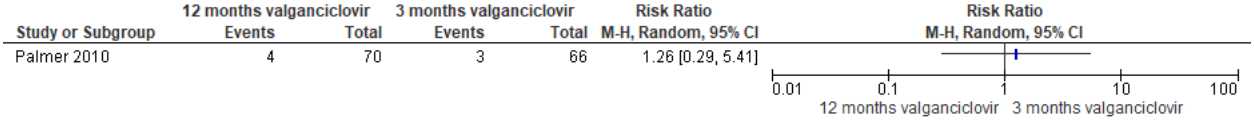
1. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
2. **Unzureichende Präzision: sehr schwerwiegend.** Very wide confidence intervals, Only data from one study, due to few events;
3. undefined
4. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
5. **Unzureichende Präzision: sehr schwerwiegend.** very wide confidence intervals, Only data from one study;
6. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
7. **Unzureichende Präzision: schwerwiegend.** Only data from one study, Wide confidence intervals;
8. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
9. **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
10. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
11. **Unzureichende Präzision: sehr schwerwiegend.** Very wide confidence intervals, Only data from one study;
12. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
13. **Unzureichende Präzision: schwerwiegend.** Only data from one study;
14. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
15. **Unzureichende Präzision: schwerwiegend.** Wide confidence intervals, Only data from one study;
16. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
17. **Unzureichende Präzision: schwerwiegend.** Only data from one study;
18. Primary study . **Baseline/Vergleichsintervention** Kontrollarm aus der Referenz für Interventionsarm . Referenzen [28].
19. **Unzureichende Präzision: schwerwiegend.** Only data from one study;

Referenzen

[28] Palmer SM, Limaye AP, Banks M., Gallup D., Chapman J., Lawrence EC, Dunitz J., Milstone A., Reynolds J., Yung GL, Chan KM, Aris R., Garrity E., Valentine V., McCall J., Chow SC, Davis RD, Avery R. : Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. Annals of Internal Medicine 152(12):761-9

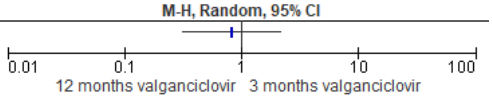
3.9.2 Analysen / Forest Plots

Mortality, 13 months after transplantation



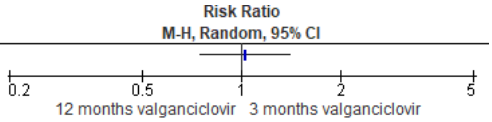
Kidney function - more than one laboratory abnormality of creatinine, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	7	70	8	66	0.82 [0.32, 2.15]



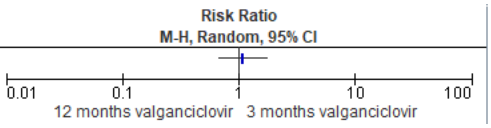
Serious adverse events, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	38	70	35	66	1.02 [0.75, 1.40]



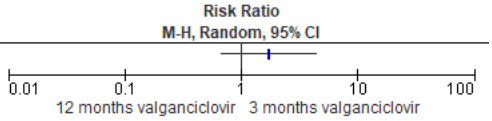
Treatment discontinuation, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	24	70	21	66	1.08 [0.67, 1.74]



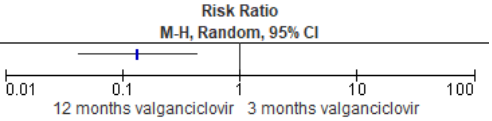
Treatment discontinuation due to AEs, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	11	70	6	66	1.73 [0.68, 4.41]



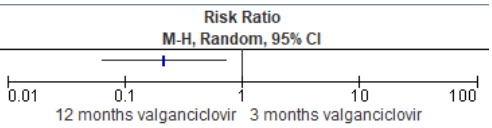
Cytomegalovirus syndrome or disease, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	3	70	21	66	0.13 [0.04, 0.43]



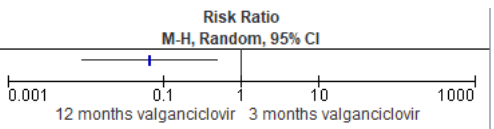
Cytomegalovirus syndrome, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	3	70	13	66	0.22 [0.06, 0.73]



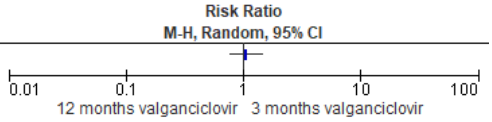
Cytomegalovirus invasive disease, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	1	70	14	66	0.07 [0.01, 0.50]



Non-cytomegalovirus infection, 13 months after transplantation

Study or Subgroup	12 months valganciclovir Events	Total	3 months valganciclovir Events	Total	Risk Ratio M-H, Random, 95% CI
Palmer 2010	39	70	35	66	1.05 [0.77, 1.43]



3.9.3 Referenzen der eingeschlossenen Studien

- Finlen Copeland CA, Davis WA, Snyder LD, Banks M, Avery R, Davis RD, Palmer SM. Long-term efficacy and safety of 12 months of valganciclovir prophylaxis compared with 3 months after lung transplantation: a single-center, long-term follow-up analysis from a randomized, controlled

cytomegalovirus prevention trial. J Heart Lung Transplant. 2011 Sep;30(9):990-6. doi: 10.1016/j.healun.2011.02.017.

- Palmer SM, Limaye AP, Banks M, Gallup D, Chapman J, Lawrence EC, Dunitz J, Milstone A, Reynolds J, Yung GL, Chan KM, Aris R, Garrity E, Valentine V, McCall J, Chow SC, Davis RD, Avery R. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. Ann Intern Med. 2010 Jun 15;152(12):761-9. doi: 10.7326/0003-4819-152-12-201006150-00003.

3.9.4 Charakteristika der eingeschlossenen Studien

Reference, study design	Population	Interventions	Outcomes	Results per outcomes	Risk of Bias (RoB 1 domains)
Palmer 2010; Finlen Copeland 2011 NCT00227370 RCT, double-blind	**Sample size:** N = 136 **Enrolment period:** July 2003 to January 2007 USA **Inclusion criteria:** Open label phase: • Lung transplant recipient • Age 18 years • At risk (donor or recipient with positive serologic status) for CMV infection • Prophylaxis with intravenous ganciclovir 2 wk immediately after transplant • Adequate hematologic, liver, and renal function • Able to tolerate oral medications • Negative baseline serum PCR and bronchoscopy results for CMV • Provide informed consent Randomized phase:	**Experimental:** Oral valganciclovir: • 900 mg (adjusted for renal insufficiency) • Daily for 9 months • Before randomisation open-label phase of ganciclovir starting within 24h after surgery, followed by open-label oral valganciclovir for 3 months • All patients received triple immunosuppression (induction and selection of specific agents followed centre practice) • N = 70 **Control:** Placebo • Before randomisation open-label phase of ganciclovir starting within 24h after surgery, followed by open-label oral valganciclovir for 3 months • All patients received triple immunosuppression (induction and selection	Mortality, 13 months after transplantation	HR 1.23 (CI 95% 0.27 to 5.5)	1. Random sequence generation: low 2. Allocation concealment: low 3. Blinding of participants and personnel: low 4. Blinding of outcome assessment: low 5. Incomplete outcome data: low 6. Selective reporting: unclear (no protocol available) 7. Other bias: low
			Retransplantation or death, 3 years after randomisation	Not reported	
			Retransplantation	Not reported	
			Chronic lung allograft dysfunction, 2 years after randomisation	Not reported	
			Kidney function - more than one laboratory abnormality of creatinine, 13 months after transplantation	RR 0.82 (CI 95% 0.32 to 2.15) Valganciclovir: 7/70 Placebo: 8/66	
			Treatment discontinuation, 13	RR 1.08 (CI 95% 0.67 to 1.74)	

	• Completion of open-label phase of study • Negative serial posttransplant serum PCR measurements for CMV • Negative bronchoscopy for CMV at day 75 measurement • Continuing to meet first-phase enrollment criteria at day 75 **Exclusion criteria:** Open-label phase: • Undergoing retransplantation • On mechanical ventilation at study entry • Previous or current intravenous or oral ganciclovir outside of the study protocol • Invasive fungal infection • Participating in another investigational study • Using disallowed anti-CMV therapy or other prohibited medications • Severe diarrhea or malabsorption, liver failure, renal failure, or pregnancy • History of severe reaction to ganciclovir Randomized phase:	of specific agents followed centre practice) • N = 66	months after transplantation	Valganciclovir: 24/70 Placebo: 21/66	
			Treatment discontinuation due to AEs, 13 months after transplantation	RR 1.73 (CI 95% 0.68 to 4.41) Valganciclovir: 11/70 Placebo: 6/66	
			Serious adverse events, 13 months after transplantation	RR 1.02 (CI 95% 0.75 to 1.40) Valganciclovir: 38/70 Placebo: 35/66	
			Adverse events – Cancer	Not reported	
			CMV syndrome or disease, 13 months after transplantation	CMV syndrome or disease RR 0.13 (CI 95% 0.04 to 0.43) Valganciclovir: 3/70 Placebo: 21/66	
			CMV invasive disease, 13 months after transplantation	RR 0.07 (CI 95% 0.01 to 0.50) Valganciclovir: 1/70 Placebo: 14/66	
			CMV syndrome, 13 months after transplantation	RR 0.22 (CI 95% 0.06 to 0.73) Valganciclovir: 3/70 Placebo: 13/66	

	• Experienced serious adverse event during open-label phase • Withdrew consent to be randomized **Characteristics** **Age (median, IQR):** • Valganciclovir: 56 (45 - 62) • Placebo: 55 (42 - 61) **Sex (% female):** • Valganciclovir: 59% • Placebo: 42% **Ethnicity:** • White o Valganciclovir: 90% o Placebo: 91% **Type of transplantation:** • SSLTx o Valganciclovir: 64% o Placebo: 70% • SLTx o Valganciclovir: 36% o Placebo: 30% • HLTx o Valganciclovir: 0% o Placebo: 0% **Respiratory medical history:** • Emphysem (COPD) o Valganciclovir: 47% o Placebo: 53%		Loss of pulmonary function by at least 10% (1 year after transplantation)	Not reported	
			Quality of life	Not reported	

	• Pulmonary fibrosis
	  ○ Valganciclovir: 23%
	  ○ Placebo: 24%
	• Cystic fibrosis
	  ○ Valganciclovir: 17%
	  ○ Placebo: 17%
	• Other
	  ○ Valganciclovir: 12%
	  ○ Placebo: 6%
	Other medical history:
	• Prior smoking
	  ○ Valganciclovir: 70%
	  ○ Placebo: 68%
	• Daily oxygen use
	  ○ Valganciclovir: 75%
	  ○ Placebo: 82%
	• History of ventilator use
	  ○ Valganciclovir: 24%
	  ○ Placebo: 20%				

3.9.5 Studienselektion: Flow Chart

Siehe 6.1.6

3.9.6 Literaturrecherche

Siehe 6.1.

Versionsnummer: 1.0

Erstveröffentlichung: 07/2025

Nächste Überprüfung geplant: 07/2030