

# Antipsychotics in the treatment of delirium in critically ill patients: a systematic review and meta-analysis of randomized-controlled trials



## INTRODUCTION

- Delirium occurs in ~50% of patients admitted to ICU<sup>1</sup>
- Negatively impacts short & long-term outcomes – prolonged hospital stay, cognitive impairment, & cause of distress<sup>2,3</sup>
- Antipsychotic medications have been used to manage symptoms, however, guidelines recommend against their use due to lack of demonstrated benefit<sup>3</sup>
- Most recent systematic reviews do not capture latest trials & looked at both prevention & treatment<sup>4-6</sup>

## OBJECTIVES

- Up to date systematic review & meta-analysis of randomized trials
- Aimed to determine whether administration of antipsychotics to critically ill adults with delirium impacts patient important outcomes

## METHOD

- Study Selection**
- Parallel-group RCTs
- Population**
- Critically ill adults with positive screen for delirium
- Intervention**
- Antipsychotic medications at any dose, frequency, initiation, time, route or duration of treatment
- Control**
- Usual care or placebo
- Outcomes**
- Delirium free days
  - Mortality
  - ICU LOS
  - Duration of IMV
  - Cognitive function/disability score
  - Disposition destination
  - Use of rescue medications
  - Adverse events
- MEDLINE, EMBASE, Cochrane, clinicaltrials.gov, WHO ICTRP from inception to November 17, 2023
  - Title/abstract, full text, data abstraction & ROB done independently in duplicate
  - Data analysed in RevMan
  - ROB using ROB2
  - PROSPERO: CRD42023397132

## AUTHORS

- K. CARAYANNOPOULOS<sup>1,2</sup>,**  
**F. ALSHAMSI<sup>3</sup>, D. CHAUDHURI<sup>1,2</sup>,**  
**L. SPATAFORA<sup>1</sup>, J. PITICARU<sup>4</sup>,**  
**K. CAMPBELL<sup>5</sup>, W. ALHAZZANI<sup>1,2</sup>,**  
**K. LEWIS<sup>1,2</sup>**
- 1 Division of Critical Care, McMaster University, Hamilton
- 2 Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton
- 3 Department of Critical Care, St. Joseph's Health Hospital, Syracuse
- 4 Department of Internal Medicine, United Arab Emirates University, Al Ain
- 5 St. Joseph's Healthcare Hamilton, Hamilton

## CONTACT INFORMATION

Kallirroi (Laiya) Carayannopoulos  
 Laiya.Carayannopoulos@medportal.ca

## RESULTS

### RCTs identified

- 5 studies included with n=1750 patients<sup>7-11</sup>
- Medications: 4 Haloperidol, 2 Quetiapine, 1 Ziprasidone
- Mean age 65.8 ±13.0years, 38% female, mean APACHE II 28.07 ±7.90
- All low risk of bias

### Antipsychotics and Outcomes

- No difference in delirium and coma-free days (Figure 1)
- No difference in mortality (Figure 2)
- No difference in duration of mechanical ventilation (Figure 3)
- No difference in adverse events (Figure 4)

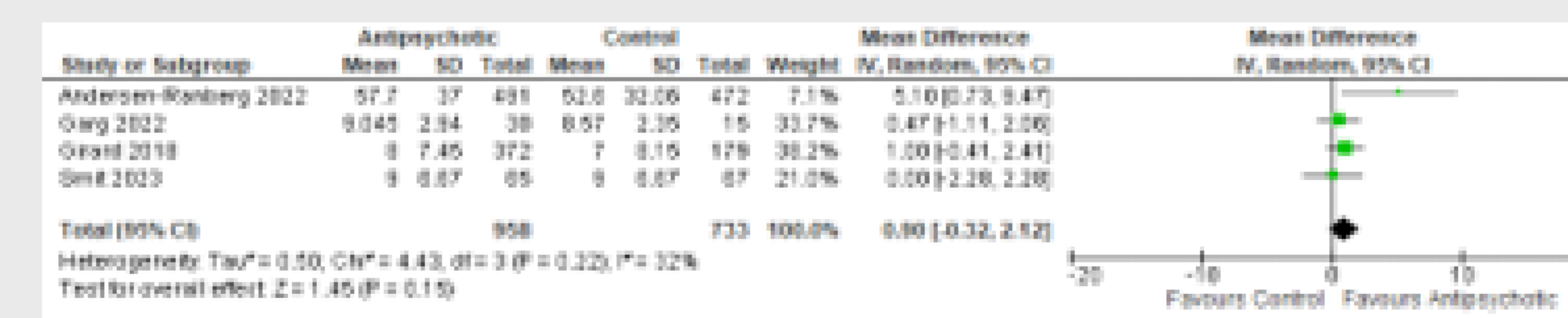


Figure 1. Forest plot showing delirium & coma-free days

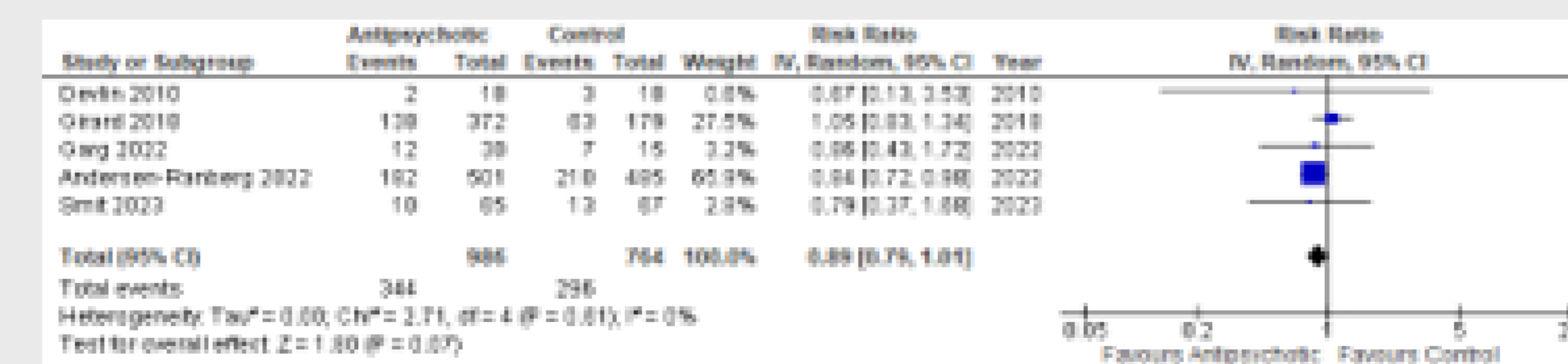


Figure 2. Forest plot showing mortality at longest follow-up

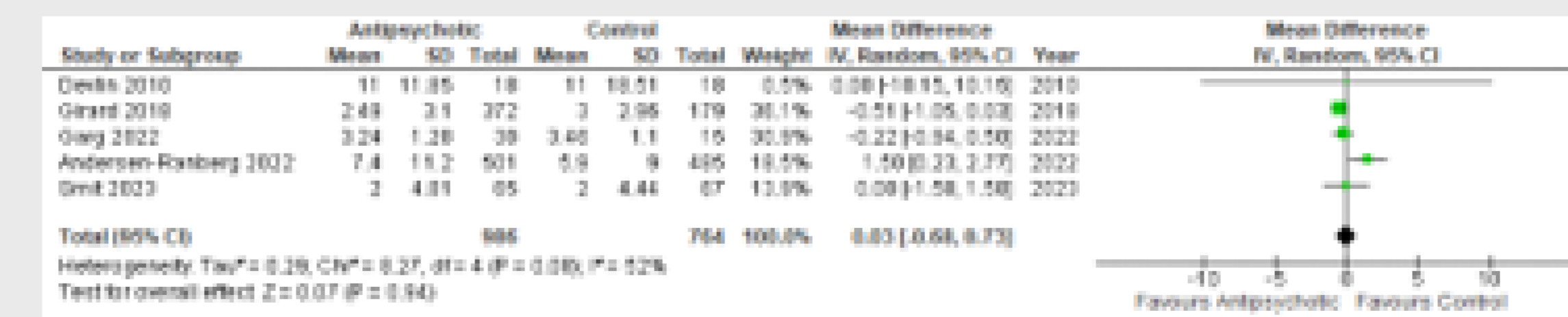


Figure 3. Forest plot showing duration of mechanical ventilation

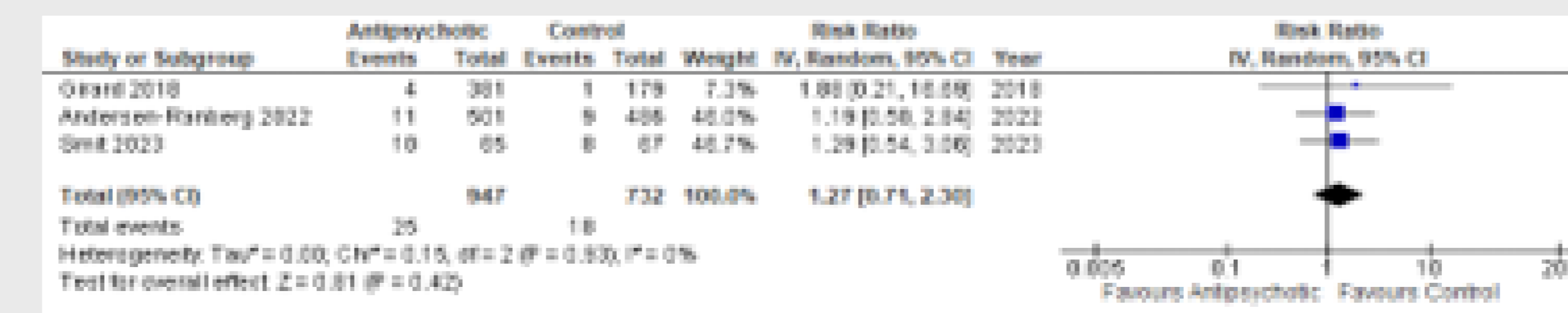


Figure 4. Forest plot showing risk of adverse events

## CONCLUSION

- Moderate certainty evidence showed that antipsychotics make no difference in delirium or coma-free days in critically ill adults with delirium
- Antipsychotics should not be administered routinely as treatment
- High certainty evidence of no difference in adverse events
- Further studies examining their use in hyper- or hypoactive delirium would be valuable

## ACKNOWLEDGEMENTS

We thank Karin Deames, MLIS (St. Joseph's Healthcare Hamilton, ON) for peer review of the Ovid search strategy.

## REFERENCES

1. Sessler DC, Wang H, Schneider EB, et al. Outcomes of delirium in critically ill patients: systematic review and meta-analysis. *BMJ*. 2015;350:g2016. doi:10.1136/bmj.g2016
2. Fink SH, Bell A, Van Leeuwen C, et al. Long-term Outcomes in ICU Patients with Delirium: A Population-based Cohort Study. *Am J Respir Crit Care Med*. 2016;194(12):1420. doi:10.1164/rccm.2016.04.0820
3. Davis JL, Sheikh V, Colwell C, et al. Clinical Practice Guidelines for the Prevention and Management of Delirium, Agitation, and Sleep Disturbance in Adult Patients in the ICU. *Crit Care Med*. 2019;47(5):e12. doi:10.1097/CCM.0000000000003208
4. Liu KB, Liu B, Chen H, et al. Delirium: Challenges for the Treatment of ICU Delirium: a systematic review and meta-analysis. *Thromb Haemostasis*. 2022;102(4):622-631. doi:10.1111/tha.15201
5. Nelson R, Naubel K, Chou S, et al. Antipsychotics for Treating Delirium in Hospitalized Adults. *Ann Intern Med*. 2016;164(11):745-752. doi:10.7326/M15-1883
6. Naubel K, Tang J, Nelson R, Naug R, Naug R. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc*. 2016;64(7):750-754. doi:10.1111/gps.12872
7. Andersen-Rasmberg MC, Phalen LM, Hansen A, et al. Haloperidol for the Treatment of Delirium in ICU Patients. *N Engl J Med*. 2022;386(25):2425-2435. doi:10.1056/NEJMoa211190
8. Garg R, Singh VK, Singh D. Comparison of Haloperidol and Quetiapine for Treatment of Delirium in Critical Care: A Protocol for Randomized Double-blind Placebo-controlled Trial. *Crit Care Res Pract*. 2022. doi:10.1016/j.ccrp.2022.100141
9. Bell A, Bell A, Bell A, et al. Effects of Haloperidol on the Duration of Delirium in Adult Intensive Care: A Randomized Clinical Trial. *Crit Care*. 2023;27(1):e1. doi:10.1186/s13054-022-04882-3
10. Graw TC, Laine MC, Cowen SW, et al. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Care. *N Engl J Med*. 2018;378(25):2500-2510. doi:10.1056/NEJMoa1801817
11. Davis JL, Sheikh V, Tang J, et al. Efficacy and safety of antipsychotics in adults with delirium: A prospective, randomised, double-blind, placebo-controlled pilot study. *Crit Care Med*. 2016;34(4):e47. doi:10.1097/CCM.0000000000001832

# INTRODUCTION

---

- Delirium occurs in ~50% of patients admitted to ICU<sup>1</sup>
- Negatively impacts short & long-term outcomes – prolonged hospital stay, cognitive impairment, & cause of distress<sup>2,3</sup>
- Antipsychotic medications have been used to manage symptoms, however, guidelines recommend against their use due to lack of demonstrated benefit<sup>3</sup>
- Most recent systematic reviews do not capture latest trials & looked at both prevention & treatment<sup>4-6</sup>

# OBJECTIVES

---

- Up to date systematic review & meta-analysis of randomized trials
- Aimed to determine whether administration of antipsychotics to critically ill adults with delirium impacts patient important outcomes

# METHOD

---

## Study Selection

- Parallel-group RCTs

## Population

- Critically ill adults with positive screen for delirium

## Intervention

- Antipsychotic medications at any dose, frequency, initiation, time, route or duration of treatment

## Control

- Usual care or placebo

## Outcomes

- Delirium free days
- Mortality
- ICU LOS
- Duration of IMV
- Cognitive function/disability score
- Disposition destination
- Use of rescue medications
- Adverse events

- MEDLINE, EMBASE, Cochrane, clinicaltrials.gov, WHO ICTRP from inception to November 17, 2023
- Title/abstract, full text, data abstraction & ROB done independently in duplicate
- Data analysed in RevMan
- ROB using ROB2
- PROSPERO: CRD42023397132

# RESULTS

## RCTs identified

- 5 studies included with n=1750 patients<sup>7-11</sup>
- Medications: 4 Haloperidol, 2 Quetiapine, 1 Ziprasidone
- Mean age 65.8 ±13.0years, 38% female, mean APACHE II 28.07 ±7.90
- All low risk of bias

## Antipsychotics and Outcomes

- No difference in delirium and coma-free days (Figure 1)
- No difference in mortality (Figure 2)
- No difference in duration of mechanical ventilation (Figure 3)
- No difference in adverse events (Figure 4)

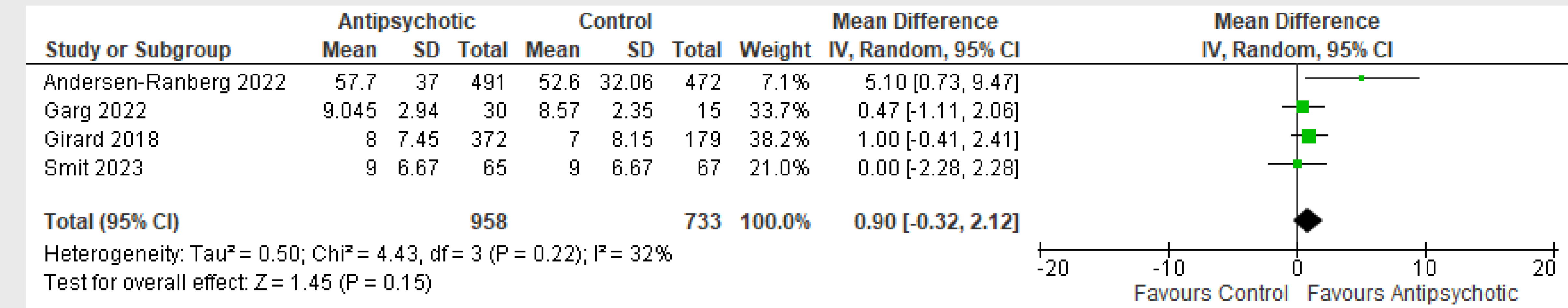


Figure 1. Forest plot showing delirium & coma-free days

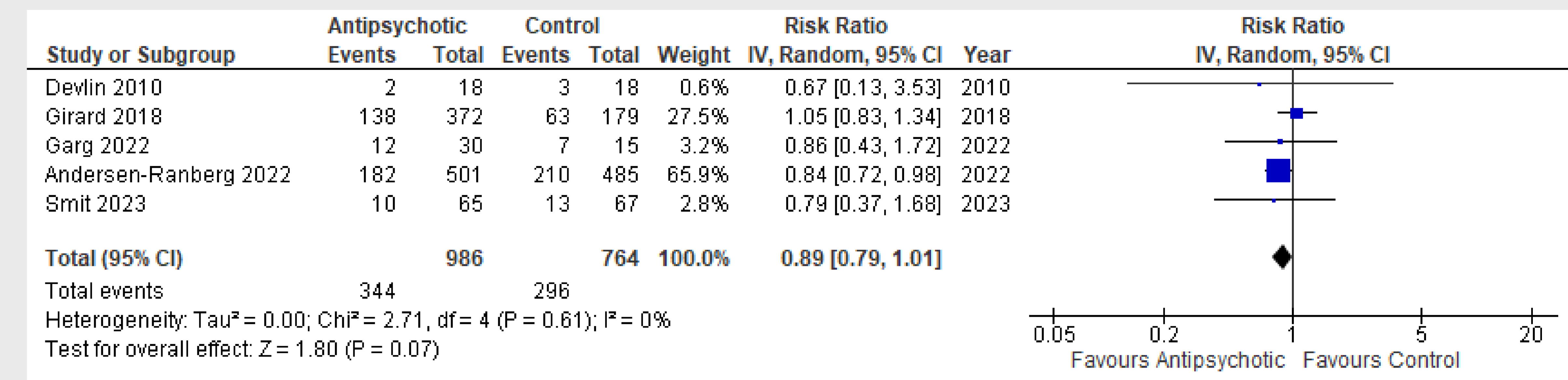


Figure 2. Forest plot showing mortality at longest follow-up

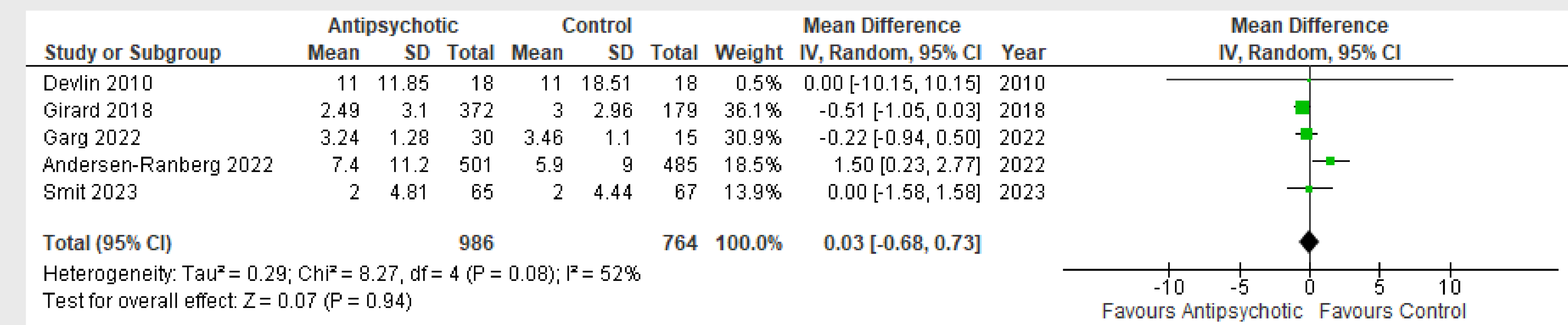


Figure 3. Forest plot showing duration of mechanical ventilation

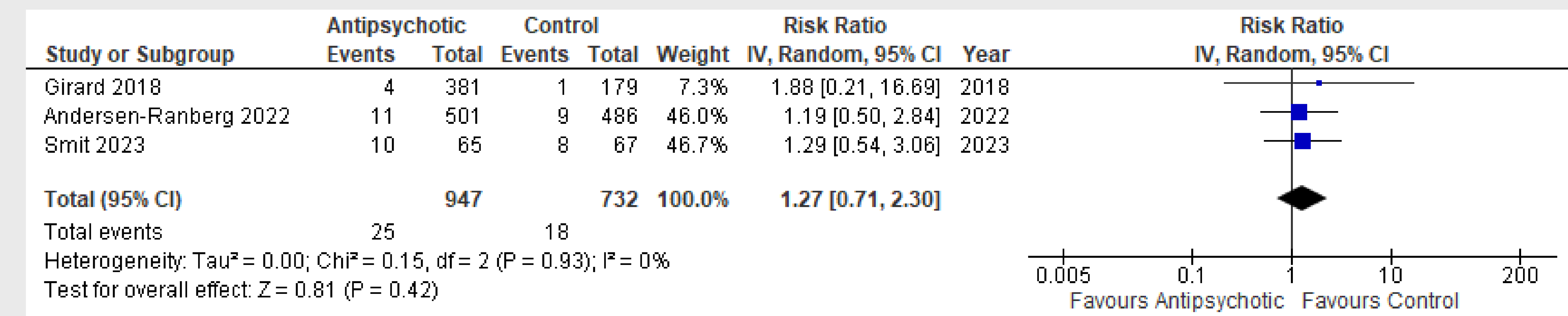


Figure 4. Forest plot showing risk of adverse events

# CONCLUSION

---

- Moderate certainty evidence showed that antipsychotics make no difference in delirium or coma-free days in critically ill adults with delirium
- Antipsychotics should not be administered routinely as treatment
- High certainty evidence of no difference in adverse events
- Further studies examining their use in hyper- or hypoactive delirium would be valuable

# ACKNOWLEDGEMENTS

---

We thank Karin Dearness, MLIS (St. Joseph's Healthcare Hamilton, ON) for peer review of the Ovid search strategy.

# REFERENCES

---

1. Salluh JIF, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ*. 2015;350:h2538. doi:10.1136/bmj.h2538
2. Fiest KM, Soo A, Hee Lee C, et al. Long-Term Outcomes in ICU Patients with Delirium: A Population-based Cohort Study. *Am J Respir Crit Care Med*. 204(4):412-420. doi:10.1164/rccm.202002-0320OC
3. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. *Crit Care Med*. 2018;46(9):e825. doi:10.1097/CCM.0000000000003299
4. Liu SB, Liu S, Gao K, Wu GZ, Zu G, Jie Liu J. Olanzapine for the treatment of ICU delirium: a systematic review and meta-analysis. *Ther Adv Psychopharmacol*. 2023;13:20451253231152113. doi:10.1177/20451253231152113
5. Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for Treating Delirium in Hospitalized Adults. *Ann Intern Med*. 2019;171(7):485-495. doi:10.7326/M19-1860
6. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc*. 2016;64(4):705-714. doi:10.1111/jgs.14076
7. Andersen-Ranberg NC, Poulsen LM, Perner A, et al. Haloperidol for the Treatment of Delirium in ICU Patients. *N Engl J Med*. 2022;387(26):2425-2435. doi:10.1056/NEJMoa2211868
8. Garg R, Singh VK, . P, Singh G. Comparison of Haloperidol and Quetiapine for Treatment of Delirium in Critical Illness: A Prospective Randomised Double-blind Placebo-controlled Trial. *J Clin Diagn Res*. Published online 2022. doi:10.7860/JCDR/2022/56141.16615
9. Smit L, Slooter AJC, Devlin JW, et al. Efficacy of haloperidol to decrease the burden of delirium in adult critically ill patients: the EuRIDICE randomized clinical trial. *Crit Care*. 2023;27(1):1-10. doi:10.1186/s13054-023-04692-3
10. Girard TD, Exline MC, Carson SS, et al. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. *N Engl J Med*. 2018;379(26):2506-2516. doi:10.1056/NEJMoa1808217
11. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: A prospective, multicenter, randomized, double-blind, placebo-controlled pilot study\*: *Crit Care Med*. 2010;38(2):419-427. doi:10.1097/CCM.0b013e3181b9e302



# CONTACT INFORMATION

---

Kallirroï (Laiya) Carayannopoulos

Laiya.Carayannopoulos@medportal.ca