**Author(s)**: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M. **Question**: Should Hydroxychloroquine + Azithromycin vs Hydroxychloroquine be used for COVID-19 patients?

Setting: Inpatient

| Certainty assessment |                       |                      |                           |              |             |                       | № of patients                            |                        | Effect                        |   | Certainty        |
|----------------------|-----------------------|----------------------|---------------------------|--------------|-------------|-----------------------|--|------------------------|-------------------------------|---|------------------|
| № of<br>studies      | Study<br>design       | Risk of<br>bias      | Inconsistency             | Indirectness | Imprecision | Other consider ations | Hydroxychloroc<br>uine +<br>Azithromycin | Hydroxych<br>loroquine | Relative<br>(95% CI)          | Absolute<br>(95% CI)                                    |                  |
| All-cause            | e mortality           |                      |                           |              |             |                       |  |                        |                               |   |                  |
| 2 <sup>1,2</sup>     | randomis<br>ed trials | serious <sup>a</sup> | not serious               | not serious  | not serious | none                  | 74/454 (16.3%)                           | 68/431<br>(15.8%)      | <b>RR 0.87</b> (0.44 to 1.71) | 21 fewer per<br>1.000<br>(from 88 fewer to<br>112 more) | ⊕⊕⊕⊖<br>MODERATE |
| Number               | of patients           | with any a           | dverse events             |              |             |                       |  |                        |                               |   |                  |
| 1 <sup>2</sup>       | randomis<br>ed trials | serious <sup>b</sup> | not serious               | not serious  | not serious | none                  | 82/217 (37.8%)                           | 74/221<br>(33.5%)      | <b>RR 1.13</b> (0.88 to 1.45) | 44 more per<br>1.000<br>(from 40 fewer to<br>151 more)  | ⊕⊕⊕⊖<br>MODERATE |
| Number               | of patients           | with serio           | us adverse event          | s            |             |                       |  |                        |                               |   |                  |
| 2 <sup>1,2</sup>     | randomis<br>ed trials | serious <sup>a</sup> | not serious               | not serious  | not serious | none                  | 105/458<br>(22.9%)                       | 77/419<br>(18.4%)      | <b>RR 1.12</b> (0.89 to 1.41) | 22 more per<br>1.000<br>(from 20 fewer to<br>75 more)   | ⊕⊕⊕⊝<br>MODERATI |
| Length o             | of stay in h          | ospital              |                           |              |             |                       |  |                        |                               |   |                  |
| 1 <sup>2</sup>       | randomis<br>ed trials | serious <sup>b</sup> | not serious               | not serious  | not serious | none                  | 217                                      | 221                    | -                             | SMD <b>0.07 higher</b> (0.12 lower to 0.26 higher)      | ⊕⊕⊕⊝<br>MODERAT  |
| Number               | of patients           | discharge            | d                         |              | L           | <u>I</u> .            |  |                        |                               |   |                  |
| 2 1,2                | randomis<br>ed trials | serious <sup>a</sup> | very serious <sup>c</sup> | not serious  | not serious | none                  | 141/454<br>(31.1%)                       | 128/431<br>(29.7%)     | <b>RR 1.04</b> (0.68 to 1.59) | 12 more per<br>1.000<br>(from 95 fewer to<br>75 more)   | ⊕○○○<br>VERY LOW |
| All-cause            | e mortality           | (non-hosp            | italized patients)        | 1            |             | 1                     | 1  |                        |                               |   |                  |
| 2 3, 4               | randomis<br>ed trials | not<br>serious       | not serious               | not serious  | not serious | none                  | No deaths reported                       |                        |                               |   | ⊕⊕⊕⊕<br>HIGH     |
| 3ARS-Co              | oV-2 cleara           | nce (non-h           | ospitalized patie         | nts)         |             |                       |  |                        |                               |   |                  |

| Certainty assessment   |                       |                 |               |              |             |                             | № of patients                            |                        | Effect                        |   | Certainty    |
|--|-----------------------|-----------------|---------------|--------------|-------------|-----------------------------|--|------------------------|-------------------------------|---|--------------|
| № of<br>studies  | Study<br>design       | Risk of<br>bias | Inconsistency | Indirectness | Imprecision | Other<br>consider<br>ations | Hydroxychlorod<br>uine +<br>Azithromycin | Hydroxych<br>loroquine | Relative<br>(95% CI)          | Absolute<br>(95% CI)                                    |              |
| 2 3, 4   | randomis<br>ed trials | not<br>serious  | not serious   | not serious  | not serious | none                        | 70/203 (34.5%)                           | 85/201<br>(42.3%)      | <b>RR 0.84</b> (0.65 to 1.09) | 68 fewer per<br>1.000<br>(from 148 fewer<br>to 38 more) | ⊕⊕⊕⊕<br>HIGH |
| Number of patients with any adverse event (non-hospitalized patients)      |                       |                 |               |              |             |                             |  |                        |                               |   |              |
| 1 <sup>3</sup>   | randomis<br>ed trials | not<br>serious  | not serious   | not serious  | not serious | none                        | 3/152 (2.0%)                             | 6/152<br>(3.9%)        | <b>RR 0.50</b> (0.13 to 1.96) | 20 fewer per<br>1.000<br>(from 34 fewer to<br>38 more)  | ⊕⊕⊕⊕<br>HIGH |
| Number of patients with serious adverse events (non-hospitalized patients) |                       |                 |               |              |             |                             |  |                        |                               |   |              |
| 2 3, 4   | randomis<br>ed trials | not<br>serious  | not serious   | not serious  | not serious | none                        | No serious adverse event reported        |                        |                               |   | ⊕⊕⊕⊕<br>HIGH |

## **Explanations**

- a. Downgraded of one level for high risk of performance bias in both studies and unclear risk of attrition bias in one study
- b. Downgraded of one level for high risk of performance bias
- c. Downgraded of one level for  $I^2=77\%$

## References

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