Renal Replacement Therapy in Acute Kidney Injury: Authors' Reply

Stéphane Gaudry, David Hajage, Agnès Dechartres, Jean-Pierre Quenot, Didier Dreyfuss

limits and upper limits were close to null effect (relative effect 1), and then did not rate down the certainty of evidence by imprecision. However, the absolute effect might suggest a different conclusion. The absolute difference in 28-day mortality between delayed RRT and early RRT ranged from 38 fewer deaths to 56 more deaths per 1000 patients (appendix). The lower limits indicate significant benefits of delayed RRT over early RRT, whereas the upper limits indicate an opposite result. Similar results were found for 60-day mortality and hospital mortality. By understanding the absolute effects, we might downgrade the certainty of evidence of the three mortality outcomes from high to moderate. Therefore, we are not sure whether the true effect of delayed RRT versus early RRT has an important clinical difference or not.

To conclude, a conservative conclusion might be more appropriate to this study—the timing of RRT initiation might not affect survival in critically ill patients with severe acute kidney injury. Considering absolute effect could be helpful in interpreting the results of this study.[1]

We declare no competing interests.

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1 Gaudry S, Hajage D, Benichou N, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet* 2020; **395:** 1506–15.
2 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64:** 383–94.
3 Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol* 2011; **64:** 1283–93.

Authors' reply

We disagree with Vincenzo Sepe and colleagues' comment about the timing and prescription of renal replacement therapy (RRT). In the randomised controlled trials included in our systematic review and individual patient data meta-analysis,[1] the protocol was precise; it mandated starting RRT as soon as Kidney Disease: Improving Global Outcomes acute kidney injury stage 2 or 3 was present in the early strategy, and it had stringent criteria for initiating RRT in the delayed strategy, such as severe hyperkalaemia or acidosis, among others. Obviously, clinicians had some degree of freedom in the interpretation of such criteria, which is scientifically and ethically desirable. If we follow Sepe and colleagues' reasoning, all randomised controlled trials in the field would be subject to the same criticism, including STARRT-AKI,[2] which is the largest trial to date.

With regards to Sepe and colleagues' second comment, indeed, most patients with severe acute kidney injury have multiple system organ failures and require care intensive care.[3] The COVID-19 pandemic is a tragic example of this situation. Do they consider that a simple renal unit or an internal medicine ward would be able to save the lives of patients with severe acute respiratory distress syndrome, septic shock, and acute kidney injury? Intensive care units (ICUs) probably do not care for the same patients as Sepe and colleagues care for, and we would be interested in having more data from their own experience. We believe that not taking care of patients who have multiple system organ failure in an ICU is not safe in a high-outcome country with modern care. Interestingly, in the only study done in a country that could not offer ICU beds for all patients, results were in favour of a delayed RRT strategy.[4]

We also do not agree with the contention by Zhenxing Lu and colleagues that considering absolute effect would modify our conclusion. We have already reported the results for mortality at day 28, our primary endpoint in terms of absolute risk difference.[1] Regardless of the endpoint definition (ie, mortality at day 28, day 60, hospital mortality), the absolute risk difference is close to 0, and the 95% CI is narrow (0·01 [95% CI −0·04 to 0·06] for mortality at day 28; 0·00 [−0·05 to 0·05] for mortality at day 60; −0·01 [−0·06 to 0·03] for hospital mortality). Our meta-analysis provides a fairly accurate estimate of the absolute difference in mortality between the groups of patients receiving delayed and early RRT. Zhenxing Lu and colleagues express these differences in number of deaths per 1000 patients, which might exaggerate the impression of imprecision (it would be even worse if expressed by millions of patients), yet this does not change our results. We wonder what degree of precision would have been considered sufficient to Zhenxing Lu and colleagues; however, we want to highlight that many non-inferiority trials in ICUs admit a non-inferiority margin for mortality equal to or higher than 0·05.[5]

We declare no competing interests.

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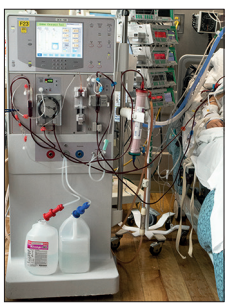
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See **Online** for appendix

1 Gaudry S, Hajage D, Benichou N, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet* 2020; **395:** 1506–15.

2 STARRT-AKI Investigators. STandard versus Accelerated initiation of Renal Replacement Therapy in Acute Kidney Injury: study protocol for a multi-national, multi-center, randomized controlled trial. *Can J Kidney Health Dis* 2019; **6:** 2054358119852937.

3 Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018; **14:** 607–25.

4 Jamale TE, Hase NK, Kulkarni M, et al. Earlier-start versus usual-start dialysis in patients with community-acquired acute kidney injury: a randomized controlled trial. *Am J Kidney Dis* 2013; **62:** 1116–21.

5 Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomized clinical trial. *JAMA* 2018; **320:** 984–94.

Triple artemisinin-based combination therapies for malaria: proceed with caution

Artemisinin-based combination therapies (ACTs) serve as the front-line treatment against malaria. Substantial evidence indicates that treatment failure of the 3-day ACT course in the Greater Mekong subregion (southeast Asia) is strongly linked to partner drug failure rather than artemisinin itself.[1] Thus, ACTs remain fully efficacious with the appropriate partner drug.[2] The fact that artemisinin is still highly efficacious is the underlying logic behind triple artemisinin-based combination therapies (TACTs).[3] However, the necessity of incorporating an additional partner drug should be evaluated in the context of the history of malaria partner drug resistance in the Greater Mekong subregion and with the presence of appropriate controls.

In Cambodia, emerging mefloquine resistance previously led to the failure of artesunate–mefloquine, which was subsequently resolved by the prescription of dihydroartemisinin–piperaquine.[4] With the presently decreasing efficacy of dihydroartemisinin–piperaquine, artesunate–mefloquine has returned to high efficacy in Cambodia, probably following the loss of selection pressure for mefloquine resistance.[2] Thus, the lack of comparison between dihydroartemisinin–piperaquine plus mefloquine and an artesunate–mefloquine control in the Vietnam, Thailand, and some sites of Cambodia data presented by Rob van der Pluijm and colleagues[3] means that it is difficult to discern how much of the increased efficacy is a result of using a triple combination, rather than the effect of simply reapplying mefloquine to a now susceptible population. Other data points for dihydroartemisinin–piperaquine plus mefloquine as well as all data for artemether–lumefantrine plus amodiaquine did not show substantial improvements over the already efficacious ACTs.[3]

Caution should be advised for the addition of new components to a still-effective therapy in a region close to malaria elimination,[2] especially considering the potential challenges associated with increased cost, compliance, and long-term complications that TACTs could bring.

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1 Tilley L, Straimer J, Gnädig NF, Ralph SA, Fidock DA. Artemisinin action and resistance in *Plasmodium falciparum*. *Trends Parasitol* 2016; **32:** 682–96.

2 WHO. World malaria report 2019. Dec 4, 2019. https://www.who.int/publications/i/item/9789241565721 (accessed Dec 4, 2019).

3 van der Pluijm RW, Tripura R, Hoglund RM, et al. Triple artemisinin-based combination therapies versus artemisinin-based combination therapies for uncomplicated *Plasmodium falciparum* malaria: a multicentre, open-label, randomised clinical trial. *Lancet* 2020; **395:** 1345–60.

4 Haldar K, Bhattacharjee S, Safeukui I. Drug resistance in Plasmodium. *Nat Rev Microbiol* 2018; **16:** 156–70.

Authors' reply

We thank Jigang Wang and colleagues for their interest in our multicentre evaluation of triple artemisinin-based combination therapies (TACTs).[1] We agree that it is self-evident that the higher the efficacy of an individual drug in clinical trials, the more difficult it is to show superiority of a corresponding combination treatment. However, equal efficacy at this moment does not mean that the individual drug will not fall to resistance in the nearby future. Combinations are designed to prevent the rare selection event that initiates the emergence and spread of resistance, and in the case of TACTs, which contain two matching partner drugs, also to reduce the selective force from reinfection during the slow partner drug elimination phase. Prevention of the emergence of resistance is safer and more effective than the current practice of waiting for resistance to emerge, and then trying to manage it.

In the specific case of Cambodia, where the majority of *Plasmodium falciparum* infections are artemisinin resistant and several artemisinin-based combination therapies (ACTs) are now failing,[2] we agree that artesunate–mefloquine is currently an effective treatment. However, in artemisinin resistant infections, there will be a much larger *P falciparum* biomass remaining after the 3-day artemisinin component of the ACT has been eliminated, and this makes the probability that resistant mutants would emerge correspondingly greater. This is illustrated by an observation on the Myanmar–Thailand border that in the presence of artemisinin resistance, mefloquine resistance developed rapidly.[3,4] Wang and colleagues are concerned about the costs and long-term challenges associated with deployment of TACTs in a region close to the elimination of malaria, but the whole objective is to reach elimination as quickly as possible and so avoid these.