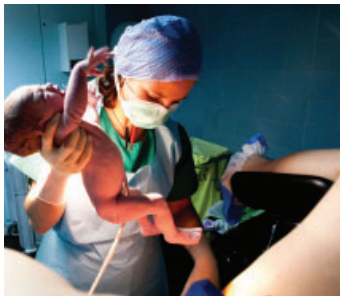
research

Angiotensin receptor blockers and severity of covid-19 p 311



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ORIGINAL RESEARCH Pragmatic, adaptive, multicentre, phase 3, RCT

Angiotensin receptor blockers for the treatment of covid-19 (CLARITY)

Jardine MJ, Kotwal SS, Bassi A, et al

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Study question Are angiotensin receptor blockers, widely used blood pressure lowering drugs, effective in reducing the severity of covid-19?

Methods CLARITY was a clinical trial performed at 17 hospitals in India and Australia. The design was adaptive, continuing until prespecified rules for efficacy or futility were met. Participants were randomly assigned with equal chance to receive an angiotensin receptor blocker or placebo for 28 days, in addition to usual care. In India, the angiotensin receptor blocker was telmisartan 40 mg/day. In Australia, placebo was not available and a standard of care group was used instead. Participants were at least 18 years old, not already receiving angiotensin receptor blockers, with a laboratory confirmed diagnosis of SARS-CoV-2 infection and admission to hospital for management of covid-19. The primary endpoint was disease severity at day 14 using a modified World Health Organization clinical progression scale of seven categories from 1 (not admitted to hospital, no limitations on activities) to 7 (death).

Study answer and limitations Between 3 May 2020 and 13 November 2021, 787 participants were randomly assigned to the angiotensin receptor blocker group (n=393, of whom 388 (99%) received telmisartan 40 mg/day) or to the control group (n=394). 778 (99%) participants were from India and nine (1%) were from Australia. The trial stopped when the prespecified futility rule was met. The median WHO scale score at day 14 was 1 (interquartile range 1-1) in 378 participants assigned to angiotensin receptor blockers and 1 (1-3) in the 377 assigned to placebo (adjusted odds ratio 1.51 (95% credible interval 1.02 to 2.23), probability of an odds ratio of >1=0.98). Participants were younger (median age 49 years (interquartile range 37-60) and had milder disease (223 (28%) required supplemental oxygen at baseline) than anticipated. Therefore, generalisability might be limited to younger patients with lower severity disease, and a benefit or harm from angiotensin receptor blockers cannot be excluded in patients with more severe disease or treated with different agents or dosing.

What this study adds Use of angiotensin receptor blockers was not beneficial in people admitted to hospital for covid-19 with lower disease severity compared with placebo or standard of care.

Funding, competing interests, and data sharing Funded by the Australian Medical Research Future Fund and University of Sydney. No direct competing interests declared. Requests for data access will be reviewed.

Study registration ClinicalTrials.gov NCT04394117.

Surveillance of maternal deaths

ORIGINAL RESEARCH Descriptive population based study

Maternal mortality in eight European countries with enhanced surveillance systems

Diguisto C, Saucedo M, Kallianidis A, et al

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Study question Do differences exist in the level and causes of maternal mortality between European countries with good quality data?

Methods This descriptive multicountry study used data from eight European countries that have enhanced permanent surveillance systems to identify, document, and review maternal deaths (Denmark (297 835 live births), Finland (301 169), France (2 435 583), Italy (1 281 986), the Netherlands (856 572), Norway (292 315), Slovakia (283 930), and the UK (2 261 090)). Maternal mortality ratios (MMRs), defined as the number of maternal deaths per 100 000 live births during a given time period, were calculated and compared with those obtained from vital statistics. Age specific MMRs; MMRs according to women's origin, citizenship, or ethnicity; and cause specific MMRs were also calculated.

Study answer and limitations MMRs up to 42 days after the end of pregnancy varied by a factor of 4 from 2.7 and 3.4 per 100 000 live births in Norway and Denmark to 9.6 in the UK and 10.9 in Slovakia. Vital statistics underestimated maternal mortality everywhere but Denmark. Age specific MMRs were higher for the youngest and oldest mothers. Except in Norway, MMRs were generally higher in women born abroad or of minoritised ethnicity, defined variously in different countries. Cardiovascular diseases and suicides were leading causes of maternal deaths in each country. The aggregate nature of the data precluded further exploration of risk factors for maternal mortality.

What this study adds Special surveillance systems are essential for gathering accurate data on maternal mortality. Differences in the level and causes of maternal mortality up to 42 days, not related to measurement of maternal mortality, exist between countries. Maternal mental and cardiovascular health need to be prioritised in all countries.

Funding, competing interests, and data sharing

No specific funding received

No competing interests declared. No additional data available

COMMENTARY Variations in maternal mortality remain one of the starkest health injustices in the world

Any death related to pregnancy is devastating. Equally shocking are the avoidable discrepancies in worldwide maternal mortality.

In their paper, Diguisto and colleagues collated data from eight European countries with dedicated surveillance systems to quantify and compare maternal mortality over three to five years.[3] They found a fourfold difference in maternal deaths per 100 000 live births (maternal mortality ratio) between countries with the highest (Slovakia, 10.9) and lowest (Norway, 2.7) rates. The value of prospective enhanced surveillance was confirmed by discrepancies found between the enhanced approach and routinely collected data, where more than a third of cases were missed. This should encourage other countries to implement similar strategies.

Differences in some countries may have been related to lack of data linkage owing to national privacy laws. Quality of maternal mortality data was linked to the presence or absence of dedicated government funding for data collection and analysis. Such funding should be considered by countries that are currently without it.

Diguisto and colleagues' eight country comparison also showed that maternal mortality in Europe is around fourfold higher among women aged 35 or older, compared with those in their 20s. In the UK, nearly one in four mothers were in this older category.[4] These findings provide important information for women and should inform evidence based strategies to improve care provision. Some variability may be explained by differences in data acquisition; international collaborative efforts must be aligned for more accurate comparisons.

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Extending accurate collection of maternal mortality data around the world must be a priority

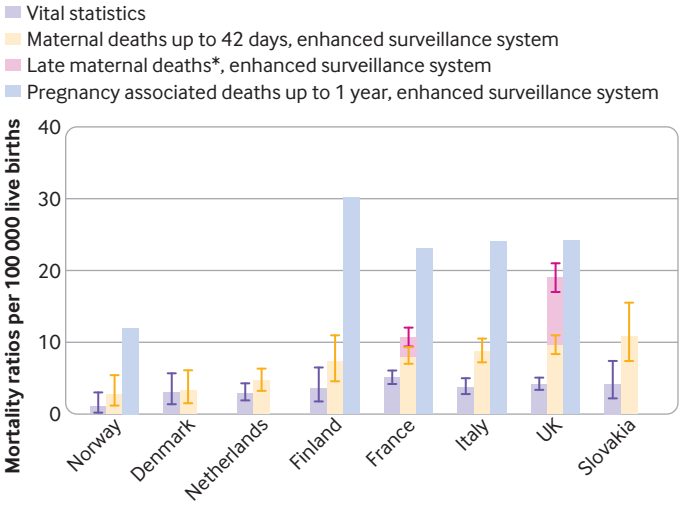
Striking disparities

The relatively low maternal mortality ratios identified in this study are striking compared with those recorded globally, with many countries still reporting more than 500 maternal deaths per 100 000 live births, despite focused efforts.[5] The overwhelming majority (99%) of preventable maternal deaths occur in low and middle income countries.[6]

Although women born abroad or from a minoritised ethnicity were 50% more likely to die in this European cohort, the discrepancy with maternal mortality rates elsewhere is revealing. A woman's lifetime risk of maternal death is defined as the probability that a 15 year old woman will eventually die from a maternal cause. In high resourced areas, lifetime risk is 1 in 5400, but the risk is more than 100 times higher for the same woman born in a low or middle income setting.[7]

Causes of death are relatively consistent across the world, and largely avoidable. Most deaths are due to haemorrhage, sepsis, and hypertensive disorders of pregnancy.[8] Interventions to prevent these deaths are effective and relatively affordable; strategies must include recognition, training, and access to care that is adequately resourced and staffed.

Deaths from pre-eclampsia are particularly avoidable, even in low income settings. Prospectively collected urban data show an eightfold difference in maternal mortality between Zambia and Sierra Leone,[9] where women are 2000 times more likely to die from



Maternal and pregnancy associated mortality ratios up to one year after end of pregnancy, in countries with enhanced surveillance systems (listed from lowest to highest maternal mortality ratio up to 42 days). Error bars represent 95% confidence intervals. *Maternal deaths between 43 and 365 days after end of pregnancy

pre-eclampsia than women in the UK.[10] As one in five babies die in utero in women with pre-eclampsia, timely delivery also has the potential to save many babies lives.[11] Extending accurate collection of maternal mortality data around the world to expose these issues must be a priority for the future.

In Europe, non-obstetric causes of death have become proportionately more common than obstetric causes, including deaths from cardiovascular disease (23%) and suicide (13%); these should be prioritised.[12] In Diguisto and colleagues' study, Finland did not report deaths related to suicide[3]; standardised datasets should be used across countries so that data are comparable.

Cardiovascular deaths and associated comorbidities such as metabolic syndrome may partly explain why mortality is higher in older women[13]; strategies to reduce these deaths will include public health education and measures to prevent cardiovascular morbidity. Mental health problems require resources and careful management in pregnancy and are related to the increase in psychosis and other serious mental health challenges that occur in pregnancy.

Ultimately, all countries should have dedicated surveillance systems; meaningful comparisons in absolute numbers of deaths by specific causes will allow strategies and policy makers to direct efforts appropriately.

This latest comparison is a valuable start and could lead the way in efforts to align methods of data collection internationally. This is a necessary prerequisite to action that will reduce these preventable deaths everywhere. Currently, maternal mortality remains one of the starkest health injustices in the world.

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APHP-COCHIN-VOISIN/PHANIE/SPL

Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community

Zheng B, Green ACA, Tazare J, et al

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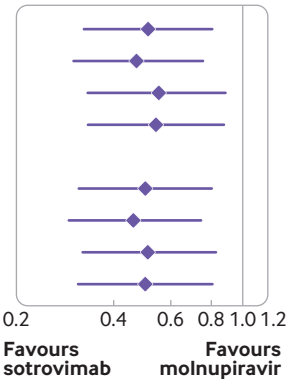
Study question Are sotrovimab (a neutralising monoclonal antibody) and molnupiravir (an antiviral) equally effective in preventing severe outcomes of covid-19 in adults infected with SARS-CoV-2 in the community and at high risk of severe outcomes from infection?

Methods With the approval of NHS England, a real world cohort study was conducted with the OpenSAFELY-TPP platform (a secure, transparent, open source software platform for analysis of NHS electronic health records), and health record data were obtained from 24 million people registered with a general practice in England that uses TPP software. Adults with covid-19 in the community at high risk of severe outcomes from covid-19, treated with sotrovimab or molnupiravir from 16 December 2021, were included in the study. The primary outcome was admission to hospital with covid-19 or death from covid-19 within 28 days of the start of treatment.

Study answer and limitations Between 16 December 2021 and 10 February 2022, 3331 and 2689 patients were treated with sotrovimab and molnupiravir, respectively. Within 28 days of the start of treatment, 87 (1.4%) patients were admitted to hospital or died of infection with SARS-CoV-2 (32 treated with sotrovimab and 55 with molnupiravir). After adjusting for demographic information, high risk cohort categories, vaccination status, calendar time, body mass index, and other comorbidities, treatment with sotrovimab was associated with a substantially lower risk of severe covid-19 outcomes than treatment with molnupiravir (hazard ratio 0.54, 95% confidence interval 0.33 to 0.88, P=0.01). The study was conducted when omicron BA.1 and BA.2 were the most prevalent variants of the virus. These findings should be interpreted with caution because of possible residual confounding bias.

Model	Hazard ratio (95% CI)	P value
Stratified Cox model		
Model 1	0.51 (0.32 to 0.81)	0.004
Model 2	0.47 (0.30 to 0.76)	0.002
Model 3	0.55 (0.33 to 0.89)	0.015
Model 4	0.54 (0.33 to 0.88)	0.014
Propensity score weighted Cox model		
Model 1	0.50 (0.31 to 0.81)	0.004
Model 2	0.46 (0.29 to 0.75)	0.002
Model 3	0.51 (0.32 to 0.83)	0.007
Model 4	0.50 (0.31 to 0.81)	0.005



Comparing risk of admission to hospital or death from covid-19 during the 28 days of follow-up between patients treated with sotrovimab versus molnupiravir. Hazard ratio (95% confidence interval) for admission to hospital for covid-19 or death from covid-19. Model 1 adjusted for age and sex; model 2 also adjusted for 10 high risk cohort categories; model 3 further adjusted for ethnic group, index of multiple deprivation (five categories), vaccination status, and calendar week; and model 4 further adjusted for body mass index category, diabetes, hypertension, and chronic cardiac and respiratory diseases

What this study adds The study suggests that in routine care of adults in England with covid-19 in the community, at high risk of severe outcomes from SARS-CoV-2 infection, sotrovimab was associated with a lower risk of severe covid-19 outcomes than molnupiravir, including in those patients who were fully vaccinated.

Funding, competing interests, and data sharing
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