COVIDMED – An early pandemic randomized clinical trial of losartan treatment for hospitalized COVID-19 patients

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ABSTRACT

Objectives: To assess the efficacy and safety of losartan for COVID-19 patients.
Methods: COVIDMED was a double-blinded, placebo-controlled platform RCT. Enrollees were randomized to standard care plus hydroxychloroquine, lopinavir/ritonavir, losartan, or placebo. Hydroxychloroquine and lopinavir/ritonavir arms were discontinued early. We report losartan data vs. combined (lopinavir-ritonavir and placebo) and prespecified placebo-only controls. The primary endpoint was the mean COVID-19 Ordinal Severity Score (COSS) slope of change. Slow enrollment prompted early termination.
Results: Fourteen patients were included in our final analysis (losartan [N = 9] vs. control [N = 5] [lopinavir-ritonavir [N = 2], placebo [N = 3]]). Most baseline parameters were balanced. Losartan treatment was not associated with a difference in mean COSS slope of change vs. combined (p = 0.4) or placebo-only control (p = 0.05) (trend favoring placebo). 60-day mortality and overall AE/SAE rates were insignificantly higher with losartan.
Conclusion: In this small RCT in hospitalized COVID-19 patients, losartan did not improve outcome and was associated with adverse safety signals.

1. Introduction
Angiotensin II receptor blockers (ARB) may benefit COVID-19 patients secondary to pneumocyte ACE-2 receptor and SARS-CoV-2 entry inhibition, vasodilation/vasoconstriction alteration, and anti-inflammatory effects [1]. Although animal studies suggest potential for benefit, safety concerns include potential for increased ACE-2 receptor expression and adverse events [2–4]. Retrospective/observational exposure-nonexposure and continuation-discontinuation trials [5–10], open-label interventional trials [11–15], and a meta-analysis [16] showed potential benefit. Two blinded RCTs, however, showed no benefit yet adverse safety signals [17,18]. COVIDMED assessed the ARB losartan in hospitalized COVID-19 patients.

2. Materials and methods
COVIDMED (NCT04340557), a parallel-design blinded platform RCT, was approved by the IRBs of Bassett Medical Center (Cooperstown, NY [April 3, 2020] [#1581969]), and two other participating sites (ClinicalTrials.gov - NCT04328012). Our objective was to compare effects of hydroxychloroquine, lopinavir/ritonavir, or losartan, vs. placebo (all investigational unlabeled uses) on a COVID-19 Ordinal Severity Score (COSS) – 1) Death; 2) Hospitalized-on mechanical ventilation/ECMO; 3) Hospitalized-on NIV; 4) Hospitalized-requiring oxygen; 5) Hospitalized-not requiring oxygen; 6) Not hospitalized-with limitations; 7) Not hospitalized-without limitations. Post-consent, patients were allocated in a 2:2:2:1 ratio in blocks to one of the above four treatment groups using a statistician/computer-generated randomization schedule (without stratification). Allocation concealment was ensured by having only the enrollment research nurse be unblinded and maintaining allocation confidentiality. All groups received standard care and were followed for 60 days. Hydroxychloroquine and lopinavir/ritonavir enrollment were halted after RCTs showed no benefit [19,20]; a 2:1 losartan:placebo allocation schedule was used thereafter. We report trial design/results for losartan vs. combined control (including 2 lopinavir/ritonavir patients) and...
placebo-only groups (per our prespecified statistical analysis plan [SAP]). Low enrollment prompted study termination May 27, 2021.

Key inclusion criteria were: hospitalized; ≥ 18 years-old; laboratory-confirmed SARS-CoV-2; and randomization within 72 h. Key losartan group exclusion criteria included: taking ACEi/ARB; hypotension; confirmed SARS-CoV-2; and randomization within 72 h. Key losartan (SAP). Low enrollment prompted study termination May 27, 2021.

An arbitrary sample size of 4000 was chosen at the pandemic onset, and 57 placebos groups subjects, however, the study was terminated beforehand.

AEs were classified in accordance with NCICCTC for Adverse Events, version 4.0. COVIDMED was carried out in accordance with principles of protection of humans participating in research, including the Declaration of Helsinki, and consent from all participants.

### Table 1
Baseline parameters/demographics. Losartan is compared with combined control (lopinavir/ritonavir and placebo) and placebo only control. Statistically significant and ‘trend’ comparisons are in bold.

| Treatment | Combined control | 95% CI | Placebo only control | 95% CI |
|-----------|------------------|--------|----------------------|--------|
| Losartan  | Lopinavir/ritonavir and placebo | p       | NA                   | NA     |
| N         | 9                 | 5      | NA                   | 3      |
| Age (mean) | 63.7              | 61.8   | 0.8                  | -17.0153 to 13.2153 |
| Male (%)  | 66.7              | 60.0   | 0.9                  | -0.8986 to 0.94319 |
| Enrollment spring 2020 | 11.1  | 60     | 0.1                  | -1.0732 to 0.0955 |
| Enrollment fall 2020 - winter 2021 | 77.8  | 20     | 0.2                  | -0.2486 to 1.4042 |
| Enrollment spring 2021 | 11.1  | 20     | 0.7                  | -0.50209 to 0.52431 |
| Caucasian ethnicity (%) | 100   | 100    | NA                   | NA     |
| COSS (mean) | 3.6               | 4.0    | 0.5                  | -0.7192 to 1.5192 |
| Symptoms duration, days (mean) | 9.3    | 7.4    | 0.3                  | -6.0157 to 2.315 |
| Comorbidities (targeted) rate (mean) | 1.0    | 2.6    | 0.02                 | 0.3255 to 2.8745 |
| Immunocompromised (%) | 22.2  | 60     | 0.3                  | -1.0311 to 0.2755 |
| Chronic heart disease (%) | 22.2  | 80     | 0.1                  | -1.2935 to 0.1379 |
| Chronic lung disease (%) | 33.3  | 60     | 0.5                  | -0.9823 to 0.449 |
| Chronic kidney disease (%) | 0     | 0      | NA                   | NA     |
| Chronic liver disease (%) | 0     | 0      | NA                   | NA     |
| Diabetes (%) | 22.2  | 25     | 0.9                  | -0.48384 to 0.52828 |
| Extreme obesity (%) | 0     | 50     | 0.03                 | -0.962 to -0.038 |
| Charlson Score (mean) | 2.5    | 4.5    | 0.08                 | -0.3196 to 4.3196 |
| qSOFA (mean) | 0.33   | 0.6    | 0.4                  | -0.3585 to 0.8985 |
| BMI (mean) | 31.0              | 31.8   | 0.4                  | -4.2764 to 9.2764 |
| Creatinine (mean) | 0.7    | 0.9    | 0.4                  | -0.2508 to 0.5708 |
| Chest x-ray opacities (%) | 88.9  | 100    | 0.9                  | -1.1646 to 0.9423 |
| Pneumonia severity index (PSI) (mean) | 54.9   | 59.3   | 0.5                  | -41.3071 to 60 |
| Treatment days (mean) | 9.6    | 13.3   | 0.3                  | -3.5454 to 10.8545 |
| Treatment with corticosteroids (%) | 88.9  | 40     | 0.3                  | -0.7949 to 0.2172 |

### Table 2
Efficacy. Losartan is compared with combined control (lopinavir/ritonavir and placebo) and placebo only control. Statistically significant and ‘trend’ comparisons are in bold. Comparison of mean COSS slope of the change was the study’s primary efficacy outcome measurement.

| Treatment | Combined control | 95% CI | Placebo only control | 95% CI |
|-----------|------------------|--------|----------------------|--------|
| Losartan  | Lopinavir/ritonavir and placebo | p       | NA                   | NA     |
| COSS slope of the change | 0.0037  | 0.0209 | 0.4                  | 0.0527 |
| COSS change day 60 | 0.7     | 1.8    | 0.6                  | -2.8175 to 5.0175 |
| Mortality, 60 days (%) | 44.4   | 20.0   | 0.9                  | -0.67123 to 0.76012 |
| First negative PCR, days (mean) | 6.5     | 10.5   | 0.7                  | -12.3243 to 16.3243 |
| Hospital LOS, days (mean) | 16.4   | 7.0    | 0.2                  | -25.2922 to 6.4922 |
| Mechanical ventilation, days (mean) | 8.5    | 0      | NA                   | NA     |
| Hospital LOS, days (mean) | 16.4   | 7.0    | 0.2                  | -25.2922 to 6.4922 |

2.1. Statistical analysis

Mean slopes of change in COSS over time served as the primary endpoint for each subject. Continuous and categorical secondary endpoints were compared using Student’s t-test and Fisher’s exact test. Small N prompted omitting adjusted and subgroup analyses. Primary outcome missingness was addressed with last-observation-carried-forward. SAP modifications included Student’s t-test use for primary analysis, losartan vs. combined control comparison, and per protocol reporting.
3. Results

3.1. Screening/enrollment

Of 448 screened patients, 15 were enrolled (3.3%), 9 receiving losartan and 6 receiving control (placebo = 4, lopinavir/ritonavir = 2); 1 placebo patient who withdrew after enrollment but prior to study drug was excluded (yielding 5 control patients [placebo = 3, lopinavir/ritonavir = 2]). Reasons for non-inclusion: patient declined (12.0%), taking ACEi/ARB (26.8%), outside enrollment window (20.1%), hypotension (1.6%), hyperkalemia (2.1%), renal disease (4.2%), altered mental status (11.5%), unrelated hospitalization (10.4%), withdrawal post-consent/pre-randomization (0.2%), and other (11.1%) (Supplement 1).

3.2. Baseline parameters/demographics

Baseline data were reasonably balanced (Table 1).

3.3. Efficacy

96–97% of COSS timepoints were recorded. Mean slopes of change for COSS were 0.00365 for losartan (p = 0.07), and 0.05268 for placebo-only control (p = 0.002). Comparisons of slopes of change for COSS (primary outcome) revealed: losartan vs. combined control (p = 0.4), losartan vs. placebo-only control (p = 0.05) (trend favoring placebo), combined control vs. placebo-only control (p = 0.267) (Supplement 2).

60-day mortality (44.4 vs. 20%, p = 0.9), mean LOS (16.4 vs. 7.0 days, p = 0.2), and mean mechanical ventilation duration (8.5 vs. 0 days) were insignificantly higher with losartan (Table 2).

3.4. Safety

The overall SAE rate was numerically higher with losartan vs. combined control (2.0 vs. 0.6%) and vs. the placebo-only control (2.0 vs. 0%). The overall AE rate trend was similar, being higher with losartan than combined control (3.9 vs. 1.0%) and vs. placebo-only control (3.9 vs. 0%). AKI AE and SAE rates were similar, but hypotension, hyperkalemia, and respiratory failure AE and SAE rates, were numerically higher with losartan than combined and placebo-only controls. No safety comparison was significantly different (Table 3).

4. Discussion

COVIDMED, the third blinded placebo-controlled RCT assessing an ARB in COVID-19, did not find significant group differences in COSS for hospitalized patients treated with losartan vs. control. An insignificant trend favoring control was found for our primary efficacy outcome, comparison of mean COSS slope of the change vs. placebo-only control (p = 0.05). Our primary safety outcome, overall SAE rate, was numerically but not significantly higher with losartan. Secondary outcomes also numerically favored placebo but no group comparisons were significantly different. We speculate that ARB class adverse effects may overcome theorized benefits making the benefit:risk ratio for these medications in COVID-19 null or negative.

Strengths of our study include: blinded RCT, minimal missingness, and baseline balance. Limitations include small N, early termination, low enrollment (reducing external validity), and SAP alterations.

5. Conclusion

Although COVIDMED was pilot-like in scope, its results add randomized, blinded, placebo-controlled data to the limited COVID-19 ACEi/ARB literature. Our results are similar to two larger blinded RCTs [17,18]. The totality of the data do not support empiric ACEi/ARB initiation in COVID-19 outside of RCTs.
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Authors’ contributions

All authors contributed to refinement of and approved the manuscript.

Authorship role

All authors collaborated in the writing/editing of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2022.100968.

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