Title: Evaluation of the effect of sofosbuvir and daclatasvir in hospitalised COVID-19 patients: A randomized double-blind clinical trial (DISCOVER).

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Panel: Research in Context

Research in context

Multiple in-vitro and in-silico studies have suggested that sofosbuvir and daclatasvir might be able to inhibit the replication of the SARS-CoV-2 virus. We searched PubMed and ClinicalTrials.gov for clinical trials investigating the use of sofosbuvir and/or daclatasvir for COVID-19, using the search terms “sofosbuvir”, “daclatasvir”, “SOF”, “DCV”, “SOFDAC” AND “coronavirus”, “COVID-19”. This search was conducted on 1st October 2020 and revealed 28 articles on PubMed and 10 on ClinicalTrials.gov. 3 published trials from Iran were identified as well as 1 unpublished trial from Egypt. These trials enrolled 426 participants. Results have been posted for the 3 Iranian trials (n = 176), 2 of which were randomised. These 3 trials showed a significant improvement in clinical recovery within 14 days on SOF/DCV [risk ratio = 1.34 (95% CI = 1.05-1.71), p = 0.020], with a significantly improved time to clinical recovery [risk ratio = 2.04 (95% CI = 1.25-3.32), p = 0.004] and significantly lower all-cause mortality [risk ratio = 0.31 (95% CI = 0.12-0.78), p = 0.013]. However, the combined sample size was relatively small and methods were not standardised.

Added value of this study

Previous research has called for larger trials investigating SOF/DCV for COVID-19. This is the first large-scale randomised controlled trial of SOF/DCV for COVID-19 and the first high powered assessment of clinical outcomes and mortality, recruiting 1083 participants. We found no significant difference between the sofosbuvir/daclatasvir group and placebo group in terms of 10-day discharge or survival. We saw no evidence of benefit of sofosbuvir/daclatasvir in any patient subgroup.

Implications of all the available evidence

Available evidence suggests that SOF/DCV improves clinical recovery in hospitalised patients with COVID-19. Our finding of no significant clinical benefit is not consistent with earlier smaller trials. Sofosbuvir/daclatasvir should be investigated in earlier stages of disease, higher doses and in combination with other antivirals.

Abstract:

Background: The combination of sofosbuvir (SOF) and daclatasvir (DCV) has shown preliminary efficacy for patients with COVID-19 in five open-label studies with small sample sizes. This larger trial aimed to assess if the addition of sofosbuvir and daclatasvir to standard care improved clinical endpoints in hospitalized patients with moderate or severe COVID-19.

Methods: This was a placebo-controlled, randomized clinical trial in adults with moderate or severe COVID-19 admitted to 19 hospitals in Iran. Patients were randomized to SOF/DCV 400/60mg once-daily or placebo in addition to standard of care. Patients were included if they had positive PCR or diagnostic chest CT, O_2 saturation <95%, and compatible symptoms. The primary endpoint was discharge from hospital within 10 days of first treatment. The trial is registered on Iran Registry of Clinical Trials under IRCT20200624047908N1 available at https://www.irct.ir/trial/49198.

Results: Between July and October 2020, 1083 patients were allocated to either the SOF/DCV treatment arm (n=541) or matching placebo (n=542). The primary endpoint was achieved by 358/541 (66%) in the SOF/DCV arm and 370/542 (68%) in controls (relative risk = 0.97, 95% CI = 0.89-1.05). The in-hospital death rates were 58/541 (11%) in the SOF/DCV group versus 53/542 (10%) in the placebo group (relative risk = 1.1, 95% CI = 0.77 to 1.56).

Conclusions: We observed no significant effect of SOF/DCV versus placebo on the rate of hospital discharge or survival in hospitalized COVID-19 patients. However, the patient population was generally severe cases that may have been too advanced for antiviral drugs to be effective.

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Introduction:

As the incidence and mortality of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to rise globally, we still lack an effective oral antiviral therapy that reduces mortality.

A strategy for tackling this fast-moving pandemic is repurposing existing antivirals or immunomodulators that could be used to treat COVID-19. This strategy takes advantage of established safety profiles and the availability of existing pharmaceuticals. Of existing antivirals being investigated, remdesivir has shown little if any overall clinical benefit and the WHO no longer recommends it for use.[1] Furthermore, it is an intravenous infusion that has logistical difficulties with up-scaling production and administration. Various other antivirals have been repurposed to be tested for effectiveness against SARS-CoV-2 including nitazoxanide and favipiravir.[2,3] Of immunomodulators, the corticosteroid treatment dexamethasone has been approved for treatment since it was found to reduce mortality in hospitalized patients in June 2020, but it is not an antiviral and is only effective at reducing the inflammation of patients with high disease severity to the point that they require oxygen, respiratory support or intubation.[4] Tocilizumab, another immunomodulator, has shown conflicting results (8,9).[5,6]

Sofosbuvir (SOF) and daclatasvir (DCV) have also been investigated for use against SARS-CoV-2.[7-11] SOF and DCV are available in a combination tablet and are approved for the treatment of Hepatitis C Virus (HCV), where they inhibit viral replication enzymes NS5B and NS5A respectively.[12,13] These direct-acting antivirals and various other nucleotide and nucleoside analogues have been predicted to be effective inhibitors of enzymes needed for replication of SARS-CoV-2 in various computer models. This *in-silico* data has predicted strong binding between SOF and DCV with RNA-dependent RNA polymerase (RdRp), Mpro, and various other enzymes needed for viral replication.[14-17] Initial *in-vitro* studies were negative for sofosbuvir when tested in certain cell lineages.[18-20] However, sofosbuvir is a pro-drug that requires intracellular metabolism to be converted to its active form.[21] More recent *in-vitro* data has shown that sofosbuvir is actually effective against SARS-CoV-2 when tested in human cells which have these necessary enzymes, and furthermore, daclatasvir was found to

be even more effective.[21,22] The EC_{50} of daclatasvir in Calu-3 cells is 812ng/ml, this is within the C_{max} values of 1409-1726ng/ml at a 60mg dose.[23] However, achievable C_{max} values at current dosing regimens for sofosbuvir are lower than the EC_{50} values required to inhibit SARS-CoV-2 *in vitro.* The EC_{50} in Calu-3 cells for sofosbuvir is 5025ng/ml whereas the C_{max} of sofosbuvir is 622ng/ml at a dose of 400mg.[24]

In early 2020 there were four small clinical trials in a total of 266 patients that tested SOF/DCV in combination with other antivirals such as lopinavir/ritonavir, hydroxychloroquine, and ribavirin in hospitalized patients with COVID-19[7-9,25] Results from these four trials were encouraging, and three have been analyzed together in a pooled meta-analysis, showing that mortality and time to clinical recovery was slightly improved in patients receiving SOF/DCV compared to those receiving SOC.[10] Trials in mild patients require thousands of patients to detect clinical effect using endpoints such as symptom alleviation or hospitalizations. However, trials in more severe, hospitalized patients require much smaller sample sizes to detect benefit on survival or hospital discharge.

In this randomized controlled trial of over 1000 patients, we aimed to see if SOF/DCV is an effective treatment for hospitalized patients with COVID-19.

Methods:

Study design: DISCOVER (DaclatasvIr and Sofosbuvir for COVid-19 in hospital Emergency Room) was a double-blind, placebo-controlled, multicenter phase 3 study in 19 different hospitals in Iran across 12 cities.

Patients: Patients with clinically diagnosed COVID-19 by either PCR positivity or COVID-19 compatible lung chest CT scan findings were considered for inclusion if they were >18 years old and provided written informed consent. In addition, patients were required to have any one of fever (oral temperature ≥ 37.8 °C), dry cough, severe fatigue, dyspnea, and oxygen saturation<95%. Patients were excluded if they had renal failure, were pregnant or breastfeeding, on amiodarone, had previous sofosbuvir use, had multi-organ failure or required intubation on admission, had significant arrhythmias, or were allergic to SOF/DCV. Subjects enrolled in other interventional trials were also excluded.

Study arms: All participants received standard care following national treatment guidelines. The treatment arm received SOF/DCV 400/60mg (Sovodak, RojanPharma, Tehran) once daily for 10 days with standard care. The control group received standard care and an identically-looking placebo tablet once daily for 10 days.

Endpoints: The primary endpoint was clinical recovery at 10 days after starting SOF/DCV. Subjects were discharged based on the managing physician's decision and when clinical recovery was evident defined as 24 hours of no fever or dyspnoea, no or improved cough and fatigue, and tolerance of oral feeding. Secondary endpoints were recovery within 14 days of randomization, mortality, time to hospital discharge, length of hospital stay, and length of intubation.

Procedures:

All patients admitted to participating hospitals with a clinical diagnosis of COVID-19 were evaluated for eligibility. Patients meeting the eligibility criteria and consenting to the study were randomized and received the first dose of study medication within 48 hours of admission. Patients were visited daily and relevant information and complications or adverse

events were recorded. All data was entered into an online system within 48 hours and was checked for consistency and errors by a central team.
If patients were discharged earlier than 10 days, they would be instructed to continue the study medication to complete the 10-day course. All subjects were contacted 14 days after discharge to ask about complience, possible re-admission or late complications.

Randomization and masking:

Block randomization was done using a computer-generated list and a block size of 4. Randomization and preparation of study medication were performed centrally and blocks were distributed among participating centers. None of the researchers or treating physicians were aware of the group allocation of subjects.

Sample size:

The sample size was calculated to provide at least 95% power to detect 5% difference in the primary endpoint of hospital discharge at day 10 with a confidence level of 95%, with a significance level of 5%. It was determined that 500 patients should be allocated to each arm (total 1,000 patients). In addition, the sample size had 80% power to detect a reduction in the death rate, from 10% in the placebo arm to 5% in the SOF/DCV arm, with a significance level of 5%. No interim analyses were planned.

Important changes to the protocol during the study:

The original inclusion and exclusion criteria were more restrictive and included only subjects with onset of symptoms in 7 days or less and those younger than 75 years. Furthermore, subjects with previous COVID infection, severe physical disability, active cancer, immune suppression, immune-compromisation, and previous or current use of experimental COVID medicine were excluded. In the first week of the study, the enrollment rate was too low so all the aforementioned limitations were removed.
Originally, the discharge criteria included a stable O_2 saturation of 95% or more. During the first weeks of the study, it became apparent that it was not possible to enforce this discharge criteria because of the shortage of hospital beds during the pandemic.

The original secondary endpoints included days admitted in the intensive care unit (ICU). Because of the shortage of ICU beds almost in all participating hospitals throughout the study, this endpoint would not have carried reliable information and was deleted.

Statistical Analysis:

Baseline characteristics were summarized using descriptive statistics. Treatment arms were compared for the Intent To Treat population including all randomized patients. Comparison of categorical variables was carried out using Chi-squared test and continuous variables were compared using Mann-Whitney U Test.

For the primary endpoint of clinical recovery within 10 days, all individuals not achieving clinical recovery within the timeframe were considered failures, including individuals self-releasing from hospital or with withdrawal of consent if they did not meet recovery criteria. Analysis was repeated for subgroups by age, time since symptom onset and use of concomitant medications. The endpoint of 'overall-mortality' includes individuals who died during the 14-day post-discharge follow-up, groups were compared using Chi-squared test.

Kaplan Meier survival curves were used to plot risk of i) hospital discharge and ii) in-hospital mortality and were compared using log-rank test. For the hospital discharge endpoint, individuals who died during hospitalization were censored at day 29. For the in-hospital mortality endpoint, patients discharged prior to day 28 will be assumed as absence of the event and were censored on day 29. Analyses censored patients self-discharging or with withdrawal of consent at day of exit. Analyses consider only the original episode of hospitalization and any hospital readmissions or deaths after the initial hospitalisation were not captured.

Logistic and Cox regression models was used to further analyze the primary and secondary endpoints. Models included an interaction term between the treatment group and baseline O_2 saturation (dichotomised as >90% or ≤90%), and included age, gender, comorbidities (diabetes, hypertension, COPD, and obesity), and concomitant medications as possible predictors.

The discussion includes a meta-analysis of available randomized trials sofosbuvir/daclatasvir trials. The endpoints of this analysis included clinical recovery within 14 days and all-cause mortality. Effects were expressed as risk ratios (RR) for binary endpoints. For each endpoint we pool the individual trial statistics using the random-effects inverse-variance model; a continuity correction of 0.5 was applied to studies with zero cells. Heterogeneity was evaluated by I^2. This meta-analysis is registered with PROSPERO and will be updated with future clinical trials of sofosbuvir/daclatasvir when more results become available in February 2021.[26]

A p-value was considered statistically significant at the $p<0.05$ threshold. Data was analysed using STATA (version 14.2) by two separate independent analysts for quality control purposes.

Ethics and Registration: The study was conducted according to the Declaration of Helsinki and Iran ministry of health requirements for clinical trials. The study protocol has been approved by the Abadan Faculty of Medicine Sciences Institutional Review Board and the Iranian Registry of Clinical Trials (IRCT) registry team. The study protocol is registered with IRCT under IRCT20200624047908N1 available at https://www.irct.ir/trial/49198

Results:

Between July and October 2020, 2404 participants were screened for eligibility, of these participants 1090 were not eligible. Causes of exclusion are given in table 1. Of the 1314 eligible patients, 231 did not consent to the study and finally, 1083 participants were enrolled and included in the intent to treat population, 541 were randomized to the intervention group, and 542 to the placebo/control group (Figure 1).

The median age of participants was 58 (IQR 45-69); 585 (54%) patients were men versus 498 (46%) women (Table 2). The most frequent comorbidities observed were diabetes (28%) and hypertension (34%). Baseline laboratory findings were balanced across treatment arms. The median time since symptom onset was eight days for both groups. COVID-19 diagnosis was based on PCR positivity or diagnostic lung CT scan. 430 participants (79%) were PCR positive at baseline in the SOF/DCV group and 426 participants (79%) in the control group. All participants had CT lung involvement; the most frequent lung percentage category was 26-50%. 429 participants (40%) had oxygen saturation less than 90% at baseline. The most frequent concomitant medications administered were interferon-beta (54%), dexamethasone (53%), lopinavir/ritonavir (33%), and remdesivir (16%). Concomitant medication administration was balanced across treatment arms (Table 3).

The study medication was discontinued prematurely in 6 patients (3 in each arm), two of which were considered to be due to study medication (one in each arm).

The primary end point of clinical recovery within 10 days was achieved by 358/541 (66%) participants in the SOF/DCV group and 370/542 (68%) in the control group. There was no significant difference between treatment arms, p=0.555 (Table 4). Figure 3a shows the time to hospital discharge. The median time to discharge was seven days (IQR 4-10) in the SOF/DCV group and six days (IQR 4-10) in the control group. There were no significant differences between groups. At day 10, 217 patients (20%) still had oxygen saturation less than 90% and 167 (15%) had respiratory rate greater than 24 breaths/minute. At day 10, 34 participants (6%) in the SOF/DCV arm and 30 (6%) in the control group still required nasal

oxygen. Furthermore, 18 participants (3%) were intubated in the SOF/DCV group and 12 (2%) in the control group. Some patients who felt well enough self-discharged before reaching the primary endpoint (and as such were considered failures in the primary analysis); in the SOF/DCV arm 5% of patients voluntarily discharged and 1% in the control arm by day 10.

In subgroup analyses of the primary endpoint there were no differences between treatment arms by sex, age, oxygen saturation at baseline, comorbidities, concomitant medications and time since symptom onset. In a multivariable analysis age, baseline oxygen saturation, and obesity were strong predictors for hospital discharge within 10 days; in addition, male sex was predictive of risk of in-hospital mortality (secondary endpoint). In the multivariable analysis or subgroup analysis there was no benefit seen for those taking dexamethasone, however, this maybe be the result of confounding factors. Individuals with dexamethasone usage tended to have more severe COVID-19 at baseline (poorer oxygen saturation and more CT lung involvement).

For the secondary endpoint of all-cause mortality, there was no significant difference between treatment arms. There were 68 (13%) deaths on the SOF/DCV group overall and 60 (11%) in the control group (considering any death at any point on the trial). Figure 3b shows the time to death by treatment group within 28 days. The median time to death was 10 days (IQR 6-16) in the SOF/DCV group and 10 (IQR 6-14) in the control group.

Discussion:

In this randomized controlled trial of 1083 patients with moderate or severe COVID-19 infection, there was no significant effect of SOF/DCV versus placebo on the rate of hospital discharge or survival. These results were consistent across different subgroups of age, sex, time since onset of symptoms, comorbidities, concomitant medications, and baseline vitals. This trial was double-blind, placebo-controlled, and investigated sofosbuvir/daclatasvir in a large sample size with the power to detect 50% reduction in mortality.

Although sofosbuvir and daclatasvir have shown some benefit in reducing viral replication *in vitro*, the EC_{50} for sofosbuvir is not within pharmacokinetic exposures and the daclatasvir EC_{50} is borderline. In this trial a large proportion of participants received dexamethasone and other corticosteroids. Dexamethasone has shown a survival benefit in severe COVID-19 patients receiving oxygen in the UK RECOVERY Trial.[4] However, dexamethasone moderately decreases daclatasvir exposure as it is a moderate CYP3A inducer.[27] Dexamethasone is not contraindicated with sofosbuvir.[28] Therefore, pharmacokinetic levels of sofosbuvir/daclatasvir may not be high enough to provide efficacy. Future trials should investigate sofosbuvir/daclatasvir at higher doses and without the use of drugs that could lower their concentration.

The results from this double-blind randomized trial are not consistent with earlier clinical trials of sofosbuvir/daclatasvir. There have been five open-label studies of sofosbuvir/daclatasvir that have shown preliminary efficacy. In a combined analysis of the four earlier randomized trials and DISCOVER, there is no significant benefit associate with sofosbuvir/daclatasvir on clinical recovery or survival (Figure 4a and 4b). Four of these trials conducted in Iran and Egypt had a total sample size of 266 patients compared to 1083 patients in the DISCOVER trial. Additionally, all of these trials were open-label and as a result investigator bias may have contributed to the positive result. In the meta-analysis of clinical recovery there was high heterogeneity (63%) and there were significant differences between subgroups of placebo-controlled and open-label studies.

In the DISCOVER trial, the median time since symptom onset was eight days in each arm. This may be too far into the course of disease for antivirals such as sofosbuvir/daclatasvir to be effective. Evidence suggests that antivirals show little benefit in late-stage disease. For example, the influenza drug, oseltamivir, shows the greatest efficacy in the early stages of the disease. The CDC recommends that this treatment is started within 48 hours of symptom onset.[29,30] Furthermore, as compared to the previous studies, the DISCOVER study was performed in a period in Iran in which the epidemy was more active and the pressure on health systems was greater. Individuals were encouraged to stay at home unless they developed severe symptoms and only the most severe patients were admitted to hospitals. For example, in DISCOVER the median oxygen saturation at baseline was 90% in both arms. Additionally, due to lack of hospital beds, patients who were deemed well enough were discharged quickly and some patients self-discharged once they felt better against the recommendation of their doctors.

Other antivirals have also been investigated against SARS-CoV-2. However, these treatments are yet to show clear benefit. The WHO SOLIDARITY trial has shown remdesivir, hydroxychloroquine, and lopinavir/ritonavir to be of no benefit. The UK RECOVERY Trial and WHO SOLIDARITY have also shown that lopinavir/ritonavir and hydroxychloroquine have no clinical benefit.[1,31,32] Furthermore, these trials have investigated antiviral monotherapies for the treatment of COVID-19. We should be assessing antivirals in combination treatments such as with favipiravir,[33] nitazoxanide,[2] bromhexine[34] or ivermectin[35] which have shown some promise in small clinical trials.

Trials should adopt a same day test and treat model wherever possible to ensure that investigational treatments are able to suppress the virus as soon as possible. For example, the FDA has granted emergency use authorization (EUA) to Eli Lilly's monoclonal antibody, bamlanivimab, for the treatment of SARS-CoV-2 in non-hospitalised patients.[36] The EUA was granted following promising preliminary results that showed significant reductions in viral load and number of hospitalizations. In the Eli Lilly Trial patients received treatment within three days of obtaining a positive SARS-CoV-2 test. Similarly to the Eli Lilly trial, future trials should investigate sofosbuvir/daclatasvir at earlier stages of disease.

The ACTION Trial is a double-blind placebo-controlled trial in 2400 outpatients which will commence in January 2021. This trial aims to determine if sofosbuvir/daclatasvir is effective in reducing hospitalizations and improving clinical recovery in earlier onset and more moderate disease. In this trial, sofosbuvir/daclatasvir will also be investigated in combination with favipiravir and at a double-dose. Using a rapid diagnostic test, participants will also be enrolled on the same day as testing.

In summary, in the DISCOVER trial there was no significant clinical benefit on sofosbuvir/daclatasvir in late-stage disease. Future trials of sofosbuvir/daclatasvir should have higher doses, be administered in combination with other antivirals, and at an earlier stage of disease.

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Author contributions:

Patient enrollment, management, and follow-up was performed by M.Abdollahi, F.Abedi, M.Afshari, E.Akbarpour, A.Ali Asgari, A.Anushiravani, Z.Arizavi, Z.Azarkar, E.Azimi, F.Babamahmoodi, A.Bahadori, E.Barahimi, A.Bonyadi, L.Davoodi, A.Davoudi Badabi, S.Dehghan Manshadi, F.Dehghani, A.Ebrahimzadeh, M.Ebrahimzadeh, G.Eslami, H.Esmaeilian, N.Hasooni Bahrini, A.Hormati, H.Hosamirudsari, S.Jelvay, N.Khajavirad, J.Khodadadi, Z.Mehrabi, H.Mirzaei, M.Mobarak, S.Mobarak, M.Moghimi, R.Moslemi, H.Mousavi, S.Mousaviasl, M.Naghipour, Z.Nekoukar, M.Noori Jangi, Z.Poormontaseri, H.Pourmasoomi, E.Radmanesh, A.Sadeghi, M.Salasi, M.Salehi, S.Salmanzadeh, S.Sayar, A.Shabani, M.Shabani, S.Shokouhi, S.Yaghoubi, S.Yeganeh,A.Zeinali, M.Ziaee, and F.Zolfaghari. Data collection was performed by E.Akbarpour, M.Hassaniazad, F.Joukar, F.Mansour-Ghanaei, L.Rezaie Keikhaie, A.Tousi, and T.Yaghubi Kalurazi. Local study management and supervision was performed by H.Abbaspour Kasgari, M.Afshari, Z.Arizavi, H.Fakheri, A.Hormati, J.Karimi, F.Mansour-Ghanaei, H.Mirzaei, M.Mobarak, L.Rezaie Keikhaie, A.Sadeghi, M.Salasi, and M.Ziaee. Central data quality control was performed by D.Merat. Randomization and blinding were managed by E.Akbarpour, A.Nateghi Baygi, H.Nateghi Baygi, and A.SadeghiStatistical analysis was performed by K.McCann, B.Simmons, and H.Wentzel. The first draft of the manuscript was prepared by S.Merat and B.Simmons. Central study supervision was performed by A.Hill and S.Merat. The study was designed by A.Hill, S.Merat, S.Mobarak, and M.Salasi. All authors have read and approved the final published manuscript.

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Tables and Figures:

Table 1: Causes of exclusion

Oxygen saturation ≥ 95%	728
Renal failure	179
Multiorgan failure	138
Significant arrhythmia	103
Age < 18 yrs	65
Previous treatment with sofosbuvir	60
Lack of compatible lung CT or PCR	55
Pregnancy or lactation	49
Requiring intubation on admission	45
Lack of required symptoms	44
Bradycardia (<50 bpm)	28
Enrolled in other interventional trials	23
Taking amiodarone	10
Reported allergy to sofosbuvir or daclatasvir	3
Total*	1090

*Some patients had more than one exclusion criteria

Table 2: Baseline Characteristics

	SOFDCV n=541	Control n=542
Baseline Demographics		
Age, Median (IQR)	57 (45,69)	59 (46,69)
Sex (female), n (%)	250 (46)	248 (46)
Days since symptom onset, median (IQR)	8 (6,10)	8 (6,10)
PCR positive, n (%)	430 (79)	426 (79)
Vitals on Admission, median (IQR)		
Oxygen Saturation %	90 (88,93)	90 (87,93)
Respiratory Rate breaths/min	20 (18,23)	20 (18,23)
Temperature °C	37 (36.70,37.50)	37 (36.80,37.50)
Height cm	168 (160,174)	168 (160,175)
Weight kg	75 (68,85)	76 (68,85)
BMI kg/m^2	27 (24,31)	27 (24,30)
Comorbidities, n(%)		
Diabetes	153 (28)	146 (27)
Hypertension	187 (35)	181 (34)
Ischaemic Heart Disease	53 (10)	46 (8)
Asthma	28 (5)	24 (4)
COPD	9 (2)	14 (3)
CT Lung Involvement		
Lung Involvement (%), median (IQR)	50 (30,60)	45 (30,60)
Lung Percentage Categories, n(%)		
0-25	94 (17)	85 (16)
26-50	267 (49)	293 (54)
51-75	138 (26)	123 (23)
76-100	42 (8)	41 (8)

Laboratory Findings, median (IQR)		
White Blood Cell	5900 (4 500,8 400)	5900 (4 400,8 640)
PMN	75 (67.20,82.50)	74 (65,82)
Lymphocyte %	18 (11.50,25.20)	18.50 (12.40,26.00)
Total lymphocyte µL	1013 (740,1425)	1068 (767,1412)
CRP	36 (20,63)	36 (20,62)

Table 3: Concomitant Medications

	SOF/DCV n=541	Control n=542
Concomitant Medications, n(%)		
Interferon-beta	293 (54%)	291 (54%)
Dexamethasone	298 (55%)	272 (50%)
Other Corticosteroids	93 (17%)	94 (17%)
Lopinavir/ritonavir	176 (33%)	183 (34%)
Azithromycin	121 (22%)	119 (22%)
Remdesivir	93 (17%)	76 (14%)
Hydroxychloroquine	70 (13%)	69 (13%)
Atazanavir	60 (11%)	57 (10%)
Naproxen	44 (8%)	52 (10%)
IVIG	5 (1%)	2 (0%)
Ribavirin	4 (1%)	0 (0%)

Table 4: Clinical Endpoints

	SOF/DCV n=541	Control n=542	p-value
Endpoints			
10-day discharge, n(%)	358 (66%)	370 (68%)	0.555[1]
Time to hospital discharge, days median	7 (4,10)	6 (4,10)	0.408[2]
Overall mortality*, n(%)	68 (13%)	60 (11%)	0.445[1]
Time to death, days median	10 (6,16)	10 (6,14)	0.581[2]

*Mortality at any point during the trial.

[1]p-value for relative risk calculated using Chi-squared test.

[2]p-value for log-rank test

Figure 1: CONSORT Flow Diagram

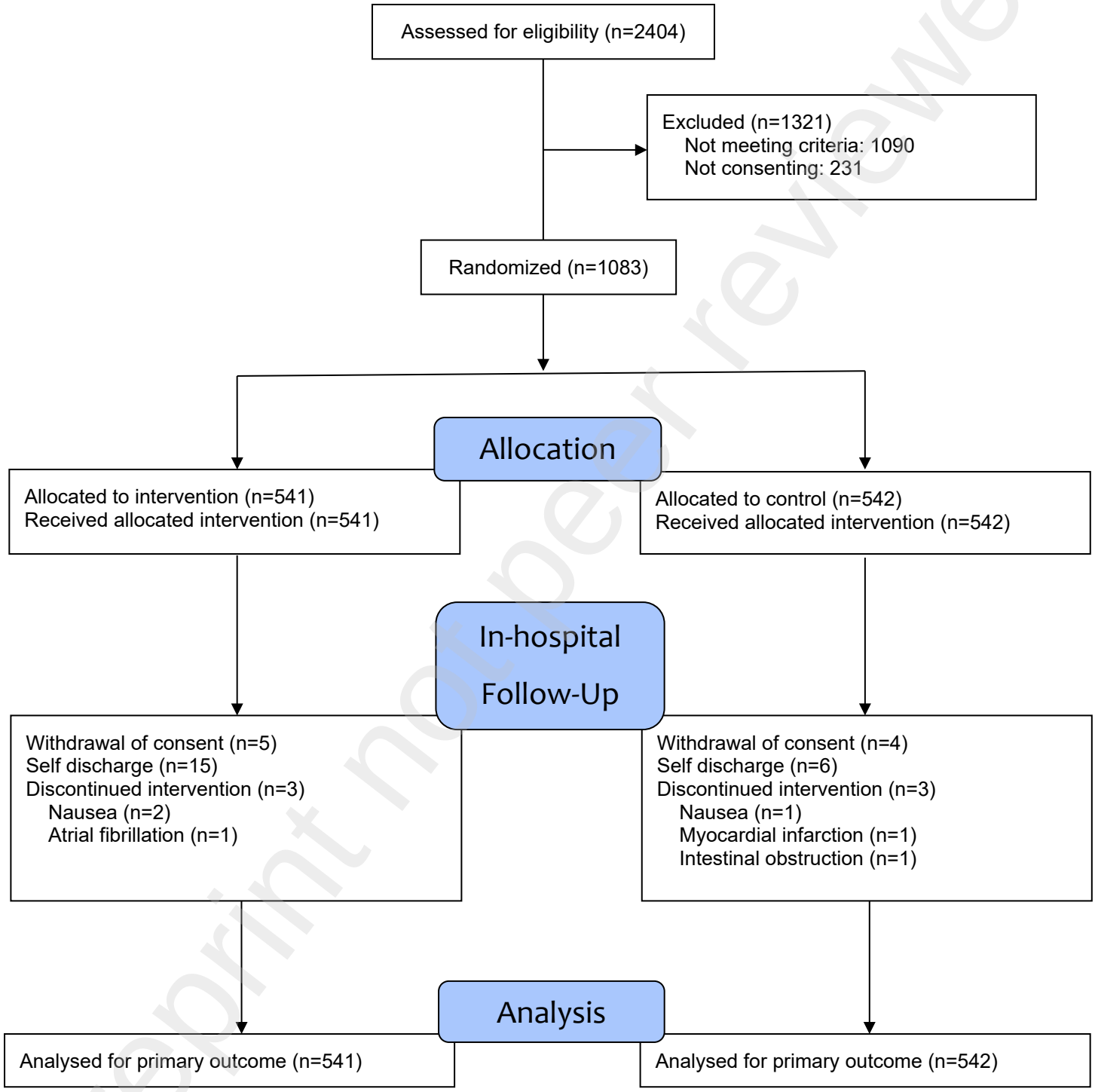

Figure 2: Subgroup Analysis of the Primary Endpoint.

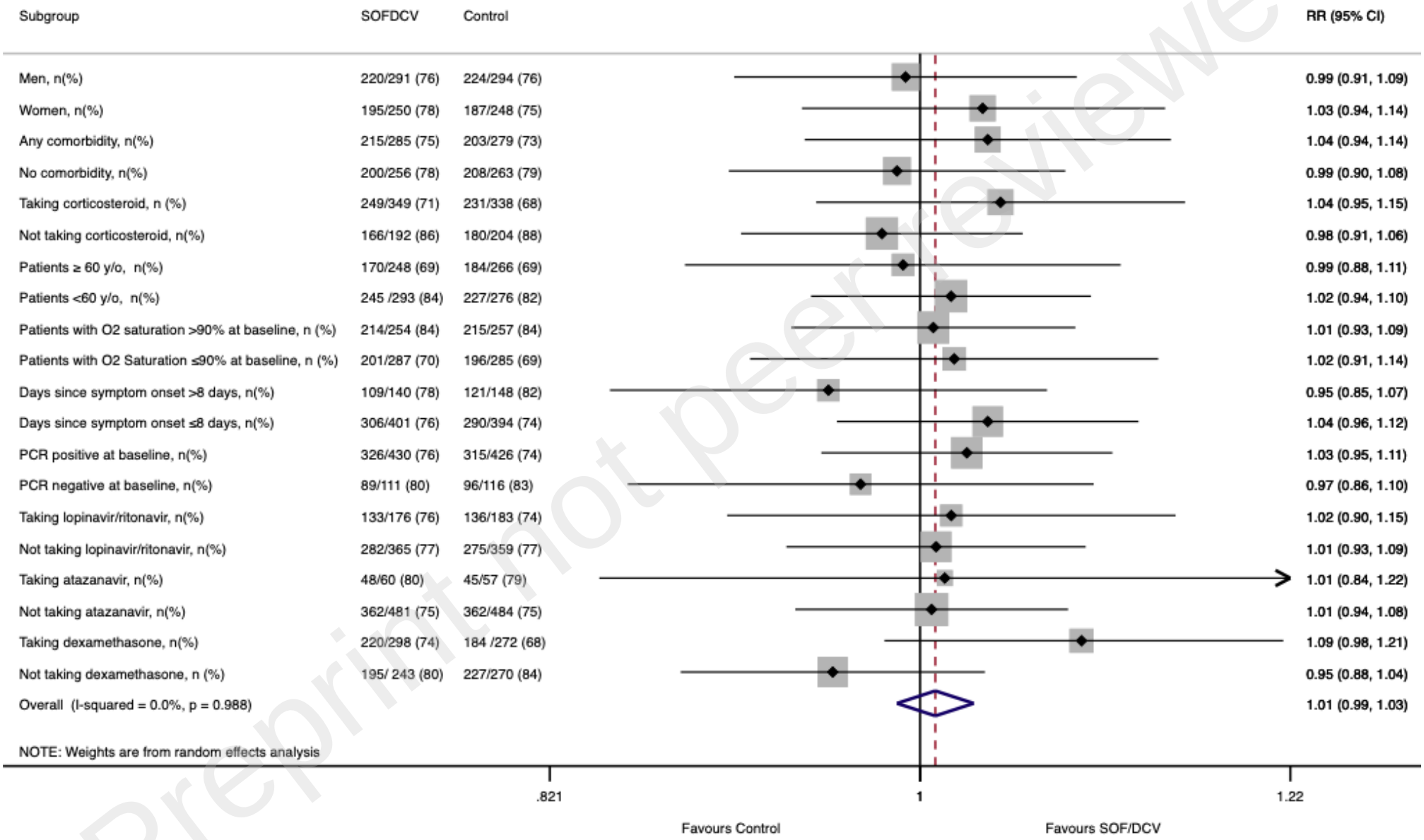

Figure 3a: Kaplan Meier graph of hospital discharge from initial hospitalisation

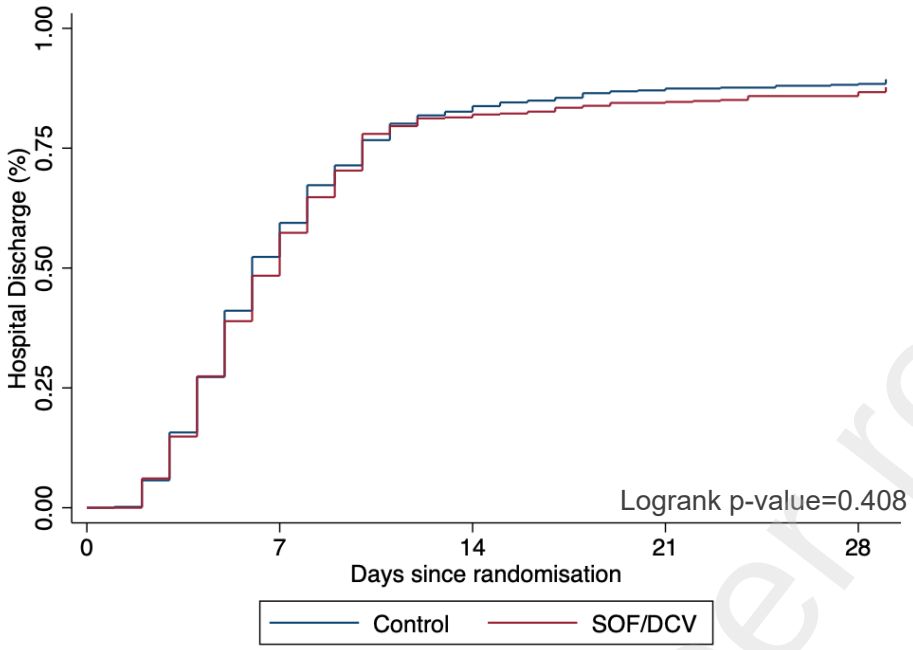

Figure 3b: Kaplan Meier graph of in-hospital mortality to day 28

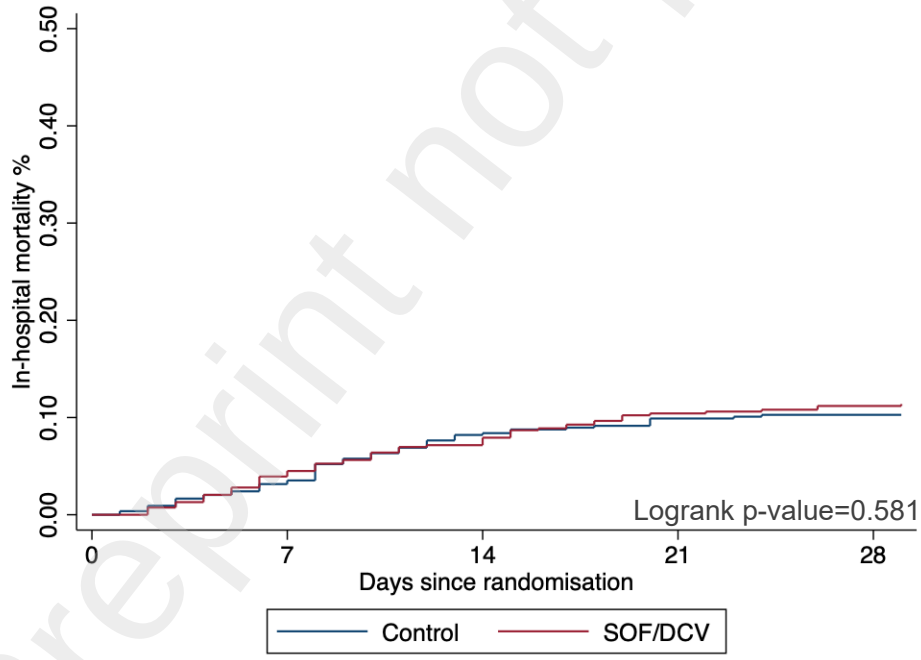

Figure 4a: Meta-analysis of clinical recovery within 14 days.

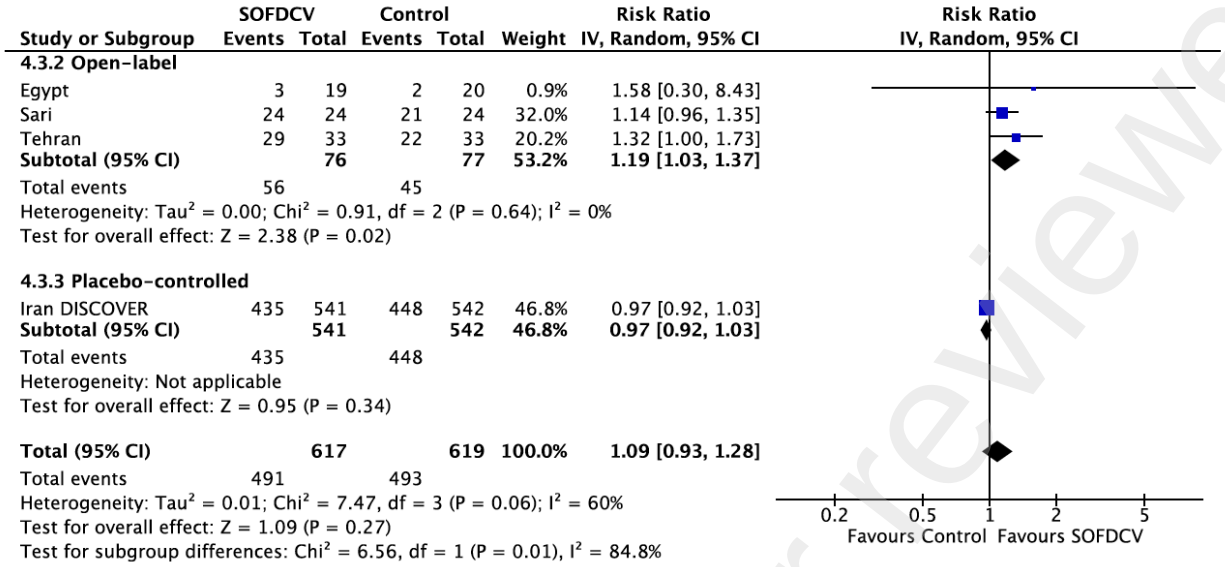

Figure 4b: Meta-analysis of all-cause mortality.