Statistical Analysis Plan (SAP)

Comparative Effects of Methylprednisolone and Prednisolone on the Risk of Acute Decompensated Heart Failure - An Emulated Target Trial

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Summary: This Statistical Analysis Plan (SAP) outlines data preparations and statistical analyses in a comprehensive health registry that spans the entire adult Norwegian population from 2008 to 2017. We aim to emulate a target trial to compare the risk of acute decompensated heart failure in users of methylprednisolone compared to prednisolone.

The exposure is prescriptions of methylprednisolone or prednisolone tablets and the primary outcome is heart failure hospitalizations within the following 6 months, i.e. acute contacts with secondary or tertiary health care resulting in a primary diagnosis of heart failure. Secondary outcomes include broader heart failure diagnoses and the initiation of loop diuretics. Data preparation includes an initial observation period of 2 years, inclusion criteria such as age, corticosteroid formulation types / dosages and prescription codes, as well as removal of duplicate prescriptions and measures to reduce potential carry-over effects.

1. Background

Corticosteroids have found widespread application in the treatment of numerous diseases, ranging from autoimmune disorders to allergic reactions. Although unified in purpose, corticosteroids differ significantly in their molecular structures and resultant effects. One defining characteristic is the balance between glucocorticoid and mineralocorticoid effects. It is primarily the glucocorticoid effects that clinicians seek when prescribing corticosteroids, owing to their pronounced anti-inflammatory and immunosuppressive properties. However, the mineralocorticoid effects are not without consequence, as they may result in sodium and fluid retention, as well as increased potassium excretion. The implications of these latter effects, particularly for patients with heart disease, have been a topic of discussion. Indeed, previous studies have reported an association between corticosteroid use and risk of heart failure decompensation (1–3). It has therefore been hypothesized that for patients with heart failure, corticosteroids with a diminished mineralocorticoid potency may be beneficial, though concrete clinical evidence remains elusive.

Prednisolone is the most frequently prescribed corticosteroid. Although methylprednisolone shares many of the therapeutic indications with prednisolone, a notable distinction between the two lies in their relative potencies: While methylprednisolone exhibits a superior glucocorticoid effect, its mineralocorticoid effects are considerably milder.

2. Objective

This Statistical Analysis Plan (SAP) outlines the methodology for an emulated target trial in a Norwegian health registry study aimed at comparing the effects of methylprednisolone and prednisolone on the risk of acute decompensated heart failure. We hypothesize that the differences in mineralocorticoid effects between the two medications will lead to lower rates of acute decompensated heart failure in patients treated with methylprednisolone compared to prednisolone. This SAP guides the statistical analysis by first detailing the target trial protocol and then the procedures that will be employed to emulate the target trial, including data handling, outcome assessment, and methodological approaches.

3. Protocol for target trial

Eligibility criteria: Individuals aged over 18 years as of January 2008, with medical conditions that indicate corticosteroid therapy (listed below) who have not had corticoid prescriptions dispensed in the preceding 6 months. Patients receiving palliative care, those

presenting with malignancy-related symptoms, medical complications or those receiving treatment post-organ transplantation will be excluded to void confounding effects.

Treatment strategies Eligible patients will be randomized into two treatment groups. One group will receive methylprednisolone tablets, while a second group will receive prednisolone tablets. The dosages for both methylprednisolone and prednisolone will be determined at the discretion of the treating physician, customized for the specific clinical need in accordance with local guidelines.

Treatment assignment The treatment strategy will be randomly assigned at baseline. Patients will be aware of which drug they have been assigned.

Outcomes The primary outcome is acute decompensated heart failure leading to acute contact with secondary or tertiary healthcare facilities during the first 6 months after treatment initiation. Secondary outcomes include the initiation or escalation of loop diuretics. A composite of both primary and secondary outcomes will also be assessed.

Follow-up Participants will be followed from the baseline until the occurrence of the primary outcome, death, emigration, loss to follow-up, or at 6 months post-baseline, whichever occurs first.

Statistical analysis The primary comparative analysis between the two treatment groups will be performed on an intention-to-treat basis, with all randomized patients in their initially assigned groups. For the primary outcome, survival plots with restricted mean survival time (RMST) differences with 95% confidence intervals will be applied to estimate the treatment effect size. Secondary outcomes will be analyzed using the appropriate statistical tests based on their distribution. Missing data will be handled appropriately using multiple imputation methods. All analyses will be two-sided, with a significance level set at 0.05.

4. Data sources for target trial emulation

This registry-based study will include data from the nationwide Norwegian Cardio-Rheuma Registry (NCRR) that encompasses the entire Norwegian adult population over a ten-year period from January 2008 to December 2017.

The registry is approved by the Norwegian General Data Protection Regulation (16/00482-11/CDG), the South East Norway Health Authority Ethical Committee (2016/588), and the Data Protection Officers at Oslo University Hospital (2016/924) and Diakonhjemmet Hospital (7/12–2019). The NCRR comprises routinely recorded administrative data, and written consent from study subjects was not required.

For this study, we will use data from three key sources: The Norwegian Prescription Registry (NPD) serves as the foundation for prescription data, The Norwegian Patient Registry (NPR) provides diagnosis data, and data regarding age and sex are extracted from Statistics Norway (SSB). The data from these registers provide accuracy up to the month and year, but not to the exact date of events, like prescriptions or diagnoses.

5. Data preparation and eligible treatment periods in the target trial emulation

To maintain comparability between the methylprednisolone and prednisolone treatment groups in the emulated study, we will apply several data management steps:

1) Individuals aged ≤ 18 years in January 2008 will be excluded
2) Analyses will be restricted to tablets, as prednisolone is only available in this form.
3) To allow for equipotent dose comparisons, we will focus only on 4 mg and 16 mg methylprednisolone and their counterparts in prednisolone at 5 mg and 20 mg, respectively. Patients with other doses will be excluded.
4) To facilitate comparisons of treatments prescribed for similar conditions, we will only include prescriptions with an International Classification of Diseases, 10th Edition (ICD10) or International Classification of Primary Care, 2nd Edition (ICPC2) refund code.
5) Patients with prescriptions for diagnosis codes including palliative care, cancer symptoms, medical complications, and organ transplants will be excluded. This exclusion aims to reduce the inherent heterogeneity within these groups, allowing for a more comparable baseline risk.
6) An initial 2-year observational period, spanning from January 2008 to December 2009, will be used to establish comorbidities. Accordingly, only prescriptions of methylprednisolone or prednisolone dispensed from January 2010, onward, will be eligible for analyses.
7) To minimize the risk of carry-over effects, we will exclude all prescriptions prescribed ≤ 6 months after another prescription for a corticosteroid. Accordingly, the same patient can contribute data on several treatment courses, provided that there was > 6 months since the last prescription was dispensed (See section 7 for justification for why a 6-month interval was chosen).
8) Duplicate prescriptions (same date, drug and dosage) will be kept in the analyses as a single treatment course. Cases of duplicate prescriptions on the same date, but where the drug or dosage is different will be excluded.

9) Baseline of the treatment course will be defined as the date when the prescription of either methylprednisolone or prednisolone was dispensed.

6. Emulated target trial matching procedure

In order to create balanced treatment groups and reduce the potential for confounding in the emulated study, we will apply a matching process for baseline characteristics including relevant comorbidities. Each methylprednisolone treatment course will be matched 1:1 with a prednisolone treatment course. The following characteristics will be matched for:

- Sex
- Age groups, defined as: < 45 years; 45 up to < 60 years; 60 up to < 75 years; 75 years or higher
- Equipotent dosage (4 mg methylprednisolone versus 5 mg prednisolone; 16 mg methylprednisolone versus 20 mg prednisolone). While prescription data from the NPD cannot provide the exact number of tablets of either medicine taken per day, we will assume that since the medications are taken by comparable populations and for comparable conditions, any differences will even out in this large dataset.
- Prescription groups based on ICD10 / ICPC2 refund codes:
    i. Pulmonary
    ii. Rheumatology and musculoskeletal
    iii. Neurology and ophthalmology
    iv. Dermatology
    v. Endocrinology and metabolic
    vi. Gastrointestinal
    vii. Hematology and immunology
    viii. Nephrology.
- Comorbidities as categorical variables (a. – e. defined as at least one ICD10 diagnosis code from a secondary or tertiary healthcare provider or at least one prescription of medication with relevant ICPC2 or ICD10 refund codes)
    a. Atherosclerotic cardiovascular disease (coronary, cerebral and peripheral artery disease)
    b. Chronic kidney disease
    c. Diabetes (type 1 and 2)
    d. Hypertension
    e. Heart failure

f. Chronic obstructive pulmonary disease, defined as at least one diagnosis code from a secondary or tertiary healthcare provider (not medication, as this is not included in the dataset).
g. Use of lipid-lowering drugs, defined as at least one prescription of lipid-lowering drugs

7. Defining time intervals for outcome measurement and new treatment courses in the emulated target trial

Data on the temporal relationships between corticosteroid therapy and heart failure decompensation are scarce. A previous nested case-control study by Souverein *et al*. found that current use of oral corticosteroids was associated with an increased risk of heart failure (adjusted OR 2.66 [CI 2.46 to 2.87]) (1). This risk was considerably higher than among patients with recent (corticosteroid prescription last 3 to 12 months) and past (corticosteroid prescription last > 12 months) corticosteroid use (adjusted OR 1.40 [CI 1.27 to 1.55] and 1.19 [CI 1.08 to 1.32], respectively). Moreover, the association was stronger in the group with higher doses, although the dose-response relation was not continuous. However, no clear association with cumulative dose was observed. Later, a Taiwanese nationwide population-based study evaluating the effect of corticosteroid bursts ($\leq$14 days treatment) in patients with heart failure also found that the risk was highest (incidence rate ratio 2.37 [CI 2.13 to 2.63]) during the first 5 to 30 days after treatment initiation, and considerably attenuated (incidence rate ratio 1.35 [CI 1.24 to 1.47]) during days 31 to 90 (2).

We must also consider the granularity of our data, which is limited to months and not days. For instance, a prescription recorded in January and an event in June could be 6 months apart (from Jan 1st to June 30th), but it could also effectively be 4 months apart (from Jan 31st to June 1st). Based on these considerations, we reason that 6-month intervals will provide a balanced period for observing medication effects on outcomes.

Due to the low granularity of our time data (limited to months and not days), the outcomes will be recorded from the first day of the month after the corticosteroid prescription. This is to make sure that the temporal relationship is in order and avoid cases where the corticosteroid prescriptions were dispensed after the outcomes.

Our understanding of potential carry-over effects from one corticosteroid treatment course to another is limited. Thus, the ideal approach for our study would involve analyzing only the first instance of corticosteroid therapy to avoid such effects. However, since our dataset begins in January 2008, tracking the initial therapy instance for each patient is not

feasible. Given the findings of Souverein *et al.* that the cumulative corticosteroid dose was not associated with heart failure, and considering that the risk did not significantly increase between months 3 and 12 compared to after 12 months, we believe that a prescription dispensed ≥6 months after the last one provides a sufficient buffer. This approach ensures minimal residual effects from the previous treatment within the constraints of our dataset.

8. Primary outcome in the emulated target trial

The primary outcome of interest is an acute hospital contact (secondary or tertiary healthcare facilities) where the patient was given a primary diagnosis code for heart failure (ICD10 code i50*) at discharge. As discussed in section 7, the outcome will be assessed from the first day of the month after the corticosteroid prescription was dispensed and the following 5 months. This window will not be extended in cases where subsequent prescriptions for the corticosteroid is made so that the treatment course is longer than 6 months.

9. Secondary outcomes in the emulated target trial

Three secondary outcomes will complement the primary analysis. As for the primary outcome, we will investigate outcomes occurring during the first 6 months following the prescription of methylprednisolone or prednisolone. The secondary outcomes are as follows:

1. Any contact (acute or elective) with secondary or tertiary healthcare facilities where a primary diagnosis of heart failure is recorded
2. Initiation of newly prescribed loop diuretics or any increase in doses within the first 6 months after the prescription of methylprednisolone or prednisolone.
3. A combination of secondary outcome 1. and 2.

10. Subgroup analyses in the emulated target trial

The primary and secondary outcomes will be analyzed for the study population as a whole and within the following subgroups:

1. Only individuals with existing heart failure
2. Only individuals with existing heart failure or established ASCVD
3. Only individuals with at least 3 comorbidities (a. to g.)

11. Statistical analysis in the in the emulated target trial

- *Descriptive Statistics*: The study will commence with descriptive statistics to provide an overview of baseline patient characteristics. This will include the calculation of means,

medians, standard deviations, and proportions to summarize key characteristics: Age, sex, comorbidities and glucocorticoid refund codes. Data will be presented in Table 1.
- *Primary and secondary outcomes:* We will employ appropriate statistical methods / survival analyses to assess the relationship between dichotomous treatment variables (methylprednisolone or prednisolone) and dichotomous outcomes of interest. These methods will be chosen based on the distribution and characteristics of the data, with consideration given to the matched nature of the study design and the requirements of each statistical test for valid results. Subgroup analyses will only be performed in the event of significant results in their respective primary and / or secondary outcome analyses. If manuscript formatting guidelines allow it, data will be presented in Figure 1 and 2. Sensitivity analyses including fatalities during follow-up will be presented in Figure 3.
- *E-value for sensitivity analyses:* To evaluate the robustness of our observed associations to potential unmeasured or residual confounding, we will calculate the E-value as described by VanderWeele and Ding (4).
- *Statistical Software:* The statistical analysis will be carried out using STATA MP16. A significance level of 0.05 will be used for all hypothesis tests.

12. Considerations about possible bias and limitations to the emulated target trial

Our emulated target trial will be subject to several sources of bias and potential limitations that merit consideration. First, the data we have is accurate only to the month and year, not to the exact date of events like prescriptions or diagnoses. This lack of precision can introduce temporal biases, particularly in the calculation of the duration between prescription dispensation and subsequent health outcomes. The imprecision in timing could either overestimate or underestimate the association between corticosteroid use and heart failure decompensation.

Second, for the purpose of matching methylprednisolone and prednisolone prescriptions, we have categorized them into broad disease groups based on ICD10/ICPC2 refund codes. While this approach is necessary due to the nature of the available data, it introduces a level of generalization that might overlook nuances in patient diagnoses. The broad categorization may not perfectly align the severity or specific characteristics of the conditions being treated, which could affect the comparability between the two treatment groups.

Third, our data includes information about comorbidities, but lacks details regarding the severity of these conditions. This gap means we cannot fully account for the potential

impact of the severity of comorbidities on the outcomes of interest. It is plausible that more severe comorbid conditions could influence the choice of medication or affect the risk of heart failure decompensation independently of the corticosteroid used.

Fourth, in clinical practice, the choice between methylprednisolone and prednisolone might be influenced by the treating physician's perception of their relative efficacy, particularly in patients with heart failure. This selection bias could mean that methylprednisolone is preferentially prescribed to patients perceived to be at higher risk of heart failure decompensation, based on the hypothesis that it might be better. By calculating the E-value the reader will be able to evaluate themselves whether the likelihood that the observed differences were due to unmeasured confounding. Should the E-value be large, this would suggest that considerable unmeasured confounding would be required to negate the observed effect. Conversely, a small E-value would indicate that our results could be more susceptible to bias from unmeasured confounding. The E-value thus complements our 1:1 matching process and provides additional context for interpreting the possible impact of unmeasured variables on our study outcomes.

This potential bias may be particularly problematic in cases where both the initiation of corticosteroid therapy and the outcome are recorded within the same calendar month. In such cases, it will be difficult to ascertain whether the heart failure event precipitated the corticosteroid prescription or, conversely, whether the corticosteroid use preceded and potentially contributed to the heart failure episode. However, we anticipate that this limitation may introduce a bias counter to our hypothesis, as clinicians are more likely to prescribe methylprednisolone to patients who have recently experienced an acute episode of decompensated heart failure under the belief that it may be safer or more beneficial in managing such patients. This prescribing tendency could result in a conservative bias in our findings, making it harder to detect a true protective effect of methylprednisolone, if one exists, in relation to heart failure decompensation.

Fifth, the definition of acute decompensated heart failure is complicated and ideally requires adjudication by experts with access to echocardiogram, biomarkers etc. By using ICD-10 codes there is a risk of both false positives and false negatives. However, we do not anticipate this bias to impact the treatment groups differently.

Recognizing these biases is crucial when interpreting our findings. If our analysis indicates that prednisolone is associated with less decompensated heart failure compared to methylprednisolone, this could be attributed to the biases mentioned. Conversely, should our results show that methylprednisolone is associated with lower rates of heart failure

decompensation, this would be particularly noteworthy. Such a finding would go against the expected bias in prescription patterns and could suggest a genuine difference in the impact of these medications on heart failure outcomes.

13. References:

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