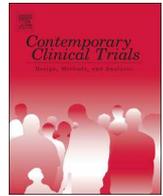




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Non-invasive Ventilation for early General Ward respiratory failure (NAVIGATE): A multicenter randomized controlled study. Protocol and statistical analysis plan

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ABSTRACT

Objective: Few randomized trials have evaluated the use of non-invasive ventilation (NIV) for early acute respiratory failure (ARF) in non-intensive care unit (ICU) wards. The aim of this study is to test the hypothesis that early NIV for mild-moderate ARF in non-ICU wards can prevent development of severe ARF.

Design: Pragmatic, parallel group, randomized, controlled, multicenter trial.

Setting: Non-intensive care wards of tertiary centers.

Patients: Non-ICU ward patients with mild to moderate ARF without an established indication for NIV.

Interventions: Patients will be randomized to receive or not receive NIV in addition to best available care.

Measurements and main results: We will enroll 520 patients, 260 in each group. The primary endpoint of the study will be the development of severe ARF. Secondary endpoints will be 28-day mortality, length of hospital stay, safety of NIV in non-ICU environments, and a composite endpoint of all in-hospital respiratory complications.

Conclusions: This trial will help determine whether the early use of NIV in non-ICU wards can prevent progression from mild-moderate ARF to severe ARF.

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1. Introduction

Non-invasive ventilation (NIV), a technique to deliver positive pressure ventilation through a non-invasive interface, is used worldwide to prevent and treat acute severe respiratory failure (ARF). [1–3] For this purpose, it is an intervention with a well-documented effect on survival in critically ill patients. [4] There are increasing reports on the effective use of NIV outside the ICU [5–9]. In this regard, the use of NIV in general wards may be cost-effective [10] and may allow treatment of patients at an earlier stage of ARF. [3,11]

Moreover, it is logical to hypothesize that the use of NIV in the early phases of ARF (when ARF is mild to moderate in severity) may be beneficial for patients outside ICUs and may avoid the development of severe ARF with its associated need for ICU admission and invasive mechanical ventilation (MV). To date, however, randomized studies of such “early” NIV use for ARF are few and limited to the setting of immunocompromised patients. [12,13]

Accordingly, we designed a controlled trial to test the hypothesis that the addition of early NIV to standard care in patients with mild to moderate ARF could reduce the rate of disease progression.

2. Rationale

ARF is the most frequent cause of deterioration in hospitalized patients assessed by medical emergency teams. [14] There is good evidence of benefit with the use of NIV in specific etiologies of ARF such as acute exacerbation of chronic obstructive pulmonary disease (COPD) [15,16] and cardiogenic pulmonary edema [17–19], and conflicting evidence in other causes of ARF, such as hypoxemic respiratory failure [20] and ARF in immunocompromised patients. [21–23] However, there is also meta-analytic evidence of a beneficial effect in ARF regardless of etiology. [24]

Most studies on the effect of NIV, however, have taken place in intensive care units (ICUs), as this is the appropriate setting for severe ARF and because in the ICU there is maximal expertise on ventilation and adequate equipment. Thus, the ICU environment provides safer and perhaps more effective treatment for patients with moderate or severe ARF.

Use of NIV as an early therapy in mild to moderate ARF to prevent progression to severe ARF, albeit appealing, has been the object of only a few small trials and mixed evidence. A small trial conducted by Hilbert et al. on 52 patients found reduced intubation rates and increased survival in ICU patients treated with NIV compared to usual care in early ARF. [21] A second trial, involving 40 ICU patients and comparing standard care with NIV in early ARF, showed that NIV was associated with a reduction in intubation rate, fatal complications and ICU length of stay, but not with better hospital survival. [25] More recently, however, Lemiale et al. performed a larger trial on 374 ICU patients, showing no difference in 28-day mortality between early NIV

and standard care for ARF. [23] These trials, however, were all conducted in the ICU.

Only two trials were conducted outside the ICU. Squadrone et al. randomized 40 patients on a hematology ward to either standard care or early use of NIV in ARF, showing a reduced progression of disease in the latter group. [12] Wermke et al. randomized 86 patients with ARF to standard therapy or standard therapy with the addition of NIV and found no difference in progression of disease or mortality. [13] However, as reported by the authors, these trials were underpowered to demonstrate differences between the two groups.

In this regard, our trial will be the largest trial on the early use of NIV outside the ICU in patients with mild to moderate ARF, with greater power to demonstrate a difference in the rate of development of severe ARF.

3. Materials and methods

3.1. Study design, approval and registration

We designed a parallel group, randomized, controlled, multicenter trial with a 1:1 allocation ratio. The study was approved by the Human Research Ethics Committees of all participating centers and was registered on clinicaltrials.gov as [NCT01572337](https://doi.org/10.1186/1745-6215-1572337) on April 6, 2012.

3.2. Study aim

The main aim of the study was to test whether the use of NIV in the early stages of ARF could reduce disease progression when compared to usual care. Secondary endpoints of the study aimed to evaluate the impact of early NIV on 28-day mortality and on length of hospital stay.

3.3. Study population/participants

We will enroll 520 adult patients with mild to moderate ARF admitted to a non-intensive-care ward. The inclusion and exclusion criteria are summarized in [Table 1](#). Contraindications to NIV include respiratory arrest, inability to fit mask, hypotensive shock, ongoing cardiac ischemia or arrhythmia, copious upper gastrointestinal bleeding, uncooperating patient, inability to protect airway, swallowing impairment, excessive secretions, multiple organ failure, recent facial, upper airway or upper gastrointestinal surgery, facial trauma/burns, life threatening hypoxemia, vomiting, bowel obstruction, undrained pneumothorax. [3,26] The aim of these criteria is to identify a group of patients with very early mild to moderate ARF and to exclude those patients who have an already established clear indication for NIV. The only etiologic exclusion criteria is COPD exacerbation (in which NIV is considered mandatory); in all other cases, inclusion and exclusion criteria are essentially based on the severity of ARF and not on its cause.

Table 1

– Inclusion and exclusion criteria.

Inclusion criteria (<i>all three have to be present</i>)	Exclusion criteria (<i>one is sufficient to exclude the patient</i>)
<ul style="list-style-type: none"> ● Age > 18 years; ● Admission to non-intensive-care department; ● Mild to moderate ARF, defined as at least one of the following: <ul style="list-style-type: none"> ○ Radiological evidence of new pulmonary consolidation or atelectasis; ○ Peripheral oxygen saturation < 92% while breathing room air or PaO₂/FiO₂ ratio < 300 on arterial blood gas analysis; ○ Decompensated hypercapnia (pCO₂ > 45 mmHg and pH < 7.35); ○ Clinical signs of respiratory distress (dyspnea, utilization of accessory respiratory muscles, paradox movements of thoraco-abdominal wall) on room air. 	<ul style="list-style-type: none"> ● Refusal to sign informed consent ● Respiratory failure due to COPD exacerbation (PaCO₂ > 45 mmHg and pH < 7.35); ● Severe, hypercapnic ARF defined as PaCO₂ > 45 mmHg and pH < 7.30; ● Severe, hypoxic ARF defined as PaO₂/FiO₂ < 200; ● Need for immediate mechanical ventilation or ICU as judged by the ICU physician in charge; ● Extremely poor short-term prognosis (imminent death with decision for palliative treatment only); ● Invasive or non-invasive mechanical ventilation during the same hospitalization due to respiratory failure. ● Contraindications to NIV treatment [3,26]

ARF – Acute Respiratory Failure; COPD – Chronic Obstructive Pulmonary Disease; ICU – Intensive Care Unit.

3.4. Study procedure

The study procedure is summarized in Fig. 1. Patients with mild to moderate ARF (defined as at least one of the following criteria: radiological evidence of new pulmonary consolidation or atelectasis; peripheral oxygen saturation < 92% while breathing room air or PaO₂/FiO₂ ratio < 300 but > 200 on arterial blood gas analysis; decompensated hypercapnia (pCO₂ > 45 mmHg and pH < 7.35) or clinical signs of respiratory distress (dyspnea, utilization of accessory respiratory muscles, paradoxical movement of thoraco-abdominal wall) on room air will be screened for eligibility. If eligible, they will then be approached to explain the study protocol and obtain written informed consent. Once the informed consent has been signed, patients will be allocated to each study group according to a web-based centralized randomization service with the use of a permuted-block design stratified according to center. Data will be collected by trained observers who will not participate in patient care.

Patients randomized to the “usual care” group will receive the best available treatment currently in use in the institution, including oxygen therapy, diuretics, antibiotics and other therapies to treat the underlying cause of the ARF. Patients in this group will not receive NIV treatment unless the medical emergency team deems it necessary. If NIV is administered outside of such restrictions, this will represent a protocol violation.

Patients assigned to the “early NIV” group will receive the same best available treatment as the “standard” group, together with two-hour cycles of NIV every eight hours. Oro-nasal, full-face and helmet NIV interface will be allowed. The preferred NIV treatment will be CPAP (PEEP 5 to 8 cmH₂O) unless the ARF is hypercapnic at enrollment or in the following days. In such cases pressure support ventilation (with a pressure support of 10 to 20 cmH₂O) will be added. Ventilatory parameters will be set (and then modified if required) by physicians on

the basis of clinical judgment and on the basis of the patient's response to the treatment with the aim of reaching a peripheral oxygen saturation > 92% and PaCO₂ < 45 mmHg, without restrictions, according to the pragmatic nature of the study. Chosen settings will be recorded.

The Medical Emergency Team (MET) was responsible for setting-up and initial deliver of NIV in accordance with the physicians of the ward. MET always included an anesthesiologist-intensivist and a nurse and/or a fellow, differing in the various participating hospitals). Monitoring of uncomplicated patients is performed by the ward staff.

Patients will be evaluated before starting each NIV cycle. Treatment with NIV will continue until at least one of the following criteria is met:

- Clinical improvement determined by the resolution of inclusion criteria;
- Patient refusal of treatment due to intolerance, or consent withdrawal;
- Clinical decision of NIV interruption for NIV contraindication or other reasons
- Development of severe ARF defined by one or more of the following criteria:
 - Hypercapnic acidemia (PaCO₂ > 45 mmHg and pH < 7.30)
 - Severe gas transfer deficit (PaO₂/FiO₂ < 200)
 - Persistent respiratory distress (persistent marked dyspnea, use of accessory respiratory muscles, paradoxical respiratory movements)
- Post-randomization decision/diagnosis of extremely poor short-term prognosis (imminent death with decision for palliative treatment only), with withdrawal of non-palliative treatment;
- Need for immediate invasive mechanical ventilation
- ICU admission
- Death

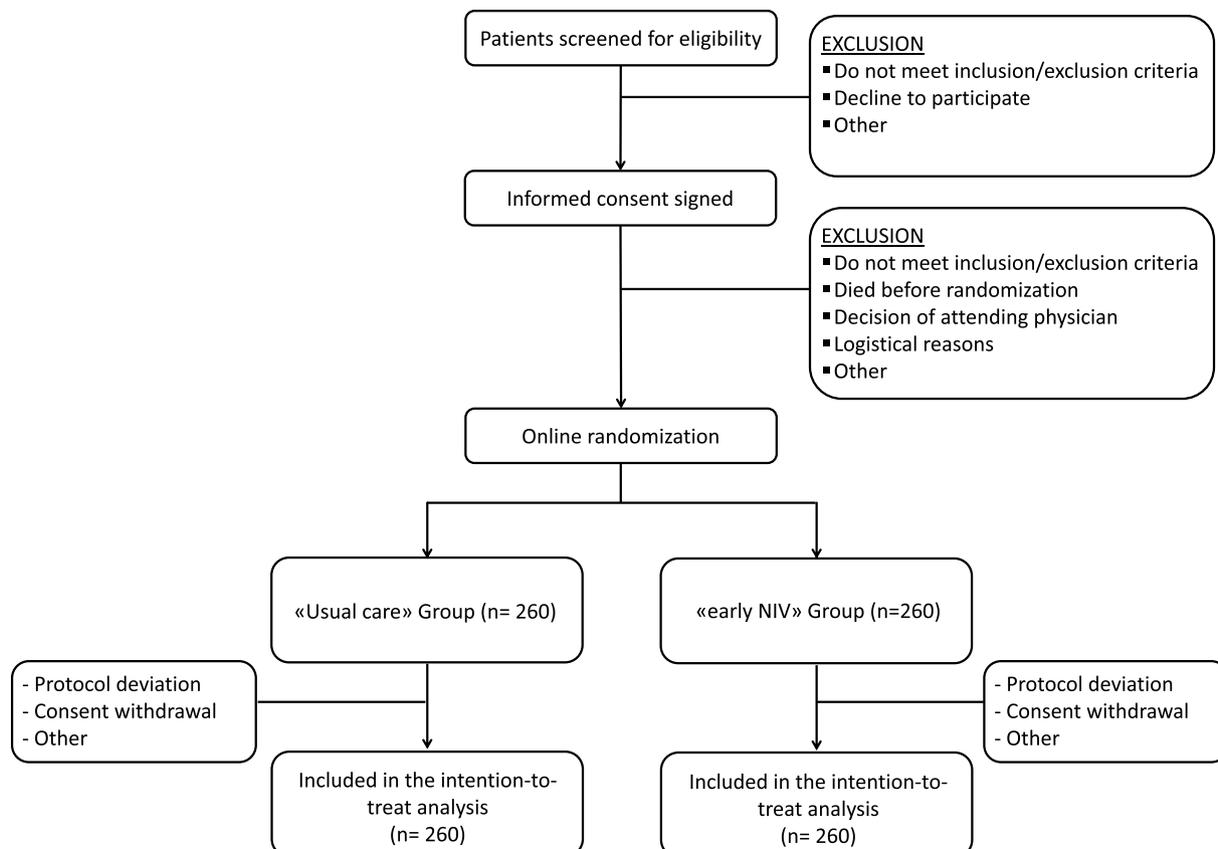


Fig. 1. Study procedure flowchart. NIV – Non-invasive ventilation.

Treatment with NIV will last for at least 24 h (3 cycles) unless interruption criteria (with the exception of clinical improvement) are met.

Target peripheral oxygen saturation will be 92–95% in both groups. Clinical re-evaluation (inclusive of re-checking for inclusion and exclusion criteria) will be performed daily by the medical emergency team or more often if deemed necessary by the ward physicians.

As the protocol is carried in general wards, an arterial catheter is never positioned. Arterial blood gas analyses are only performed upon clinical judgment by means of single shot arterial punctures.

NIV treatment will continue for 4-day periods. At the end of each period, patients will undergo a 6-h screening test during which they will breath room air. If their SaO₂ decreases below 95%, or the respiratory rate increases to > 25 breaths/min, patients will be returned to the assigned treatment for another 4-day period. The treatment protocol will be discontinued when the patient has a SaO₂ > 95% and respiratory rate < 25 breaths/min. [12] This does not apply to patients who have already reached the primary endpoint or one of the above-mentioned reasons for NIV discontinuation. (Fig. 2).

3.5. Data collection

We will collect demographic data (age, sex), as well as baseline pathophysiological data (height, weight, comorbidities). Two independent Investigators will assess and record the main cause of acute respiratory failure, as well as concomitant causes and the therapy the patient is receiving. Vital signs (respiratory rate, peripheral oxygen saturation, Glasgow Coma Score, arterial blood pressure, heart rate) and arterial blood gas data (where available) will be recorded at all

scheduled time points if the patient will be not yet discharged from the hospital. Information on ventilator parameters, along with complications and potential contraindications to NIV treatment, will also be collected.

Follow-up will be performed at 28, 90 and 365 days after randomization either via direct visit or telephone call.

Individual participant data that underlie the results reported in the trial's final results article, after deidentification, agreement of the privacy office of the Institute and ethical committee approval will be shared upon request 9 months to five years after the publication of the trial's final results. Study protocol and informed consent form will also be available upon request. Requesters must have a demonstrated experience in medical research, with no conflict of interest that may potentially influence their interpretation of any analyses. The data sharing will be only for the purposes of health and medical research and within the constraints of the consent under which the data were originally gathered. Requester will be required to enter into a Data Sharing Agreement which will follow the Ethical Committee and Privacy Office updated indications.

3.6. Study endpoints/outcomes

According to the recommendations of the European Society of Anaesthesiology (ESA) and the European Society of Intensive Care Medicine (ESICM) joint task force [27], the study will also focus on clinically relevant outcomes such as mortality, need for invasive mechanical ventilation, length of hospital stay and ICU admission.

The primary outcome will be the development of severe ARF defined by one or more of the criteria described above. Prespecified

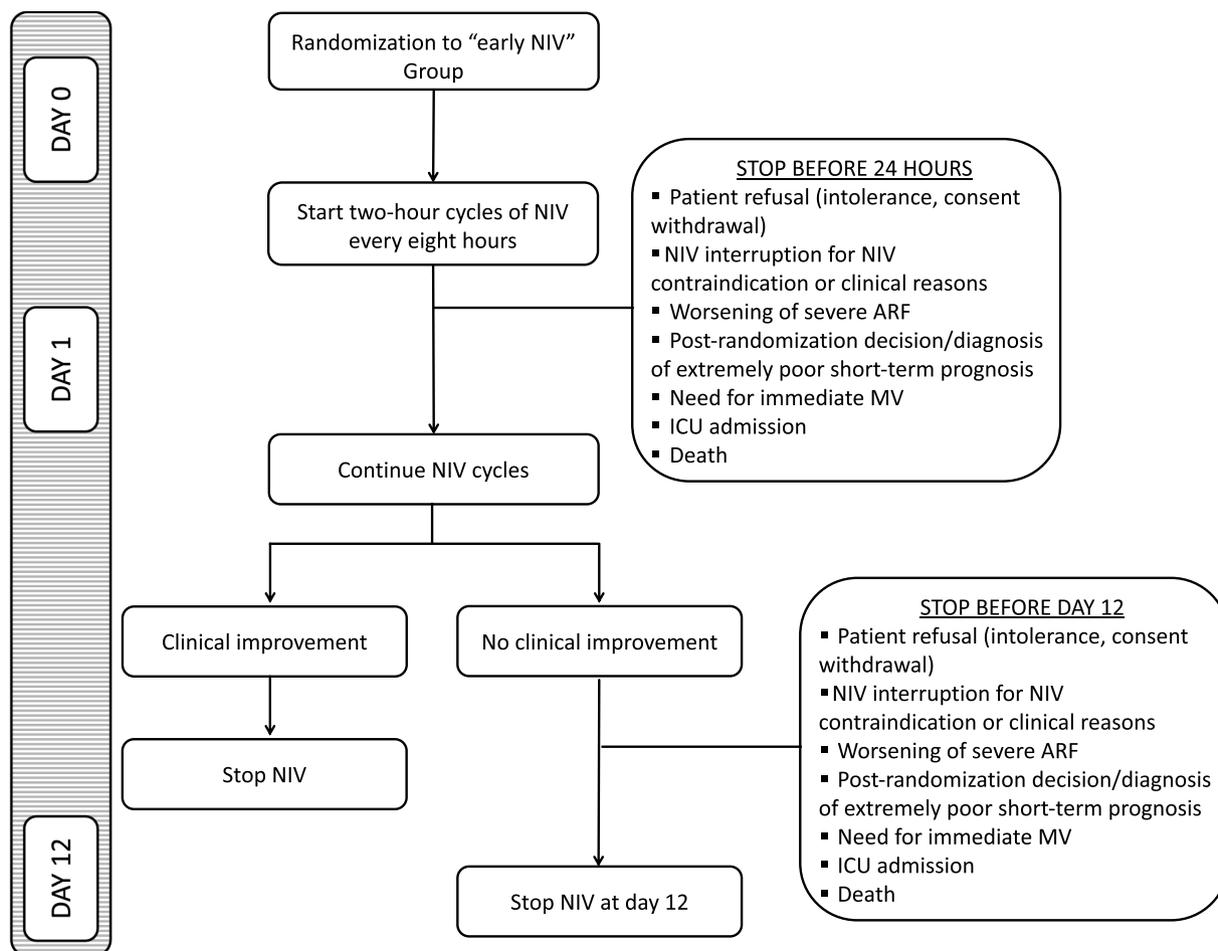


Fig. 2. Intervention diagram.

subgroups analyses for the primary endpoint will be: age < 75 years old; $20 \leq \text{BMI} < 30 \text{ kg/m}^2$; respiratory rate < 25 per minute; post-operative patients.

Secondary outcomes will include 28-day mortality, length of hospital stay, as well as a composite endpoint of all in-hospital respiratory complications (comprising atelectasis, nosocomial pneumonia, new pneumothorax, pleural effusion, intubation, tracheostomy and acute respiratory distress syndrome as defined by the Berlin definition). [28]

Atelectasis will be defined as lung opacification with a shift of the mediastinum, hilum or hemi-diaphragm, and compensatory over inflation in the adjacent non- atelectatic lung. [29]

Nosocomial pneumonia will be defined as two or more serial chest radiographs with at least one of the following findings (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease): (i) New or progressive and persistent infiltrates, (ii) consolidation, (iii) cavitation; AND at least one of the following: (a) fever ($> 38^\circ\text{C}$) with no other recognized cause, (b) leukopenia (white cell count $< 4 \times 10^9/\text{l}$) or leukocytosis (white cell count $> 12 \times 10^9/\text{l}$), (c) for > 70 -year old adults, altered mental status with no other recognized cause; AND at least two of the following: (a) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, (b) new onset or worsening cough, or dyspnea, or tachypnoea, (c) rales or bronchial breath sounds, (d) worsening gas exchange (hypoxemia, increased oxygen requirement, increased ventilator demand) occurring > 48 h after hospital admission and not appearing to be incubating at the time of admission. [30]

Pneumothorax will be defined as air in the pleural space with no vascular markings surrounding the visceral pleura. [29]

Pleural effusion will be defined as chest X-ray demonstrating blunting of the costo-phrenic angle, loss of the sharp silhouette of the ipsilateral hemi-diaphragm when upright, displacement of adjacent anatomical structures, or a hazy opacity in one hemithorax with preserved vascular shadows when supine. [29]

3.7. Statistical analysis and sample size estimates

Data will be collected by the investigators and stored electronically in a digital Excel spreadsheet (version 2010, Microsoft Corporation, Redmond, WA, USA) and analyzed using STATA (Stata Statistical Software: version 15, College Station, TX, USA). Statistical analysis will be performed by an epidemiologist. All analysis will be performed by an independent statistician blinded to intervention allocation. We will not apply any imputation for missing data. All data will be analyzed according to the intention-to-treat principle. The only exception will be those patients that, after randomization, are declared terminally ill and only receive palliative interventions: this decision will be taken as standard practice by the MET in conjunction with the caring ward staff and shared with the patient and his/her family.

Demographic and baseline disease characteristics will be summarized with the use of descriptive statistics. Categorical variables will be reported as absolute numbers and percentages. Unadjusted univariate analyses to compare the two groups will be performed using Pearson's χ^2 test or Fisher's exact test as appropriate. Risk differences and 95% confidence intervals will be calculated by means of the two-by-two table. Continuous variables will be reported as mean \pm standard deviation or median and interquartile range, based on the distribution. Normality will be evaluated with the Shapiro-Wilk normality test, along with visual histogram evaluation and a Q-Q plot, and differences between groups will be tested using Student's *t*-test or the Wilcoxon signed rank test, as appropriate.

A logistic regression model using a stepwise selection will be used to estimate the treatment effect with respect to primary and secondary endpoints and predictors of mortality. The pre-randomization clinical data (e.g. demographic and baseline pathophysiological data) and center will be entered into the model if their univariate *p* value is < 0.2 .

Collinearity and overfitting will be assessed using a stepwise regression model and Pearson correlation test. The treatment group will be forced into the multivariate model. A classic logistic regression will be performed with a consistent number of events and the number of covariates in the model will be decided based on the number of outcome events. In the multivariate analyses, clinical factors or potential confounding variables will be expressed as odds ratio with 95% confidence interval (CI).

We will compare patients receiving NIV with those assigned to standard care for time to event with the log-rank test and display such comparison with Kaplan-Meier survival curves. A time to event analysis with a Cox regression will be performed to adjust for key baseline characteristics.

Two *interim* analyses performed by an independent safety committee after recruiting 25% ($n = 130$) and 50% ($n = 260$) of patients are planned. Data evaluation at each interim analysis will be based on the alpha spending function concept, according to DeMets, [31] and will employ O'Brien-Fleming Z-test boundaries. [32] During the first *interim* analysis the efficacy stopping rule will require a *p* value ($p < .005$), while a higher value ($p < .014$) will be required for the second analysis. Investigators will be kept blind to the interim analysis results.

The independent safety committee will also perform conditional power analyses in order to evaluate potential interruption for futility issues in the trial. Conditional power will be calculated by assuming that the proportion of outcomes will follow the observed trend.

Based on available literature [12,13], we have hypothesized that the primary endpoint will be reached by 22% of patients in the "usual care" group and in 11% of patients in the "early-NIV" group. We based the sample size computation on a two-sided alpha error of 0.05 and a power of 90% using Pearson's χ^2 test. Therefore, we calculated 256 patients per group using the continuity correction (260 considering possible protocol deviations) for a total of 520 patients.

3.8. Monitoring of the study

Study auditors will verify the strict adherence to the clinical trial protocol and will confirm accurate data collection according to Good Clinical Practice guidelines. [33] Study monitoring and follow-up, from initial set-up to final reporting, will be fulfilled according to national and international requirements.

3.9. Ethical aspects

It is important to evaluate the role of early initiation of NIV in addition to standard therapy as this may prevent progression to severe ARF in patients, as previously reported, [12,15,34] and consequently might improve outcomes and reduce healthcare costs.

The exclusion of patients with acute exacerbation of COPD is due to the fact that NIV is first-line therapy in these patients [26] and it would be unethical to deprive them of this treatment. Data will be stored in an electronic database with no patient identifiers (a unique numeric code will be used) to address privacy issues.

3.10. Study initiation, timing and participating centers, source of funding

The study started after Ethical Committee approval from each contributing recruiting center. Recruitment started in April 2012 as a single center trial to assess feasibility. The study became multicentric in 2016. Consecutive participants who meet eligibility criteria and sign the written informed consent are enrolled. The study progress will be updated monthly. Currently, six hospitals have randomized a total of 175 patients.

The authors are solely responsible for the design and conduct of the study, all study analyses and drafting and editing of the final research paper.

The trial is funded with departmental funds only.

4. Expected results

In the present study, we will test the hypothesis that the early addition of NIV in non-ICU patients with mild-moderate ARF would reduce development of severe ARF from 22% to 11%. Our trial will help determine whether NIV can play a wider role in the treatment of ARF than it currently does, possibly reducing short-term mortality and length of hospital stay.

4.1. Limitations

A possible limitation of the study is the absence of a strictly defined “usual care” in the control group, leaving the definition of best available treatment to the single participating centers. We believe, however, that this pragmatic approach can also be seen as a strength of our study, which will allow us to capture the complex reality of tertiary centers and allow each patient to be treated according to best available local expertise and logistics. In this context, for example, echocardiography is only performed in those with a positive history or clinical features of cardiac dysfunction (severe right ventricular dysfunction is a contraindication to NIV) and lung ultrasound for pleural effusion is only performed at discretion of clinicians caring for the patients.

Moreover, as the study will take place in ordinary, non-intensive general medical or surgical wards, that do not have the resource and staffing of ICUs, we anticipate that the adherence to study protocols, both by patients and by staff, may not be perfect. However, we believe this is also a potential strength of the study, as it would investigate and measure use of NIV in a “real world” environment and not solely as part of a tightly controlled experimental protocol. Furthermore, due to the nature of NIV treatment, blinding is not an option in this setting. Also, the exclusion criteria cut out from the present study some of the patients who might benefit more from NIV: COPD exacerbation. As NIV has been already demonstrated extremely beneficial in this setting, in many centers, it is used immediately as first-line therapy in this population. Therefore, we decided to exclude these patients, even if this may reduce the magnitude of our findings. However, this might be seen as a strength more than a limitation, as it is more ethical and improves the validity of our eventual positive findings. Lastly, the hypothesized effect size might be considered too big, but we consider it very prudent since, following the results of Squadrone et al. [12] the sample size should have been 49 patients per group only and following the results of Wermke et al., [13] the sample size should have been 213 per group. Our prudent decision of enrolling 520 patients is driven by the heterogeneity of our population, that represents the daily complexity of large hospitals.

5. Conclusions

This will be the first large randomized controlled trial performed outside the ICU and comparing the effect of the early addition of NIV to usual care in patients with mild to moderate ARF. Evidence resulting from this study will potentially be of value in the effective early management of patients with ARF.

Conflict of interest

Prof. Biondi-Zoccai has consulted for Abbott Vascular and Bayer.

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