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ORIGINAL ARTICLES

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ORIGINAL ARTICLE

Evaluation of intra-abdominal pressure as an early marker of diuretic response in patients with cardiorenal syndrome

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Abstract

Introduction: Renal dysfunction and heart failure (HF) are closely intermingled, even though their pathophysiology is not fully understood. Recently, abdominal congestion, through an increase of intra-abdominal pressure (IAP), has been proposed as a novel and important factor in cardiorenal interactions. In this study, we postulated that IAP is linked to renal function and diuretic response in acute heart failure (AHF) patients. **Objectives:** The objectives of this study were to analyze whether IAP variations in AHF patients are associated with changes in renal function and diuretic response during the first 72 h of admission. **Methods:** The prospective, observational, and single-center cohort study in AHF patients admitted at the Internal Medicine department. Multiparametric congestion assessment, including X-rays, point of care ultrasoung, serum biomarkers and IAP, will be performed during the first 72 h. **Conclusions:** We aim to broaden the knowledge about IAP changes and its correlation with renal function and diuretic response in patients admitted with AHF.

Keywords: Intra-abdominal pressure. Cardiorenal syndrome. Congestion. Diuretic response.

Introduction

The link between heart and kidney has been currently named as cardiorenal syndrome[1] and interpreted as a multisystemic complex with an essential role in patients with HF[2]. Conventionally, the presence of acute kidney injury (AKI) or worsening renal function (WRF) in AHF has been explained through the activation of renin-angiotensin-aldosterone system and sympathetic nervous system[3,4]. However, congestion, defined as intravascular volume expansion and increased central venous pressure (CVP), has been shown as another important pathophysiological mechanism in cardiorenal interactions[5,6]. The novel concept of congestive nephropathy has been proposed to define AKI and/or WRF caused by congestion in the context of AHF[7,8], an so, new tools are needed to detect renal congestion in clinical practice. In this context, diuretic response might be essential to improve outcomes and avoid "truth" WRF, and some new strategies have been developed to standardize endovenous loop diuretics during the 1st days after an AHF admission. Specifically, Testani et al.[9] developed a new equation that has been subsequently validated[10],

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Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Age ≥ 18 years. 2. Patients with a previous or new onset diagnosis of heart failure, according to the latest ESC Guidelines. 3. Presence of symptoms (dyspnea in NYHA functional class II, III, IV) and/or congestive signs (edema, ascites, jugular engorgement, lung crackles, or pulmonary congestion signs on chest X-ray). 4. NT-proBNP concentration at baseline ≥ 1000 pg/mL. 5. Candidates for the administration of intravenous diuretics according to routine clinical practice. 6. A transthoracic echocardiogram performed in a period < 12 months or during hospitalization. 7. Written and signed informed consent.
Exclusion criteria
1. Direct admission to the intensive care unit. 2. Significant functional dependence (Barthel scale < 50 points). 3. Moderate or severe cognitive impairment (Pfeiffer scale). 4. Need for renal replacement therapy. 5. Active contraindication for bladder catheterization.

capable of predicting early natriuresis, with a spot urine sample collected 2 h after loop diuretic administration.

Otherwise, intra-abdominal hypertension, defined as an increase of intra-abdominal pressure (IAP) above 12 mmHg[11], has been postulated as a potential mechanism of AKI which contributes to worsen outcomes in AHF[11-15].

Nonetheless, the link between IAP, diuretic response, and AKI are still far from been elucidated. Although some studies have related IAP to the occurrence AKI and/or worse outcomes[14], most of them were not specifically designed to seek the relation among them[11,13-15]. Whether IAP might be used for guiding diuretic therapy which is still to be demonstrated.

We hypothesize that the insufficient reduction or maintenance of IAP after the initial doses of intravenous (i.v.) furosemide, during the first 72 h of admission for an AHF, correlates with WRF and worse diuretic response. The aims of this study are to analyze IAP variations in patients with AHF and their correlation with the occurrence of AKI, diuretic response, biomarkers of congestion, and major outcomes (death from any cause, readmission for HF, and/or anticipated need for i.v. diuretics) 90 days after discharge.

Methods

Study design

The prospective, observational, and single-center cohort study to be carried out at the Internal Medicine Department of a tertiary hospital. Inclusion and exclusion criteria are shown in table 1.

Protocol

In those patients who fulfill inclusion criteria, the protocol will be explained and informed consent will be provided.

Timetable of study:

- Admission: defined as first 24 h after hospital admission.
- Assessment at 48 h
- Assessment at 72 h
- Post-discharge assessment: 30 days after discharge, on an ambulatory basis at internal medicine out-clinic.
- Final assessment: 90 days after discharge.

All variables analyzed at each checkpoint are listed and presented in table 2 and moreover, the subsequent variables will be recorded: (1) date of admission, (2) date of discharge, (3) number of admissions for AHF at 30 and 90 days after discharge, (4) death at 90 days, (5) cause of death, and (6) WRF (increase of creatinine > 0.3 mg/dL after discharge) at 30 and 90 days.

Some of the procedures and measurements will be explained as follows.

Laboratory samples

Serum and plasma samples will be collected following routine clinical practice. Biochemistry and blood counts (Table 3) will be performed at local laboratories, following the manufacturer's recommendations for each of the techniques.

Table 2. Variables analyzed at each checkpoint

	Admission	48 h control	72 h control
Demographic data	X		
Clinical record	X		
NYHA score	X		X
VAS scale (dyspnea)	X		X
Weight	X	X	X
Urine output		X	X
Dose of intravenous diuretic		X	X
Vital signs	X		X
Congestion assessment	X		X
Renal doppler ultrasound	X		X
Inferior vena cava ultrasound	X		X
Intra-abdominal pressure mesurement	X		X
Urine sodium levels	X		X
NT-proBNP plasma concentrations	X		X
CA125 plasma concentrations	X		X
Blood chemistries	X		X
Blood count	X		X
Iron metabolism	X		
Biobank	X		X
	Post-discharge control after 30 days		**Post-discharge control after 90 days**
Hospital admissions due to HF	X		X
Intravenous diuretic requirement	X		X
Death	X		X
Cause of death	X		X
Deterioration of renal function	X		X
NT-proBNP plasma concentrations	X		X
CA125 plasma concentrations	X		X
Blood chemistries	X		X
Blood count	X		X
Electrolytes in urine	X		X

NYHA score: New York Heart Association score; VAS: visual analog scale; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; CA125: cancer antigen 125; HF: heart failure.

Table 3. Blood test parameters determined in the study

Blood chemistries	Urea (g/dL) Creatinine (mg/dL) Sodium (mmol/L) Potassium (mmol/L) Chlorine (mmol/L) LDH (U/L) CPK (U/L) AST (U/L) ALT (U/L) C-reactive protein (mg/L) Albumin (g/L) Ferritin (microg/dL)
Blood count	Hemoglobin (g/dL) Hematocrit (%) Total leukocytes (mm^3) Total lymphocytes (mm^3) Platelets (mm^3)
Qualitative urine analysis	Sodium (mmol/L) Potassium (mmol/L) Chlorine (mmol/L) Creatinine (mg/dL) Urea (mg/dL)
Biomarkers	NT-pro BNP CA125

Congestion assessment

Chest X-ray

The arrival chest X-ray will be review to grade pulmonary congestion.

The following findings will be recorded: cardiomegaly, pulmonary venous congestion, pulmonary interstitial edema, pulmonary alveolar edema, or pleural effusion.

Lung ultrasound

Lung ultrasound will be carried out evaluating the presence of B-lines (using the 8 fields method[16]) or pleural effusion.

IAP measurement

IAP will be measured through the bladder catheter technique[17]. A bladder catheter has to be placed in every case, and so, those patients with no medical indication for the utilization of bladder catheterization, who accept to participate in this study, will signed a voluntary and specific inform consent for bladder catheterization with research uses. IAP will be measured using the Unometer Abdo-pressure® system specifically designed for this purpose; this will be connected to the urine catheter, and, using a fluid column, it will estimate the IAP (Fig. 1).

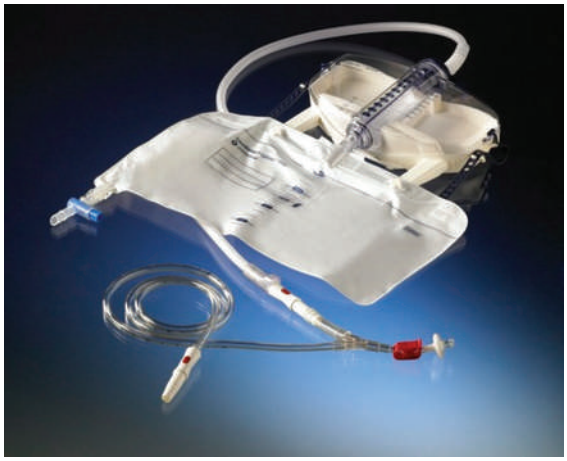

Figure 1. Unometer Abdo-pressure® system.

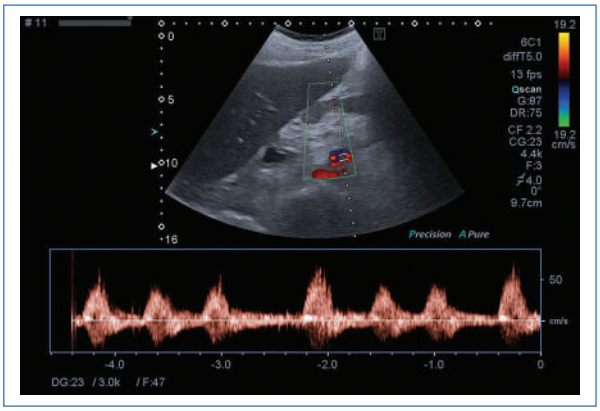

Figure 2. Renal doppler as part of VeXus protocol.

Inferior vena cava (IVC) measurement

Within the first 72 h, the IVC diameter will be measured as well as its collapse on inspiration[18]. This assessment will be performed through ultrasonography: a LOGIQ F6 ultrasound (General Electrics Healthcare©) with a transducer probe G3S of 1.7-3.8 MHz will be used.

Renal Doppler ultrasound

Doppler ultrasound will be performed on the right kidney with the patient in the left lateral decubitus using a convex probe. Color Doppler will be used to locate the interlobar vessels and pulsed Doppler will be used,

to record arterial and venous flow simultaneously. After the examination, venous Doppler patterns will be classified into continuous or discontinuous flow. An example is available in figure 2.

Database and statistical analysis

An exploratory sample size of 100 patients has been selected for this preliminary study.

Patients' data will be collected on paper. The statistical analysis, including descriptive, univariate, and multivariate comparative studies and multivariate comparative studies (using regression analysis) as well as survival analysis using Kaplan–Meier curves and Cox regression analysis, will be performed using the program SPSS, version 24.0 (IBM Corp., Armonk, NK).

The clinical and analytical data collected will be stored together with a written copy of the informed consent.

Ethical issues

The study will be carried out under the fundamental guidelines of the International Declaration of Helsinki and, on May 5, 2021. In addition, the study protocol has been approved by the Clinical Research Ethics Committee of Aragon, encoded as PI21/226. The creation of the collection of biological samples has also been approved by the same Committee, encoded as COL21/003.

Discussion

A large proportion of patients with HF have antecedents of chronic kidney disease (CKD)[1]. This background contributes to their short and long-term prognosis[19]. The high prevalence of CKD in patients with HF is due to the number of shared etiologies and pathophysiological mechanisms which contribute to the onset, maintenance, and progression of renal and cardiac dysfunction (cardiorenal syndrome)[2,3].

Hypoperfusion has been traditionally argued as one of the mechanisms to explain WRF during AHF[3]. Nevertheless, other studies such as Mullens et al. in 2009[20] outlined the idea that venous congestion might be an important factor, and not only a consequence, of renal function impairment. This link between WRF and CVP was not found with other variables related with systolic function, such as systemic blood pressure or estimated glomerular filtration rates[20].

In spite of the undisputable association between venous congestion and WRF, the mechanisms by which congestion leads to kidney dysfunction are still poorly understood.

Several mechanisms have been suggested as a possible explanation. Over the past few years, IAP has been related to WRF in patients with AHF[13-15], although its actual role is not fully clarified. The IAP study[11] was a prospective study which aimed to assess the relation between IAP and WRF. In this study, decompensated HF patients who did not show a significant IAP reduction (< 12 mmHg) after the first 72 h of loop diuretic treatment, were more congested (clinical congestion score), had larger IVC diameter and higher intravascular volume. Furthermore, this group of patients had worse prognosis in terms of all-cause mortality and/or rehospitalizations for AHF during the following 180 days after discharge[11,14].

Another study by Abu-Saleh et al.[15], based on a CHF rat model, analyzed the role of increased IAP and the development of WRF. In this study, rats were divided according to IAP levels (10 mmHg vs 14 mmHg). They demonstrated that elevated IAP contributed to kidney dysfunction in both high- and low-cardiac output CHF. Several parameters regarding urine metrics, such as urine flow, Na+ excretion, and glomerular filtration rate were found closely associated: those animals in the latter group showed significant decreases in these parameters.

Finally, Boorsma et al.[21] have recently proposed a novel contributing factor to explain the interplay between cardiac and renal dysfunction. These authors suggest that WRF is not only affected by hypoperfusion or increased CVP but a third factor, in which they called the renal tamponade theory. They hypothesize that renal dysfunction may be caused by compression of renal structures cloistered inside renal capsule with limited ability for expansion. In fact, renal decapsulation in animal models of HF and renal ischemia showed improvement in alleviating pressure-related injury.

Despite all of the aforementioned theories, the link between intra-abdominal hypertension and congestive nephropathy remains to be elucidated. Furthermore, whether IAP could have a role in clinical practice which is not yet known. The European Society of Cardiology, and more specifically the Cardiorenal group[22], has proposed a new diagnostic algorithm that includes the use of IAP measurement for HF patients with poor diuretic response, persistent clinical congestion, and impaired renal function. However, the role of IAP to guide loop diuretic treatment is based in small studies of patients with advanced HF[23,24] and should be interpreted carefully. New studies to assess the utility of IAP in patients

with cardiorenal syndrome and diuretic resistance are needed. On the other hand, new tools in addition to IAP are now being investigated to improve the assessment of congestive nephropathy. Venous excess ultrasound grading system, known as VExUS protocol[25], is a novel approach that analyzes venous pulse wave at different locations (suprahepatic, portal, and renal veins), in the context of AHF and probably could help to identify patients with congestive nephropathy on clinical basis.

This study has potential limitations. It will be conducted as a single-center study which may narrow down the sample characteristics and, consequently, the results. Given the details of the design, it might be challenging to meet the recruitment target, especially as every patient has to agree in the use of a bladder catheter.

Conclusions

In the present prospective study, we aim to investigate and deepen the knowledge about IAP changes and its correlation with renal function and diuretic response in patients admitted with AHF.

Funding

No funding was received for this study.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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ORIGINAL ARTICLE

Observational study on telemonitoring of patients with heart failure

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Abstract

Introduction: Patients with cardiovascular disease require continuous monitoring throughout their lives. Studies have shown that remote monitoring improves assessments of these patients, leading to more accurate prevention and lower hospitalization rates. The aim of this study is to evaluate the impact of monitoring patients with heart failure (HF) using different devices and to make a comparison with standard clinical practice, mainly based on hospital readmissions and patients' quality of life by improving their self-care strategy. **Methods:** The study involved 32 patients previously discharged from hospital, divided into two groups: a study group underwent telemonitoring for 3 months using their mobile phone and various portable devices, and a control group followed standard clinical practice for the same period. The physiological variables analyzed were heart rate, blood oxygen saturation, blood pressure, physical activity, sleep patterns, weight, height, and fluid intake. To assess the impact of monitoring on HF patients, the number of outpatient visits, emergency room visits, and hospital readmissions were taken into account. The impact on quality of life, self-care, and patient satisfaction was also assessed by analyzing patient reported outcomes measures and patient reported experience measures. **Results:** The results showed that the study group had a lower readmission rate than the control group (40% vs 60%) and fewer visits to the Emergency Department (relative risk 0.667). On the other hand, it is important to note that in the control group, 60% of patients were readmitted during the follow-up period, while in the experimental group, this percentage was reduced to 40%. At the same time, the telemonitored patients have improved their self-care, have greater adherence to the taking of constants, and feel more confident and calmer. In addition, professionals have been able to take different actions proactively, due to the possibility of obtaining information in real time. **Conclusions:** Telemonitoring patients have achieved a better quality of life and improved health status through continuous, real-time monitoring.

Keywords: Telemonitoring. Heart failure. Wearables.

Introduction

The current moment in which we live has shown that, now more than ever, it is possible to provide increasingly digital healthcare, as digital platforms for patient monitoring have been found to be of great use in improving intervention and adherence.

In fact, focusing on remote monitoring in patients with cardiovascular disease, it has been shown that information from behavioral and physiological sensor data

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leads to more accurate prevention[1-3] and the benefits of these digital health interventions have even been compared to non-intervention[4,5].

In terms of monitoring heart failure (HF) patients in particular, improved adherence to physical activity[6,7] and reduced hospitalization have also been demonstrated[8]. Furthermore, improvements in self-care[9] and quality of life have been found using wearables[10].

Due to all this emerging research, an observational study of telemonitoring of HF patients, specifically in the comprehensive management unit for patients with HF, was proposed to explore the usefulness of these telemonitoring platforms. To this end, a solution has been customized to configure a telemonitoring program tailored to each disease.

Objectives

The purpose of this report is to provide the results obtained from the project "Analysis of the pilot study of remote telemonitoring of patients with HF", considering the experience of the patient as well as that of the professional.

In addition, the main objective of this study is to assess the impact of monitoring in patients with HF on readmissions, quality of life and self-care, as well as to assess the impact of monitoring with respect to the control group, the preliminary hypothesis being that the health status of patients improves with the use of telemedicine and in comparison, with the control group.

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In addition, the main objective of this study is to assess the impact of monitoring in patients with HF on readmissions, quality of life and self-care, as well as to assess the impact of monitoring with respect to the control group, the preliminary hypothesis being that the health status of patients improves with the use of telemedicine and in comparison, with the control group.

Methods

Study design

The study was conducted at the University Hospital of Torrevieja (level III hospital). The study design was randomized case-control (1:1). The study group (case group) underwent telemonitoring for 3 months through their mobile device and various wearables, while the control group followed usual clinical practice for the same period. Each patient was randomly assigned to a particular group.

Participants

Patient inclusion criteria are described in detail in table 1.

Timeline

The phases carried out in the single-center study are described below (Fig. 1):

- **Recruitment phase**: this took place between May and October 2020, of those patients discharged from the Internal Medicine Department who met the selection criteria.
- **Study development phase**: participants completed the study phases as follows:
  - **Initial face-to-face visit**: patients are informed about the project and their rights are explained to them. In addition, they sign the informed consent and the study group participant is provided with the application and the electronic devices. The measurement of:
    - Sociodemographic variables: age, gender, educational level, and marital status.
    - Clinical variables: height, medication use, medical comorbidities, and substance use (alcohol, drugs, or medication abuse).
    - Analytical parameters.
    - Scales: New York Heart Association (NYHA), Functional (classification of HF severity), Quality of Life (SF12), PROFUND (prediction of annual mortality risk), and Self-Care.
  - **Recording of variables:** the fluid intake and the measurement of the different physiological variables are recorded daily from the application. If any parameter measured by the device reaches abnormal values, alerts warn the medical team. Patients in the control group carry out this function in a notebook that they are given in normal clinical practice.
  - **Questionnaires**: patients answer two questionnaires on quality of life and self-care at 1 week, 1 month and 3 months after inclusion in the study.
  - **Final face-to-face visit**: patients return the devices. The last patient f completed follow-up in January 2021.

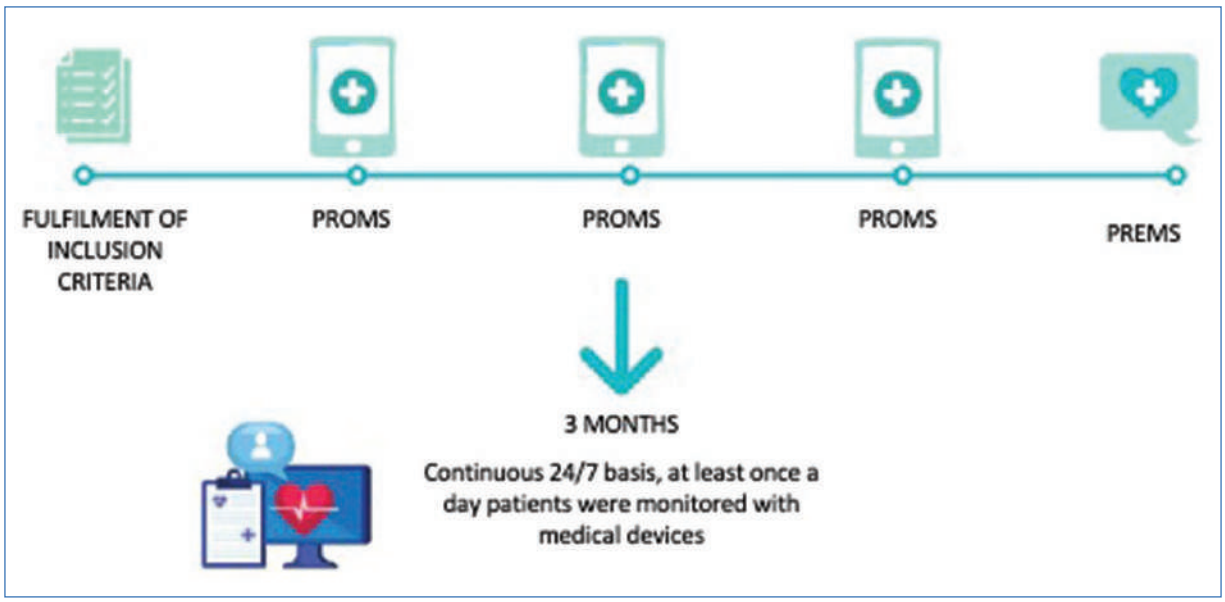

Figure 1. Timeline.

Table 1. Selection criteria

Inclusion criteria	Exclusion criteria
– Hospitalization for HF – NT-proBNP > 1800 pg/mL or BNP > 400 pg/mL – NYHA class II to IV – Echocardiogram performed within the previous 12 months – PROFUND index < 11 points – Belonging to the Torrevieja Department (per capita)	– Oncological disease – Inclusion in another study or clinical trial – Refusal to participate – Body weight over 150 kg – Not speaking Spanish or English – Patients who do not have a mobile phone

NYHA: New York Heart Association.

- **Patient satisfaction**: analyzed through various questionnaires:
  - Control group: before the study and after the study.
  - Study group: during the 3 months, data reported by patients or patient reported outcomes measures (PROMS) and their experience or patient reported experience measures (PREMS) are included in the study.

The visual summary shows the PROMS and PREMS described above.

Variables measured

As mentioned above, during the study, different variables were obtained periodically through the different devices (Table 2): heart rate, blood oxygen saturation, blood pressure, physical activity, sleep patterns, weight, height, and fluid intake (manually entered into the App).

Questionnaires and scales used

Questionnaires provided by the medical team

- NYHA functional scale[11]
- PROFUND scale[12]

PROMS analysis

- European scale of self-care in HF[13]
- Quality of life scale SF-12[14]

PREMS analysis

The items assessed by the patients in the study group were the degree of satisfaction and the usability of the application which were measured through adaptations of the "post-study system usability questionnaire (PSSUQ)"[15] and the "system usability scale (SUS) (Brooke, 1986)"[16,17], respectively.

The experience was also analyzed from the point of view of the healthcare staff, who were asked to answer a questionnaire resulting from an adaptation of the telehealth usability questionnaire (TUQ) scale for telemonitoring.

Table 2. Technical table of devices

Type	Model	Usability	Variables measured
Activity Wrist	Fitbit Inspire HR	Very good	– Physical activity – Sleep patterns
Digital Sphygmomanometer	Beurer BM-85	Good	– Blood pressure
Pulse Oximeter	LifeVit	Very good	– Heart rate – Blood oxygen saturation
Pulse Oximeter	Beurer PO60	Good	– Heart rate – Blood oxygen saturation
Weighing scale	Beurer BF600	Normal	– Weight

Statistical analysis

To obtain results from the data collected and thus be able to accept or reject the hypothesis put forward, the use was made of the non-parametric Mann–Whitney U-test (as the number of cases was < 30) for the comparison of the means of the quantitative variables and the relative risk (RR) with 95% confidence interval was obtained to indicate the probability of an event occurring in one group compared to the other group.

Results

Patients

During the recruitment period, a total of 32 patients were enrolled in the study; however, only 28 patients completed the follow-up period (14 patients in each study arm).

Sociodemographic data showed that 62.5% of the patients were male; the mean age and height were 77 years and 166 cm, respectively, and the mean body mass index was 31.89 kg/m^2. Of the patients, 35.5% had a university education, 54.8% had a basic education and the rest had a high school education. About 96.88% were married, 100% of the patients were taking medication, 87.50% had medical comorbidities, and 34.38% consumed toxic substances (tobacco, alcohol, narcotics, etc.).

Impact on health-care activity

Impact on face-to-face consultations and emergencies

The health-care activity is largely marked by medical consultations and emergency visits. For this reason, a comparison of these aspects was carried out between the two groups.

The number of face-to-face visits to the doctor's office did not differ significantly between groups (p = 0.533), as more than 85% of the visits were routine appointments. Regarding visits to the Emergency Department, the mean number of visits per patient in the control group was 1.125 while in the study group, it was 0.875, thus concluding that telemonitored patients were 33% less likely to return to the Emergency Department, RR = 0.667 (95% IC 0.27–0.41; p = 0.663). On the other hand, it is important to note that in the control group, 60% of patients were readmitted during the follow-up period, while in the experimental group, this percentage was reduced to 40%.

Analysis of re-admissions and average length of stay

Although the difference in the admission rate per patient (p = 0.850) is also not statistically significant (α = 0.05), it is possible to highlight the difference in the readmission rate of patients who have been admitted at least once. In the control group, 57.14% of patients (n = 8) were readmitted during the follow-up period, while in the experimental group, this percentage was reduced to 35.7% (n = 5).

On a patient-by-patient basis, the mean length of stay for readmissions was determined to be 5.78 days in the control group versus 4.75 days in the experimental group (p = 0.626), with mean length of stay and group being independent variables.

Alarms received through the platform

During the study period, exactly 30 alarms were generated for changes in the patient's vital signs and three

alarms for failure to take records. The alarms received by the medical team through the platform provided real-time information on the patient's state of health, which allowed different actions to be taken immediately, such as re-educating on the use of oxygen therapy or modifying the treatment.

PROMS analysis

The European scale of self-care in HF has a range of 12-60, with lower values indicating better self-care. A positive evolution in this aspect has been observed in patients who have made use of the tool (Fig. 2).

After analyzing the results obtained through the self-care scale, it was observed that patients acquired greater training in self-care strategies and that telephone contact with professionals was earlier and more frequent, for example, in situations of respiratory difficulty or significant weight gain: 85% of patients stated that they contacted their doctor in these situations 1 week after inclusion in the study, while after 3 months, 100% of them did so. In terms of quality of life, greater efficiency in performing tasks, and better pain and mood management were detected.

On the SF-12 Quality of Life Scale, the score ranges from 0 to 100, where a higher score implies a better health-related quality of life. In this case, an improvement was also observed in the group of telemonitored patients over time and with respect to the control group (Fig. 3).

Finally, analysis of fluid intake indicated a lower consumption of alcoholic beverages and stimulant drinks over time. In addition, it allowed the medical team to observe the patient's lifestyle habits in more detail, while the patient himself became more aware of his consumption.

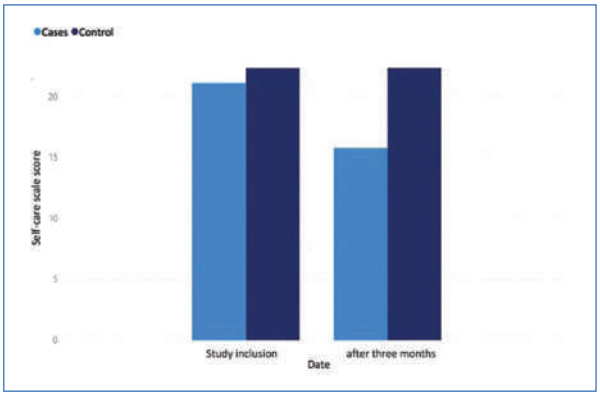

Figure 2. Comparison of the self-care scale.

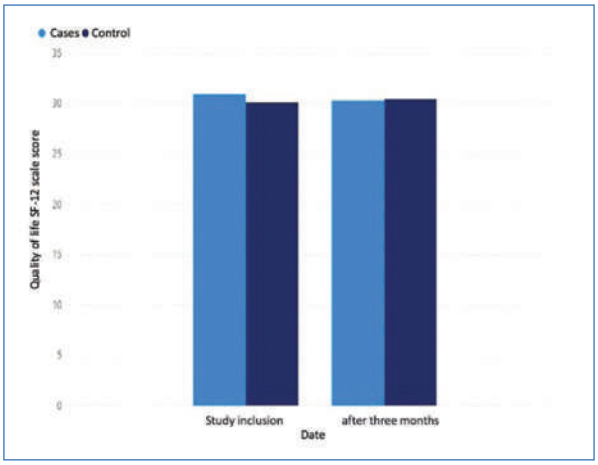

Figure 3. SF-12 Life Scale Comparison.

PREMS analysis

PREMS, PATIENTS

The items assessed by the patients in the study group were the degree of satisfaction and the usability of the application, which were measured through adaptations of the "PSSUQ" and the "SUS (Brooke, 1986)", respectively. In addition, open-ended questions were introduced to acquire additional information.

The PSSUQ questionnaire is based on 16 questions, among which issues such as the simplicity of the application or the performance of the application are raised. Considering that 6 corresponds to strongly agree, patients assigned an average score of 5.6 to the question on the ease of answering questions and more than 70% (n = 10) of patients stated that answering the questions was effortless.

Patients gave a score of 4.8 to the information provided by the application on whether there were questionnaires to be answered and gave the highest score to the organization of the items. Thus, 70% of patients said they were very satisfied with the application in general.

Through the app usability questionnaire, a SUS score of 78.3 was achieved, which places the app above average[18]. In this questionnaire, 100% of the patients agree that they would use the app frequently to monitor their health symptoms and highlight the ease of use of the app. All patients think that the functions are well integrated while 15% of them agree with the statement: "The application is very inconsistent".

Additional questions revealed that 92% of patients would recommend the app and that all patients would like to see their medical history data included in the study.

PREMS, HEALTH STAFF

The experience was also analyzed from the point of view of health-care staff through the TUQ scale, with 100% of professionals reporting that the platform improves care and health services, saves time during visits, and satisfies remote medical care. In addition, all professionals agreed positively on the ease of use and learnability.

Finally, all health-care staff reported feeling comfortable communicating with the patient using the platform, stating that they would use it again and reporting their overall satisfaction.

Discussion

Today, thanks to constant advances in technology, telemedicine has expanded to multiple fields, with marked utility in the management of chronic diseases that represent an excessive cost for the public health system. There are studies that analyze the nature and magnitude of the results of telemonitoring in chronic diseases which, without being conclusive, show more consistent results for pulmonary and cardiac diseases, in which a reduction in Emergency Department visits, hospital admissions, and average hospital stay is achieved[19]. Telemedicine has demonstrated numerous applications, including diagnosis, treatment, and rehabilitation of HF.

First, we must highlight the importance of HF as a major public health problem worldwide, since 8% of patients over 75 years of age in Spain suffer from this condition due to the increase in its prevalence with the progressive ageing of the population[19]. The fact that its target population is the elderly means that in Spain, it is responsible for 3% of hospital admissions and a high mortality rate, accounting for 10% of deaths in men and 16% of deaths in women in 2010. It thus accounts for a large part of health care expenditure, constituting 2% of the same in developed countries, its main component being hospital expenditure. Thus, the importance of telemedicine lies in the early detection of signs and symptoms of worsening of the condition of these patients and in the early modification of treatment, with the aim of intervening early to avoid the large economic burden secondary to the management of these complications, as well as the deterioration of the quality of life of patients[20].

Thus, reducing the impact of exacerbations can reduce the risk of hospitalization and improve quality of life. Given that HF exacerbations have a gradual increase preceding the externalization of symptoms, it follows that early detection could prevent their occurrence leading to a milder clinical presentation. Therefore, the presence of detection systems could be very cost-effective in reducing the cost of these interventions[21].

However, telemonitoring systems based solely on the completion of periodic questionnaires screening for cardiac symptoms, quality of life, and general condition did not show significant results in reducing the risk of admission, average length of stay or mortality[22], highlighting the need for greater technological involvement. And so, in other studies, in which physiological measurements were taken in addition to these questionnaires, encouraging results were obtained in terms of reducing admissions and length of stay[23-26], and, to a lesser extent, in terms of mortality[23,24].

In terms of predictive modeling, home telemonitoring is a promising management approach by reproducing accurate data to establish trends, facilitate the development of personalized strategies, and empower patients by making them proactive in their management[24]. However, in most cases, these systems were implemented in multidisciplinary management units where patients had personalized care provided by HF experts[27] and more positive clinical outcomes were to be expected as part of a specialized HF management unit. Despite this, even in those studies where patients were not part of a multidisciplinary management unit, numerous benefits were found in relation to the use of telemedicine.

Through the present observational pilot study, we have tried, although the sample was small, to show the great impact on care activity of telemonitoring in patients with HF. Thus, over 3 months, using real-time telemonitoring of these patients, we observed that they are 33% (RR = 0.667, 95% CI 0.27-0.41; p = 0.663) less likely to visit the Emergency Department for their condition, the readmission rate is reduced by 20% compared to the average and the average hospital stay of patients is 1 day less (4.7 days in telemonitored patients compared to 5.7 days in the rest, p = 0.626).

Through PROMS, greater adherence and increased self-care strategies as well as improved quality of life and mood were observed. Therefore, a general improvement was observed in the group of telemonitored patients over time and with respect to the control group.

Finally, the real opinion of patients and professionals revealed that they rate the application above average and that they consider its usability to be very good.

Conclusions

Although it is true that over the years telemonitoring has become established as one of the most cost-effective interventions in reducing admissions and related costs[24], larger population-based studies are still needed to confirm the results obtained in our study.

Throughout the study, some points for improvement were discovered, such as the internet connection of both users and the institution itself, or the use of other portable devices instead of mobile phones.

Despite the limitations mentioned above, it was possible to evaluate the impact of telemonitoring on care activity. In this way, continuous monitoring improves the health status and quality of life of patients with HF.

The telemonitoring platform could be implemented in other chronic pathologies, other hospitals and as support for the home hospitalization unit.

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Conflicts of interest

None.

Ethical disclosures

Protection of humans and animals. The authors declare that no experiments on humans or animals have been carried out for this research.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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REVIEW ARTICLE

Estimands: a new way of interpreting the results of clinical essays

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Abstract

Considering the need to homogenize and strengthen the principles of statistical methodology in clinical trials, and to prevent biases in trial design and losses in results, regulatory authorities have encouraged the use of new statistical concepts that help avoid these problems. Based on this idea, *estimands* were developed with the special purpose of solving the problem of missing data at the end of clinical trials, a fact that conditions the reliability of the results and the fulfillment of the objectives of a study. *Estimands* can be seen as a bridge between objectives and statistical tools, allowing a clear and coherent presentation of results. In this article, we explain in simple terms the concept of *estimands*, and the benefits of incorporating them into the interpretation of clinical trials.

Keywords: Estimands. Clinical trials. Statistical methodology. Intercurrent events.

Introduction

Most clinical trials are conducted to assess the effect of an intervention in a target population. The true effect of an intervention may be altered by study limitations, such as loss to follow-up, non-adherence, or poor data quality.

To homogenize and reinforce the principles of statistical methodology in clinical trials, in 1998, the Steering Committee of the International Conference on Harmonization (ICH) published the document ICH E9, which addresses all methodological aspects that should be described in a clinical trial protocol and establishes the statistical foundations for the design, analysis, interpretation, and presentation of trial results[1,2]. An addendum to ICH E9, last revised in 2020[3], was published in 2014, defining the term *estimand* and the process of sensitivity analysis of study objectives. This proposal underlines the formulation of the basic concepts of a clinical trial, such as population, objectives, endpoints, and quantification of effects. The term *estimand* has become widespread in clinical research and it is the element of analysis often required by regulators to approve clinical trials (Fig. 1). To illustrate the concepts related to this term, we will use the design and results of the PIONEER 2[4] clinical trial (Fig. 2).

Estimand, estimator, and estimate

The *estimand* of a trial is defined as the actual outcome of an intervention. In statistical terms, the estimate is a parameter of a probability distribution which has been

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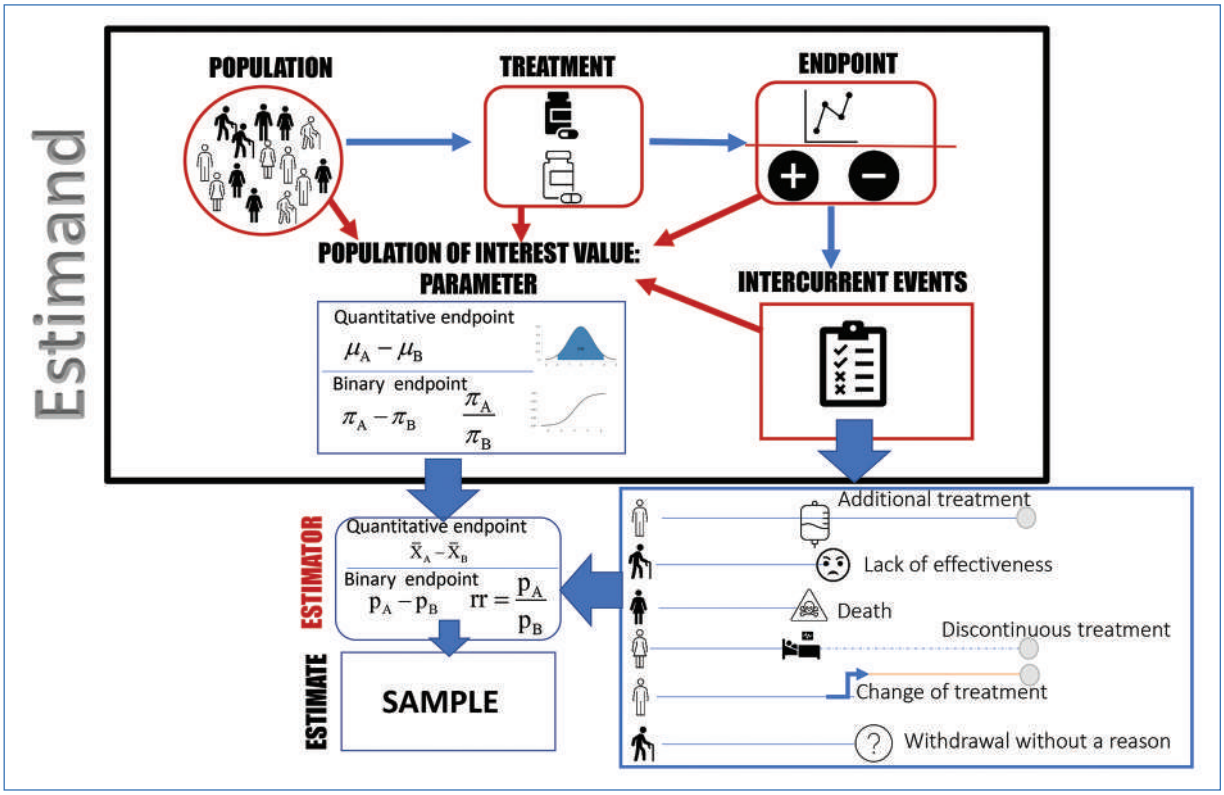

Figure 1. Diagram of the definition of estimand, estimator, and estimate in the analysis of the effect of a new treatment **(A)** on a standard treatment **(B)** when the variables of interest are quantitative and qualitative.

defined over a random variable. For example, the population means (μ) or variance (σ^2) of a continuous variable or the probability of the presence of an event (π) in a binomial distribution. While there are several definitions of *estimand*, the most literal one would be "what is to be estimated". Russek-Cohen and Petullo define it as "quantities used to capture treatment effects within a clinical trial"[5] and Lundberg et al. in the context of social science, refer to it as the "*quantitative target*"[6].

In a two-treatment comparison study, provided that the outcome measure (variable) is continuous, the *estimand* could be defined as the effect on the main variable of a new treatment on a standard treatment, or the difference of two population means referred to the treatments. In case, the variable being analyzed is dichotomous (mortality or improvement vs. no improvement), the effect of the new treatment compared to the standard can be measured in several ways: population risk difference (absolute risk), population relative risk, or population odds-ratio.

An *estimand* is determined on the basis of five attributes that perfectly delineate what population effect size is intended to assess[7,8], and this is where part of its value lies:

- The target population: which sets of individuals is the study aimed at?
- The variable or endpoint: what and how will outcome be measured for each patient?
- Treatments of interest: clearly establish the treatments that will determine the experimental groups.
- The specification and treatment of intercurrent events (ICE): distorting events that may occur throughout the study and that may affect the comparison of experimental groups.
- The definition of the value of population interest obtained in the variable analyzed. This is the materialization of the *estimand* in a statistical measure.

The choice of the *estimand* and the target population should reflect the goals of the study, since the *estimands* and the selected population will determine how the outcomes of the intervention under analysis will be measured. Once the *estimand* is clearly defined, its best estimator (calculated on the basis of the representative sample obtained from the accessible population) should be proposed. The estimator should be the best expression of the *estimand* in the chosen sample. While the *estimand* is unique, the estimator changes according

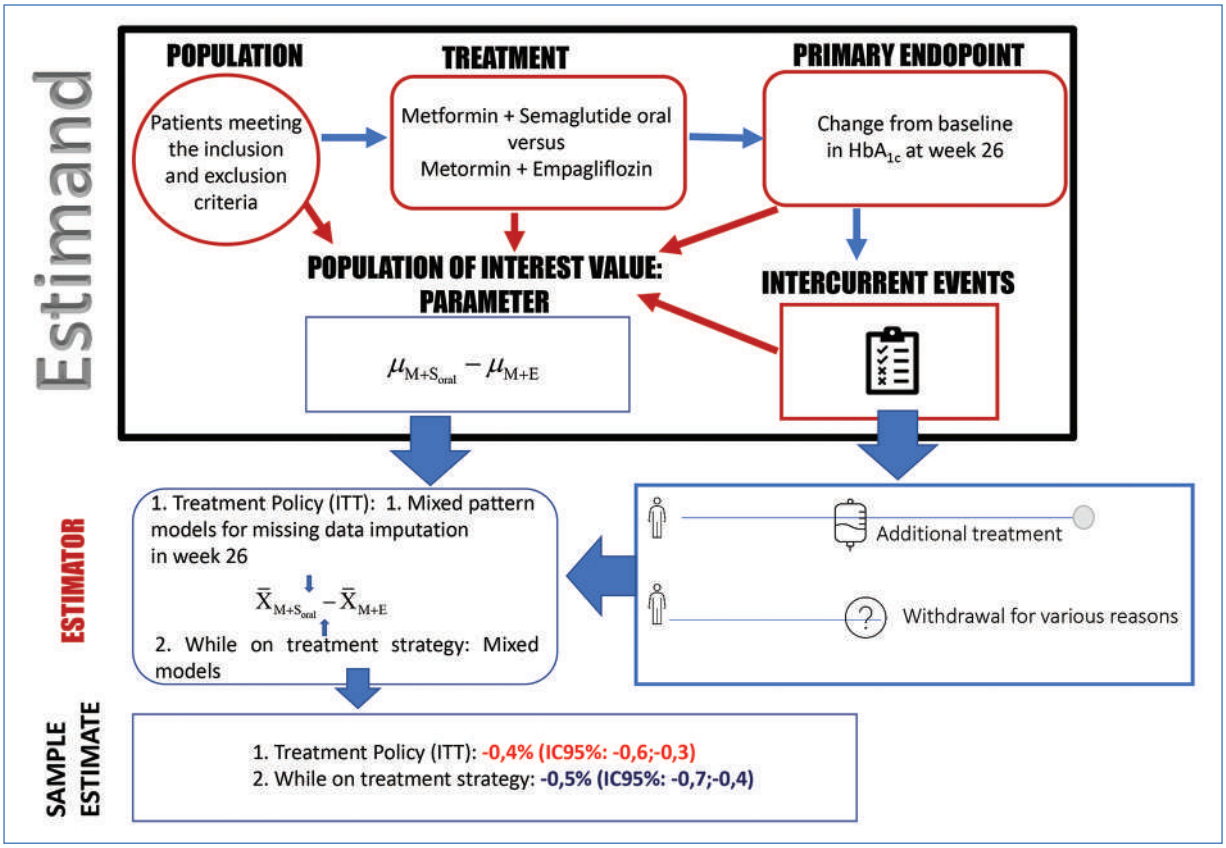

Figure 2. Diagram of estimand, estimator, and estimate definition from the PIONEER 2 clinical trial for the primary endpoint.

to the sample chosen in each experimental study. That is, if the purpose of a clinical trial is to ascertain the effect of a new treatment versus a standard treatment by assessing a marker or a quantitative variable that is normally distributed, the *estimand* would be the difference in population means as long as there is no ICE. In our example, the best proposed estimator due to its statistical properties would be the difference between sample means. The estimations will be the concrete values of these estimators in a given experimental study.

The problem arises with the occurrence of ICE, such as drop outs due to adverse effects of treatments or the clinical situation of patients, and the introduction of supplementary treatments. These events may alter the causal effect of the treatments on the chosen endpoint due to the lack of homogeneity of the experimental groups. One of the procedures that has usually been used to solve the missing data problem is the so-called "last observation carried forward (LOCF)". However, the statistical community has warned about the limitations of this approach[9]. Several strategies for the determination of the *estimands* and the choice of the estimator in the presence of ICE have been described[3,9,10] (Fig. 3).

Little et al. point out what should define an *estimand* and its estimator. The *estimand* should outline the causal effects in terms of benefits and risks of the treatment in the target population. This is particularly important when using surrogate variables (e.g., HbA_{1c}) instead of clinical variables, such as mortality or rate/frequency of cardiovascular events. Estimators should show a valid and unbiased estimate of the *estimand*. For this reason, estimators must present good internal and external quality. Randomization increases internal validity and, therefore, moving away from this condition should be avoided[11].

Estimand, estimator, and estimate from the PIONEER 2 trial

The primary aim of this study was to evaluate the efficacy and safety of two oral antidiabetic drugs, semaglutide, and empagliflozin, in patients with type 2 diabetes not controlled by metformin.

The target population for the study consisted of selected patients with type 2 diabetes and an HbA_{1c} of 7-10%, receiving a stable dose of metformin (> 1500 mg

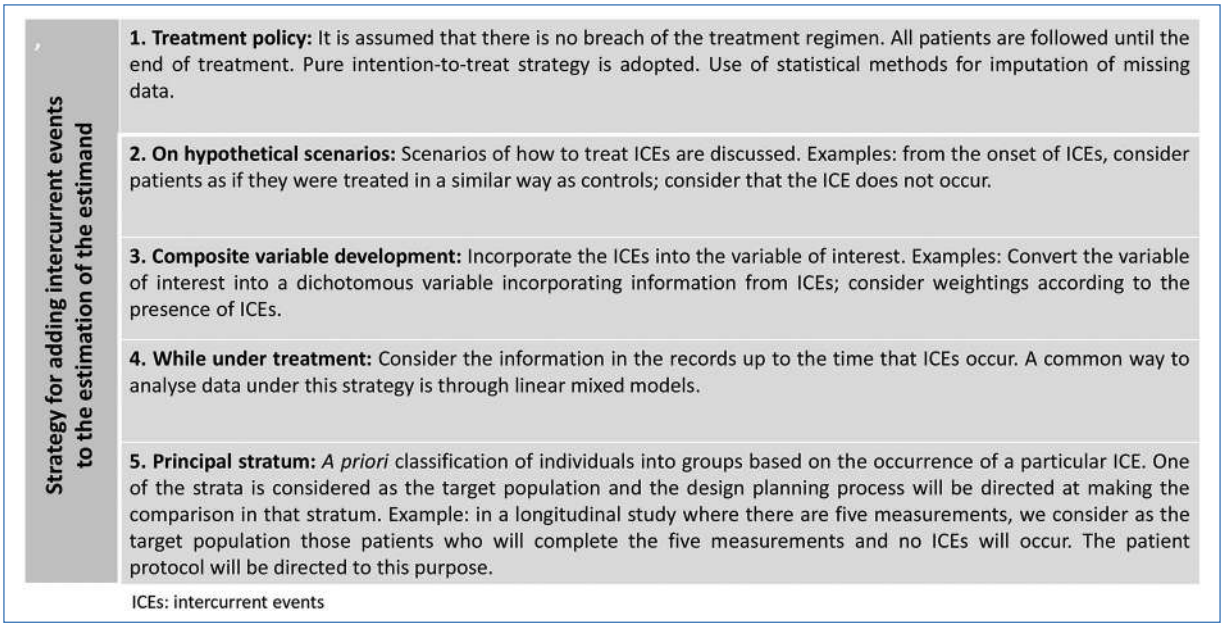

Figure 3. Strategies for the management of intercurrent events in clinical trials.

or the maximum tolerated dose), based on exclusion criteria defined in the protocol of the trial. The treatments to be compared were metformin + oral semaglutide versus metformin + empagliflozin.

The main endpoint was defined as the change from baseline in HbA_{1c} at week 26. The ICE described were withdrawals during the 26 weeks of the study and the use of other rescue antidiabetic treatments. The population of interest value was defined as the difference in population means of HbA_{1c} change between the two experimental groups. In this case, the estimator was the difference in sample means of the change in HbA_{1c}.

The authors presented two strategies for data analysis in the presence of the ICE, to maintain the randomization process that increases the validity of the effect in the population, where the *estimand* was defined. The first strategy, "treatment policy strategy" (under intention-to-treat [ITT] principle), is a statistical procedure to estimate missing HbA_{1c} values (whether the intercurrent event has occurred) and, thus, calculate the differences from baseline values for all patients in the trial. The estimate obtained with this strategy was −0.4 (95% CI: −0.6, −0.3). Contrasts from this estimate were also analyzed under conditions of superiority and non-inferiority, and in both cases, the results were significant.

The second strategy, called "while on treatment" (per protocol trial product *estimand*), also referred to as "tested product estimator" or "efficacy estimator", involves analyzing results only until an ICE occurs. That is, if a subject has dropped out at week 14, this subject may not be removed from the test, but only the last HbA_{1c} value is considered in the calculation of the *estimand*. This strategy uses mixed models, which allow for the analysis of non-balanced data (a series of data over time that do not show the same number of observations for each individual). The population of interest value, or main outcome variable of the study, remains the population mean difference in HbA_{1c} between the two experimental groups. What varies is the statistical procedure used to define the estimator, using a mixed model to calculate it. The estimate, that is, the difference in the means of the HbA_{1c} change for this study was −0.5% (−0.7%; −0.4%).

In addition, in PIONEER 2, three secondary endpoints were analyzed under the same conditions used for the previous *estimand*:

- Change in weight from baseline at week 26 (the difference between groups was −0.9 kg, p = 0.0114, by product estimator, vs. −0.2 kg, p = 0.6231, by ITT).
- Change in HbA_{1c} from baseline at week 56.
- Change in weight from baseline at week 56.

Finally, the study made a descriptive analysis of safety in terms of adverse effects, for which no *estimand* is defined. The use of more than one *estimand* in the analysis adds validity and robustness to the results (when concordance is observed). On the other hand, the finding of clear discrepancies should require

Table 1. Example of the formulation of different estimands as a function of strategies for the management of intercurrent events on the PIONEER 2 trial

	Ideal	Treatment policy	While on treatment	Composite variable	Hypothetical scenary	Principal stratum
ICEs	No Withdrawal	Withdrawal	Withdrawal	Withdrawal	Withdrawal	Withdrawal
Population	Patients with type 2 diabetes and Hba of 7-10% who meet the inclusion and exclusion criteria.	Patients with type 2 diabetes and Hba of 7-10% who meet the inclusion and exclusion criteria.	Patients with type 2 diabetes and Hba of 7-10% who meet the inclusion and exclusion criteria.	Patients with type 2 diabetes and Hba of 7-10% who meet the inclusion and exclusion criteria.	Patients with type 2 diabetes and Hba of 7-10% who meet the inclusion and exclusion criteria and received treatment for 26 weeks.	Patients with type 2 diabetes and Hba of 7-10% who meet the inclusion and exclusion criteria and patients not likely to drop out of trial.
Treatments	Metformin + oral semaglutide vs. metformin + empagliflozin.	Metformin + oral semaglutide vs. metformin + empagliflozin.	Metformin + oral semaglutide vs. metformin + empagliflozin.	Metformin + oral semaglutide vs. metformin + empagliflozin.	Metformin + oral semaglutide vs. metformin + empagliflozin.	Metformin + oral semaglutide vs. metformin + empagliflozin.
Primary Endpoint	The change from baseline in HbA_{1c} at week 26.	The change from baseline in HbA_{1c} at week 26.	The change from baseline in HbA_{1c} at week 26.	Treatment success or failure. Treatment success was defined as no withdrawal and 7% or more reduction from baseline in HbA_{1c} at week 26.	Change in weight from baseline at week 26 without withdrawal.	Change in weight from baseline at week 26 without withdrawal.
Population value	Mean difference	Mean difference under the assumption of missing data not at random (MNAR).	Mean difference at the last time point while on treatment.	Difference rates between treatment groups.	Mean difference	Mean difference
Estimate	Sample mean difference	Sample means difference by Pattern-Mixture Model using multiple imputation.	Sample means from linear mixed model.	Sample difference in response rates between treatment groups.	Sample mean difference	Sample mean difference

additional interpretation by the authors. Table 1 shows, in addition to the strategies on the management of ICE used in the PIOONER 2 trial, other possible definitions of estimation under the other three types of strategies proposed.

Limitations and advantages of the *estimands*

The concept of *estimand* arises from the need to address the issue of missing data in clinical trials. The presence of ICE renders the experimental groups non-comparable since the randomization effect disappears. On the other hand, statistical analyses that only include individuals who are adherent to treatment, without considering those lost to treatment (*per protocol estimand*), overestimate the effectiveness of the intervention. A first effort to avoid this problem was made by introducing the concept of ITT analysis, which attempts to maintain the randomization process used in a given population regardless of its adherence, but this approach can lead to a biased interpretation of the effect if not performed rigorously[12,13].

A limitation in the use of *estimands* is the possible pretension to replace flaws in study design with the use of statistical techniques that are increasingly sophisticated, but not sufficiently documented in the study methodology. The emergence of new terms such as

"*predictimand*"[14] may end up producing more noise, distorting the meaning of the concept, and thus leading to misinterpretations and deformations of the concept.

Mitroiu et al. in their narrative review of estimands, question whether this concept is "old wine in new barrels".

"In this sense, we share their view: the *estimands* are new and old at the same time, and missing data are a problem that has always existed in medical research"[15]. The *estimand* is a concept as old as clinical research, but it provides an innovative solution for developing the fundamental aspects of a clinical trial (as long as the homogenization of the concept is not lost).

Conclusion

The *estimand* provides advantages when it comes to presenting information related to the fulfillment of a study objectives in a reliable way. It can be seen as a bridge between the objectives and the statistical tools, allowing for a clear and consistent presentation of the results[16] so that readers or evaluators of a study can get a more accurate picture of what is actually being measured and the possible biases affecting the results.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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