Early on-demand drainage versus standard management among acute necrotizing pancreatitis patients complicated by persistent organ failure: the protocol for an open-label multicenter randomized controlled trial

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Short title： Early On-demand Drainage in Acute Necrotizing Pancreatitis

ABSTRACT

Introduction and aim: Pancreatic necrosis occurs in a quarter of patients with acute pancreatitis, many of whom form an acute necrotic collection (ANC). The current standard treatment of these collections is to defer percutaneous drainage (PCD) until the latter becomes 'walled off' necrosis (WON), which takes 4 weeks, by arbitrary definition. The majority of patients that develop persistent organ failure (POF), the primary determinant of mortality, do so within 4 weeks, and over half within the first week. To defer PCD until after 4 weeks may result in a worse outcome because of a missed opportunity to treat patients with early infected ANC (<4 weeks duration) and thereby reduce the severity and/or duration of POF.

The aim of this study is to compare the clinical outcome of the current standard approach of delaying PCD for 4 weeks with early on-demand PCD in acute necrotizing pancreatitis (ANP) patients with ANC and OF.

Methods/Design： This study is an open-label, multicenter, parallel, randomized, controlled trial to determine whether early on-demand PCD offers an advantage. All patients with ANP who develop POF during the first week of onset will be screened for eligibility. In total, 120 study subjects will be recruited and randomized to either (1) early on-demand PCD or (2) standard care with deferred intervention until after 4 weeks. Different from standard treatment, patients assigned to the early on-demand group will receive PCD when they show signs of decompensation like new-onset OF, aggravation of pre existent OF and persistent OF for more than a week. The primary composite endpoint is major complication and/or death. Patients will be followed until discharge or death with an additional followup 90 days after randomization if discharged before that.

Discussion: This study challenges the standard 4 week delay before PCD in ANP patients complicated by POF and will answer the question whether early on-demand PCD is associated with a lower incidence of major complications and/or death.

Keywords： Acute pancreatitis, necrosis, persistent organ failure, percutaneous drainage, acute necrotic collection, walled-off necrosis, on-demand

Introduction

The re-classification of acute pancreatitis and its complications in the Revised Atlanta Classification (RAC) has been an important advance[1]. The definition of 'severe acute pancreatitis' is now based on the presence of 'persistent organ failure' (POF). The RAC also defined "acute necrotic collection" (ANC) as a local pancreatic complication "containing variable amounts of both fluid and necrosis associated with necrotizing pancreatitis" [1]. Both POF and ANC can and commonly occur early in the course of acute pancreatitis.

It is known that most ANCs remain sterile and will spontaneously resolve over time, which means that fine needle aspiration (to determine the presence of infection) and percutaneous drainage (PCD, to drain infected fluid) have been contraindicated because of the concern about introducing infection into a sterile collection[2]. The ACG guidelines (2013) state that no intervention is indicated for "asymptomatic pancreatic and/or extra-pancreatic necrosis regardless of size, location, and/or extension" [3]. The Dutch Acute Pancreatitis Group have promoted the importance of delay to allow encapsulation of the collection[2] and intervention should only be considered after 3-4 weeks. In contrast, the IAP/APA guidelines (2012) state that intervention should be considered when organ failure persists 'for weeks in patients with sterile ANC' [4], but they did not state how many weeks. Further, the European Society of Gastrointestinal Endoscopy (ESGE) recommended invasive intervention for patients with POF or "failure to thrive" for "several weeks" [5], but they also did not state how many weeks. When taken together, these guidelines raise the question as to whether early (less than 3-4 weeks) intervention for ANC in some patients with POF is justified, even with a risk of introducing infection. This can be argued because ANC is one of the drivers of POF and even when sterile, it contains inflammatory mediators and pancreatic enzymes, which contribute to the systemic inflammatory response and end-organ dysfunction[6].

There is an additional concern that waiting an arbitrary 4 or more weeks may mean that early infection is missed, given the challenge of diagnosing early infected ANC. The Dutch group have stated that intervention in the first week is not indicated[2, 7]. But they have shown that clinically relevant walled off necrosis (largely or fully

encapsulated) and gas configuration (indicating infection) can occurr in 43% and 12% patients within the first 3 weeks, respectively[8].

If PCD for sterile or early infected ANC is justified in the presence of POF, the question then arises as to when this should occur and who would benefit from early drainage. It is known that the duration of OF is related to the risk of mortality[9] and the risk of infection [10]. Early endoscopic and/or percutaneous drainage had been shown to be effective in patients with signs of clinical deterioration with new onset organ failure[11]. On this basis we proposed 'early on-demand PCD' for patients with acute necrotizing pancreatitis (ANP), ANC and POF. As an alternative to standard drainage with a wait of 4 weeks, this approach would be indicated in patients showing signs of deterioration or failure to progress in relation to OF. This would include new-onset POF, aggravation of pre-existent POF and persistent OF for more than a week. Based on the available data, we suggest that the optimal timing of PCD for ANC in patients with POF is not known, that encapsulation and infection can occur before 4 weeks, and that arbitrarily waiting 4 weeks results in the undertreatment in a proportion of patients. We have therefore framed an hypothesis that early on-demand PCD in patients with ANP, ANC and POF will result in improved clinical outcomes. This will be tested in a randomized controlled multi-center clinical trial designed to compare this approach with currently standard (delayed) percutaneous drainage.

METHODS

Design

This TIMING trial is an open-label, multicenter, parallel, randomized, controlled trial. The overalls study design is shown in Figure 1.

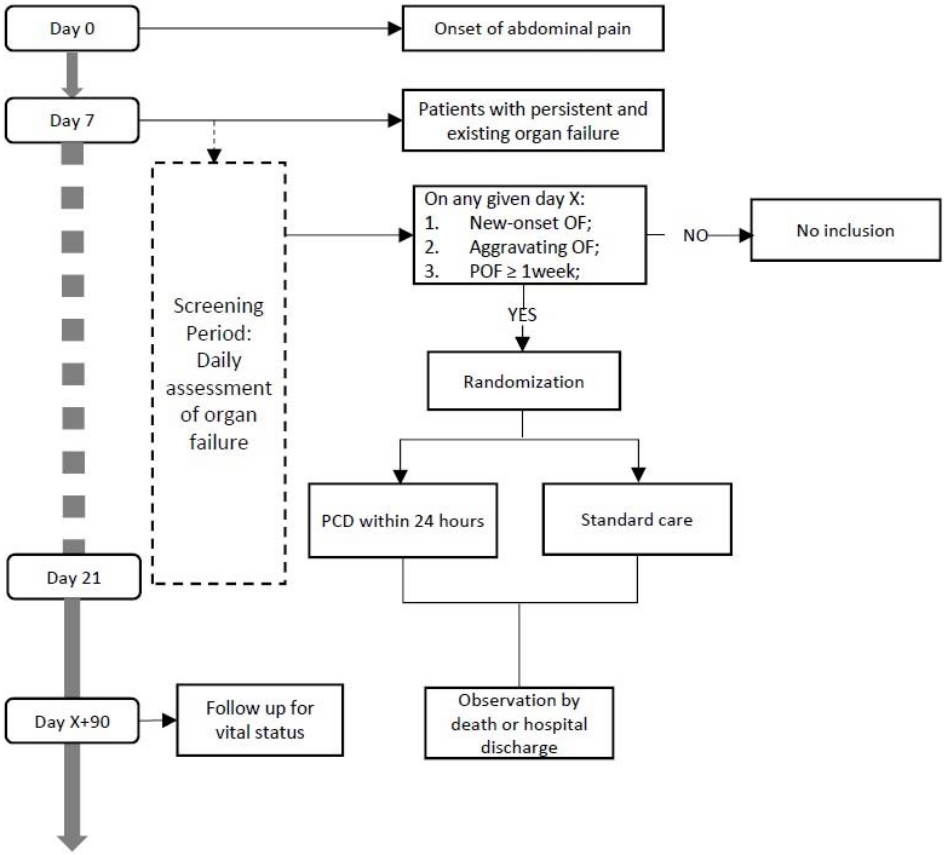

Fig.1: The study design, including schedule of enrollment, interventions, and assessments

Trial committees

A Trial Management Committee (TMC) will be formed comprising the Chief Investigators, supported by all the co-investigators (clinical and non-clinical) as needed and members of the Chinese Acute Pancreatitis Clinical Trials Group (CAPCTG) coordinating center. The TMC will be responsible for the day-to-day running and management of the trial.

An expert clinical panel including 5 members from each of the participating sites(Jinling Hospial, Xijing Hospital, Xiangya Hospital, Sir Run Run Shaw Hospital, First Affiliated Hospital of Nanchang University) was formed to provide governance and audit the study. This panel will also assist with making and major clinical decisions such as whether rescue intervention were required.

A writing and publication committee will also be organized for drafting the manuscript and submission of the manuscript to adequate journals. It will also decide on the authorship of this study.

Study population

Patients with ANP complicated by ANC and POF will be informed of the possibility of taking part in the TIMING trial at admission. After signing informed consent, participants meeting all the inclusion criteria and no exclusion criteria will be randomized.

Eligibility criteria

In the TIMING trial, the day of onset of symptoms will be defined as Day 0 and the second day Day 1 and so on. OF in this study will be defined as a modified Marshall score (respiratory and renal) or SOFA score≥2 (cardiovascular) for each individual organ system. Patients enrolled for screening will be assessed for these three organ systems on a daily basis from Day 8 to Day 21, namely, the second and the third week to evaluate eligibility for randomization.

The inclusion criterion are:

1. Aged 18 to 70 years
2. Able to provide informed consent
3. Confirmed diagnosis of AP[1]
4. CT diagnosis of acute necrotic collection (ANC)
5. Technically able to be drained percutaneously, by ultrasound or CT guidance.
6. Confirmed persistent organ failure (either respiratory, renal and/or cardiovascular lasting for more than 48 hours) that had not resolved by Day 7;
7. During Day 8-Day 21, one or more of these criteria:

(a) New-onset organ failure not present on Day 7 (no alleviation within 24 hours);

(b) Organ failure (either single or multiple, modified Marshall score or SOFA score≥2) persist for seven natural days from Day 1;

(c) Aggravation of organ failure from that on Day 7 evidenced by increased

modified Marshall score or SOFA score (no alleviation within 24 hours);

The exclusion criteria are:

1. Pregnant pancreatitis;
2. Chronic pancreatitis;
3. Pancreatic tumor-related pancreatitis;
4. Percutaneous or transluminal drainage or surgery is undertaken before admission;
5. Patients had a history of cardio-pulmonary resuscitation during this episode;
6. Patients with a known history of severe cardiovascular, respiratory, renal or hepatic disease defined as (1) greater than New York Heart Association class II heart failure, (2) active myocardial ischemia or (3) cardiovascular intervention within previous 60 days, (4) history of cirrhosis or (5) chronic kidney disease with creatinine clearance< 40 mL/min, or (6) chronic obstructive pulmonary disease with requirement for home oxygen;

Consent and confidentiality

Informed consent is required for each participant of this study, either signed by the patient himself or next of kin. All the data stored in the electronic database are de-identified to guarantee patients' privacy.

Randomization and blinding method

Permuted block randomization, stratified by the participating site, will be used according to a computer generated randomization list. The randomization assignments will be put in sequentially numbered, sealed, opaque envelopes, which will be opened sequentially upon enrollment of a study participant in each site. This study is an open-label study, therefore no blinding method will be applied for both the participants and the investigators. However, the outcome assessors will be blinded to patients allocation.

Sample size, centres and recruitment

On the basis of our previous studies [12, 13] and the results of our pilot study

(unpublished), it is estimated that 50% of patients with ANC and POF meeting the randomization criteria could have the primary endpoint (death or major complications). We estimated that a sample size of 116 participants could provide 80% power at a two-sided alpha level of 0.05 to detect >=50% reduction in the primary endpoint from the intervention treatment. In our study, we plan to randomize 120 patients in total (60 per group) after allowing for a 4% lost follow up.

The centres and estimated number of participants are as follows: Jinling Hospital (40 participants), the Xijing Hospital (20 participants), the Xiangya Hospital (20 participants), the Sir Run Run Shaw Hospital (20 participants)and the First Affiliated Hospital of Nanchang University (20 participants). According to the audited volume of eligible cases an 18-24 months period will be required to recruit 120 patients. The starting date of the study was March 2019, and the planned finishing date is March 2021.

Endpoints

Composite primary endpoint

Death and/ or major complications during the index admission (from randomization to hospital discharge or death) will be the primary endpoint. Major complications refer to new-onset organ failure (cardiovascular, renal and respiratory), bleeding requiring intervention and gastrointestinal perforation or fistula requiring intervention (see the definitions below).

Secondary endpoints:

The secondary endpoints will be assessed at two time points: before the time of hospital discharge or death and day90 after randomization. The following endpoints will be collected before the time of hospital discharge or death: (1) New-onset organ failure, (2) Bleeding requiring intervention, (3) Gastrointestinal perforation or fistula requiring intervention, (4) Deteriorated organ failure, (5) Organ failure score assessed at 14 and 21 days after randomization, (5) Organ failure-free days during the 21-day period following randomization, (6) Intra-abdominal pressure for seven consecutive days after randomization and 14, 21 days after randomization, (7) Incidence of infected

pancreatic necrosis, (8) Incidence of sepsis, (9) New prescription of mechanical ventilation, renal replacement therapy and vasoactive agents; (9) Incidence of pancreatic fistula, (10) Incidence of symptomatic SVT, (11) Requirement of minimally invasive debridement, (12) Requirement of open surgery, (13) Duration of ICU admission, (14) Duration of hospital admission, (15) Total cost. On 90 days after randomization, an additional follow-up will be arranged to determine the vital status of the participants, which will also be served as a secondary endpoint.

General management regimen

All patients will receive standardized management based on the IAP/APA acute pancreatitis guidelines[4]. This includes adequate fluid resuscitation, early enteral nutrition, routine medical treatment (blood glucose control, antibiotics if needed and sedatives if required), mechanical ventilation if needed, CRRT if needed and other organ support measures, etc. OF would be assessed on a daily basis according to the modified Marshall score (respiratory and renal) or SOFA score(cardiovascular). All patients included in this trial will be treated with either surgical or endoscopic step-up approach(except the study intervention which must be PCD when randomized) based on the location of the necrotic collection and technical availability in each participating center when infected pancreatic necrosis is suspected or confirmed. Either percutaneous catheter drainage or endoscopic transluminal placement of double pigtail stents, are acceptable primary interventions.

Intervention

The patients will be randomized into one of two groups:

Early on-demand PCD group (the EOD group):

In addition to the standard treatment, ultrasound or computed tomography(CT) guided PCD will be performed within 24 hours of randomization. Early on demand endoscopic drainage is not permitted in this arm, as we can not monitor daily volume of the endoscopic drain. At least one drainage catheter with size from 12F to 16F will be placed to drain the ANC, and the content drained from the site will be cultured to determine whether it is sterile or infected. More drains are permitted if deemed clinically necessary based on patient status and extent of the collection. The treating

physician is responsible for choosing the access routes, size, and the number of drains. The percutaneous drains will be audited every day and removed to reduce the unnecessary risk for introducing infection when the volume of a given catheter is less than 50ml (including 50ml) for three consecutive days and infection has not been suspected or confirmed. Debridement of the infected necrosis (necrosectomy) will be performed once there is encapsulation and as scheduled by the treating physician. For minimally-invasive techniques, both percutaneous and endoscopic necrosectomy are acceptable based on the technical preference and availability within each participating center.

Standard-care group (the standard group):

No intervention will be immediately applied if the participant is randomized to this group unless meeting the "rescue intervention criteria" shown below. Interventions, including PCD and necrosectomy, will be delayed until high suspicion or diagnosis of infection associated with WON and preferably at least four weeks following admission. Both percutaneous drainage and endoscopic transluminal drainage can be selected for the initial step, and necrosectomy would be undertaken when necessary.

Rescue intervention criteria

An important part of this trial is to ensure the safety of patients, and this is more important than ensuring compliance with research protocol. Any participant who shows significant deterioration such that an intervention is required the expert clinical panel will be contacted. They will be available 24/7 through the trial period and will make the final decision regarding intervention, in consultation with the treating physician. Significant deterioration requiring rescue intervention includes:

(1) Bleeding that has failed to be controlled by interventional radiology
(2) Abdominal compartment syndrome refractory to conservative treatment
(3) Evidence of intestinal ischaemia/necrosis/perforation
(4) Mechanical bowel obstruction that has not responded to conservative measures.

Monitored parameters and Data collection

A web-based electrical database (Huifang Tech, Wuxi, China) will be used for data

collection and storage. All data will be input by the primary investigator or nominated investigators (less than two for each participating center) approved by the primary investigator. Training for data entry will be performed by the provider of the electrical database and the CAPCTG coordinating center.

The study consists of two periods: the screening period before randomization (day8 to day21 from the onset of abdominal pain) and the observational period after randomization (randomization to hospital death or discharge). The data required to be collected during different phases are shown below（Fig 2）:

Data management and Statistical Analysis

The coordinating center from the CAPCTG will be responsible for data safety, privacy, and quality.

General principles

All statistical analyses will be described in detail in the Statistical Analysis Plan (SAP) and finalized and signed before the data lock. The study is designed as a superiority trial, so all tests will be two-sided, and P-values <0.05 will be used to define statistical significance. The analysis will be done using SAS and/or Stata.

Analyses populations

Primary analyses will be based on intention-to-treat (ITT) population, and secondary supportive analyses will be done on the PP population. The safety analysis will be performed on the safety population.

1. ITT population: This population consists of all randomized subjects;
2. Per-protocol (PP) population: This population is a subset of the ITT population. Subjects with major protocol deviations will be excluded from the PP population. Major protocol deviations will be defined in the SAP.
3. Safety population: This population will be the same as the ITT population, which consists of all randomized subjects.

Interim analysis

We will not perform interim analysis for efficacy. However, data safety and monitoring board (DSMB) will be formed to monitor the safety at regular intervals

(every 6 months) or based on suggested intervals by DSMB. The trial recruitment can then be stopped unless the DSMB advises. Otherwise, statistics will not be the sole basis for the decision to stop or continue, and the DSMB can advise to continue recruiting in the trial or stop recruiting but continue to complete the intervention as per randomization in order to continue collecting more safety information or data for further sub-group analyses etc.

Primary endpoint analyses

The generalized linear model (GLM) with the log-link function and binomial distribution (log-binomial regression) will be used to analyze the primary endpoint. The GLM model will have the treatment arm as the only predictor and 5 sites as the control variable, from which (unadjusted) risk ratio (RR) and its 95% confidence intervals (CI) of having a primary endpoint will be derived. Covariate-adjusted analyses for the primary endpoint will also be conducted by adding pre-specified covariates into the above unadjusted GLM analysis to derive the adjusted RR (95% CI). Imputation for baseline missing covariates will be made for covariate-adjusted analysis.

Secondary endpoints analyses

These will also be analyzed using GLMs with the treatment arm as the single predictor and 5 sites as the control variable. The point estimate of the treatment effects with 95% CI will be derived via the specification of a GLM model for each secondary outcome depending on its distribution. For a binary outcome such as the components of the primary endpoint, similar analysis to the primary endpoint analysis will be performed, and the treatment effects measured as RR will be generated. For a continuous outcome like the organ failure score, a Gaussian distribution will be assumed and identity link function will be used. Correspondingly the mean difference and its 95%CI between two arms will be calculated. For a count outcome, Poisson distribution and log link function will be used, from which incidence rate ratio (IRR) and its 95% CI will be computed.

Adverse events

Adverse events (AEs) are defined in accordance with the National Cancer Institute-

Common Terminology Criteria for Adverse Events as any untoward medical occurrence in a patient, or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment.

It is recognized that the patient population (acute pancreatitis complicated by ANC and POF) will experience a number of common aberrations in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator's clinical judgment.

In all cases, the condition or disease underlying the symptom, sign, or laboratory value should be reported, e.g., renal failure rather than hyperkalemia, and agitation rather than self-extubation.

Discussion

The current recommendations suggest that it is important to delay intervention until the ANC becomes WON, which has arbitrarily been determined to be 4 weeks. But it is appreciated that 43% of patients have encapsulated and 12% of patients have developed infection in the collection before 4 weeks. This provides a rationale for intervention in some patients. This study selects a subgroup of patients for intervention: those with ANP who have an ANC (of drainable size and location) and POF. It is argued that these patients may benefit from earlier drainage and will be randomized to early on-demand PCD versus delayed drainage, after 4 weeks(standard care). Given the widespread practice of waiting 4 weeks before any intervention, it is reasonable to consider early as being less than 4 weeks from the onset of symptoms and thus we set the interventional window at the second and the third week after onset.

The primary endpoint will be a composite of major complications and/or death. The results of this TIMING trial will therefore be to answer a clinical question: whether patients with severe acute pancreatitis and showing signs of clinical decompensation despite maximum intensive care treatment but no overt evidence of infection should

have on-demand early drainage of ANC.

Strengths and limitations:

Strengths

1. This is a randomized, multi-center, controlled trial providing level 1 evidence concerning the efficacy and safety of early on-demand intervention in patients with ANP, ANC and POF.
2. An expert clinical panel will be available to assist with decisions regarding rescue interventions for major complications, ensuring the safety of patients is paramount
3. An interim analysis will be applied and the data will be handled by an independent data safety monitoring board (DSMB) to ensure the safety of the participants.

Limitations

1. Lack of blinding methods, as “sham” intervention may introduce additional risk to the study objects;
2. Due to the available expertise and equipment and treating physician preference there will be different approaches to intervention in different centres, including surgical and endoscopic drainage, which may introduce some bias on clinical outcomes.

Ethics and dissemination

This study has been approved by the ethics committee of the Jinling Hospital (2018NZKY-009-04). Ethics approval of each participating center is required before initiation of enrollment.

Dissemination policy

All the investigators and the sponsor(The Center of Severe Acute Pancreatitis, Jinling Hospital, Nanjing University) will have full access to the data after the conclusion of the study. Anyone who wants to do a post-hoc analysis needs to submit a formal writing proposal to the TMC. Only approved authors can have access to the database.

Trial status

The TIMING trial was registered on the Chinese Clinical Trial Registry (ChiCTR1800014963) and ISRCTN(91106416). The first patient was randomized on 13 March 2019. To date, 45 of the 120 patients have been randomized and the inclusion of patients is on schedule.

List Of Abbreviations

AP	Acute Pancreatitis
ANC	Acute Necrotic Collection
IPN	Infected Pancreatic Necrosis
TMC	Trial Management Committee
DSMB	Data and Safety Monitoring Board
SAEs	Serious Adverse Events
AEs	Adverse Events
ICU	Intensive Care Unit
SOFA	Sequential Organ Failure Assessment
CRRT	Continuous Renal Replacement Therapy
MV	Mechanical Ventilation
POF	Persistent Organ Failure
CAPCTG	Chinese Acute Pancreatitis Clinical Trials Group
ITT	Intention-To-Treat
SAP	Statistical Analysis Plan
GLM	Generalized Linear Model

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	Study period						Follow-up
	Pre-Recruitment		Screening period	Randomization	Observational period		
Course date	Day0[a] - Day 6	Day 7	Day 8- Day X	Day X	DayX+1~ DayX+21	Discharge/ death	DayX+90
Study date	D-1			D0	D1-D21	Discharge/ death	D90
Description	Identifying potential patients for enrollment		Identifying patients for randomization		Assessing endpoints		
Pre-enrollment							
Pre-screening	X						
Prior consent discussion	X	X	X				
Enrollment							
Eligibility screen		X	X				
Informed consent				X			
Study code issued		X					
Laboratory test[b]				X	X		
Allocation				X			
Interventions[c]				X			
Assessments							
Organ failure[d]		X	X	X	X[e]	X[f]	
Major complications					← →		
Major interventions					← →		
Vital status							X

Fig. 2: Schedule of enrolment, interventions and assessments

a: Course date Day0 is defined as the day when abdominal pain starts.

b: Laboratory test is indicated at randomization(course date DayX and study date Day0) and 1,7,14,and 21days after randomization.

c: Percutaneous catheter drainage of ANC should be performed in patients assigned to the early on-demand drainage group within 24h after randomization.

d. Organ failure assessments include respiratory and renal failure based on the Modified Marshall Score and cardiovascular failure based on the SOFA score.

e. Organ failure assessments during this period need to be repeated on a daily basis.

f. Only new-onset organ failure which is part of the primary endpoint will be recorded during this period.

New-onset denotes what is not present 24h before randomization.