

Limiting Acute Kidney Injury Progression In Sepsis: Study Protocol and Trial Simulation*

OBJECTIVES: To describe study design considerations and to simulate a trial of biomarker-guided sepsis management aimed to reduce acute kidney injury (acute kidney injury). Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7, urinary biomarkers of cell-cycle arrest, and indicators of kidney stress can detect acute kidney injury before clinical manifestations. We sought to determine the event rates for acute kidney injury as a function of serial measurements of urinary (tissue inhibitor of metalloproteinases-2)•(insulin-like growth factor-binding protein 7) in patients at risk of sepsis-associated acute kidney injury, so that an escalating series of kidney-sparing sepsis bundles based on international guidelines could be applied.

DESIGN: We described the study protocol of “Limiting acute kidney injury Progression In Sepsis,” a phase 4, multicenter, adaptive, randomized controlled trial. We performed simulations to estimate the rates for the trial’s primary endpoint using patient-level data from two previous studies (Sapphire and Protocolized Care for Early Septic Shock).

SETTING: Academic and community ICUs.

PATIENTS: Critically ill patients with sepsis or septic shock, without evidence of stage 2/3 acute kidney injury at enrollment.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Our primary endpoint is progression of two or more stages of acute kidney injury, death, or dialysis within 72 hours after enrollment. In the Sapphire simulation, 45 of 203 patients (22%) with sepsis met the endpoint. In Protocolized Care for Early Septic Shock, 144 of 607 patients (24%) with septic shock met the endpoint. In both simulations, (tissue inhibitor of metalloproteinases-2)•(insulin-like growth factor-binding protein 7) patterns, suggested by Limiting acute kidney injury Progression In Sepsis protocol, stratified the risk for the endpoint from 6% (three negative tests) to 41% (for patients eligible for the highest level of kidney-sparing sepsis bundle) in Sapphire, and 14% (two negative tests) to 46% (for the highest level of kidney-sparing sepsis bundle) in Protocolized Care for Early Septic Shock.

CONCLUSIONS: Findings of our Limiting acute kidney injury Progression In Sepsis trial simulation confirmed that (tissue inhibitor of metalloproteinases-2)•(insulin-like growth factor-binding protein 7) could identify patients with different rates of progression to moderate/severe acute kidney injury, death, or dialysis in 72 hours. The Limiting acute kidney injury Progression In Sepsis protocol algorithm is therefore feasible in terms of identifying suitably high-risk individuals for kidney-sparing sepsis bundle.

KEY WORDS: acute kidney injury; biomarkers; insulin-like growth factor-binding protein 7; randomized controlled trial; sepsis; tissue inhibitor of metalloproteinases-2

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*See also p. 1822.

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Acute kidney injury (AKI) is a clinical syndrome with multiple etiologies (1) afflicting 18–39 people per thousand population (2). It occurs in approximately 11–13% of hospital admissions (3) and over 50% of patients in ICUs (4). AKI is an important risk factor for chronic kidney disease and accelerated progression to end-stage kidney disease, leading to poor quality of life, disability, and increased costs (5).

Early recognition and management of patients at risk for or with AKI but prior to clinical manifestations are likely to translate into better outcomes (1, 5). Even when identifying risk factors for AKI (e.g., advanced age and underlying disease, sepsis, radiocontrast, nephrotoxic drugs), there is no reliable way for a clinician to use this information to establish a clear and actionable risk profile (6). Furthermore, AKI is usually silent, with no early signs or symptoms, and serum creatinine may only increase once significant injury has occurred (7). All this leads to delays in recognizing AKI and applying treatments to preserve kidney function (6).

Sepsis is the most common cause of AKI in critically ill patients, playing a role in 40–50% of AKI cases (8). Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (9). The Global Burden of Disease Study estimated that in 2017 sepsis caused almost 20% of all global preventable deaths (10). The development of sepsis-associated AKI (SA-AKI) is associated with reduced survival and longer hospital/ICU stay (11).

Biomarkers that provide an early indicator of kidney stress could be useful in clinical practice to detect silent episodes of AKI or for early identification of patients at risk (6, 12). Two such biomarkers, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) (13, 14), are measured by a commercial test (NephroCheck Test; Astute Medical, San Diego, CA) and are combined into a risk score ([TIMP-2]•[IGFBP7]) that can predict the development of moderate or severe AKI (Kidney Disease: Improving Global Outcomes [KDIGO] stages 2–3) within 12 hours (13, 15, 16).

Currently, no study has assessed the clinical utility and economic effects of [TIMP-2]•[IGFBP7] in patients at risk of SA-AKI. We designed “Limiting AKI Progression In Sepsis” (LAPIS), a phase 4, multicenter, adaptive, randomized controlled trial (RCT) of

biomarker-guided delivery of kidney-sparing care measures in patients with sepsis admitted to the ICU. Here, we sought to describe the LAPIS trial design and to estimate the rates of the primary endpoint as a function of the biomarker patterns by simulating the study protocol using similar cohorts from the Sapphire study (13) and the Protocolized Care for Early Septic Shock (ProCESS) trial (17).

MATERIAL AND METHODS

Study Protocol

The study will be performed in accordance with the Declaration of Helsinki, the International Council for Harmonization Good Clinical Practice, and all applicable laws and regulations of the countries in which the trial is conducted. An independent Data and Safety Monitoring Board will review the progress of the study. More details are provided in the Supplemental Digital Content (<http://links.lww.com/CCM/G472>). Trial registration is available at ClinicalTrials.gov number NCT04434209.

Objectives. The primary objective of the LAPIS study is to evaluate the effects of biomarker-guided implementation of kidney-sparing care measures (intervention arm) in comparison with standard of care (SOC) assessment and treatment (control arm) on clinical outcomes in patients with sepsis. The secondary objective is to evaluate the effect of the intervention on economic outcomes.

Endpoints. The primary endpoint is a composite of progression of two or more stages of AKI (from KDIGO stage 0 to 2/3 or from stage 1 to 3), death, or dialysis within 72 hours after enrollment. For the purposes of the endpoint, dialysis is defined as any form of renal replacement therapy (RRT).

Secondary endpoints are as follows: 1) death, dialysis, or AKI stage 2/3 within 48 and 72 hours of enrollment; 2) stage 2 or 3 AKI within 72 hours of enrollment; and 3) ICU length of stay. A detailed description of all the endpoints is in the Supplemental Digital Content (<http://links.lww.com/CCM/G472>).

Study Design and Study Population. LAPIS is an adaptive, multicenter, open label, RCT of patients with sepsis. We plan to enroll approximately 540 patients at 18 sites in Europe and the United States. The study will compare SOC patient management with management guided by [TIMP-2]•[IGFBP7] using protocol-defined

care measures. After any eligible patient is diagnosed with sepsis, the patient may be approached for study participation (**Supplemental Fig. S1**, <http://links.lww.com/CCM/G472>).

We will consider eligible adults (age 21 or older) with a diagnosis of sepsis or septic shock according to Sepsis-3 definitions (9) without AKI stage 2/3 at the time of screening. Patients must be admitted to the ICU or have a planned admission to the ICU with an expected stay in the hospital of more than 48 hours. The full list of inclusion and exclusion criteria is reported in **Supplemental Table S1** (<http://links.lww.com/CCM/G472>), and a more detailed discussion is provided in the Supplemental Digital Content-Study Population (<http://links.lww.com/CCM/G472>). Consented patients will be randomly assigned 1:1 to either intervention or control (**Supplemental Fig. S2**, <http://links.lww.com/CCM/G472>).

Study Interventions. *Control arm*—SOC. Patients randomly assigned to the control arm will be treated according to the caring team plan and any site approaches for treating sepsis patients.

Intervention arm—SOC. As it is SOC to promote the deescalation of care in low-risk patients for SA-AKI, when subjects have three negative [TIMP-2]•[IGFBP7] values, and if medically appropriate according to their judgment, the treating clinician may consider deescalation of care.

Intervention arm—kidney-sparing sepsis bundles. Patients with any (TIMP-2)•(IGFBP7) test result greater than 0.3 will be recommended for kidney-sparing sepsis bundles (KSSBs) with three possible levels of care depending on the quantitative value of the test results and test result trends over time (**Fig. 1**). Once started, the assigned KSSB level will not deescalate to a lower level for at least 72 hours after enrollment. KSSB interventions are based on the international KDIGO guidelines for the prevention of AKI (1) routinely used in ICUs around the world. The treating clinician has the option to decline the use of any KSSB intervention, if they feel it is not in the best interest of the patient. The three levels of the KSSB interventions are listed in **Table 1** and described in the Supplemental Digital Content (<http://links.lww.com/CCM/G472>).

Adaptive Design. This study will use an adaptive design using prespecified changes to the protocol based on the observed relative risk reduction (RRR). If the RRR is different from the assumed 30%, the sample size will be modified as detailed in the Supplemental

Digital Content (<http://links.lww.com/CCM/G472>). Furthermore, if the overall RRR is less than 17%, the effect of excluding septic shock patients will be evaluated.

Trial Simulations

We selected two cohorts of patients from the Sapphire (13) and ProCESS (17) studies to simulate and inform the event rate estimates for the LAPIS primary endpoint in association with urinary [TIMP-2]•[IGFBP7] values over time. The Sapphire study (13) included 723 adults admitted to the ICU within 24 hours of enrollment. Among these patients, we considered only those with sepsis. For [TIMP-2]•[IGFBP7] measurements, the first urine sample was collected at enrollment, the second sample 12 ± 6 hours later, and the third sample at 24 ± 6 hours after enrollment. Time of enrollment varied among patients, but for most, it was when the patient was already admitted in the ICU and/or completed the first resuscitative treatments. For this reason and for the purposes of our trial simulation, these time points represent 6, 18, and 30 hours from sepsis diagnosis and start of the treatment.

The ProCESS trial (17) enrolled 1,341 patients 18 years or older, recruited in the emergency department within 2 hours after the detection of septic shock. For [TIMP-2]•[IGFBP7] measurements, the first urine sample was collected at 6 hours after enrollment and a second sample at 24 hours after enrollment.

From both cohorts, we excluded patients with AKI stage 2 or 3 at enrollment. Further details on inclusion and exclusion criteria and on the sensitivity analysis for the ProCESS trial are provided in the Supplemental Digital Content-LAPIS simulation (<http://links.lww.com/CCM/G472>). In both studies, urine samples were centrifuged, and supernatants were frozen and stored at less than -70°C ; the supernatant was then thawed immediately prior to testing for [TIMP-2]•[IGFBP7].

We assessed the primary endpoint for each cohort as a whole and for all branches created using the protocol treatment algorithm (**Fig. 1**). We described the general characteristics of each cohort overall and according to the presence or absence of the primary endpoint. We used Pearson's chi-square test to compare categorical variables, and we used Mann-Whitney *U* test to compare continuous variables. Logistic regression for the primary endpoint was performed in both cohorts. Among the statistically significant variables ($p < 0.05$) at univariate

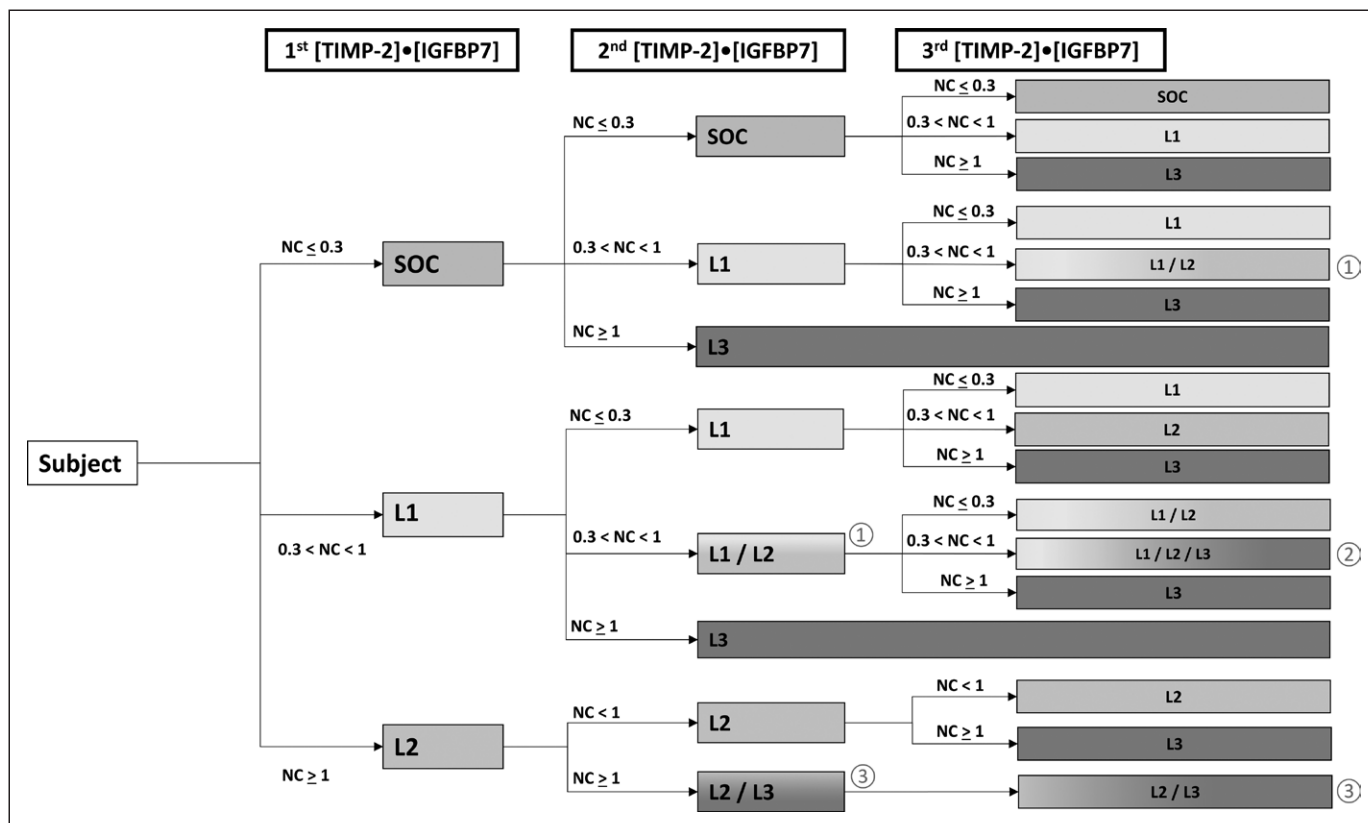


Figure 1. Protocol treatment algorithm. The figure shows the protocol treatment algorithm. After every [TIMP-2]•[IGFBP7] test, the patients are allocated to a different level of treatment (standard of care [SOC], L1, L2, and L3) according to the [TIMP-2]•[IGFBP7] value (e.g., ≤ 0.3 , $0.3-1.0$, or ≥ 1.0 ; < 1.0 or ≥ 1.0 [ng/mL]²/1,000). The first [TIMP-2]•[IGFBP7] draw will be performed at 6–9 hr from sepsis diagnosis, the second one after 6–9 hr from the first one (around 12–18 hr from sepsis diagnosis), whereas the third one after 12–15 hr from the second one (around 24–33 hr from sepsis diagnosis). The red circled numbers represent special rules applied to that specific protocol hub. The rules are as follows: ① If the patient's [TIMP-2]•[IGFBP7] results remain in the same category range, but the quantitative score increases or remains the same, the next higher kidney-sparing sepsis bundle (KSSB) level will be instituted. ② If the third [TIMP-2]•[IGFBP7] quantitative score increases or remains the same as the second [TIMP-2]•[IGFBP7] test, then the next higher KSSB level will be instituted. If the third [TIMP-2]•[IGFBP7] test quantitative score is lower than the second [TIMP-2]•[IGFBP7] test, then the patient's care will remain at the KSSB level assigned after the second test. ③ If the patient's second [TIMP-2]•[IGFBP7] result is greater than or equal to 1 but shows a decline by 50% or more, then the patient's care will remain at KSSB Level 2. If the patient's third [TIMP-2]•[IGFBP7] result remains greater than or equal to 1 but shows a decline by 50% or more in comparison with the second [TIMP-2]•[IGFBP7] value, then the patient's care will remain at KSSB Level 2. IGFBP7 = insulin-like growth factor-binding protein 7, L = level of the kidney-sparing sepsis bundle, NC = NephroCheck, [TIMP-2]•[IGFBP7], TIMP-2 = tissue inhibitor of metalloproteinases-2.

analysis (Supplemental Tables S3 and S4, <http://links.lww.com/CCM/G472>), we chose least absolute shrinkage and selection operator (LASSO) regularization to select the best covariates for the logistic regression models. Analyses were conducted using SPSS Statistics Version 26 (IBM Corp., Armonk, NY) and R 4.0.2 (R Foundation for Statistical Computer, Vienna, Austria) with alpha set at two-tailed p value of less than 0.05.

RESULTS

Characteristics of the Two Cohorts

The Sapphire evaluation cohort consisted of 203 patients (of 723). In this cohort, 22% of patients (45/203)

experienced the primary endpoint. Supplemental Table S3 (<http://links.lww.com/CCM/G472>) shows the general characteristics of the Sapphire cohort and compares patients with and without the primary endpoint. Age, sex, and race did not differ in the two groups nor did comorbidities. Acute Physiology and Chronic Health Evaluation (APACHE) III score, but not SOFA score, was higher in the endpoint positive group (median 93 vs 73; $p = 0.002$). All three [TIMP-2]•[IGFBP7] median values were higher in the endpoint positive group.

The ProCESS evaluation cohort consisted of 607 patients (of 1,341). In this cohort, 24% of patients (144/607) experienced the primary endpoint. Supplemental Table S4 (<http://links.lww.com/CCM/G472>) shows the general

TABLE 1.**Summary and List of the Interventions of Limiting acute kidney injury Progression In Sepsis Trial**

Trial summary (PICO)	
P	Critically ill patients with sepsis or septic shock at risk for AKI.
I	Serial tests of urinary [TIMP-2]•[IGFBP7] to guide and escalating series of interventions (see Level 1–3 KSSB below).
C	Clinicians blinded to [TIMP-2]•[IGFBP7] results; application of standard of care for sepsis.
O	Progression of 2 or more Kidney Disease: Improving Global Outcomes stages of AKI, death, or dialysis within 72 hr after enrollment.
Level 1 KSSB	
1	Discontinuation of potentially nephrotoxic agents (full list in Supplemental Table S2 , [http://links.lww.com/CCM/G472]).
2	Discontinuation of nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aminoglycosides, radiocontrast agents.
3	Vancomycin or aminoglycosides dosing based upon therapeutic drug level monitoring.
4	Review all medications for potential nephrotoxicity as soon as possible in consultation with available hospital resources (e.g., clinical pharmacists).
5	Use of only balanced crystalloid for fluid boluses.
6	Accurate daily measurement of total fluids intake and output.
7	Limit use of diuretics and fluids only after determining fluid status and need.
8	Provision of alternative options to radiocontrast procedures (consideration of alternative imaging methods, use of the lowest possible dose of contrast medium, and avoidance of all unnecessary IV iodinated contrast dye).
Level 2 KSSB	
1	institution of functional hemodynamic monitoring (e.g., with FloTrac, Pulse Contour Cardiac Output, ultrasound) to optimize the volume status and hemodynamic variables and to assess fluid responsiveness
Level 3 KSSB	
1	Review the study subject's kidney status with available hospital resources chiefly to identify any unrecognized cause of AKI (e.g., consultation with nephrologist)
2	Review the study subject's infectious disease management with available hospital resources (e.g., infectious disease specialist).
3	Consideration of seeking other sources of infection (interventions could include imaging procedures, skin examination, etc.)

AKI = acute kidney injury, IGFBP7 = insulin-like growth factor-binding protein 7, KSSB = kidney-sparing sepsis bundle, TIMP-2 = tissue inhibitor of metalloproteinases-2, PICO = Population-Intervention-Comparison-Outcome.

characteristics of the ProCESS cohort and compares patients with and without the primary endpoint. Patients who developed the primary endpoint were older and had a higher prevalence of chronic heart failure, history

of renal disease, cerebral vascular disease, and dementia. Furthermore, APACHE II score, SOFA score, and both the [TIMP-2]•[IGFBP7] median values were higher in the endpoint positive group.

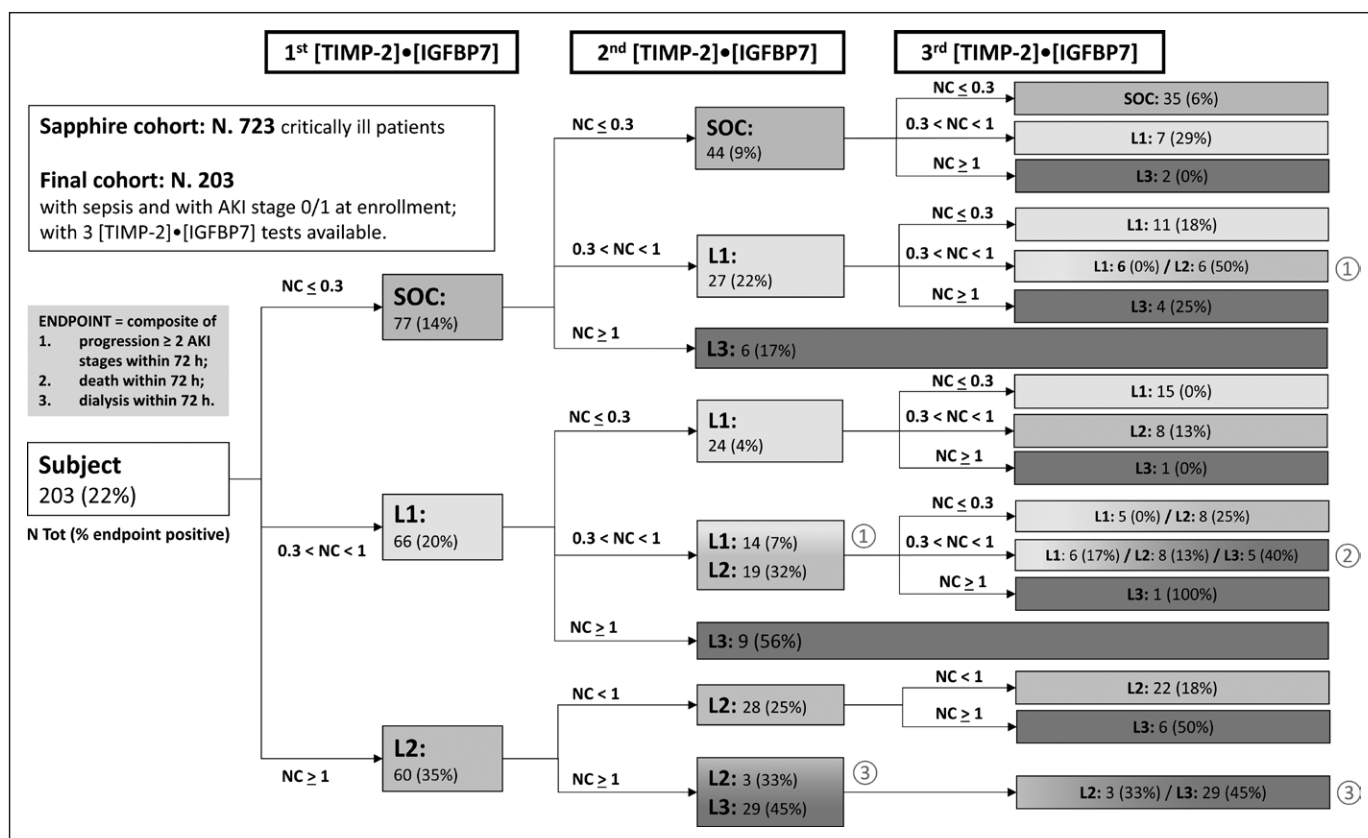


Figure 2. Protocol simulation in Sapphire study. The figure shows the protocol algorithm simulated in Sapphire study cohort. These patients did not receive these levels of kidney-sparing sepsis bundle, but these interventions would have been recommended based on the biomarker results. In each *box*, it is shown the total number of patients in this level of treatment, whereas in the *round brackets*, it is shown the percentage of these patients that reach the primary endpoint. The first [TIMP-2]•[IGFBP7] test was performed at enrollment, the second 12 hr later, and the third 24 after enrollment. Since time of enrollment varied among patients, but for most of them, it was when the patient was already admitted in the ICU and/or completed the first resuscitative treatments, for the purposes of our trial simulation, these timepoints will represent 6, 18, and 30 hr from sepsis diagnosis and start of the treatment. If any [TIMP-2]•[IGFBP7] result was missing or unavailable, we applied the last of the general rules planned also for Limiting acute kidney injury Progression In Sepsis trial: the subject will remain at the current treatment level and use the appropriate decision rules according to the next test in the algorithm (see Supplemental Digital Content, chapter “Study Interventions,” paragraph “General Rules,” <http://links.lww.com/CCM/G472>). For the rules of the *red circled numbers*, see legend of Figure 1. AKI = acute kidney injury, IGFBP7 = insulin-like growth factor-binding protein 7, L = level of the kidney-sparing sepsis bundle, NC = NephroCheck, [TIMP-2]•[IGFBP7], SOC = standard of care, TIMP-2 = tissue inhibitor of metalloproteinases-2.

Finally, LASSO regularization yielded a reduced model with the [TIMP-2]•[IGFBP7] measurement as covariates. In Sapphire, only the third [TIMP-2]•[IGFBP7] test had a statistically significant odds ratio of 2.29 (95% CI, 1.37–4.08; $p = 0.003$) after adjustment for the other two [TIMP-2]•[IGFBP7] tests in the model (**Supplemental Table S5**, <http://links.lww.com/CCM/G472>), whereas for the ProCESS cohort, both tests were significant (**Supplemental Table S6**, <http://links.lww.com/CCM/G472>).

Figure 2 shows in detail the results of simulating LAPIS protocol algorithm using the Sapphire cohort. The percentage of patients who met the primary endpoint ranged from 14% when the “first” [TIMP-2]•[IGFBP7] value was less than or equal to 0.3 (ng/mL)²/1,000, to 25%

20% for values between 0.3 and 1.0, and finally to 35% when the value was greater than or equal to 1.0. **Figure 3** shows in detail the results of simulating LAPIS protocol algorithm using the ProCESS cohort. The percentage of patients who met the primary endpoint ranged from 16% when the “first” [TIMP-2]•[IGFBP7] value was less than or equal to 0.3 (ng/mL)²/1,000, to 25% for values between 0.3 and 1.0, and finally to 40% when the value was greater than or equal to 1.0.

Table 2 summarized the results of both simulations. We pooled together all patients who should have reached the same level of treatment at the end of the algorithm according to their [TIMP-2]•[IGFBP7] values. In Sapphire, only 6% of patients with three consecutive [TIMP-2]•[IGFBP7] less than or equal to 0.3 (ng/

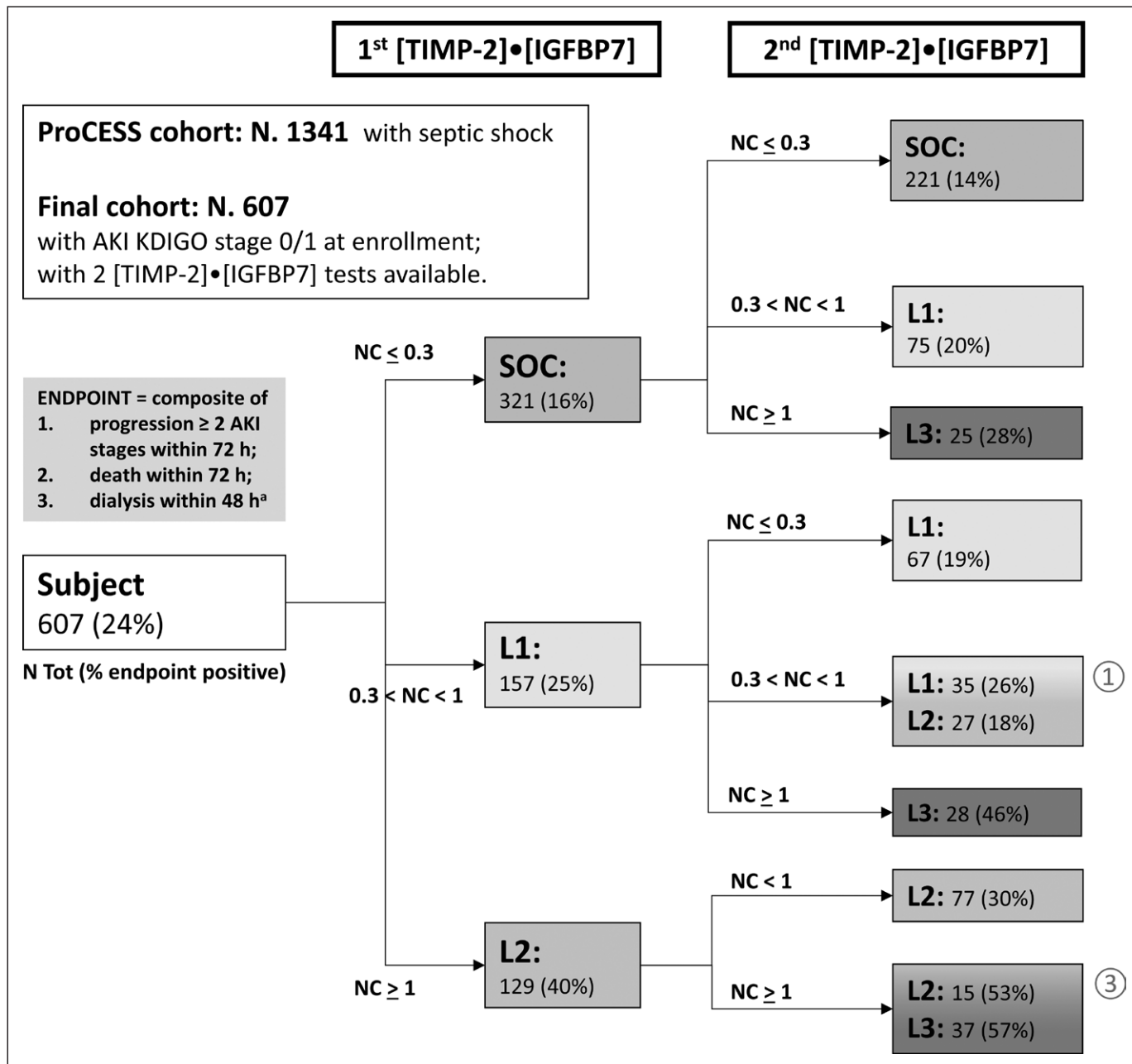


Figure 3. Protocol simulation in Protocolized Care for Early Septic Shock (ProCESS) trial. The figure shows the protocol algorithm simulated in ProCESS. These patients did not receive these levels of kidney-sparing sepsis bundle, but these interventions would have been recommended based on the biomarker results. In each *box*, it is shown the total number of patients in this level of treatment, whereas in the *round brackets*, it is shown the percentage of these patients that reach the primary endpoint. The first[TIMP-2]•[IGFBP7] test was performed at 6 hr from enrollment/sepsis diagnosis, whereas the second at 24 hr from enrollment/sepsis diagnosis. For the rules of the *red circled numbers*, see legend of Figure 1. ^aIn ProCESS, the dialysis endpoint was evaluated at 48 hr from enrollment instead of 72 hr. AKI = acute kidney injury, IGFBP7 = insulin-like growth factor-binding protein 7, KDIGO = Kidney Disease: Improving Global Outcomes, L = level of the kidney-sparing sepsis bundle, NC = NephroCheck, [TIMP-2]•[IGFBP7], SOC = standard of care, TIMP-2 = tissue inhibitor of metalloproteinases-2.

mL)²/1,000 developed the primary endpoint, whereas in ProCESS, 14% of patients with two consecutive values less than or equal to 0.3 developed the primary endpoint. In addition, the results indicate that the LAPIS algorithm proposes increased complexity of care (reflected by a higher level of KSSB) for patients with a higher risk

of developing the primary endpoint. At the end of the simulation, the endpoint positivity rate increased from 10% for level 1 KSSB to 41% for level 3 KSSB in Sapphire cohort, and from 21% for level 1 KSSB to 46% for level 3 KSSB in ProCESS. **Supplemental Table S7** (<http://links.lww.com/CCM/G472>) and **Supplemental Figure S3**

TABLE 2.**Summary of Protocol Simulation in Sapphire and Protocolized Care for Early Septic Shock Studies**

Treatment Levels After [Tissue Inhibitor of Metalloproteinases-2]•[Insulin-Like Growth Factor-Binding Protein 7] Tests ^a	n (%)	Progression of 2 Acute Kidney Injury Stages ^b	Death ^b	Dialysis ^c	Primary Endpoint ^d
Sapphire study					
SOC	35 (17)	1/35 (3)	1/35 (3)	0/35 (0)	2/35 (6)
L1 KSSB	50 (25)	4/50 (8)	1/50 (2)	0/50 (0)	5/50 (10)
L2 KSSB	55 (27)	8/55 (15)	4/55 (7)	1/55 (2)	12/55 (22)
L3 KSSB	63 (31)	23/63 (37)	5/63 (8)	6/63 (10)	26/63 (41)
Total	203 (100)	36/203 (18)	11/203 (5)	7/203 (3)	45/203 (22)
Protocolized Care for Early Septic Shock trial ^e					
SOC	221 (36)	30/221 (14)	0/221 (0)	0/221 (0)	30/221 (14)
L1 KSSB	177 (29)	32/177 (18)	3/177 (2)	2/177 (1)	37/177 (21)
L2 KSSB	119 (20)	34/119 (29)	3/119 (3)	1/119 (1)	36/119 (30)
L3 KSSB	90 (15)	37/90 (41)	11/90 (12)	0/90 (0)	41/90 (46)
Total	607 (100)	133/607 (22)	17/607 (3)	3/607 (0.5)	144/607 (24)

KSSB = kidney-sparing sepsis bundle, L = level of the kidney-sparing sepsis bundle, SOC = standard of care.

^aPatients in neither study received these interventions but these interventions would have been recommended based on the biomarker results.

^bWithin 72 hr from enrollment.

^cFor Sapphire study within 72 hr from enrollment. For Protocolized Care for Early Septic Shock trial within 48 hr from enrollment.

^dPresence of at least one between progression of two or more stages of acute kidney injury, death, or dialysis.

^eBased only on two [tissue inhibitor of metalloproteinases-2]•[insulin-like growth factor-binding protein 7] tests.

(<http://links.lww.com/CCM/G472>) show similar results for the simulation in the sensitivity analysis cohort for ProCESS trial, and they are discussed in the Supplemental Digital Content (<http://links.lww.com/CCM/G472>).

DISCUSSION

Our simulation helps inform the upcoming LAPIS trial and adds insight into AKI development in septic patients. The aim of the LAPIS trial is to assess the effects of a biomarker-guided kidney-sparing sepsis protocol on patient outcomes. Previous trials in patients undergoing major surgery measured [TIMP-2]•[IGFBP7] to enrich for patients at higher risk of AKI, and patients testing positive were randomized to interventions (18, 19), whereas LAPIS will be

the first trial that randomizes patients to receive the biomarker test itself. Furthermore, LAPIS will be the first to use serial [TIMP-2]•[IGFBP7] measurements, and our algorithm was specifically designed to consider biomarker trends over time. Recent observational studies have supported this approach (20, 21).

The 0.3 cut off is the only Food and Drug Administration–approved cut off for its high sensitivity in identifying patients at higher risk for moderate-severe AKI. This cut off will be sensitive enough to provide at least level 1 interventions to most of our patients (around 64–83% according to our simulations). In addition, the higher 1.0 cut off has a higher specificity (22) that will allow us to select patients deserving a higher level of treatment.

We chose to obtain our first biomarker sample at approximately 6 hours from sepsis diagnosis because, in

sepsis, patients with high [TIMP-2]•[IGFBP7] values upon presentation that decline with resuscitation have much better outcomes compared with patients with high [TIMP-2]•[IGFBP7] values after the initial 6–12 hours of therapy suggesting that a high value after 6 hours may be more predictive of outcome (21, 23). In addition, a 6-hour sepsis bundle is already a well-established practice at many hospitals, and it would be quite difficult to enroll patients in time to modify this practice.

In our simulation, patients with sepsis in Sapphire were quite similar to patients in ProCESS, a study that exclusively enrolled septic shock, with regard to both the general patient characteristics (Supplemental Tables S3 and S4, <http://links.lww.com/CCM/G472>) and the overall proportion of patients who experience the primary endpoint. In ProCESS, the definition of septic shock was based on the presence of systemic inflammatory response syndrome criteria plus shock, so we are cautious in generalizing these data since LAPIS will use Sepsis-3 criteria; it is also for this reason that we designed the specific adaptation regarding septic shock. Also, both regression models for prediction of the primary endpoint included only [TIMP-2]•[IGFBP7] and no other clinical variables; [TIMP-2]•[IGFBP7] values were all associated with the endpoint at univariate analysis, but when combined in a model, the association was strongest for the last [TIMP-2]•[IGFBP7] likely because this value was the closest to the time the patient developed the endpoint.

Table 2 emphasizes the LAPIS protocol's ability to appropriately increase the complexity and intensity of care, corresponding to a higher level of KSSB, for patients who have a higher risk of experiencing the endpoint. The endpoint rates for level 3 KSSB were similar in the two simulations (41% vs 46%), whereas the higher difference in the other levels could be because ProCESS simulation was based only on two [TIMP-2]•[IGFBP7] measurements.

The KSSB interventions were derived from the KDIGO AKI clinical practice guideline (1) and represent an implementation plan for therapies (e.g., balanced fluids). Other KDIGO care bundles (e.g., optimization of fluid status, maintenance of perfusion pressure, discontinuation of nephrotoxic agents) have been implemented for different types of

patients—cardiac (18) and major abdominal surgery (19)—and have been shown to reduce AKI rates compared with standard of care.

Experts from Europe and North America have recommended many of the interventions proposed in LAPIS trial guided by the results of [TIMP-2]•[IGFBP7] (24). KDIGO bundles applied after interpreting the results of [TIMP-2]•[IGFBP7] seem to be effective in reducing AKI both in real-life (25) and in clinical trials settings (18, 19, 26). In particular, nephrotoxic exposure (e.g., vancomycin, piperacillin/tazobactam, nonsteroidal anti-inflammatory drugs, radiocontrast agents) is known to be frequent in ICU patients and may lead to drug-associated AKI in around 15–25% of the patients (27). Cumulative and longer nephrotoxic exposures further increase the risk for AKI; additionally, [TIMP-2]•[IGFBP7] seems to be able to identify patients at risk of developing AKI after this kind of exposure (27, 28).

We assigned functional hemodynamic monitoring as part of the level 2 KSSB because we think it plays a crucial role in the management of patients with sepsis at higher risk of AKI and because this intervention was included in other previous studies (18, 26). Furthermore, a recent trial underlined how using fluid responsiveness assessment to guide resuscitation therapy is able to reduce the rates of RRT and mechanical ventilation without compromising safety (29).

As a level 3 KSSB, we suggest nephrology and infectious disease consultation. Early nephrologist involvement in managing patients with AKI is likely to be beneficial (30), as delayed consultation is associated with higher mortality in patients with AKI (31). Similarly, infectious disease consultation may be helpful in patients with sepsis and septic shock who are not responding to standard therapy (32–34). These subspecialists are normally brought in when cases are complex or refractory, but, as also suggested by our simulation, a situation of high-risk of death, dialysis, or progression of AKI should warrant their early involvement. We are aware that a potential limitation of our study, with a complex intervention with different levels of KSSB, is that we will not know the relative contribution of each component to the final effect. However, we will be able to determine the effect of a consecutive biomarker-guided protocol in patients with sepsis, which is our primary goal.

CONCLUSIONS

We described our study rationale, protocol, intervention, and analysis approach before starting the LAPIS trial. Our simulation of the LAPIS protocol algorithm using patient-level data from two prior studies allowed us to better understand the role of urinary [TIMP-2]•[IGFBP7] in selecting patients with markedly different rates of progression to moderate/severe AKI, death, or dialysis in 72 hours.

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