Original research

Prospective RandOmised Trial of Emergency Cardiac Computerised Tomography (PROTECCT)

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ABSTRACT

Objective Many patients presenting with suspected acute coronary syndrome (ACS) have high-sensitivity cardiac troponin (hs-cTn) concentrations between rule-in and rule-out thresholds and hence need serial testing, which is time consuming. The Prospective RandOmised Trial of Emergency Cardiac Computerised Tomography (PROTECCT) assessed the utility of coronary CT angiography (CCTA) in patients with suspected ACS, non-ischaemic ECG and intermediate initial hs-cTn concentration.

Methods Patients were randomised to CCTA-guided management versus standard of care (SOC). The primary outcome was hospital length of stay (LOS). Secondary outcomes included cost of in-hospital stay and major adverse cardiac events (MACE) at 12 months of follow-up. Data are mean (SD); for LOS harmonic means, IQRs are shown.

Results 250 (aged 55 (14) years, 25% women) patients were randomised. Harmonic mean (IQR) LOS was 7.53 (6.0–9.6) hours in the CCTA arm and 8.14 (6.3–9.8) hours in the SOC arm (p=0.13). Inpatient cost was £1285 (£2216) and £1108 (£3573), respectively, p=0.68. Los was shorter in the CCTA group in patients with <25% stenosis, compared with SOC; 6.6 (5.6–7.8) hours vs 7.5 (6.1–9.4) hours, respectively; p=0.021. More referrals for cardiology outpatient clinic review and cardiac CT-related outpatient referrals occurred in the SOC arm (p=0.01). 12-month MACE rates were similar between the two arms (7 (5.6%) in the CCTA arm and 8 (6.5%) in the SOC arm—log-rank p=0.78).

Conclusions CCTA did not lead to reduced hospital LOS or cost, largely because these outcomes were influenced by the detection of ≥25% grade stenosis in a proportion of patients.

Trial registration number NCT03583320.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Only two randomised controlled trials (RCTs) of emergency coronary CT angiography (CCTA) have been published during the era of high-sensitivity troponin assays—one including predominantly lower risk troponin negative patients and the other including higher risk patients with non-ST acute coronary syndrome (ACS).

⇒ Patients presenting with suspected ACS, who fall in between the above two risk categories, specifically with intermediate concentration of high-sensitivity troponin on initial blood-draw and non-ischaemic ECG, pose a diagnostic and logistical challenge to clinicians working in emergency department with the need for time-consuming serial troponin/ECG testing, thus contributing to increased hospital stay.

WHAT THIS STUDY ADDS

⇒ The additional use of CCTA did not decrease hospital length of stay (LOS) (CCTA vs standard of care (SOC): harmonic mean (IQR) LOS 7.53 (6.0–9.6) vs 8.14 (6.3–9.8) hours; p=0.13) or inpatient cost (CCTA vs SOC: mean (SD) cost £1285 (£2216) and £1108 (£3573), respectively, p=0.68). On 12 months of follow-up, cumulative major adverse cardiac events did not differ between the two arms—log-rank p=0.78. However, CCTA was associated with significantly reduced outpatient referrals/investigations (p=0.01) and also significantly increased discharge prescription of aspirin (p=0.008).

INTRODUCTION

Acute chest pain is a significant health burden and its accurate and safe assessment in the emergency department (ED) is a key determinant of clinical outcomes and resource utilisation.1 In recent years, high-sensitivity cardiac troponin (hs-cTn) assays have received approval for clinical use in international practice guidelines for evaluation of patients with suspected acute coronary syndrome (ACS). The European Society of Cardiology guidelines advocate the use of hs-cTn testing to rule-in or rule-out ACS with one blood draw,2 but a substantial proportion of patients have an equivocal initial result (between rule-out and rule-in thresholds) and therefore serial hs-cTn measurement is required.3 Furthermore, even after serial hs-cTn measurement, a significant proportion of patients remain between those thresholds (referred to as the observational zone), and this is associated with increased mortality and adverse cardiac event risks compared with patients in the rule-out category.3,4,7
The use of coronary CT angiography (CCTA) in patients with acute chest pain in the era of conventional troponin has been shown to be safe with high sensitivity and negative predictive value for coronary artery disease (CAD) and cost-effective with decreased time to diagnosis and earlier discharge from the ED. While CCTA may help, there are conflicting data on its utility. On the one hand, the American Heart Association guidelines recommend the use of CCTA in patients with acute chest pain—although this is largely based on evidence gathered during the era of conventional troponin assays. On the other hand, two randomised clinical trials carried out in the hs-cTn era suggest that CCTA may not be beneficial.

The Better Evaluation of Acute Chest Pain with Computed Tomography Angiography (BEACON) trial, which enrolled a highly selected and relatively low-risk cohort (95% had hs-Tn levels below the reference level), found no difference in the number of patients requiring revascularisation at 30 days. The Rapid Assessment of Potential Ischaemic Heart Disease with computed tomography coronary angiography (RAPID-CTCA) trial enrolled a higher risk cohort (67% had elevated hs-Tn levels, 61% had abnormal ECG) and found that a CCTA (done up to 24 hours following presentation) did not reduce the rate of death or myocardial infarction at 1 year. While these two multicentre trials have advanced our understanding of the utility of CCTA in managing ACS, they leave several pertinent questions unanswered. First, the patients who pose the greatest management challenge, and are also the most frequent presenters to ED with suspected ACS, are those who fall between the ends of the spectrum represented by BEACON and RAPID-CTCA; patients with hs-cTn concentrations above the rule-out threshold (and may be discharged by ED physicians) but lacking ECG changes or rule-in information for coronary artery disease (CAD) and cost-effective with decreased time to diagnosis and earlier discharge from the ED. While CCTA may help, there are conflicting data on its utility. On the one hand, the American Heart Association guidelines recommend the use of CCTA in patients with acute chest pain—although this is largely based on evidence gathered during the era of conventional troponin assays. On the other hand, two randomised clinical trials carried out in the hs-cTn era suggest that CCTA may not be beneficial.

Results of performing CCTA and/or calcium score only were excluded from the healthcare costs evaluation of the SOC arm. In the SOC arm, we ensured that the CCTA was carried out during a time window where patients would normally have been waiting for their serial hs-cTnT blood draw/result and hence hospital length of stay (LOS) would not be affected. In cases with minimal or no atheroma (<25% diameter stenosis), the CCTA report stated that the patient’s presentation was unlikely to be due to ACS, but subsequent management (including the need for serial hs-cTnT) in both groups was left to the discretion of the treating physician. In the CCTA arm, scan reports were made available to clinicians involved in patient care in real time. Reports for patients recruited to the SOC arm were only made available to clinicians during the acute hospital setting if the patient was found to have >50% stenosis in the left main stem and/or proximal left anterior descending artery or for serious non-cardiac pathology (such as an acute pulmonary embolism).

CCTA protocol
All CCTA studies were performed using a third-generation dual-source CT (Siemens Healthcare, Forchheim, Germany) with ECG synchronisation. The acquired images were interpreted by readers who had level III certification in CCTA, and reports issued according to the Society of Cardiovascular Computed Tomography guidelines—additional information in online supplemental material.

Outcome measures
The primary outcome was hospital LOS, defined as the time from hospital presentation to hospital discharge or inpatient death. Secondary outcomes included the cost of inpatient stay, rates of invasive coronary angiography (ICA)/revascularisation, confirmed diagnosis of ACS during index hospital visit (as recorded on discharge summary) and rate of planned cardiac outpatient review at discharge. Using the information from the blinded CCTAs as control data, we also aimed to investigate the impact of CCTA reports, classified by the aforementioned 25% stenosis cut-off, on hospital LOS.

The cost of hospital LOS was obtained from the hospital finance department, where the hospital ED and/or inpatient stays were recorded as individualised ED and/or inpatient episode codes. These codes corresponded to the overall cost of hospital stay and included cost of inpatient diagnostics (including haematological/radiology tests, etc) and management of each patient (including medications given, any interventional procedures, etc). The costs of performing CCTA and/or calcium score only were excluded from the healthcare costs evaluation of the SOC arm.
Major adverse cardiac events (MACE), defined as myocardial infarction, coronary revascularisation or all-cause mortality, were assessed at 12 months by a combination of telephone follow-up and electronic patient records linked to UK Office for National Statistics database. Causes of death were ascertained by retrieving death certificates and/or from hospital and primary care health records. The end of the study was defined as 12 months after recruitment of the final patient.

Statistics
Sample size calculations
LOS was expected to be highly skewed and so sample size calculations were based on simulations using the Mann-Whitney U test as follows: data from a random sample of 49 real patients with suspected ACS managed as per-usual SOC and calculated the multiplication factor needed to reduce their median LOS by 1 hour in a putative experimental population; this constant was found to be 0.799. For a given sample size n, 10 000 Monte Carlo simulations were performed by sampling n patients with replacement from each of the two groups, and the p value from a Mann-Whitney U test was calculated for each simulation. The proportion of these 10 000 simulations with a p value below 0.05 was recorded as the power for that sample size n. The sample size was varied until a power of 0.8 was obtained. Based on reported reductions in hospital LOS from previous studies, we theorised that CCTA may lead to reduction in mean hospital LOS by 20% and this corresponded to a reduction in median LOS of 1 hour. The target sample size was 250 (125 in each arm), which would provide 80% power at a 5% significance level to detect a difference in median LOS of 1 hour.

Analysis
Hospital LOS was compared in the two groups using a two-sample t-test after using an inverse transformation to correct the skewness. LOS results are reported as the harmonic means (IQR) following back transformation. To assess differences in mean cost of hospital LOS between the two arms, we used a generalised linear model (gamma family, identity link) with bootstrapped CIs. Pearson \( \chi^2 \) test or Fisher’s exact test (small frequencies) was used to assess differences in the dichotomous outcomes between the two arms. Kaplan-Meier curves were used to examine cumulative MACE rate and differences between the arms were tested using a log-rank test. The primary analyses were conducted on an intention to treat basis. Analyses were done using SPSS V.26 and Stata V.16.

Patient and public involvement
Patients or the public were not involved in the design, conduct, reporting or dissemination of this research study.

RESULTS
Study participants
During the period from 11 January 2018 to 4 April 2019, five hundred patients presenting with suspected ACS were screened, of whom 250 were recruited (figure 1). Patient characteristics were similar between the two arms (table 1). Seven patients from the SOC arm had CCTAs unblinded during their inpatient hospital stay, including two cases of protocol violation (please see online supplemental material for further details).

Mean (SD) CCTA scanning duration was 12(3.4) min. In the CCTA arm, CCTA versus hs-cTnT mean (SD) turnaround times were similar (from request time to reporting time); 96(11.3) min vs 105(60) min; p=0.28. In the CCTA arm, mean (SD) door to CCTA time was 4.2 (0.99) hours and mean (SD) door to CCTA reporting time was 5.3 (1.06) hours. In the CCTA arm, 31 (26%) out of 118 contrast-enhanced scans were reported before blood draw for second troponin or uploading of the result. Overall mean effective radiation dose was 4.9(2.25) mSv (conversion factor of 0.014 mSv/mGy).

![Flow chart of recruitment, randomisation and follow-up of participants. CAD, coronary artery disease; CCTA, coronary CT angiography; hs-cTnT, high-sensitivity cardiac troponin T; SOC, standard of care.](image)

| Table 1 Baseline characteristics of study participants |
|------------------------------------------------------|
| **CCTA arm** (n=125) | **SOC arm** (n=125) |
| Age mean (SD), years | 54.7 (13.3) | 56.0 (14.0) |
| Gender | | |
| Male: | 93 (74%) | 95 (77%) |
| Female: | | |
| Diabetes | 24 (19%) | 23 (18%) |
| Hypertension | 56 (45%) | 59 (47%) |
| Dyslipidaemia | 52 (42%) | 50 (40%) |
| Current or ex-smoker | 59 (47%) | 63 (50%) |
| Family history of ischaemic heart disease | 35 (28%) | 32 (25.6%) |
| Initial troponin concentration mean (SD), ng/L | 11.11 (8.56) | 11.52 (7.36) |
| Initial troponin concentration >99th percentile (14 ng/L) of a healthy reference population | 24 (19.2%) | 28 (22.4%) |
| Mean (SD) heart rate (beats/min) | 78 (14) | 78 (15) |
| Mean (SD) blood pressure (mm Hg) | | |
| Systolic | 141 (21) | 143 (22) |
| Diastolic | 85 (15) | 86 (14) |
| Medications | | |
| (n=124) | (n=123) |
| Antiplatelet therapy | 16 (13%) | 21 (17%) |
| Statin | 29 (23%) | 45 (36.6%) |
| ACE inhibitor | 29 (23%) | 24 (19.5%) |
| Angiotensin receptor blocker | 14 (11%) | 10 (8%) |
| Beta blocker | 13 (10%) | 20 (16%) |
| Calcium channel blocker | 30 (24%) | 30 (24%) |
| Diuretic agent | 11 (9%) | 16 (13%) |
| Oral diabetic agent | 21 (17%) | 22 (18%) |
| Insulin | 7 (5.6%) | 10 (8%) |
| Oral anticoagulant agent | 7 (5.6%) | 6 (5%) |
| Proton pump inhibitor | 22 (18%) | 25 (20%) |

CCTA, coronary CT angiography; SOC, standard of care.
Fifteen patients had very high calcium scores (mean (SD) calcium score = 1122.82 (606) Agatston units) and did not proceed to a contrast-enhanced study, as these would have yielded suboptimal CCTA results (Table 2).

**Outcomes**

There was no significant difference in the primary outcome between the two arms: the harmonic mean (IQR) LOS was 7.53 (6.0–9.6) hours in the CCTA arm and 8.14 (6.3–9.8) hours in the SOC arm (p = 0.13). Median hospital LOS was 7.35 hours in the CCTA arm and 8.05 hours in the SOC arm. In the CCTA arm, LOS for patients with <25% stenoses was significantly shorter than for patients with at least mild (≥25%) stenoses (6.6 (5.6–7.8) hours vs 8.8 (6.5–10.7) hours; p < 0.005). LOS in patients with <25% stenoses was significantly shorter in the CCTA+SOC arm, compared with the SOC arm; 6.64 (5.6–7.8) hours vs 7.5 (6.1–9.4) hours; p = 0.021, while there was no significant difference in LOS between the two arms among patients with ≥25% stenoses; p = 0.609 (Figure 2).

Of patients who had serial hs-cTnT blood draw (n = 236), 77 were still found to be in the intermediate or observational zone risk category (n = 33 in the CCTA arm vs 44 in the SOC arm). Among this group, we found no difference in LOS—harmonic mean (IQR) LOS was 8.54 (7.1–10.6) hours in the CCTA arm and 9.43 (6.9–12.3) hours in the SOC arm (p = 0.36). Based solely on serial second hs-cTnT profiles, 154 patients could be categorised as “rule-out” (n = 78 in the CCTA arm vs 76 in the SOC arm) and again we found no difference in LOS—harmonic mean (IQR) LOS was 7.05 (5.8–8.01) hours in the CCTA arm and 7.5 (6.1–9.2) hours in the SOC arm (p = 0.23).

The mean (SD) cost of inpatient hospital stay was not significantly different between the two arms (CCTA vs SOC: £1285 (£2216) vs £1108 (£3573); p = 0.68). There were significantly more referrals for cardiology outpatient clinic review and cardiac CT-related outpatient referrals in the SOC arm than the CCTA+SOC arm (60 vs 40; p = 0.01). There were no differences between groups in terms of discharge diagnosis of ACS or in the rates of inpatient ICA and revascularisation. There were no inpatient deaths (Table 3).

Significantly more patients were prescribed aspirin in the CCTA arm at discharge compared with on admission: n = 11 (9%) on admission vs n = 26 (21%) on discharge (p = 0.008). No such difference was observed in aspirin prescription in the SOC arm: n = 18 (15%) on admission vs 25 (21%) on discharge (p = 0.23). Furthermore, there were no differences in rates of prescription (between admission and discharge) of other antiplatelet agents or statins in either arm. Medications on discharge are tabulated in the online supplemental material.

Post-discharge 12-month MACE follow-up data were available for 249/250 (99.6%) of patients. Overall, there were seven MACE events in the CCTA+SOC arm and eight in the SOC arm (log-rank p = 0.78).

**DISCUSSION**

We found that a CCTA-guided strategy in ED did not reduce the duration or cost of the in-hospital stay, compared with conventional biomarker-based diagnosis and triage of patients who present with a suspected ACS (Figure 2). There are two main reasons why CCTA may have failed to impact on the main outcome events. First, while the finding of little or no CAD gave clinicians the confidence to discharge patients early (as reflected in shorter LOS when the CCTA result was available compared with SOC in these patients), the converse was also true—the finding of at least mild CAD appeared to compound the ambiguity that had arisen from the finding of intermediate initial hs-cTnT concentrations, leading to neither expedited nor delayed discharge. This may have diluted the beneficial impact

### Table 2  
**CCTA findings of study participants**

|                        | CCTA arm (n=125) | SOC arm (n=125) |
|------------------------|------------------|-----------------|
| Calcium score mean (SD) | 6 (3.514)       | 158.3 (350.2)   |
| CT scan not carried out | 0               | 4 (3.2%)        |
| Calcium score only     | 7 (5%)           | 8 (6.4%)        |
| ≥50% stenosis          | 11 (9%)          | 15 (12%)        |
| 1%–24% stenosis        | 26 (21%)         | 29 (23%)        |
| 25%–49% stenosis       | 24 (19%)         | 19 (15%)        |
| No stenoses on CCTA    | 46 (37%)         | 38 (30.4%)      |
| Calcium score only     | 7 (5%)           | 8 (6.4%)        |
| CT scan not carried out| 0               | 4 (3.2%)        |
| Calcium score only     | 7 (5%)           | 8 (6.4%)        |
| CT scan not carried out| 0               | 4 (3.2%)        |

**Figure 2**  
Trial overview. CAD, coronary artery disease; CCTA, coronary CT angiography; FU, follow-up; hs-cTnT, high-sensitivity cardiac troponin T; MACE, major adverse cardiac event; OP, outpatient.

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1975
of CCTA of patients with little or no disease, and thus contributed to the lack of impact overall.

The second reason may be that the protocol left the interpretation of the CCTA result and subsequent management to the discretion of the clinicians responsible for these patients. While this is reflective of real-world practice, it may have resulted in a lower rate of discharge than might have been achieved with a more didactic protocol. For instance, although 72 (58%) of patients in the CCTA arm had minimal or no coronary disease, only 31 (25%) were discharged early either without the need for serial hs-cTnT testing or without waiting for hs-cTnT results. Investigators of the BEACON trial also left final medical management decision-making to the treating physicians and similarly found that the addition of CCTA was not associated with a reduction in hospital LOS despite the fact that 42% of patients had no detectable CAD on CCTA (the hospital LOS in both arms was 6.3 hours; p=0.80). 17 However, the reasons for this disparity are likely to be pertinent to future pathways and may include the heterogeneity of patient care among physicians, cautious adoption of CCTA in the ED fraternity and the challenging logistics of everyday practice in busy EDs.

Our findings also contrast with clinical trials performed during the era of conventional troponin such as the American College of Radiology Imaging Network-Pennsylvania and Rule Out Myocardial Infarction/Ischemia Using Computer Assisted Tomography (ROMICAT II), where the CCTA arms showed significantly reduced hospital LOS. 22–24 We selected a more conservative value of <25% stenosis to rule out ACS to further safeguard patient safety. One hundred and thirty-nine patients (table 2), and among these patients only one had a MACE event at 12 months of follow-up (patient died of disseminated cancer). Notwithstanding the limited power of our study to detect small differences in mortality, it appears that ruling out ACS based on <25% maximal stenosis cut-off on CCTA may be safe. In our study, 12 months of mortality among observational zone patients based on serial hs-cTnT testing, 3/76 (4%) is similar to that reported (3.5%–9.6%) in observational zone cohorts in previous studies. 5 7

| Table 3 Secondary endpoints |
|-----------------------------|
| Outcomes | CCTA arm (n=125) | SOC arm (n=125) | Difference CCTA-SOC (95% CI)* | P value |
| Mean (SD) cost of hospital stay | £1285 (£2216) n=124 | £1108 (£3573) n=124 | £177 (~650 to 1003) | 0.68 |
| Cardiac or CCTA-related outpatient referrals (clinical and/or investigations) | 40 (32%) | 60 (48%) | −16% points (~28% to ~4.0%) | 0.01 |
| Inpatient invasive coronary angiography | 6 (4.8%) | 7 (5.6%) | −0.8% points | >0.99 |
| Discharge diagnosis of ACS | 5 (4.0%) | 4 (3.2%) | 0.8% points | >0.99 |
| Inpatient revascularisation | 5 (4.0%) | 4 (3.2%) | 0.8% points | >0.99 |
| Inpatient death | 0 | 0 | − | − |
| Post-discharge ACS events at 12 months | 1 (0.8%) | 2 (1.6%) | −0.8% points | 0.62 |
| Post-discharge revascularisation events at 12 months | 2 (1.6%)† | 3 (2.4%)‡ | −0.8% points | 0.68 |
| Post-discharge death events at 12 months | 1 (0.8%) | 2 (1.6%) | −0.8% points | 0.62 |

*95% CI given where it could be calculated.
†One patient had both ACS and revascularisation (this patient also previously had inpatient ACS and revascularisation).
‡Two patients had both ACS and revascularisation after discharge and one patient also previously had inpatient ACS and revascularisation.

ACS, acute coronary syndrome; CCTA, coronary CT angiography; SOC, standard of care.

Limitations
First, ours was a single-centre study and hence the results may not be as generalisable as a multicentre study. On the other hand, the enrolment of consecutive patients has meant that we have enlisted a cohort of real-world patients which may therefore be more representative than larger but more highly selected case series. Second, our study was conducted in a large tertiary...
hospital during working hours with a dedicated research fellow available to enable a rapid pathway incorporating the use of acute CCTA. This pathway may not be replicable in routine clinical care without such logistical support. Due to the existence of different tariffs for investigations in other regions, the healthcare costs in our study may not be extrapolated to all other healthcare regions, as these differing tariffs may translate to a dissimilar influence on overall healthcare costs elsewhere. It could be queried whether CCTA could have fared better in terms of LOS if it were evaluated among patients found to be still in the observational zone after second hs-cTn rather than among patients with intermediate hs-cTn concentrations on initial blood draw. Here again, we found no significant difference in LOS among these patients. However, our study was not adequately powered to investigate this specifically. The study protocol stated that a scan report would be made available if significant findings were identified in the SOC group. In certain instances, this could have resulted in a ‘reassurance bias’ because clinicians looking after patients randomised to the SOC arm could have potentially assumed that the lack of unblinding meant that there were no significant findings on the CCTA scans that needed immediate attention. Finally, our study was powered to look at differences in process outcomes rather than clinical events.

CONCLUSION
Performing CCTA in ED to triage and guide management of patients with suspected ACS did not reduce median hospital LOS or inpatient healthcare costs. Further focused research may be of benefit to determine whether the reduction observed in downstream referrals and investigations with CCTA translates to a long-term healthcare economic benefit.

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Contributors
WA, TR, NB-H, RP, LH, KO’K, RN, MM, RRaz, RRaj and DP contributed to the conception and design of the trial. WA, MM, OMD, AS, TR, RP, SMM, GB, AV, EW and RRaj were involved in the acquisition of data. GC, W, MM and TI were involved in the data and safety monitoring committee. RRaj, RRaz, RH and DP were involved in the trial steering committee. WA, RRaz, TI, DP, NB-H and JP were involved in statistical analyses in the study. All authors participated in the work and reviewed and agreed with the content of the manuscript. DP is responsible for the overall content as guarantor.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

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The study protocol was approved by the UK National Health Service Research Ethics Committee (ref: 17/EM/0375).

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Not commissioned; externally peer reviewed.

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All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material
This content has been supplied by the author(s).

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