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**Concept and design:** Markman, Hamilton, Marchlinski.

**Acquisition, analysis, or interpretation of data:** Markman, Nazarian.

**Drafting of the manuscript:** Markman.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Markman, Nazarian.

**Obtained funding:** Marchlinski, Nazarian.

**Administrative, technical, or material support:** Markman, Hamilton, Nazarian.

**Supervision:** Marchlinski, Nazarian.

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## COMMENT & RESPONSE

### Surgery vs Endoscopy for Early Treatment of Chronic Pancreatitis

**To the Editor** In the ESCAPE randomized clinical trial, Dr Issa and colleagues concluded that early surgery compared with an endoscopy-first approach resulted in significantly less pain over 18 months among patients with chronic pancreatitis.<sup>1</sup> We are concerned about the generalizability of the finding.

First, the endoscopic intervention in the study was inconsistent with international guidelines, in which extracorporeal shock-wave lithotripsy is recommended for the treatment of pancreatic stones 5 mm or larger obstructing the pancreatic duct, followed by endoscopic stone extraction, with a single stent maintained for 1 full year only when symptoms persist or signs of stent dysfunction are detected with imaging at least every 6 months.<sup>2</sup> A previous study reported that 85.5% of 5124 patients with chronic pancreatitis and painful calculi larger than 5 mm required 3 or fewer sessions of extracorporeal shock-wave lithotripsy, and 4%

required 5 to 8 sessions, with complete stone clearance achieved in 72.6%.<sup>3</sup> Thus, we doubt that fragmentation of stones with a diameter of 7 mm or greater with 3 sessions of extracorporeal shock-wave lithotripsy and successful removal of intraductal stones under direct endoscopic retrograde pancreatography was effective. These factors may have contributed to the low complete duct clearance and high endoscopy failure rate because complete duct clearance was associated with better pain control. In addition, elective endoscopic retrograde pancreatography performed every 3 months may cause complications with plastic stents, including worsening of pancreatic pain, which was the most commonly reported complication.<sup>2</sup>

Second, of the 88 patients enrolled, more than 80% were diagnosed with exocrine pancreatic insufficiency at randomization and should be categorized as stage IIb or an even more advanced stage.<sup>4</sup> According to the “burnout” hypothesis, a majority of patients achieve lasting pain-free status because of progressive parenchymal destruction, and surgery may greatly accelerate the clinical course. Also, successful treatment of painful chronic pancreatitis is argued to be maintained if endoscopy was performed at an early stage.<sup>4</sup> Furthermore, nearly half of the participants presented with an enlarged pancreatic head, a high proportion with no subgroup analysis performed. An inflammatory mass in the head of the pancreas develops in nearly one-third of patients with chronic pancreatitis, and intractable pain is believed to originate from this region. Enlargement of the pancreatic head may lead to locoregional complications, making combined drainage and resection procedures preferred in these patients.<sup>5</sup> Given these considerations, the benefit of surgery in this study may be overestimated.

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**In Reply** Dr Qian and colleagues are concerned about the generalizability of the ESCAPE trial and call for a standardized endoscopy strategy for better control of painful chronic pancreatitis.<sup>1</sup>

We acknowledge that international guidelines set the pancreatic stone size for extracorporeal shock-wave lithotripsy at 5 mm or greater instead of 7 mm or greater, as in the trial.<sup>2,3</sup> However, this difference did not lead to another treatment strategy in the trial because the median diameter of stones in the endoscopy-first approach was 10 mm, and only 3 patients had stones between 5 and 7 mm, of whom 2 underwent extracorporeal shock-wave lithotripsy. The 3-session extracorporeal shock-wave lithotripsy technique for stone fragmentation before endoscopic retrograde pancreatography is common practice in many countries and is also the dominant technique in the study of 5000 patients undergoing extracorporeal shock-wave lithotripsy<sup>4</sup> referred to in the letter.

Regarding the stent exchange schedule, international guidelines advise changing stents at regular intervals or when necessary in patients with symptoms of stent dysfunction.<sup>2,3</sup> This is exactly what was done in the trial. The low-quality evidence regarding stent exchange discussed in these guidelines showed no differences in complication rates for both schedule strategies.<sup>2</sup>

The endoscopic duct clearance was somewhat lower in the trial compared with the literature; in the endoscopy-first approach, patients with persistent pain due to failed endoscopy were referred according to protocol for surgery in the short term to achieve complete duct clearance.

Qian and colleagues suggest that in the trial, the majority of the patients may have had end-stage disease with progressive parenchymal destruction and that, according to the burnout theory, they may have been close to pain-free status with surgery accelerating this course. The burnout theory was proposed 20 years ago, after some small studies showed a correlation between pain relief and longer disease duration, but it is unproven and likely outdated. Recent large studies do not show any correlation between duration of disease and pain.<sup>5</sup> Moreover, a correlation between morphologic abnormalities and pain in chronic pancreatitis is variable and contradictory in the literature. This absence of a correlation among duration of disease, morphologic abnormalities, and duration and intensity of pain is also apparent in our trial. Most patients had extensive morphological abnormalities but had only been diagnosed with chronic pancreatitis for 1 year with worsening of pain for which opioid medication was initiated for a maximum of 8 weeks before study inclusion.

The authors propose that the beneficial effect of early surgery could be partly due to the large proportion of patients with an enlarged pancreatic head. Our cohort was a representative sample of all patients with painful ductal obstruction presenting to Dutch hospitals, and we deliberately chose not to exclude patients with an enlarged pancreatic head. We performed an additional post hoc subgroup analysis that showed that in the endoscopy-first approach, patients with an enlarged pancreatic head had less pain during follow-up (mean area-under-the-curve Izbicki score, 45 [SD, 25]) compared with patients with a nonenlarged pancreatic head (mean area-under-the-curve Izbicki score, 54 [SD, 25]), indicating the variable cor-

relation between morphologic abnormalities and clinical response to treatment.

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## Vitamin C, Hydrocortisone, and Thiamine for Septic Shock

**To the Editor** The Vitamin C, Hydrocortisone, and Thiamine in Patients With Septic Shock (VITAMINS) trial found that vitamin C, hydrocortisone, and thiamine, compared with hydrocortisone alone, did not improve outcomes in patients with septic shock.<sup>1</sup>

In randomized trials in sepsis, time spent to select and stabilize patients by initiating early interventions such as antibiotics, fluids, and vasopressors must precede patient enrollment, randomization, and administration of study drug. The VITAMINS trial reflects this—although hydrocortisone use was standardized and presumptively administered quickly, thiamine and vitamin C were delayed.

The idea that early, resuscitative therapy in septic shock is distinct from day-to-day drug selections is supported by the sepsis bundle time limits from the Centers for Medicare & Medicaid Services. It would be expected that interventions targeting prevention of progression of multiorgan dysfunction by treating microvascular dysfunction, mitochondrial injury, and the oxidative burst and stress of sepsis would have time-dependent efficacy. In a before-after study, almost all patients were treated within 6 hours.<sup>2</sup> Another retrospective study found that delays in the administration of hydrocortisone, vitamin C,