

# Effectiveness of Colonoscopy for Colorectal Cancer Screening in Reducing Cancer-Related Mortality: Interpreting the Results From Two Ongoing Randomized Trials

Bretthauer M, Loberg M, Wieszczy M, et al; NordICC Study Group. Effect of colonoscopy screening on risks of colorectal cancer and related death. *N Engl J Med*. 2022;387(17):1547-1556. doi:10.1056/NEJMoa2208375

Forsberg A, Westerberg M, Metcalfe C, et al; SCREESCO investigators. Once-only colonoscopy or two rounds of faecal immunochemical testing 2 years apart for colorectal cancer screening (SCREESCO): preliminary report of a randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2022;7(6):513-521. doi:10.1016/S2468-1253(21)00473-8

## Study 1 Overview (Bretthauer et al)

**Objective:** To evaluate the impact of screening colonoscopy on colon cancer-related death.

**Design:** Randomized trial conducted in 4 European countries.

**Setting and participants:** Presumptively healthy men and women between the ages of 55 and 64 years were selected from population registries in Poland, Norway, Sweden, and the Netherlands between 2009 and 2014. Eligible participants had not previously undergone screening. Patients with a diagnosis of colon cancer before trial entry were excluded.

**Intervention:** Participants were randomly assigned in a 1:2 ratio to undergo colonoscopy screening by invitation or to no invitation and no screening. Participants were randomized using a computer-generated allocation algorithm. Patients were stratified by age, sex, and municipality.

**Main outcome measures:** The primary endpoint of the study was risk of colorectal cancer and related death after a median follow-up of 10 to 15 years. The main secondary endpoint was death from any cause.

**Main results:** The study reported follow-up data from 84,585 participants (89.1% of all participants originally included in the trial). The remaining participants were either excluded or data could not be included due to lack of follow-up data from the usual-care group. Men (50.1%) and women (49.9%) were equally represented. The median age at entry was 59 years. The median follow-up was 10 years. Characteristics were otherwise balanced. Good bowel preparation was reported in 91% of all participants. Cecal intubation was achieved in 96.8% of all participants. The percentage of patients who underwent screening was 42% for the group, but screening rates varied by country (33%-60%). Colorectal cancer was diagnosed at screening in 62 participants (0.5% of screening group). Adenomas were detected in 30.7% of participants; 15 patients had polypectomy-related major bleeding. There were no perforations.

The risk of colorectal cancer at 10 years was 0.98% in the invited-to-screen group and 1.2% in the usual-care group (risk ratio, 0.82; 95% CI, 0.7-0.93). The reported number needed to invite to prevent 1 case of colon cancer

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in a 10-year period was 455. The risk of colorectal cancer–related death at 10 years was 0.28% in the invited-to-screen group and 0.31% in the usual-care group (risk ratio, 0.9; 95% CI, 0.64-1.16). An adjusted per-protocol analysis was performed to account for the estimated effect of screening if all participants assigned to the screening group underwent screening. In this analysis, the risk of colorectal cancer at 10 years was decreased from 1.22% to 0.84% (risk ratio, 0.69; 95% CI, 0.66-0.83).

**Conclusion:** Based on the results of this European randomized trial, the risk of colorectal cancer at 10 years was lower among those who were invited to undergo screening.

## Study 2 Overview (Forsberg et al)

**Objective:** To investigate the effect of colorectal cancer screening with once-only colonoscopy or fecal immunochemical testing (FIT) on colorectal cancer mortality and incidence.

**Design:** Randomized controlled trial in Sweden utilizing a population registry.

**Setting and participants:** Patients aged 60 years at the time of entry were identified from a population-based registry from the Swedish Tax Agency.

**Intervention:** Individuals were assigned by an independent statistician to once-only colonoscopy, 2 rounds of FIT 2 years apart, or a control group in which no intervention was performed. Patients were assigned in a 1:6 ratio for colonoscopy vs control and a 1:2 ratio for FIT vs control.

**Main outcome measures:** The primary endpoint of the trial was colorectal cancer incidence and mortality.

**Main results:** A total of 278,280 participants were included in the study from March 1, 2014, through December 31, 2020 (31,140 in the colonoscopy group, 60,300 in the FIT group, and 186,840 in the control group). Of those in the colonoscopy group, 35% underwent colonoscopy, and 55% of those in the FIT group participated in testing. Colorectal cancer was detected in 0.16% (49) of people in the colonoscopy group and 0.2% (121) of people in the FIT test group (relative risk, 0.78; 95% CI, 0.56-1.09). The advanced adenoma detection rate was 2.05% in the colonoscopy group and 1.61% in the FIT group (relative risk, 1.27; 95% CI, 1.15-1.41). There were 2 perforations noted

in the colonoscopy group and 15 major bleeding events. More right-sided adenomas were detected in the colonoscopy group.

**Conclusion:** The results of the current study highlight similar detection rates in the colonoscopy and FIT group. Should further follow-up show a benefit in disease-specific mortality, such screening strategies could be translated into population-based screening programs.

## Commentary

The first colonoscopy screening recommendations were established in the mid 1990s in the United States, and over the subsequent 2 decades colonoscopy has been the recommended method and main modality for colorectal cancer screening in this country. The advantage of colonoscopy over other screening modalities (sigmoidoscopy and fecal-based testing) is that it can examine the entire large bowel and allow for removal of potential precancerous lesions. However, data to support colonoscopy as a screening modality for colorectal cancer are largely based on cohort studies.<sup>1,2</sup> These studies have reported a significant reduction in the incidence of colon cancer. Additionally, colorectal cancer mortality was notably lower in the screened populations. For example, one study among health professionals found a nearly 70% reduction in colorectal cancer mortality in those who underwent at least 1 screening colonoscopy.<sup>3</sup>

There has been a lack of randomized clinical data to validate the efficacy of colonoscopy screening for reducing colorectal cancer–related deaths. The current study by Bretthauer et al addresses an important need and enhances our understanding of the efficacy of colorectal cancer screening with colonoscopy. In this randomized trial involving more than 84,000 participants from Poland, Norway, Sweden, and the Netherlands, there was a noted 18% decrease in the risk of colorectal cancer over a 10-year period in the intention-to-screen population. The reduction in the risk of death from colorectal cancer was not statistically significant (risk ratio, 0.90; 95% CI, 0.64-1.16). These results are surprising and certainly raise the question as to whether previous studies overestimated the effectiveness of colonoscopy in reducing the risk of colorectal cancer–related deaths. There are several limitations to the Bretthauer et al study, however.

Perhaps the most important limitation is the fact that only 42% of participants in the invited-to-screen cohort underwent screening colonoscopy. Therefore, this raises the question of whether the efficacy noted is simply due to a lack of participation in the screening protocol. In the adjusted per-protocol analysis, colonoscopy was estimated to reduce the risk of colorectal cancer by 31% and the risk of colorectal cancer–related death by around 50%. These findings are more in line with prior published studies regarding the efficacy of colorectal cancer screening. The authors plan to repeat this analysis at 15 years, and it is possible that the risk of colorectal cancer and colorectal cancer–related death can be reduced on subsequent follow-up.

While the results of the Bretthauer et al trial are important, randomized trials that directly compare the effectiveness of different colorectal cancer screening strategies are lacking. The Forsberg et al trial, also an ongoing study, seeks to address this vitally important gap in our current data. The SCREESCO trial is a study that compares the efficacy of colonoscopy with FIT every 2 years or no screening. The currently reported data are preliminary but show a similarly low rate of colonoscopy screening in those invited to do so (35%). This is a similar limitation to that noted in the Bretthauer et al study. Furthermore, there is some question regarding colonoscopy quality in this study, which had a very low reported adenoma detection rate.

While the current studies are important and provide quality randomized data on the effect of colorectal cancer screening, there remain many unanswered questions. Should the results presented by Bretthauer et al represent the current real-world scenario, then colonoscopy screening may not be viewed as an effective screening tool compared to simpler, less-invasive modalities (ie, FIT). Further follow-up from the SCREESCO trial will help shed light on this question. However, there are concerns with this study, including a very low participation rate, which could greatly underestimate the effectiveness of screening. Additional analysis and longer follow-up will be

vital to fully understand the benefits of screening colonoscopy. In the meantime, screening remains an important tool for early detection of colorectal cancer and remains a category A recommendation by the United States Preventive Services Task Force.<sup>4</sup>

### Applications for Clinical Practice and System Implementation

Current guidelines continue to strongly recommend screening for colorectal cancer for persons between 45 and 75 years of age (category B recommendation for those aged 45 to 49 years per the United States Preventive Services Task Force). Stool-based tests and direct visualization tests are both endorsed as screening options. Further follow-up from the presented studies is needed to help shed light on the magnitude of benefit of these modalities.

### Practice Points

- Current guidelines continue to strongly recommend screening for colon cancer in those aged 45 to 75 years.
- The optimal modality for screening and the impact of screening on cancer-related mortality requires longer-term follow-up from these ongoing studies.

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# Anesthetic Choices and Postoperative Delirium Incidence: Propofol vs Sevoflurane

Chang JE, Min SW, Kim H, et al. Association between anesthetics and postoperative delirium in elderly patients undergoing spine surgery: propofol versus sevoflurane. *Global Spine J.* 2022 Jun 22;21925682221110828. doi:10.1177/21925682221110828

Mei X, Zheng HL, Li C, et al. The effects of propofol and sevoflurane on postoperative delirium in older patients: a randomized clinical trial study. *J Alzheimers Dis.* 2020;76(4):1627-1636. doi:10.3233/JAD-200322

## Study 1 Overview (Chang et al)

**Objective:** To assess the incidence of postoperative delirium (POD) following propofol- vs sevoflurane-based anesthesia in geriatric spine surgery patients.

**Design:** Retrospective, single-blinded observational study of propofol- and sevoflurane-based anesthesia cohorts.

**Setting and participants:** Patients eligible for this study were aged 65 years or older admitted to the SMG-SNU Boramae Medical Center (Seoul, South Korea). All patients underwent general anesthesia either via intravenous propofol or inhalational sevoflurane for spine surgery between January 2015 and December 2019. Patients were retrospectively identified via electronic medical records. Patient exclusion criteria included preoperative delirium, history of dementia, psychiatric disease, alcoholism, hepatic or renal dysfunction, postoperative mechanical ventilation dependence, other surgery within the recent 6 months, maintenance of intraoperative anesthesia with combined anesthetics, or incomplete medical record.

**Main outcome measures:** The primary outcome was the incidence of POD after administration of propofol- and sevoflurane-based anesthesia during hospitalization. Patients were screened for POD regularly by attending nurses using the Nursing Delirium Screening Scale (disorientation, inappropriate behavior, inappropriate communication, hallucination, and psychomotor retardation) during the entirety of the patient's hospital stay; if 1 or more screening criteria were met, a psychiatrist was consulted for the proper diagnosis and management of delirium. A psychiatric diagnosis was required for a case to be counted toward the incidence of POD in this study. Secondary outcomes included postoperative 30-day

complications (angina, myocardial infarction, transient ischemic attack/stroke, pneumonia, deep vein thrombosis, pulmonary embolism, acute kidney injury, or infection) and length of postoperative hospital stay.

**Main results:** POD occurred in 29 patients (10.3%) out of the total cohort of 281. POD was more common in the sevoflurane group than in the propofol group (15.7% vs 5.0%;  $P = .003$ ). Using multivariable logistic regression, inhalational sevoflurane was associated with an increased risk of POD as compared to propofol-based anesthesia (odds ratio [OR], 4.120; 95% CI, 1.549-10.954;  $P = .005$ ). There was no association between choice of anesthetic and postoperative 30-day complications or the length of postoperative hospital stay. Both older age (OR, 1.242; 95% CI, 1.130-1.366;  $P < .001$ ) and higher pain score at postoperative day 1 (OR, 1.338; 95% CI, 1.056-1.696;  $P = .016$ ) were associated with increased risk of POD.

**Conclusion:** Propofol-based anesthesia was associated with a lower incidence of and risk for POD than sevoflurane-based anesthesia in older patients undergoing spine surgery.

## Study 2 Overview (Mei et al)

**Objective:** To determine the incidence and duration of POD in older patients after total knee/hip replacement (TKR/THR) under intravenous propofol or inhalational sevoflurane general anesthesia.

**Design:** Randomized clinical trial of propofol and sevoflurane groups.

**Setting and participants:** This study was conducted at the Shanghai Tenth People's Hospital and involved 209 participants enrolled between June 2016 and November 2019.

All participants were 60 years of age or older, scheduled for TKR/THR surgery under general anesthesia, American Society of Anesthesiologists (ASA) class I to III, and assessed to be of normal cognitive function preoperatively via a Mini-Mental State Examination. Participant exclusion criteria included preexisting delirium as assessed by the Confusion Assessment Method (CAM), prior diagnosed neurological diseases (eg, Parkinson's disease), prior diagnosed mental disorders (eg, schizophrenia), or impaired vision or hearing that would influence cognitive assessments. All participants were randomly assigned to either sevoflurane or propofol anesthesia for their surgery via a computer-generated list. Of these, 103 received inhalational sevoflurane and 106 received intravenous propofol. All participants received standardized postoperative care.

**Main outcome measures:** All participants were interviewed by investigators, who were blinded to the anesthesia regimen, twice daily on postoperative days 1, 2, and 3 using CAM and a CAM-based scoring system (CAM-S) to assess delirium severity. The CAM encapsulated 4 criteria: acute onset and fluctuating course, agitation, disorganized thinking, and altered level of consciousness. To diagnose delirium, both the first and second criteria must be met, in addition to either the third or fourth criterion. The averages of the scores across the 3 postoperative days indicated delirium severity, while the incidence and duration of delirium was assessed by the presence of delirium as determined by CAM on any postoperative day.

**Main results:** All eligible participants (N=209; mean [SD] age 71.2 [6.7] years; 29.2% male) were included in the final analysis. The incidence of POD was not statistically different between the propofol and sevoflurane groups (33.0% vs 23.3%;  $P=.119$ , Chi-square test). It was estimated that 316 participants in each arm of the study were needed to detect statistical differences. The number of days of POD per person were higher with propofol anesthesia as compared to sevoflurane (0.5 [0.8] vs 0.3 [0.5];  $P=.049$ , Student's  $t$ -test).

**Conclusion:** This underpowered study showed a 9.7% difference in the incidence of POD between older adults who received propofol (33.0%) and sevoflurane (23.3%) after THR/TKR. Further studies with a larger sample size

are needed to compare general anesthetics and their role in POD.

### Commentary

Delirium is characterized by an acute state of confusion with fluctuating mental status, inattention, disorganized thinking, and altered level of consciousness. It is often caused by medications and/or their related adverse effects, infections, electrolyte imbalances, and other clinical etiologies. Delirium often manifests in post-surgical settings, disproportionately affecting older patients and leading to increased risk of morbidity, mortality, hospital length of stay, and health care costs.<sup>1</sup> Intraoperative risk factors for POD are determined by the degree of operative stress (eg, lower-risk surgeries put the patient at reduced risk for POD as compared to higher-risk surgeries) and are additive to preexisting patient-specific risk factors, such as older age and functional impairment.<sup>1</sup> Because operative stress is associated with risk for POD, limiting operative stress in controlled ways, such as through the choice of anesthetic agent administered, may be a pragmatic way to manage operative risks and optimize outcomes, especially when serving a surgically vulnerable population.

In Study 1, Chang et al sought to assess whether 2 commonly utilized general anesthetics, propofol and sevoflurane, in older patients undergoing spine surgery differentially affected the incidence of POD. In this retrospective, single-blinded observational study of 281 geriatric patients, the researchers found that sevoflurane was associated with a higher risk of POD as compared to propofol. However, these anesthetics were not associated with surgical outcomes such as postoperative 30-day complications or the length of postoperative hospital stay. While these findings added new knowledge to this field of research, several limitations should be kept in mind when interpreting this study's results. For instance, the sample size was relatively small, with all cases selected from a single center utilizing a retrospective analysis. In addition, although a standardized nursing screening tool was used as a method for delirium detection, hypoactive delirium or less symptomatic delirium may have been missed, which in turn would lead to an underestimation of POD incidence. The latter is a common limitation in delirium research.

In Study 2, Mei et al similarly explored the effects of general anesthetics on POD in older surgical patients. Specifically, using a randomized clinical trial design, the investigators compared propofol with sevoflurane in older patients who underwent TKR/THR, and their roles in POD severity and duration. Although the incidence of POD was higher in those who received propofol compared to sevoflurane, this trial was underpowered and the results did not reach statistical significance. In addition, while the duration of POD was slightly longer in the propofol group compared to the sevoflurane group (0.5 vs 0.3 days), it was unclear if this finding was clinically significant. Similar to many research studies in POD, limitations of Study 2 included a small sample size of 209 patients, with all participants enrolled from a single center. On the other hand, this study illustrated the feasibility of a method that allowed reproducible prospective assessment of POD time course using CAM and CAM-S.

### Applications for Clinical Practice and System Implementation

The delineation of risk factors that contribute to delirium after surgery in older patients is key to mitigating risks for POD and improving clinical outcomes. An important step towards a better understanding of these modifiable risk factors is to clearly quantify intraoperative risk of POD attributable to specific anesthetics. While preclinical studies have shown differential neurotoxicity effects of propofol and sevoflurane, their impact on clinically important neurologic outcomes such as delirium and cognitive decline remains poorly understood. Although Studies 1 and 2 both provided head-to-head comparisons of propofol and sevoflurane as risk factors for POD in high-operative-stress surgeries in older patients, the results were inconsistent. That being said, this small incremental increase in knowledge was not unexpected in the course of discovery around a clinically complex research question. Importantly, these studies provided evidence regarding the methodological approaches that could be taken to further this line of research.

The mediating factors of the differences on neurologic outcomes between anesthetic agents are likely pharmacological, biological, and methodological. Pharmacologically, the differences between target receptors, such as GABAA (propofol, etomidate) or NMDA

(ketamine), could be a defining feature in the difference in incidence of POD. Additionally, secondary actions of anesthetic agents on glycine, nicotinic, and acetylcholine receptors could play a role as well. Biologically, genes such as *CYP2E1*, *CYP2B6*, *CYP2C9*, *GSTP1*, *UGT1A9*, *SULT1A1*, and *NQO1* have all been identified as genetic factors in the metabolism of anesthetics, and variations in such genes could result in different responses to anesthetics.<sup>2</sup> Methodologically, routes of anesthetic administration (eg, inhalation vs intravenous), preexisting anatomical structures, or confounding medical conditions (eg, lower respiratory volume due to older age) may influence POD incidence, duration, or severity. Moreover, methodological differences between Studies 1 and 2, such as surgeries performed (spinal vs TKR/THR), patient populations (South Korean vs Chinese), and the diagnosis and monitoring of delirium (retrospective screening and diagnosis vs prospective CAM/CAM-S) may impact delirium outcomes. Thus, these factors should be considered in the design of future clinical trials undertaken to investigate the effects of anesthetics on POD.

Given the high prevalence of delirium and its associated adverse outcomes in the immediate postoperative period in older patients, further research is warranted to determine how anesthetics affect POD in order to optimize perioperative care and mitigate risks in this vulnerable population. Moreover, parallel investigations into how anesthetics differentially impact the development of transient or longer-term cognitive impairment after a surgical procedure (ie, postoperative cognitive dysfunction) in older adults are urgently needed in order to improve their cognitive health.

### Practice Points

- Intravenous propofol and inhalational sevoflurane may be differentially associated with incidence, duration, and severity of POD in geriatric surgical patients.
- Further larger-scale studies are warranted to clarify the role of anesthetic choice in POD in order to optimize surgical outcomes in older patients.

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# The Role of Revascularization and Viability Testing in Patients With Multivessel Coronary Artery Disease and Severely Reduced Ejection Fraction

Velazquez E, Lee KL, Jones RH, et al; STICHES Investigators. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med.* 2016;374(16):1511-1520. doi:10.1056/NEJMoa1602001

Perera D, Clayton T, O'Kane P, et al; REVIVED-BCIS Investigators. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med.* 2022;387(15):1351-1360. doi:10.1056/NEJMoa2206606

## Study 1 Overview (STICHES Investigators)

**Objective:** To assess the survival benefit of coronary-artery bypass grafting (CABG) added to guideline-directed medical therapy, compared to optimal medical therapy (OMT) alone, in patients with coronary artery disease, heart failure, and severe left ventricular dysfunction.

**Design:** Multicenter, randomized, prospective study with extended follow-up (median duration of 9.8 years).

**Setting and participants:** A total of 1212 patients with left ventricular ejection fraction (LVEF) of 35% or less and coronary artery disease were randomized to medical therapy plus CABG or OMT alone at 127 clinical sites in 26 countries.

**Main outcome measures:** The primary endpoint was death from any cause. Main secondary endpoints were death from cardiovascular causes and a composite outcome of death from any cause or hospitalization for cardiovascular causes.

**Main results:** There were 359 primary outcome all-cause deaths (58.9%) in the CABG group and 398 (66.1%) in the medical therapy group (hazard ratio [HR], 0.84; 95% CI, 0.73-0.97;  $P = .02$ ). Death from cardiovascular causes was reported in 247 patients (40.5%) in the

CABG group and 297 patients (49.3%) in the medical therapy group (HR, 0.79; 95% CI, 0.66-0.93;  $P < .01$ ). The composite outcome of death from any cause or hospitalization for cardiovascular causes occurred in 467 patients (76.6%) in the CABG group and 467 patients (87.0%) in the medical therapy group (HR, 0.72; 95% CI, 0.64-0.82;  $P < .01$ ).

**Conclusion:** Over a median follow-up of 9.8 years in patients with ischemic cardiomyopathy with severely reduced ejection fraction, the rates of death from any cause, death from cardiovascular causes, and the composite of death from any cause or hospitalization for cardiovascular causes were significantly lower in patients undergoing CABG than in patients receiving medical therapy alone.

## Study 2 Overview (REVIVED BCIS Trial Group)

**Objective:** To assess whether percutaneous coronary intervention (PCI) can improve survival and left ventricular function in patients with severe left ventricular systolic dysfunction as compared to OMT alone.

**Design:** Multicenter, randomized, prospective study.

**Setting and participants:** A total of 700 patients with LVEF <35% with severe coronary artery disease amenable to

PCI and demonstrable myocardial viability were randomly assigned to either PCI plus optimal medical therapy (PCI group) or OMT alone (OMT group).

**Main outcome measures:** The primary outcome was death from any cause or hospitalization for heart failure. The main secondary outcomes were LVEF at 6 and 12 months and quality of life (QOL) scores.

**Main results:** Over a median follow-up of 41 months, the primary outcome was reported in 129 patients (37.2%) in the PCI group and in 134 patients (38.0%) in the OMT group (HR, 0.99; 95% CI, 0.78-1.27;  $P=.96$ ). The LVEF was similar in the 2 groups at 6 months (mean difference,  $-1.6$  percentage points; 95% CI,  $-3.7$  to  $0.5$ ) and at 12 months (mean difference,  $0.9$  percentage points; 95% CI,  $-1.7$  to  $3.4$ ). QOL scores at 6 and 12 months favored the PCI group, but the difference had diminished at 24 months.

**Conclusion:** In patients with severe ischemic cardiomyopathy, revascularization by PCI in addition to OMT did not result in a lower incidence of death from any cause or hospitalization from heart failure.

### Commentary

Coronary artery disease is the most common cause of heart failure with reduced ejection fraction and an important cause of mortality.<sup>1</sup> Patients with ischemic cardiomyopathy with reduced ejection fraction are often considered for revascularization in addition to OMT and device therapies. Although there have been multiple retrospective studies and registries suggesting that cardiac outcomes and LVEF improve with revascularization, the number of large-scale prospective studies that assessed this clinical question and randomized patients to revascularization plus OMT compared to OMT alone has been limited.

In the Surgical Treatment for Ischemic Heart Failure (STICH) study,<sup>2,3</sup> eligible patients had coronary artery disease amenable to CABG and a LVEF of 35% or less. Patients ( $N=1212$ ) were randomly assigned to CABG plus OMT or OMT alone between July 2002 and May 2007. The original study, with a median follow-up of 5 years, did not show survival benefit, but the investigators reported that the primary outcome of death from any cause was significantly lower in the CABG group compared to OMT alone when follow-up of the same study population was

extended to 9.8 years (58.9% vs 66.1%,  $P=.02$ ). The findings from this study led to a class I guideline recommendation of CABG over medical therapy in patients with multivessel disease and low ejection fraction.<sup>4</sup>

Since the STICH trial was designed, there have been significant improvements in devices and techniques used for PCI, and the procedure is now widely performed in patients with multivessel disease.<sup>5</sup> The advantages of PCI over CABG include shorter recovery times and lower risk of immediate complications. In this context, the recently reported Revascularization for Ischemic Ventricular Dysfunction (REVIVED) study assessed clinical outcomes in patients with severe coronary artery disease and reduced ejection fraction by randomizing patients to either PCI with OMT or OMT alone.<sup>6</sup> At a median follow-up of 3.5 years, the investigators found no difference in the primary outcome of death from any cause or hospitalization for heart failure (37.2% vs 38.0%; 95% CI, 0.78-1.28;  $P=.96$ ). Moreover, the degree of LVEF improvement, assessed by follow-up echocardiogram read by the core lab, showed no difference in the degree of LVEF improvement between groups at 6 and 12 months. Finally, although results of the QOL assessment using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated, patient-reported, heart-failure-specific QOL scale, favored the PCI group at 6 and 12 months of follow-up, the difference had diminished at 24 months.

The main strength of the REVIVED study was that it targeted a patient population with severe coronary artery disease, including left main disease and severely reduced ejection fraction, that historically have been excluded from large-scale randomized controlled studies evaluating PCI with OMT compared to OMT alone.<sup>7</sup> However, there are several points to consider when interpreting the results of this study. First, further details of the PCI procedures are necessary. The REVIVED study recommended revascularization of all territories with viable myocardium; the anatomical revascularization index utilizing the British Cardiovascular Intervention Society (BCIS) Jeopardy Score was 71%. It is important to note that this jeopardy score was operator-reported and the core-lab adjudicated anatomical revascularization rate may be lower. Although viability testing primarily utilizing cardiac magnetic resonance imaging was performed in



most patients, correlation between the revascularization territory and the viable segments has yet to be reported. Moreover, procedural details such as use of intravascular ultrasound and physiological testing, known to improve clinical outcome, need to be reported.<sup>8,9</sup>

Second, there is a high prevalence of ischemic cardiomyopathy, and it is important to note that the patients included in this study were highly selected from daily clinical practice, as evidenced by the prolonged enrollment period (8 years). Individuals were largely stable patients with less complex coronary anatomy as evidenced by the median interval from angiography to randomization of 80 days. Taking into consideration the degree of left ventricular dysfunction for patients included in the trial, only 14% of the patients had left main disease and half of the patients only had 2-vessel disease. The severity of the left main disease also needs to be clarified as it is likely that patients the operator determined to be critical were not enrolled in the study. Furthermore, the standard of care based on the STICH trial is to refer patients with severe multivessel coronary artery disease to CABG, making it more likely that patients with more severe and complex disease were not included in this trial. It is also important to note that this study enrolled patients with stable ischemic heart disease, and the data do not apply to patients presenting with acute coronary syndrome.

Third, although the primary outcome was similar between the groups, the secondary outcome of unplanned revascularization was lower in the PCI group. In addition, the rate of acute myocardial infarction (MI) was similar between the 2 groups, but the rate of spontaneous MI was lower in the PCI group compared to the OMT group (5.2% vs 9.3%) as 40% of MI cases in the PCI group were periprocedural MIs. The correlation between periprocedural MI and long-term outcomes has been modest compared to spontaneous MI. Moreover, with the longer follow-up, the number of spontaneous MI cases is expected to rise while the number of periprocedural MI cases is not. Extending the follow-up period is also important, as the STICH extension trial showed a statistically significant difference at 10-year follow up despite negative results at the time of the original publication.

Fourth, the REVIVED trial randomized a significantly lower number of patients compared to the STICH trial,

and the authors reported fewer primary-outcome events than the estimated number needed to achieve the power to assess the primary hypothesis. In addition, significant improvements in medical treatment for heart failure with reduced ejection fraction since the STICH trial make comparison of PCI vs CABG in this patient population unfeasible.

Finally, although severe angina was not an exclusion criterion, two-thirds of the patients enrolled had no angina, and only 2% of the patients had baseline severe angina. This is important to consider when interpreting the results of the patient-reported health status as previous studies have shown that patients with worse angina at baseline derive the largest improvement in their QOL,<sup>10,11</sup> and symptom improvement is the main indication for PCI in patients with stable ischemic heart disease.

### Applications for Clinical Practice and System Implementation

In patients with severe left ventricular systolic dysfunction and multivessel stable ischemic heart disease who are well compensated and have little or no angina at baseline, OMT alone as an initial strategy may be considered against the addition of PCI after careful risk and benefit discussion. Further details about revascularization and extended follow-up data from the REVIVED trial are necessary.

### Practice Points

- Patients with ischemic cardiomyopathy with reduced ejection fraction have been an understudied population in previous studies.
- Further studies are necessary to understand the benefits of revascularization and the role of viability testing in this population.

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# Call for Contributions

JCOM is seeking submissions of original research and descriptive reports of quality improvement projects.

Original research submissions can include reports of investigations that address questions about clinical care or the organization of health care and its impact on outcomes.

Descriptions and evaluations of quality improvement efforts will be considered for JCOM’s “Reports from the Field” section. The section features reports on actions being taken to improve quality of care. Such reports may include, but are not limited to, the following items:

- Motivation for the project, including the role of research findings or internal or external benchmarking data
- Setting/demographics
- Intervention/implementation process
- Measurements
- Results
- Similarities to other approaches studied, limitations, applicability in other settings, etc.

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