

Non-Culprit Lesion PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock

Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med* 2017;377:2419–32.

STUDY OVERVIEW

Objective. To determine if percutaneous coronary intervention (PCI) of non-culprit vessels should be performed in patients with acute myocardial infarction and cardiogenic shock.

Design. Multicenter randomized controlled trial.

Setting and participants. 706 patients who had multivessel disease, acute myocardial infarction, and cardiogenic shock were assigned to one of 2 revascularization strategies: PCI of the culprit lesion only with the option of staged revascularization of non-culprit lesions, or immediate multivessel PCI.

Main outcome measures. The primary endpoint was the composite of death or severe renal failure leading to renal replacement therapy within 30 days after randomization. Safety endpoints included bleeding and stroke.

Main results. The primary endpoint of death or renal replacement therapy occurred in 158 /344 patients (45.9%) in the culprit lesion-only PCI group and 189/341 patients (55.4%) in the multivessel PCI group (relative risk [RR]

0.83, 95% CI 0.72–0.96, $P = 0.01$). The rate of death from any cause was lower in the culprit lesion-only PCI group compared to multivessel PCI group (RR 0.84, 95% CI 0.72–0.98, $P = 0.03$). There was no difference in stroke and numerically lower risk of bleeding in culprit lesion-only PCI group (RR 0.75, 95% CI 0.55–1.03).

Conclusion. Among patients who had multivessel coronary artery disease and acute myocardial infarction with cardiogenic shock, the 30-day risk of death or severe renal failure leading to renal replacement therapy was lower in patients who initially underwent PCI of the culprit lesion only compared with patients who underwent immediate multivessel PCI.

Commentary

Patients presenting with cardiogenic shock at the time of acute myocardial infarction have the highest mortality—up to 50%. Since the original SHOCK trial in 1999, it is known that the mortality can be reduced by early revascularization of the culprit vessel [1]. However, whether the non-culprit vessel should be revascularized at the time of presentation with acute myocardial infarction is unknown.

Recently, there have been multiple trials suggesting the

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benefit of non-culprit vessel revascularization in patients with acute myocardial infarction who are hemodynamically stable at the time of their presentation. Three recent trials—PRAMI, CvPRIT and DANAMI-PRIMULTI—investigated this clinical question and found benefit of non-culprit vessel revascularization [2–4]. The results of these trials led to a focused update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention in 2015 [5]. Non-infarct-related artery PCI in hemodynamically stable patients presenting with acute myocardial infarction was upgraded to class IIb from class III [5]. Whether these findings can be extended to hemodynamically unstable (cardiogenic shock) patients is not mentioned in the guidelines.

In the current CULPRIT-SHOCK trial, Thiele et al investigated this clinical question by performing a well-designed clinical trial in patients with acute myocardial infarction and cardiogenic shock. They found that the composite endpoint of death and renal replacement therapy at 30 days occurred more frequently in the multivessel PCI group compared with the culprit lesion–only group (relative risk [RR] 0.83, 95% CI 0.71–0.96, $P = 0.01$). The composite endpoint was mainly driven by death (43.3% vs 51.6%, RR 0.84, 95% CI 0.72–0.98, $P = 0.03$), and the rate of renal replacement therapy was numerically higher in the multivessel PCI group (11.6% vs 16.4%, $P = 0.07$). The study was conducted in the sickest population compared to prior trials as evidenced by high rate of mechanical ventilation (~80%), requirement of catecholamine support (~90%), and long ICU stay (median 5 days). The significance of non-culprit lesion was determined by angiogram (stenosis > 70%). The culprit vessel–only group had treatment of the culprit vessel only initially, but the staged intervention for non-culprit vessel was encouraged.

A unique point of this trial is that patients with chronic total occlusion (CTO) were included in the study and it was encouraged to attempt revascularization of CTO lesions, contrary to previous trials. Although CTO intervention improves angina and ejection fraction [6,7], whether CTO intervention has a mortality benefit needs further investigation. In the CULPRIT-SHOCK trial, 24% of patients had one or more CTO lesions. This most likely contributed to the increased contrast use in the multivessel PCI group (250 vs 190 mL, $P < 0.01$). CTO is considered a most challenging lesion to treat, and expertise and skill level vary among operators. In the hybrid CTO intervention model, it is recommended to

stage the intervention as much as possible, as this type of intervention requires meticulous planning [8]. There is a possibility that attempting CTO intervention in this acute setting caused more harm than benefit. Furthermore, the investigators did not report the success rate of CTO intervention.

Another interesting finding of this trial is that the mortality of both groups was high (43.3% vs 51.6%). The revascularization arm of the original shock trial almost 20 years ago had a 30-day mortality of 46.7%, which is almost identical with the current CULPRIT-SHOCK study. Despite improvement in hemodynamic support such as Impella, TandemHeart, extracorporeal membrane oxygenation device, and improvement in medical therapy over the years, patients with cardiogenic shock with acute myocardial infarction have a dismal prognosis.

The CULPRIT-SHOCK trial has number of strengths, including low drop-out rate (3%) and adequate power, however, there are some limitations. Some patients crossed over from culprit-vessel only to multivessel PCI group due to lack of hemodynamic improvement, plaque shifts, and newly detected lesions after treatment of the culprit lesion. On the other hand, some patients crossed over from multivessel PCI from culprit lesion only due to multiple reasons, including technical difficulty of intervention.

Applications for Clinical Practice

In patients presenting with cardiogenic shock and acute myocardial infarction, culprit lesion–only intervention and focusing on hemodynamic support with a staged intervention if necessary seems to be better strategy than immediate multivessel PCI, including non-culprit vessel PCI.

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References

1. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999;341:625–34.
2. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013;369:1115–23.
3. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. *J Am Coll Cardiol* 2015;65:963–72.
4. Engstrom T, Kelbaek H, Helqvist S, et al. Complete revasculari-

- sation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3-PRIMULTI): an open-label, randomised controlled trial. *Lancet* 2015;386:665–71.
5. Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI Focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol* 2016;67:1235–50.
 6. Sapontis J, Salisbury AC, Yeh RW, et al. Early procedural and health status outcomes after chronic total occlusion angioplasty: a report from the OPEN-CTO Registry (Outcomes, Patient Health Status, and Efficiency in Chronic Total Occlusion Hybrid Procedures). *JACC Cardiovasc Interv* 2017;10:1523–34.
 7. Henriques JP, Hoebbers LP, Ramunddal T, et al. Percutaneous intervention for concurrent chronic total occlusions in patients with STEMI: the EXPLORE trial. *J Am Coll Cardiol* 2016;68:1622–32.
 8. Brilakis ES, Grantham JA, Rinfret S, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. *JACC Cardiovasc Interv* 2012;5:367–79.

Which Herpes Zoster Vaccine is Most Cost-Effective?

Le P, Rothberg MB. Cost-effectiveness of the adjuvanted herpes zoster subunit vaccine in older adults. JAMA Intern Med 2018;178:248–58.

Objective. To assess the cost-effectiveness of the new adjuvanted herpes zoster subunit vaccine (HZ/su) as compared with that of the current live attenuated herpes zoster vaccine (ZVL), or no vaccine.

Design. Markov decision model evaluating 3 strategies from a societal perspective: (1) no vaccination, (2) vaccination with single dose ZVL, and (3) vaccination with 2-dose series of HZ/su.

Setting and participants. Data for the model were extracted from the US medical literature using PubMed through January 2015. Data were derived from studies of fewer than 100 patients to more than 30,000 patients, depending on the variable assessed. Variables included epidemiologic parameters, vaccine efficacy and adverse events, quality-adjusted life-years (QALYs), and costs. Because there is no standard willingness-to-pay (WTP) threshold for cost-effectiveness in the United States, \$50,000 per QALY was chosen.

Main outcome measures. Total costs and QALYs.

Main results. At all ages, no vaccination was always the least expensive and least effective option, while HZ/su was always the most effective and less expensive than ZVL. At

a proposed price of \$280 per series (\$140 per dose), HZ/su was more effective and less expensive than ZVL at all ages. The incremental cost-effectiveness ratios compared with no vaccination ranged from \$20,038 to \$30,084 per QALY, depending on vaccination age. The cost-effectiveness of HZ/su was insensitive to the waning rate of either vaccine due to its high efficacy, with initial level of protection close to 90% even among people 70 years or older.

Conclusion. At a manufacturer suggested price of \$280 per series (\$140 per dose), HZ/su would cost less than ZVL and has a high probability of offering good value.

Commentary

Herpes zoster is a localized, usually painful, cutaneous eruption resulting from reactivation of latent varicella zoster virus. It is a common disease with approximately one million cases occurring each year in the United States [1]. The incidence increases with age, from 5 cases per 1000 population in adults aged 50–59 years to 11 cases per 1000 population in persons aged ≥ 80 years. Postherpetic neuralgia, commonly defined as persistent pain for at least 90 days following the resolution of the herpes zoster rash, is the most common complication and occurs in 10% to 13% of herpes zoster cases in persons aged > 50 years [2,3].

In 2006, the US Food and Drug Administration (FDA)

approved the ZVL vaccine Zostavax (Merck) for prevention of postherpetic neuralgia. By 2016, 33% of adults aged ≥ 60 years reported receipt of the vaccine [4]. However, ZVL does not prevent all herpes zoster, particularly among the elderly. Moreover, the efficacy wanes completely after approximately 10 years [5]. To address these shortcomings, a 2-dose HZ/su (Shingrix; GlaxoSmithKline) containing recombinant glycoprotein E in combination with a novel adjuvant (AS01_B) was approved by the FDA in adults aged ≥ 50 years. In randomized controlled trials, HZ/su has an efficacy of close to 97%, even after age 70 years [6].

With the approval of the new attenuated herpes zoster vaccine, clinicians and patients face the question of which vaccine to get and when. The cost-effectiveness analysis published by Le and Rothberg in this study compare the value of HZ/su with ZVL vaccine and a no-vaccine strategy for individuals 60 years or older from the US societal perspective. The results suggest that, at \$140 per dose, using HZ/su vaccine compared with no vaccine would cost between \$20,038 and \$30,084 per QALY and thus is a cost-effective strategy. The deterministic sensitivity analysis indicates that the overall results do not change under different assumptions about model input parameters, even if patients are nonadherent to the second dose of HZ/su vaccine.

As with any simulation study, the major limitation of this study is the accuracy of the model and the assumptions on which it is based. The body of evidence for benefits of ZVL was large, including multiple pre-licensure and post-licensure RCTs, as well as observational studies of effectiveness. On the other hand, the body of evidence for benefits of RZV was primarily informed by one high-quality RCT that studied vaccine efficacy through 4 years post-vaccination [4,6]. Currently, 3 other independent cost-effectiveness analysis are available. The Centers for Disease Control and Prevention model estimated HZ/su vaccine cost per QALY of \$31,000 when vaccination occurred at age ≥ 50 years. The GlaxoSmithKline model, manufacturer of HZ/su vaccine, estimated a HZ/su vaccine cost per QALY of \$12,000. While the Merck model, manufacturer of the ZVL vaccine, estimated a HZ/su vaccine cost per QALY of \$107,000 [4]. In addition to model variables, the key assumption by Le and Rothberg are based on the HZ/su vaccine cost at \$140 per dose and ZVL at

\$213. The study results need to be interpreted carefully if the vaccine prices turn out to be different in the future.

Applications for Clinical Practice

The current study by Le and Rothberg demonstrated the cost-effectiveness of the new HZ/su vaccine. Since the study's publication, the CDC has updated their recommendations on immunization practices for use of herpes zoster vaccine [4]. HZ/su vaccine, also known as the recombinant zoster vaccine (RZV), is now preferred over ZVL for the prevention of herpes zoster and related complications. RZV is recommended for immunocompetent adults age 50 or older, 10 years earlier than previously for the ZVL. In addition, RZV is recommended for adults who previously received ZVL. Finally, RZV can be administered concomitantly with other adult vaccines, does not require screening for a history of varicella, and is likely safe for immunocompromised persons.

—Ka Ming Gordon Ngai, MD, MPH

References

1. Insinga RP, Itzler RF, Pellissier JM, et al. The incidence of herpes zoster in a United States administrative database. *J Gen Intern Med* 2005;20:748–53.
2. Yawn BP, Saddier P, Wollan PC, et al. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007;82:1341–9.
3. Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Eng J Med* 2005;352:2271–84.
4. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep* 2018;67:103–8.
5. Morrison VA, Johnson GR, Schmader KE, et al; Shingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis* 2015;60:900–9.
6. Lai H, Cunningham AL, Godeaux O, et al; ZOE-50 Study Group. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med* 2015;372:2087–96.

HIPEC for Ovarian Cancer: Standard of Care or Experimental Approach?

van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 2018;378:230–40.

Study Overview

Objective. To evaluate whether the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery would improve outcomes among patients who were receiving neoadjuvant chemotherapy for stage III epithelial ovarian cancer.

Design. Phase 3 prospective randomized clinical trial.

Setting and participants. The trial was conducted at 8 hospitals in the Netherlands and Belgium at which medical personnel had experience in administering HIPEC in patients with peritoneal disease from colon cancer or from pseudomyxoma peritonei. Eligible patients had newly diagnosed stage III epithelial ovarian, fallopian tube, or peritoneal cancer and were referred for neoadjuvant chemotherapy because of extensive abdominal disease or incomplete cytoreductive surgery (one or more residual tumors measuring > 1 cm in diameter). Eligibility criteria also including performance status score of 0 to 2, normal blood counts, and adequate renal function.

Intervention. At the time of surgery, patients were randomly assigned in a 1:1 ratio to undergo interval cytoreductive surgery either with HIPEC (surgery-plus-HIPEC group) or without HIPEC (surgery group). HIPEC was administered at the end of the cytoreductive surgical procedure. The abdomen was filled with saline that circulated continuously with the use of a roller pump through a heat exchanger. Perfusion with cisplatin at a dose of 100 mg per square meter and at a flow rate of 1 liter per minute was then initiated. The procedure took 120 minutes in total. To prevent nephrotoxicity, sodium thiosulphate was administered at the start of perfusion as an intravenous bolus (9 g per square meter in 200 mL), followed by a continuous infusion (12 g per square meter in 1000 mL) over 6 hours. Patient received in addition 3 cycles of

carboplatin and paclitaxel after surgery. During follow-up, physical examinations and measurement of CA-125 level were repeated every 3 months for 2 years and then every 6 months until 5 years after the completion of chemotherapy. Computed tomography was performed at 1, 6, 12, and 24 months after the last cycle of chemotherapy.

Main outcome measure. The primary endpoint was recurrence-free survival in the intent-to-treat population. Secondary endpoints included overall survival, the side-effect profile, and health-related quality of life.

Main results. A total of 245 women were randomized between April 2007 and April 2016. The median follow-up at the time of recurrence-free survival analysis was 4.7 years. Recurrence-free survival events occurred in 81% of the HIPEC group vs 89% of the control group; median recurrence-free survival was 14.2 months vs 10.7 months, respectively (hazard ratio [HR] 0.66, $P = 0.003$). The benefit of HIPEC was consistent across stratification factors and post hoc subgroups. Hazard ratios (none reaching statistical significance) were 0.63 and 0.72 for those aged ≥ 65 and < 65 years; 0.69 and 0.56 for those with high-grade serous and other histology; 0.71 and 0.47 for those with no previous surgery and previous surgery; 0.64 and 0.66 for those with 0 to 5 and 6 to 8 involved regions; and 0.69 and 0.61 for those with no laparoscopy vs laparoscopy before surgery. Death occurred in 50% of the hyperthermic intraperitoneal chemotherapy group vs 62% of the control group; median overall survival was 45.7 vs 33.9 months (HR 0.67, $P = 0.02$).

No significant differences between the HIPEC and control groups were observed in the incidence of adverse events of any grade. The most common adverse events of any grade in the HIPEC group were nausea (63% vs 57%), abdominal pain (60% vs 57%), and fatigue (37% vs 30%). Grade ≥ 3 adverse events occurred in 27% vs 25% of patients ($P = 0.76$). The most common grade 3 or 4

adverse events in the HIPEC group were infection (6% vs 2%), abdominal pain (5% vs 6%), and ileus (4% vs 2%). Among the patients who underwent bowel resection, a colostomy or ileostomy was performed more commonly among patients in the surgery-plus-HIPEC group (21 of 29 patients [72%]) than among those in the surgery group (13 of 30 patients [43%]) ($P = 0.04$).

Conclusion. Among patients with stage III epithelial ovarian cancer, the addition of hyperthermic intraperitoneal chemotherapy to interval cytoreductive surgery resulted in longer recurrence-free survival and overall survival than surgery alone and did not result in higher rates of side effects.

Commentary

Ovarian cancer is associated with the highest mortality of all gynecologic cancers in the Western world [1]. The majority of the patients have advanced disease at diagnosis and the most effective treatment for advanced disease involved maximum debulking surgery followed by chemotherapy. For those patients for whom primary surgery is not feasible, primary chemotherapy is given, which is followed by interval debulking after 3 courses of chemotherapy [2]. However, outcome remains dismal for patients with advanced disease. Regional (intraperitoneal) chemotherapy theoretically results in a decreased rate of systemic toxic effects and may improve outcomes by eliminating residual microscopic disease more effectively than intravenous chemotherapy [3].

Intraperitoneal chemotherapy during surgery that can be delivered under hyperthermic conditions is termed hyperthermic intraperitoneal chemotherapy. Rationale for using hyperthermic conditions when delivering intraperitoneal chemotherapy is multifactorial. Clinical hyperthermia is defined as the use of temperatures of 41°C and higher. Hyperthermia itself has a direct cytotoxic effects on cells caused by impaired DNA repair, denaturation of proteins, inductions of heat-shock proteins which may serve as receptors for natural killer-cells, induction of apoptosis, and inhibition of angiogenesis. In addition to its intrinsic cytotoxic effect, hyperthermia acts in synergy with some chemotherapeutic agents and increase peritoneal and tumour drug penetration [4].

The study by van Driel et al evaluates the impact of addition of HIPEC to interval cytoreductive surgery in patients who received neoadjuvant chemotherapy for stage III epithelial ovarian cancer. Authors found that addition of HIPEC resulted in 11.8 months improvement in overall survival compared to surgery alone without increased rate of side effects.

The outcomes of the trial by van Driel et al are encouraging, but questions remain about how to apply these results in everyday clinical practice. First, with the extensive reported experience with HIPEC in select single center or multicenter trials, it is reasonable to conclude the procedure can be successfully undertaken by well-trained surgical/gynecologic oncologists and at institutions experienced in the approach. However, clinical trials have limited external validity, and while providing evidence regarding efficacy (ie, the effect of the intervention under highly selected conditions), they generally do not provide evidence of effectiveness (ie, the benefit to the general population of patients with the disease). Can the same results be reproduced in hospitals across the country? Second, what part of HIPEC was responsible for benefit? Was it merely administration of chemotherapy through intraperitoneal route? Is hyperthermia necessary to see the observed benefit in this trial? The answers to these questions are not known. Third, the assessment of cost-benefit ratio warrants serious consideration as well. As authors pointed, the addition of HIPEC resulted in extension of duration of surgery by 2 hours and a perfusionist was needed. Additional standard costs are incurred due to the use of HIPEC machine, the disposable products needed to administer HIPEC, and the 1-day stay in the ICU. Increased use of diverting colostomy and ileostomy will also increase the overall cost of the treatment.

Applications for Clinical Practice

This trial is an important step in establishing the efficacy of adding HIPEC to interval cytoreductive surgery without increasing the side effects. However, whether the same results can be reproduced at centers at which surgeons do not have as much expertise in administering HIPEC remains to be seen. New confirmatory clinical trials of HIPEC are needed before it can be recommended as a common treatment strategy.

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References

1. Levi F, Lucchini F, Negri E, La Vecchia C. Trends in mortality from major cancers in the European Union, including acceding countries, in 2004. *Cancer* 2006;101:2843–50.
2. van der Burg MEL, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. *N Engl J Med* 1995;332:629–34.
3. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 2006;354:34–43.
4. Ohno S, Siddik ZH, Kido Y, et al. Thermal enhancement of drug uptake and DNA adducts as a possible mechanism for the effect of sequencing hyperthermia on cisplatin-induced cytotoxicity in L1210 cells. *Cancer Chemother Pharmacol* 1994;34:302–6.

Effect of Romosozumab vs. Alendronate on Osteoporosis Fracture Risk

Saag K, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *The ARCH trial. N Engl J Med* 2017;377:1417–27.

Study Overview

Objective. To determine if romosuzumab, an antiscle-rostin antibody, is superior to alendronate in reducing the incidence of fracture in postmenopausal women with osteoporosis at high-risk for fracture.

Design. Multicenter, international, double-blind, randomized clinical trial.

Setting and participants. 4093 postmenopausal women with osteoporosis and a previous fragility fracture were enrolled from over 40 countries worldwide. Patients were eligible for the study if they were 55 to 90 years old and were deemed at high risk for future fracture based on bone mineral density (BMD) T score at the total hip or femoral neck and fracture history. This included T score ≤ -2.5 and ≥ 1 moderate or severe vertebral fractures or ≥ 2 mild vertebral fractures; T score ≤ -2.0 and either ≥ 2 moderate or severe vertebral fractures or proximal femur fracture within 3 to 24 months before randomization. Subjects with a history of prior use of medications that affect bone metabolism were excluded, as were those with other metabolic bone disease, vitamin D deficiency, uncontrolled metabolic disease, malabsorption syndromes, history of transplant, severe renal insufficiency, malignancy or severe illness.

Intervention. Patients were randomized to either subcutaneous romosuzumab 210 mg monthly or oral alendro-

nate 70 mg weekly for 12 months. Following the 12-month double-blind period, all patients received open-label weekly alendronate until the end of the trial, with maintenance of blinding to the initial treatment assignment. Primary analysis occurred when all subjects had completed the 24-month visit and clinical fractures had been confirmed in at least 330 patients. All patients received daily calcium and vitamin D. Lateral radiographs of the thoracic and lumbar spine were obtained at screening and months 12 and 24. The BMD at the lumbar spine and proximal femur was evaluated by dual-energy x-ray absorptiometry at baseline and every 12 months thereafter. Serum concentrations of bone-turnover markers were measured in a subgroup of patients.

Main outcome measures. The primary outcomes were the incidence of new vertebral fracture and the incidence of clinical fracture at 24 months. Clinical fractures included symptomatic vertebral fracture and nonvertebral fractures. The secondary outcomes were the BMD at the lumbar spine, total hip, and femoral neck at 12 and 24 months, the incidence of nonvertebral fracture, and fracture category. Safety outcomes included the incidence of adjudicated clinical events, including serious cardiovascular adverse events, osteonecrosis of the jaw, and atypical femoral fracture. Serious cardiovascular events were defined as cardiac ischemic event, cerebrovascular event, heart failure, death, non-coronary revascularization

and peripheral vascular ischemic event not requiring revascularization.

Analysis. An intention to treat approach was used for data analysis. For the incidence of fractures, the treatment groups were compared using a Cox proportional-hazards model and the Mantel-Haenszel method with adjustment for age (< 75 vs ≥ 75 years), the presence or absence of severe vertebral fracture at baseline, and baseline BMD T score at the total hip. Between-group comparisons of the percentage change in BMD from baseline were analyzed by means of a repeated-measures model with adjustment for treatment, age category, baseline severe vertebral fracture, visit, treatment-by-visit interaction, and baseline BMD. Percentage changes from baseline in bone turnover were assessed using a Wilcoxon rank-sum test. The safety analysis included cumulated incidence rates of adverse outcomes. Odds ratios and confidence intervals were estimated for serious cardiovascular adverse events with the use of a logistic regression model.

Main results. 2046 participants were randomized to the romosozumab group and 2047 to the alendronate group. A total of 3654 participants from both groups (89.3%) completed 12 months of the trial, and 3150 (77.0%) completed the primary analysis period. The treatment groups were similar in baseline age, ethnicity, and fracture history. The majority of patients in both groups were non-Hispanic (> 60%) and ≥ 75 years old (> 50%). The mean age of the patients was 74.3 years. Baseline mean bone mineral density T scores were -2.96 at the lumbar spine, -2.8 at the total hip, and -2.9 at the femoral neck.

After 24 months of treatment, 6.2% of patients in the romosozumab-alendronate group had a new vertebral fracture as compared to 11.9% in the alendronate-alendronate group. This represents a 48% lower risk (risk ratio 0.52, 95% confidence interval [CI] 0.4–0.66; $P < 0.001$) of new vertebral fractures with romosozumab. At the time of the primary analysis, romosozumab followed by alendronate resulted in a 27% lower risk of clinical fracture than alendronate alone (hazard ratio 0.73, 95% CI 0.61–0.88; $P < 0.001$). 8.7% of the romosozumab-alendronate group had a nonvertebral fracture versus 10.6% in the alendronate-alendronate group, representing a 19% lower risk

with romosozumab (hazard ratio 0.81, 95% CI 0.66–0.99; $P = 0.04$). Hip fractures occurred in 2.0% of the romosozumab-alendronate group as compared with 3.2% in the alendronate-alendronate group, representing a 38% lower risk with romosozumab (hazard ratio 0.62, 95% CI 0.42–0.92; $P = 0.02$).

Patients in the romosozumab-alendronate group had greater gains in BMD from baseline at the lumbar spine (14.9% vs 8.5%) and total hip (7% vs 3.6%) compared to the alendronate-alendronate group. ($P < 0.001$ for all comparisons). At 12 months, romosozumab treatment resulted in decreased levels of bone resorption marker β -CTX and increased levels of bone formation marker P1NP. β -CTX and P1NP decreased and remained below baseline levels after transitioning to alendronate. In the alendronate-alendronate group, P1NP and β -CTX decreased within 1 month and remained below baseline levels at 36 months.

Overall, the adverse events and serious event rates were similar between the 2 treatment groups during the double-blind period with 2 exceptions. In the first 12 months, injection-site reactions were reported in 4.4% of patients receiving romosozumab compared to 2.6% in those receiving alendronate. Patients in the romosozumab group had an increased incidence of adjudicated serious cardiovascular outcomes during the double-blind period, 2.5% (50 of 2040 patients) compared to 1.9% (38 of 2014 patients) in the alendronate group. During the open-label period, osteonecrosis of the jaw occurred in one patient in each group. Two atypical femoral fractures occurred in the romosozumab-alendronate group, compared to 4 in the alendronate-alendronate group. During the first 18 months of the study, binding anti-romosozumab antibodies were observed in 15.3% of the romosozumab group, with neutralizing antibodies in 0.6%.

Conclusion. In postmenopausal woman with osteoporosis and high fracture risk, 12 months of romosozumab treatment followed by alendronate resulted in significantly lower risk of fracture than use of alendronate alone.

Commentary

Osteoporosis-related fragility fractures carry a substantial risk of morbidity and mortality [1]. The goal of osteoporosis

treatment is to ameliorate this risk. The current FDA-approved medications for osteoporosis can be divided into anabolic (teriparatide, abaloparatide) and anti-resorptive (bisphosphonate, denosumab, selective estrogen receptor modulators) categories. Sclerostin is a glycoprotein produced by osteocytes that inhibits the Wnt signaling pathway, thereby impeding osteoblast proliferation and activity. Romosozumab is a monoclonal antisclerostin antibody that results in both increased bone formation and decreased bone resorption [1]. By apparently uncoupling bone formation and resorption to increase bone mass, this medication holds promise to become the ideal osteoporosis drug.

Initial studies have shown that 12 months of romosozumab treatment significantly increased BMD at the lumbar spine (+11.3%), as compared to placebo (-0.1%), alendronate (+4.1%), and teriparatide (+7.1%) [2]. The Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) was a large (7180 patients) randomized controlled trial that demonstrated that 12 months of romosozumab resulted in a 73% lower risk of vertebral fracture and 36% lower risk of clinical fracture compared to placebo [3]. However, there was no significant reduction in non-vertebral fracture [3]. This may be due to the fact that FRAME excluded women at the highest risk for fracture. That is, exclusion criteria included history of hip fracture, any severe vertebral fracture, or more than 2 moderate vertebral fractures. The current phase 3 ARCH trial (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) attempts to clarify the potential benefit of romosozumab treatment in this very high-risk patient population, compared to a common first-line osteoporosis treatment, alendronate.

Indeed, ARCH demonstrates that sequential therapy with romosozumab followed by alendronate is superior to alendronate alone in improving BMD at all sites and preventing new vertebral, clinical, and non-vertebral fractures in postmenopausal women with osteoporosis and a history of fragility fracture. While ARCH was not designed as a cardiovascular outcomes trial, the higher rate of serious cardiovascular adverse events in the romosozumab group raises concern that romosozumab may have a negative effect on vascular tissue. Sclerostin is expressed in vascular smooth muscle [4] and upregulated at sites of

vascular calcification [5]. It is possible that inhibiting sclerostin activity could alter vascular remodeling or increase vascular calcification. However, it is interesting that in the larger FRAME trial, no increase in adverse cardiovascular events was seen in the romosozumab group compared to placebo. This may be due to the fact that the average age of patients in FRAME was lower than ARCH. However, it also raises the hypothesis that alendronate itself may be protective in terms of cardiovascular risk. It has been postulated that bisphosphonates may have cardiovascular protective effects, given animal studies have demonstrated that alendronate downregulates monocyte chemoattractant protein 1 and macrophage inflammatory protein 1 [6]. However no cardioprotective benefit was seen in meta-analysis [7].

ARCH has several strengths, including its design as an international, double-blind, and randomized clinical trial. The primary outcome of cumulative fracture incidence is a hard endpoint and is clinically relevant. The intervention is simple and the results are clearly defined. The statistical assessment yields significant results. However, there are some limitations to the study. The lead author has received research support from Amgen and UCB Pharma, the makers of romosuzumab. Amgen and UCB Pharma designed the trial, and Amgen was responsible for trial oversight and data analyses per a pre-specified statistical analysis plan. An external independent data monitoring committee monitored unblinded safety data. Because there was no placebo-controlled arm, it is difficult to determine whether the unexpected cardiovascular signal was due to romosuzumab itself or a protective effect of alendronate. In addition, the majority of study participants were non-Hispanic from Central or Eastern Europe and Latin America, with only ~2% of patients from North America. As a result, ARCH findings may not be generalizable to other regional or ethnic populations. Furthermore, the majority of the patients were ≥ 75 years of age and were at very high fracture risk. It is unclear if younger patients or those with lower risk of fracture would see the same fracture prevention and BMD gain. In addition, because of the relatively short length of the trial, the durability of the metabolic bone benefit and cardiovascular risk is unknown. While the authors reported the increased anti-romosozumab antibodies in the romo-

sozumab group had no detectable effect on efficacy or safety, given the short duration of the trial, this has not been proven.

Applications for Clinical Practice

The dual anti-resorptive and anabolic effect of romosozumab makes it an attractive and promising new osteoporosis therapy. ARCH suggests that sequential therapy with romosozumab and alendronate is superior in terms of fracture prevention to alendronate alone in elderly postmenopausal women with osteoporosis and a history of fragility fractures, although longer term studies are needed to define the durability of this effect. While the absolute number of serious adjudicated cardiovascular events was low, the increased incidence in the romosozumab group will likely prevent the FDA from approving this medication for widespread use at this time. Additional studies are needed to clarify the cause and magnitude of this cardiovascular risk and to determine whether prevention of fracture-associated morbidity and mortality is enough to mitigate it.

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References

1. Cummings SR, Melton IJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; 359:176107.
2. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2014;370:412–20.
3. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016;375:1532–43.
4. Zhu D, Mackenzie NCW, Millán JL, et al. The appearance and modulation of osteocyte marker expression during calcification of vascular smooth muscle cells. *PLoS One* 2011;6:e19595.
5. Evenepoel P, Goffin E, Meijers B, et al. Sclerostin serum levels and vascular calcification progression in prevalent renal transplant recipients. *J Clin Endocrinol Metab* 2015;100:4669–76.
6. Masuda T, Deng X, Tamai R. Mouse macrophages primed with alendronate down-regulate monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1alpha (MIP-1alpha) production in response to Toll-like receptor (TLR) 2 and TLR4 agonist via Smad3 activation. *Int Immunopharmacol* 2009;9:1115–21.
7. Kim DH, Rogers JR, Fulchino LA, et al. Bisphosphonates and risk of cardiovascular events: a meta-analysis. *PLoS One* 2015;10:e0122646.