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September 2024

Optimal Care Forum for Evidence-Based Medicine

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Learning objectives	• Examine the new peripheral artery disease practice guidelines and recognize the emphasis on avoiding screening for peripheral artery disease (PAD) in asymptomatic patients with no risk factors guideline-directed medical therapy, and revascularization surgery only for specific indications. • Identify current pharmacotherapies, the utilization of these drugs and their outcomes for chronic obstructive pulmonary disease (COPD) and nonarteritic anterior ischemic optic neuropathy (NAION). • Evaluate and compare routine functional stress testing and guideline directed medical therapy for coronary artery disease (CAD). • Determine the risk and mortality reduction with a colonoscopy screening.

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Peripheral artery disease practice guideline update from American College of Cardiology (ACC) and American Heart Association (AHA)

The American College of Cardiology and American Heart Association have recently updated their 2016 practice guidelines on management of lower extremity PAD with a new 2024 version.[1] Based on the evidence of poor outcomes, these updated guidelines caution providers to not use procedural interventions for asymptomatic or below popliteal PAD except in extremely rare circumstances. The guidelines categorize lower limb PAD as asymptomatic, chronic symptomatic, chronic limb-threatening ischemia and acute limb ischemia. Limb-threatening ischemia remains the primary indication for procedural intervention, whereas asymptomatic disease and infrapopliteal disease other than limb-threatening ischemia are best managed medically. For those with chronic activity-limiting symptoms unresponsive to an adequate trial of medical management and exercise therapy, invasive procedures may also be considered. All patients with considerations for surgery should be referred to a multidisciplinary team.

Since many of the underlying pathophysiological mechanisms leading to PAD are the same as for other atherosclerotic vascular diseases, medical management follows similar principles. Anti-lipid, anti-platelet and anti-thrombotic medications, exercise and nutrition therapy, blood pressure control, diabetes management (when present) and smoking cessation are all cornerstones of treatment.

Diagnosis of PAD is based on a careful history, physical exam and ankle-brachial index (ABI) measurement. Universal screening of asymptomatic patients with no risk factors is not recommended. Those patients who have diabetes mellitus, are over age 65, or have evidence of atherosclerosis in one or more vascular beds are considered at risk. Those with symptoms of claudication, or with physical exam findings consistent with PAD, should undergo further workup with an ABI and additional physiological testing. Advanced imaging should be reserved for pre-surgery planning, but it's not typically ordered in the primary care setting.

Figure 4, below, is from the published guideline. It shows medical management of PAD. The green color represents class 1 (strong) recommendations, magenta class 2a (moderate), and purple class 2b (weak). Specific medications and dosage recommendations are available for each class in the full guideline.

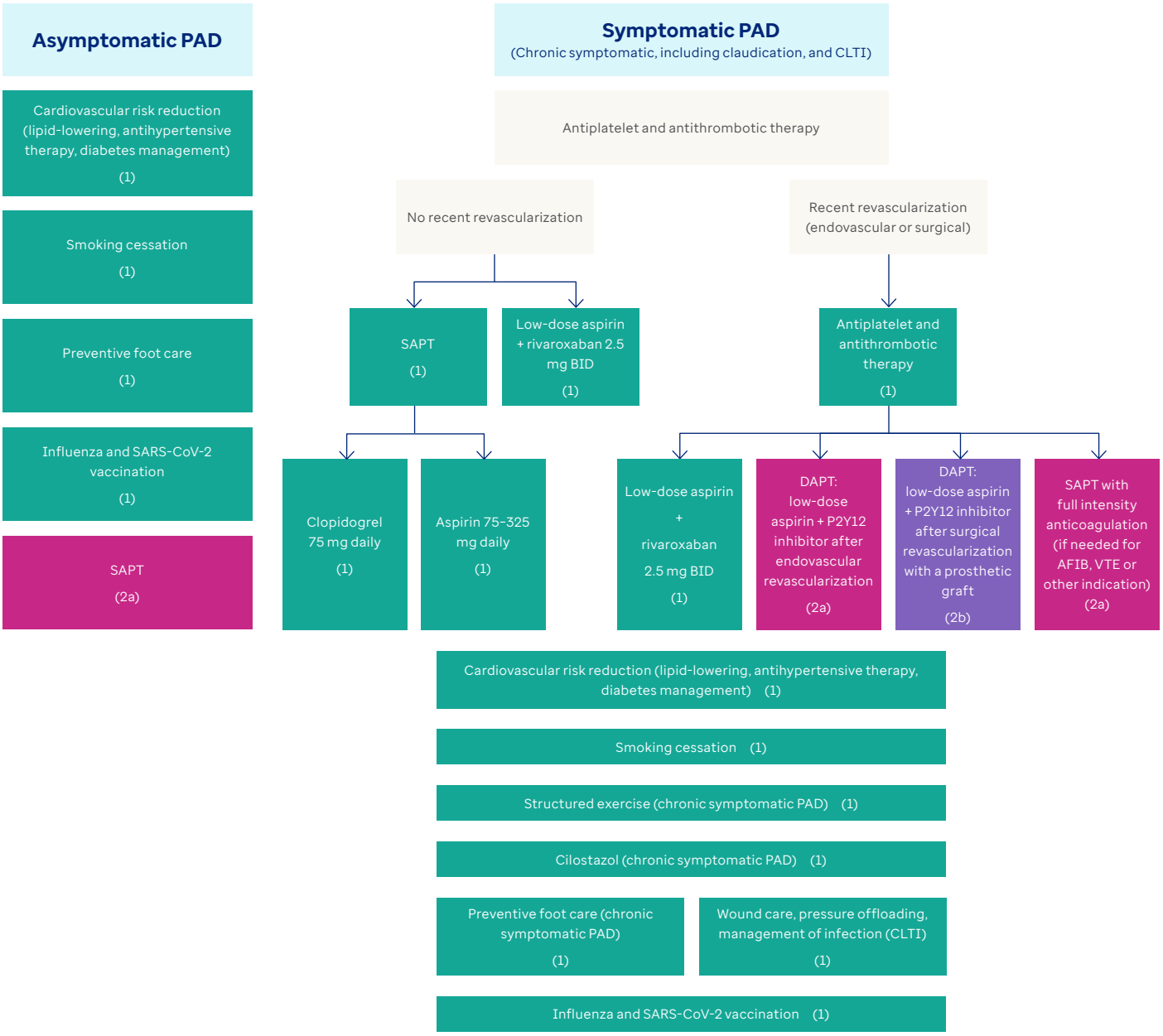

Figure 4. Medical Therapy and Foot Care for PAD.

Colors correspond to Table 3. Afib indicates atrial fibrillation; BID, 2 times daily; CLTI, chronic limb-threatening ischemia; DAPT, dual antiplatelet therapy; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; and VTE, venous thromboembolism.

Figure 5, below, is also from the published guideline. It shows that revascularization for chronic symptomatic PAD is a magenta class 2a (moderate), and purple class 2b (weak) recommendation when benefits outweigh risks, and an orange class 3 (no benefit, not recommended) when risks outweigh benefits.

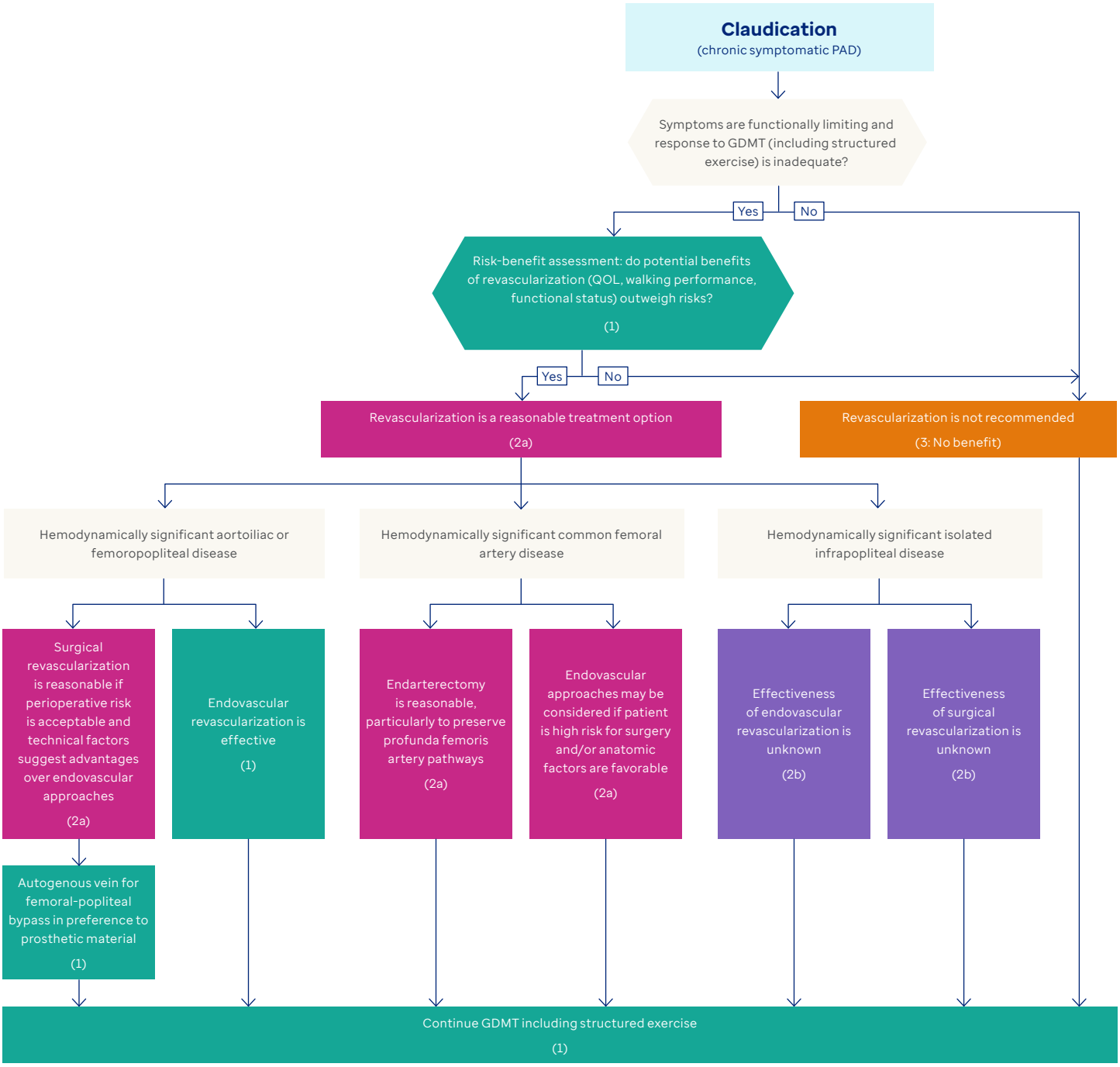

Figure 5. Algorithm for Revascularization for Claudication (Chronic Symptomatic PAD).

Colors correspond to Table 3. GDMT indicates guideline-directed management and therapy; PAD, peripheral artery disease; and COL, quality of life.

This is particularly important as studies have shown increased adverse outcomes, including increased amputation rates, with aggressive procedural management of infrapopliteal disease.[2]

In summary, the new guidelines:

- Reiterate avoiding screening for PAD in asymptomatic patients with no risk factors
- Encourage guideline-directed medical therapy for both symptomatic and asymptomatic PAD
- Endorse revascularization surgery only for specific indications

Association of sudden onset blindness with semaglutide

Nonarteritic anterior ischemic optic neuropathy (NAION) is the second most common form of optic neuropathy and is of unknown pathogenesis. The incidence is from 2–10/100,000, making it the second most common cause of blindness due to optic nerve damage, with glaucoma being the most common cause.

Based on anecdotal concerns over a relationship between the GLP1-RAs and NAION, investigators at the Massachusetts Eye and Ear Institute conducted a retrospective propensity matched cohort study. To estimate the relative risk of NAION developing in patients taking semaglutide, they examined patients referred to neuro-ophthalmology from 2017 to 2023.[3]

710 patients with myotonic dystrophy type 2 (DM2) and 979 patients with obesity who were taking semaglutide were propensity matched 2:1 to a cohort of patients not taking semaglutide.

In the diabetes population, NAION occurred in 17 patients in the semaglutide cohort versus 6 in the comparative cohort. The median age was 57 (49–63) years for the semaglutide cohort and 58 (47–66) years for the non-semaglutide cohort.

In the obese cohort, NAION occurred in 20 patients in the semaglutide cohort versus 3 in the comparative cohort. The median age was 46 (35–58) years for the semaglutide cohort and 44 (29–59) years for the non-semaglutide cohort. The hazard rate for the development of NAION in the diabetes cohort was 4.28, and for the obesity cohort was 7.64.

It is important to recognize that this relationship is not necessarily causal, but rather reflects only an association in a retrospective analysis. However, the strength of the association was strong and the sample size of 629 NAION cases over 6 years was a substantial fraction of expected cases from the Boston area. With a relatively low baseline annual incidence of NAION, the risk/benefit analysis for most patients initiating therapy would still favor the use of a GLP1-RA. However, due to the increasing utilization of these drugs and the devastating outcome of sudden blindness, further studies need to be done to confirm or refute this relationship and also to define the magnitude of the increased risk if present. The authors propose the options of a much larger, retrospective, multicenter population-based cohort study; a prospective, randomized clinical study; or a post-market analysis of all GLP-1 RA drugs.

New therapies for COPD — high cost, limited value

Over 15 million Americans are affected by COPD. It is the fourth leading cause of death and generally among the top 5 reasons for inpatient admission in the Medicare population. Available inhaler therapies have a modest effect on improving symptoms and reducing the frequency of moderate to severe exacerbations. They have a more limited effect on reduction of mortality or progressive loss of lung function. Two new drug classes of treatment will soon be added to the current armamentarium of pharmacotherapies. The first is ensifentrine, which was recently approved by the FDA. The second will be dupilumab (Dupixent), a biological therapy, which has been approved in Europe, with U.S. approval expected soon.

Ensifentrine was recently evaluated by the Institute for Clinical and Economic Review (ICER) and that information formed the basis of this review.[4] It is a novel inhaled dual inhibitor of PDE3 and PDE4 enzymes that relaxes the airway's smooth muscle and decreases inflammation. Treatment is twice daily via nebulizer. It has been evaluated in two 24-week randomized controlled trials (RCTs). About 1,500 patients were included in the combined group with a 2:1 ratio of active drug versus placebo. Since study design and participants were similar, the results have been combined. Participants had moderate to severe COPD and were on stable background therapy, including no therapy or LAMA or LABA, with or without inhaled corticosteroids (ICS). Patients on dual LAMA+LABA therapy or triple LAMA+LABA+ICS were excluded from the trials.

In terms of lung function in the 2 trials, the FEV-1 improvement was between 87 ml and 94 ml, which did not meet the minimal clinically important difference (MCID) of 100 ml. With respect to patient symptom scores, as examples, one of the studies did not show benefit in the Evaluating Respiratory Symptoms (E-RS) score and the other showed a median reduction of 1.0, with the MCID being >2.0. The scores on the dyspnea index just met the threshold for the MCID. The reduction in moderate to severe exacerbations equated to one less exacerbation every 6 years, approximately. Importantly, the subset of severe exacerbations (those requiring hospitalization) was not provided.

Ensifentrine was not found to be cost effective. At a wholesale acquisition cost of $35,400 per year, the incremental cost effectiveness ratio was $492,000 per QALY gained, or close to 5 times the accepted QALY threshold. ICER estimated that the cost was between 3- to 5-fold higher than would be needed to be cost effective. Importantly, when considering the above small benefits, it is emphasized that patients were not permitted to be on a LABA/LAMA combination or triple inhaler therapy in these 2 trials. Therefore, it is unknown whether there would be any benefit of ensifentrine for patients on these 2 regimens, which encompasses most of the patients with moderate to severe COPD.

Dupilumab (Dupixent) is a biological therapy which has been approved for asthma and atopic dermatitis. It has also been studied for use in COPD and in 2 RCTs – BOREAS and NOTUS.[5,6] These trials each enrolled approximately 1,000 patients with a 1:1 drug versus placebo ratio. Both studies evaluated the same patient population. Patients had moderate to severe COPD, blood eosinophil count ≥ 300 cells/μL, were current or former smokers, and with a history of high exacerbation risk. They were on a background of ICS+LAMA+LABA (or LAMA+LABA if ICS was contraindicated), and patients with asthma were excluded. The primary outcome was the rate of moderate to severe exacerbations per year. In BOREAS, the reduction in exacerbations equated to one less exacerbation per 3 years on therapy. For NOTUS, the reduction equated to one less exacerbation per 2.3 years. FEV1 results showed improvements of 83ml and 62 ml, once again not meeting the MCID criteria. Results were more significant for the subpopulation of patients with a baseline fractional exhaled nitric oxide (FeNO) ≥ 20 ppb. Elevated levels of FeNO are correlated with greater degrees of airways inflammation. One of three measurement scores of patient symptoms exceeded the MCID for improvement. There were no mortality improvements in either trial.

Importantly, less than 10% of exacerbations were severe, enough to require hospitalization, with the remainder being treated in the office with corticosteroids +/- antibiotics. ICER has not yet reviewed dupilumab as it is not yet FDA approved. But our Value and Therapeutics committee looked at the number needed to treat per year (NNT) to prevent one severe exacerbation and multiplied this by the yearly cost of the drug, which is approximately $50,000. The results were approximately $3 million per prevented severe exacerbation based on BOREAS results and approximately $2 million based on NOTUS results. Both results are clearly not cost effective. Whether there is a subset of patients with more severe airways inflammation, analogous to a severe asthma population, in which treatment might be cost effective is not known at this time.

Routine functional stress testing not indicated for patients after PCI following acute coronary syndrome

We now have extensive literature supporting the equivalency of guideline-directed medical therapy and invasive management of stable coronary artery disease (CAD) with respect to future major adverse coronary events.[7,8] Therefore, routine ischemia testing is no longer recommended for patients with stable CAD.

Patients who have cardiovascular disease warranting them to undergo percutaneous coronary interventions (PCI) are presumed to be at elevated risk of future major adverse coronary events (MACE). The subset of these patients who undergo PCI due to an acute coronary syndrome could be presumed to have an even higher risk. A recent study examined the effect of routine functional stress testing at 12 months after PCI compared to guideline directed medical therapy (GDMT) alone. Additional analyses were performed to examine outcomes of those patients who had a PCI following ACS versus those who underwent a PCI without a preceding ACS.[9]

The primary outcome was assessed for a 2-year period and was a composite of death, myocardial infarction or hospitalization for unstable angina. Of the 1,706 patients who underwent PCI, 526 presented with ACS. The primary outcome was similar between those who underwent routine functional testing versus those who received GDMT (functional testing: 16 of 251[6.6%]; standard care: 23 of 275 [8.5%]; HR, 0.76; 95% CI, 0.40–1.44; P = 0.39). Those who presented with ACS had higher incidence of the primary outcome compared with those who did not present with ACS (HR, 1.55; 95% CI, 1.03–2.33; P = 0.03). In other words, those who presented with ACS and underwent PCI had a higher risk of the primary outcome compared to those who did not present with ACS, but the use of routine functional stress testing in this group did not significantly change the outcomes. Those who underwent PCI without preceding ACS also did not benefit from routine functional stress testing (functional testing: 30 of 598 [5.1%]; standard care: 28 of 582 [4.9%]; HR, 1.04; 95% CI, 0.62–1.74; P = 0.88).

Patients with stable CAD do not require, nor benefit from, routine ischemia testing. For those patients who develop new stable chest pain, functional stress testing is still not preferred. Rather, coronary CT angiography (CCTA) can help guide subsequent work-up and medical versus procedural treatment.[10] The routine use of functional stress testing is of limited value in these settings.

Reduction of colorectal cancer mortality with the use of the fecal immunochemical test (FIT)

Following the publication of the NordICC trial,[11] we have a better understanding of the CRC risk reduction and mortality reduction with colonoscopy screening. Recall that using an intention-to-screen analysis, over a 10-year period, the colonoscopy group had a relative risk reduction of 18% in the incidence of colorectal cancer (CRC) compared to the control group. The risk of dying from CRC was not significantly different between the 2 groups. Since only 42% of those in the colonoscopy-invited group ultimately underwent a screening colonoscopy, additional per-protocol analyses were done looking only at patients who actually underwent colonoscopy. These showed a 31% relative risk reduction in CRC and a 50% relative reduction in death from CRC.

A recent nested, case control study evaluated whether the risk of dying from CRC was reduced with the use of FIT screening.[12] The study was conducted at Kaiser Permanente, which mails FIT kits to all eligible patients who are not otherwise up to date on CRC screening. From an underlying population of 2,127,128 members during 2011 to 2017, there were 1,279 patients identified who had died of CRC and 10,226 matched CRC-free persons.

During the 10-year period prior to the reference date, among control persons, 6,101 (63.5%) completed at least one FIT screening and 4,404 (45.8%) completed 2 or more FITs. The cumulative FIT positive rate among control persons was 12.6% (768 controls), of whom 610 (79.4%) had a colonoscopy within 12 months of the result date. In unconditional logistic regression analyses, completing FIT screening was associated with a 33% lower risk of death from overall CRC (adjusted odds ratio [aOR], 0.67; 95% CI, 0.59–0.76).

In stratified analyses, there was no statistically significant difference in CRC for right colon cancers (aOR, 0.83; 95% CI, 0.69–1.01), but there was a significant 42% lower risk of death for left colon and rectum cancers (aOR, 0.58; 95% CI, 0.48–0.71). The difference in the estimates between the right colon and left colon or rectum was statistically significant (P = .01). Interestingly, a prior study found that the mean stool hemoglobin concentration was 60.0 µg/g for left colon cancers and 12.4 µg/g for right colon cancers. More cancers in the right colon than in the left colon would be expected to generate hemoglobin concentrations below the positivity threshold.[13]

In summary, this nested case-control study found that completing one or more FIT screenings within the prior 5 years was associated with a 33% lower risk of death from colorectal adenocarcinoma. The reduction in mortality risk was significant for those with left colon or rectum cancers (42%). Although the results of this study cannot be directly compared to the colonoscopy results of the NordICC trial, it is interesting that in the invited-to-treat-cohort of NordICC, 42% of patients completed a colonoscopy and, in this study, 46% of patients completed 2 or more FIT tests. The overall reduction in CRC mortality was higher in this trial than in the invited-to-treat-cohort of NordICC. It is a reminder that FIT testing is an appropriate approach to reduce mortality from CRC.

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Dr. Kenneth Cohen is an experienced physician leader, practicing internist and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of Optum Care. He served as chief medical officer from 1995–2020. He now serves as the executive director of Translational Research for Optum Care and co-leads the Optum Center for Research and Innovation. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship, New West Physicians was awarded the AMGA Acclaim award in 2015 and the CDC Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine and School of Pharmacy. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

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