Nonculprit Lesion PCI Strategies in Patients With STEMI Without Cardiogenic Shock

Mehta S, Wood D, Cairns J, et al. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med. 2019;381:1411-1421.

Study Overview

Objective. To determine whether percutaneous coronary intervention (PCI) of a nonculprit lesion in patients with ST-segment elevation myocardial infarction (STEMI) reduces the risk of cardiovascular death or myocardial infarction.

Design. International, multicenter, randomized controlled trial blinded to outcome.

Setting and participants. Patients with STEMI who had multivessel coronary disease and had undergone successful PCI to the culprit lesion.

Intervention. A total of 4041 patients were randomly assigned to either PCI of angiographically significant nonculprit lesions or optimal medical therapy without further revascularization. Randomization was stratified according to intended timing of nonculprit lesion PCI (either during or after the index hospitalization).

Main outcome measures. The first co-primary endpoint was the composite of cardiovascular death or myocardial infarction (MI). The second co-primary endpoint was the composite of cardiovascular death, MI or ischemia-driven revascularization.

Main results. At a median follow-up of 3 years, the composite of cardiovascular death or MI occurred in 158 of the 2016 patients (7.8%) in the nonculprit PCI group and in 213 of the 2025 patients (10.5%) in the culprit-lesion-only group (hazard ratio, 0.73; 95% confidence interval [CI], 0.60-0.91; $P = 0.004$). The second co-primary endpoint occurred in 179 patients (8.9%) in the nonculprit PCI group and in 339 patients (16.7%) in the culprit-lesion-only group (hazard ratio, 0.51; 95% CI, 0.43-0.61; $P < 0.001$).

Conclusion. Among patients with STEMI and multivessel disease, those who underwent complete revascularization with nonculprit lesion PCI had lower rates of cardiovascular death or MI compared to patients with culprit-lesion-only revascularization.

Commentary

Patients presenting with STEMI often have multivessel disease.[1] Although it is known that mortality can be reduced by early revascularization of the culprit vessel,[2] whether the nonculprit vessel should be revascularized at the time of presentation with STEMI remains controversial.

Recently, multiple studies have reported the benefit of nonculprit vessel revascularization in patients presenting

with hemodynamically stable STEMI. Four trials (PRAMI, CvPRIT, DANAMI-PRIMULTI, and COMPARE ACUTE) investigated this clinical question with different designs, and all reported benefit of nonculprit vessel revascularization compared to a culprit-only strategy.[3-6] However, the differences in the composite endpoints were mainly driven by the softer endpoints used in these trials, such as refractory angina and ischemia-driven revascularization, and none of these previous trials had adequate power to evaluate differences in hard outcomes, such as death or MI.

In this context, Mehta et al investigated whether achieving complete revascularization by performing PCI on nonculprit vessels would improve the composite of cardiovascular death or MI compared to the culprit-only strategy by conducting a well-designed randomized controlled study. At median follow-up of 3 years, patients who underwent nonculprit vessel PCI had a lower incidence of death or MI compared to those who received the culprit-only strategy (7.8% versus 10.5%). The second co-primary endpoint (composite of death, MI, or ischemia-driven revascularization) also occurred significantly less frequently in the nonculprit PCI group than in the culprit-only PCI group (8.9% versus 16.7%).

The current study has a number of strengths. First, this was a multicenter, international study, and a large number of patients were enrolled (> 4000), achieving adequate power to evaluate for the composite of death and MI. Second, the treatments the patients received reflect contemporary medical therapy and interventional practice: the third-generation thienopyridine ticagrelor, high-dose statins, and ACE inhibitors were prescribed at high rates, and radial access (> 80%) and current-generation drug-eluting stents were used at high rates as well. Third, all angiograms were reviewed by the core lab to evaluate for completeness of revascularization. Fourth, the trial mandated use of fractional flow reserve to assess lesion stenosis 50% to 69% before considering revascularization, ensuring that only ischemic or very-high-grade lesions were revascularized. Fifth, the crossover rate in each group was low compared to the previous studies (4.7% into the complete revascularization group, 3.9% into the lesion-only group). Finally, this study evaluated the timing of the nonculprit PCI. Randomization to each group was stratified according to the intended timing of the nonculprit PCI during the index hospitalization or after hospital discharge (within 45 days). They found that benefit was consistent regardless of when the nonculprit PCI was performed.

Although the COMPLETE study's design has a number of strengths, it is important to note that patients enrolled in this trial represent a lower-risk STEMI population. Patients with complex anatomy likely were not included, as evidenced by a lower SYNTAX score (mean, 16). Furthermore, no patients who presented with STEMI complicated by cardiogenic shock were enrolled. In the recent CULPRIT SHOCK trial, which focused on patients who had multivessel disease, acute MI, and cardiogenic shock, patients who underwent the culprit-only strategy had a lower rate of death or renal replacement therapy, as compared to patients who underwent immediate complete revascularization.[7] Therefore, whether the findings from the COMPLETE study can be extended to a sicker population requires further study.

In 2015, the results from the previous trials, such as PRAMI and CvPRIT, led to a focused update of US PCI guidelines.[8] Recommendations for noninfarct-related artery PCI in hemodynamically stable patients presenting with acute MI were upgraded from class III to class IIb. The results from the COMPLETE trial will likely influence the future guidelines, with stronger recommendations toward complete revascularization in patients presenting with hemodynamically stable STEMI.

Applications for Clinical Practice

In patients presenting with hemodynamically stable STEMI, staged complete revascularization, including the nonculprit vessel, should be considered.

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Switching from TDF- to TAF-Containing Antiretroviral Therapy: Impact on Bone Mineral Density in Older Patients Living With HIV

Maggiolo F, Rizzardini G, Raffi F, et al. Bone mineral density in virologically suppressed people aged 60 years or older with HIV-1 switching from a regimen containing tenofovir disoproxil fumarate to an elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide single-tablet regimen: a multicentre, open-label, phase 3b, randomised trial. Lancet HIV. 2019;6(10):e655-e666.

Study Overview

Objective. To evaluate the effect of changing from tenofovir disoproxil fumarate (TDF) –containing antiretroviral therapy (ART) to tenofovir alafenamide (TAF) –containing ART in patients ages 60 years and older living with HIV.

Design. Prospective, open-label, multicenter, randomized controlled trial.

Setting and participants. The study was completed across 36 European centers over 48 weeks. Patients were enrolled from December 12, 2015, to March 21, 2018, and were eligible to participate if they were diagnosed with HIV-1; virologically suppressed to < 50 copies/mL; on a TDF-containing ART regimen; and ≥ 60 years of age.

Intervention. Participants (n = 167) were randomly assigned in a 2:1 ratio to ART with TAF (10 mg), elvitegravir (EVG; 150 mg), cobicistat (COB; 150 mg), and emtricitabine (FTC; 200 mg) or to continued therapy with a TDF-containing ART regimen (300 mg TDF).

Main outcome measures. Primary outcome measures were the change in spine and hip bone mineral density from baseline at week 48. Secondary outcome measures included bone mineral density changes from baseline at week 24, HIV viral suppression and change in CD4 count at weeks 24 and 48, and the assessment of safety and tolerability of each ART regimen until week 48.

Main results. At 48 weeks, patients (n = 111) in the TAF+EVG+COB+FTC group had a mean 2.24% (SD, 3.27) increase in spine bone mineral density, while those in the TDF-containing group (n = 56) had a mean 0.10% decrease (SD, 3.39), a difference of 2.43% (95% confidence interval [CI], 1.34-3.52; $P < 0.0001$). In addition, at 48 weeks patients in the TAF+EVG+COB+FTC group had a mean 1.33% increase (SD, 2.20) in hip bone mineral density, as compared with a mean 0.73% decrease (SD, 3.21) in the TDF-containing group, a difference of 2.04% (95% CI, 1.17-2.90; $P < 0.0001$).

Similar results were seen in spine and hip bone mineral density in the TAF+EVG+COB+FTC group at week

24, with increases of 1.75% (P = 0.00080) and 1.35% (P = 0.00040), respectively. Both treatment groups maintained high virologic suppression. The TAF+EVG+COB+FTC group maintained 94.5% virologic suppression at week 24 and 93.6% at week 48, as compared with virologic suppression of 100% and 94.5% at weeks 24 and 48, respectively, in the TDF-containing group. However, the TAF+EVG+COB+FTC group had an increase in CD4 count from baseline (56 cells/μL), with no real change in the TDF-containing group (–1 cell/μL). Patients in the TAF+EVG+COB+FTC group had a mean 27.8 mg/g decrease in urine albumin-to-creatinine ratio (UACR) versus a 7.7 mg/g decrease in the TDF-containing group (P = 0.0042). In addition, patients in the TAF+EVG+COB+FTC group had a mean 49.8 mg/g decrease in urine protein-to-creatinine ratio (UPCR) versus a 3.8 mg/g decrease in the TDF-containing group (P = 0.0042).

Conclusion. Patients 60 years of age or older living with virologically suppressed HIV may benefit from improved bone mineral density by switching from a TDF-containing ART regimen to a TAF-containing regimen after 48 weeks, which, in turn, may help to reduce the risk for osteoporosis. Patients who were switched to a TAF-containing regimen also had favorable improvements in UACR and UPCR, which could indicate better renal function.

Commentary

The Centers for Disease Control and Prevention estimated that in 2018 nearly half of those living with HIV in the United States were older than 50 years.[1] Today, the life expectancy of patients living with HIV on ART in developed countries is similar to that of patients not living with HIV. A meta-analysis published in 2017 estimated that patients diagnosed with HIV at age 20 beginning ART have a life expectancy of 63 years, and another study estimated that life expectancy in such patients is 89.1% of that of the general population in Canada.[2,3] Overall, most people living with HIV infection are aging and at risk for medical conditions similar to persons without HIV disease. However, rates of osteoporosis in elderly patients with HIV are estimated to be 3 times greater than rates in persons without HIV.[4] As a result, it is becoming increasingly important to find ways to decrease the risk of osteoporosis in these patients.

ART typically includes a nucleoside reverse transcriptase inhibitor (NRTI) combination and a third agent, such as an integrase strand inhibitor. Tenofovir is a commonly used backbone NRTI that comes in 2 forms, TDF (tenofovir disoproxil fumarate) and TAF (tenofovir alafenamide). Both are prodrugs that are converted to tenofovir diphosphate. TDF specifically is associated with an increased risk of bone loss and nephrotoxicity. The loss in bone mineral density is most similar to the bone loss seen with oral glucocorticoids.[5] TDF has been shown to increase plasma levels of RANKL and tumor necrosis factor-α, leading to increased bone resorption.[6] The long-term effects of TDF- versus TAF-containing ART on bone mineral density have, to our knowledge, not been compared previously in a randomized control study. The significance of demonstrating an increase in bone mineral density in the prevention of osteoporotic bone fracture in people living with HIV is less clear. A long-term cohort study completed in Japan looking at patients on TDF showed an increased risk of bone fractures in both older postmenopausal women and younger men.[7] However, a retrospective cohort study looking at 1981 patients with HIV found no association between bone fractures and TDF.[8]

This randomized controlled trial used appropriate methods to measure the reported primary and secondary endpoints; however, it would be of benefit to continue following these patients to measure their true long-term risk of osteoporosis-related complications. In terms of the study's secondary endpoints, it is notable that the patients maintained HIV viral suppression after the switch and CD4 counts remained stable (with a slight increase observed in the TAF-containing ART cohort).

In regard to the patient's renal function, patients in the TAF group had significantly improved UACR and UPCR, which likely reflects improved glomerular filtration. Improved renal function is also increasingly important for patients with HIV, as up to 48.5% have some form of chronic kidney disease.[9]

Applications for Clinical Practice

This study shows that making the switch from TDF- to TAF-containing ART can lead to improved bone mineral density. We can extrapolate that switching may lead to a decreased risk of osteoporosis and osteoporosis-related

complications, such as bone fracture, but this needs to be investigated in more detail. As demonstrated in this study, switching from a TDF- to a TAF-containing regimen can also lead to improved renal function while maintaining HIV viral suppression and CD4 counts.

Unfortunately, the regimen selected with TAF in this study (elvitegravir, cobicistat, and emtricitabine) includes cobicistat, which is no longer recommended as initial therapy due to its risk of drug-drug interactions, and elvitegravir, which has a lower barrier to resistance than other integrase strand inhibitors.[10,11] The United States Department of Health and Human Services guidelines and the International Antiviral Society-USA Panel suggest using several other TAF-containing regimens for beginning or even switching therapy in older patients.[10,11]

When choosing between either a TAF- or a TDF-containing regimen to treat HIV infection in older patients, increasing evidence shows that using a TAF-containing ART regimen may be more beneficial for people living and aging with virologically suppressed HIV infection.

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Collaborative Dementia Care via Telephone and Internet Improves Quality of Life and Reduces Caregiver Burden

Possin KL, Merrilees JJ, Dulaney S, et al. Effect of collaborative dementia care via telephone and internet on quality of life, caregiver well-being, and health care use. JAMA Intern Med. 2019;179:1658-1667.

Study Overview

Objective. To examine the effectiveness of a hub site–based care delivery system in delivering a dementia care management program to persons with dementia and their caregivers.

Design. Randomized pragmatic clinical trial enrolling dyads of persons with dementia and their caregiver. Study participants were randomly assigned to the dementia care management program and usual care in a 2:1 ratio.

Setting and participants. The study was conducted from 2 hub sites: the University of California, San Francisco, and the University of Nebraska Medical Center in Omaha. Each hub-site team served persons with dementia and their caregivers in California, Nebraska, and Iowa in both urban and rural areas. Participants were recruited through referral by treating providers or self-referral in response to advertising presented through a community outreach event, in the news, or on the internet. Eligibility requirements included: having a dementia diagnosis made by a treating provider; age older than 45 years; Medicare or Medicaid enrollment or eligibility; presence of a caregiver willing to enroll in the study; fluency in English, Spanish, or Cantonese; and residence in California, Nebraska, or Iowa. Exclusion criteria included residence in a nursing home. Out of 2585 referred dyads of persons with dementia and caregivers, 780 met inclusion criteria and were enrolled. A 2:1 randomization yielded 512 dyads in the intervention group and 268 dyads in the control group.

Intervention. The dementia care management program was implemented through the Care Ecosystem, a telephone- and internet-based supportive care intervention delivered by care team navigators. The navigators were unlicensed but trained dementia care guides working under the supervision of an advanced practice nurse, social worker, and pharmacist. The intervention consisted of telephone calls, monthly or at a frequency determined by needs and preferences, placed by navigators over a 12-month period; the content of the calls included response to immediate needs of persons with dementia and their caregiver, screening for common problems, and provision of support and education using care plan protocols. Caregivers and persons with dementia were encouraged to initiate contact through email, mail, or telephone for dementia-related questions. Additional support was provided by an advanced practice nurse, social worker, or pharmacist, as needed, and these health care professionals conducted further communication with the persons with dementia, caregiver, or outside professionals, such as physicians, for the persons with dementia, as needed. The average number of telephone calls over the 12-month period was 15.3 (standard deviation, 11.3). Participants assigned to usual care were offered contact information on dementia and aging-related organizations, including the Alzheimer's Association and the Area Agencies on Aging, and also were sent a quarterly newsletter with general information about dementia.

Main outcome measures. The primary outcome measure was the Quality of Life in Alzheimer's Disease score obtained by caregiver interview. This quality of life measure includes the following aspects, each rated on an ordinal scale of 1 to 4: physical health, energy level, mood, living situation, memory, family, closest relationship, friends, self, ability to do things for fun, finances, and life as a whole. The scores range from 13 to 52, with a higher score indicating

better quality of life for persons with dementia. Other outcomes included frequency of emergency room visits, hospital use, and ambulance use; caregiver depression score from the Patient Health Questionnaire scale; caregiver burden score using the 12-item Zarit Burden Interview; caregiver self-efficacy; and caregiver satisfaction.

Main results. The study found that the quality of life for persons with dementia declined more in the usual care group than in the intervention group during the 12-month study period (difference of 0.53; 95% confidence interval, 0.25-1.3; $P = 0.04$). Persons with dementia also had fewer emergency room visits, with a number needed to treat to prevent 1 emergency room visit of 5. The intervention did not reduce ambulance use or hospital use. Caregivers in the intervention group had a greater decline in depression when compared to usual care; the frequency of moderate to severe depression decreased from 13.4% at baseline to 7.9% at 12 months ($P = 0.004$). Caregiver burden declined more in the intervention group than in the control group at 12 months ($P = 0.046$). In terms of caregiver satisfaction, 97% of caregivers surveyed in the intervention group said they would recommend the intervention to another caregiver; 45% indicated they were very satisfied, and 33% that they were satisfied.

Conclusion. Delivering dementia care via telephone and internet through a collaborative program with care navigators can improve caregiver burden and well-being and improve quality of life, emergency room utilization, and depression for persons with dementia. In addition, the program was well received.

Commentary

Dementia, including Alzheimer's disease, primarily affects older adults and is characterized by declines in memory and cognitive function. It is often accompanied by neuropsychological symptoms such as agitation, wandering, and physical and verbal outbursts, which are debilitating for persons living with dementia and difficult to cope with for caregivers.[1] These symptoms are often the source of caregiver stress, potentially leading to caregiver depression and eventual need for long-term institution-based care, such as nursing home placement.[2]

Prior literature has established the potential effect of support in improving caregiver outcomes, including caregiver stress and burden, through interventions such as enhancing resources for caregivers, teaching coping strategies to caregivers, and teaching caregivers how to manage support for their loved ones.[3,4] However, wider adoption of these interventions may be limited if the interventions involve in-person meetings or activities that take caregivers away from caregiving; the scalability of these programs is also limited by their ability to reach persons with dementia and their caregivers. These barriers are particularly important for older adults living in rural areas, where the availability of resources and distance from access to quality care may be particularly limiting.[5] Leveraging advances in technology and telecommunication, this study examined the effects of providing dementia care support via telephone and internet using a trained, unlicensed care navigator as the main point of contact. The results showed improved quality of life for persons with dementia, reduced need for emergency room visits, and reduced caregiver burden and depression. The intervention is promising as a scalable intervention that may impact dementia care nationwide.

Despite the promising results, there are several issues regarding the intervention's applicability and impact that future studies may help to further clarify. Although the improvement in quality of life in persons with dementia is important to document, it is unclear whether this difference is clinically significant. Also, it may be important to examine whether the 12-month program has sustained impact beyond the study period, although the intervention could be conceived as a long-term care solution. If the intervention is sustained beyond 12 months, future studies may look at other clinical outcomes, such as incidence of institutionalization and perhaps time to institutionalization. The study population consisted of persons with dementia of various stages, half of whom had mild disease. Future studies may further clarify at which stage of dementia the intervention is most useful. Other changes that occurred during the study period, such as change in the use of paid home-based support services and referrals to other relevant evaluations and treatment, may provide further clues about how the dementia care intervention achieved its beneficial effects.

Applications for Clinical Practice

From the health systems perspective, dementia care accounts for significant resources, and these costs are expected to grow as the population ages and dementia prevalence increases. Identifying potentially scalable interventions that yield clinical benefits and are sustainable from a cost perspective is an important step forward in improving care for persons with dementia and their caregivers across the nation. The use of centralized hubs to deliver this intervention and the novel use of telecommunications advances make this intervention applicable across large areas. Policy makers should explore how an intervention such as this could be established and sustained in our health care system.

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