Adjuvant Olaparib Improves Outcomes in High-Risk, HER2-Negative Early Breast Cancer Patients With Germline *BRCA1* and *BRCA2* Mutations

Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-2405. doi:10.1056/NEJM0a2105215

Study Overview

Objective. To assess the efficacy and safety of olaparib as an adjuvant treatment in patients with *BRCA1* or *BRCA2* germline mutations who are at a high-risk for relapse.

Design. A randomized, double-blind, placebo-controlled, multicenter phase III study. The published results are from the prespecified interim analysis.

Intervention. Patients were randomized in 1:1 ratio to either receive 300 mg of olaparib orally twice daily or to receive a matching placebo. Randomization was stratified by hormone receptor status (estrogen receptor and/or progesterone receptor positive/HER2-negative vs triple negative), prior neoadjuvant vs adjuvant chemotherapy, and prior platinum use for breast cancer. Treatment was continued for 52 weeks.

Setting and participants. A total of 1836 patients were randomized in a 1:1 fashion to receive olaparib or a placebo. Eligible patients had a germline *BRCA1* or *BRCA1* pathogenic or likely pathogenic variant. Patients had high-risk, HER2-negative primary breast cancers and all had received definitive local therapy and neoadjuvant or adjuvant chemotherapy. Patients were enrolled between 2 to 12 weeks after completion of all local therapy. Platinum chemotherapy was allowed. Patients received adjuvant endocrine therapy for hormone receptor positive disease as well as adjuvant bisphosphonates per institutional guidelines. Patients with triple negative disease who received adjuvant chemotherapy were required to be lymph node positive or have at least 2 cm invasive disease. Patients who received neoadjuvant chemotherapy were required to have residual invasive disease to be eligible. For hormone receptor positive patients receiving adjuvant chemotherapy to be eligible they had to have at least 4 pathologically confirmed lymph nodes involved. Hormone receptor positive patients who had neoadjuvant chemotherapy were required to have had residual invasive disease.

Main outcome measures. The primary endpoint for the study was invasive disease-free survival which was defined as time from randomization to date of recurrence or death from any cause. The secondary endpoints included overall survival (OS), distant disease-free survival, safety, and tolerability of olaparib.

Main results. At the time of data cutoff, 284 events had occurred with a median follow-up of 2.5 years in the intention to treat population. A total of 81% of patients had triple negative breast cancer. Most patients (94% in the olaparib group and 92% in the placebo group) received both taxane and anthracycline based chemotherapy regimens. Platinum based chemotherapy was used in 26% of patients in each group. The groups were otherwise well balanced. Germline mutations in *BRCA1* were present in 72% of patients and *BRCA2* in 27% of patients. These were balanced between groups.

At the time of this analysis, adjuvant olaparib reduced the risk of invasive disease-free survival by 42% compared with placebo ($P < .001$). At 3 years, invasive disease-free survival was 85.9% in the olaparib group and 77.1% in the placebo group (difference, 8.8 percentage points; 95% CI, 4.5-13.0; hazard ratio [HR], 0.58; 99.5% CI, 0.41-0.82; $P < .001$). The 3-year distant disease-free survival was 87.5% in the olaparib group and 80.4% in the placebo group (HR 0.57; 99.5% CI, 0.39-0.83; $P < .001$). Results also showed that olaparib was associated with fewer deaths than placebo (59 and 86, respectively) (HR, 0.68; 99% CI, 0.44-1.05; $P = .02$); however, there was no significant difference between treatment arms at the time of this interim analysis. Subgroup analysis showed a consistent benefit across all groups with no difference noted regarding *BRCA* mutation, hormone receptor status or use of neoadjuvant vs adjuvant chemotherapy.

The side effects were consistent with the safety profile of olaparib. Adverse events of grade 3 or higher more common with olaparib included anemia (8.7%), leukopenia (3%), and fatigue (1.8%). Early discontinuation of trial regimen due to adverse events of disease recurrence occurred in 25.9% in the olaparib group and 20.7% in the placebo group. Blood transfusions were required in 5.8% of patients in the olaparib group. Myelodysplasia or acute myeloid leukemia was observed in 2 patients in the olaparib group and 3 patients in the placebo group. Adverse events leading to death occurred in 1 patient in the olaparib group and 2 patients in the placebo group.

Conclusion. Among patients with high-risk, HER2-negative early breast cancer and germline *BRCA1* or *BRCA2* pathogenic or likely pathogenic variants, adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy was associated with significantly longer invasive disease-free and distant disease-free survival compared with placebo.

Commentary

The results from the current OlympiA trial provide the first evidence that adjuvant therapy with poly adenosine diphosphate-ribose polymerase (PARP) inhibitors can improve outcomes in high-risk, HER2-negative breast cancer in patients with pathogenic *BRCA1* and *BRCA2* mutations. The OS, while favoring olaparib, is not yet mature at the time of this analysis. Nevertheless, these results represent an important step forward in improving outcomes in this patient population. The efficacy and safety of PARP inhibitors in *BRCA*-mutated breast cancer has previously been shown in patients with advanced disease leading to FDA approval of both olaparib and talazoparib in this setting.[1,2] With the current results, PARP inhibitors will certainly play an important role in the adjuvant setting in patients with deleterious *BRCA1* or *BRCA2* mutations at high risk for relapse. Importantly, the side effect profile appears acceptable with no unexpected events and a very low rate of secondary myeloid malignancies.

Subgroup analysis appears to indicate a benefit across all groups including hormone receptor–positive disease and triple negative breast cancer. Interestingly, approximately 25% of patients in both cohorts received platinum-based chemotherapy. The efficacy of adjuvant olaparib did not appear to be impacted by prior use of platinum-containing chemotherapy regimens. It is important to consider that postneoadjuvant capecitabine, per the results of the CREATE-X trial, in triple-negative patients was not permitted in the current study. Although, this has been widely adopted in clinical practice.[3] The CREATE-X trial did not specify the benefit of adjuvant capecitabine in the *BRCA*-mutated cohort, thus, it is not clear how this subgroup fares with this approach. Thus, one cannot extrapolate the relative efficacy of olaparib compared with capecitabine, as pointed out by the authors, and whether we consider the use of capecitabine and/or olaparib in triple-negative patients with residual invasive disease after neoadjuvant chemotherapy is not clear at this time.

Nevertheless, the magnitude of benefit seen in this trial certainly provide clinically relevant and potentially practice changing results. It will be imperative to follow these results as the survival data matures and ensure no further long-term toxicity, particularly secondary myeloid malignancies, develop. These results should be discussed with each patient and informed decisions regarding the use of adjuvant olaparib should be considered for this patient population. Lastly, these results highlight the importance of germline testing for patients with breast cancer in accordance with national guideline recommendations. Moreover, these results certainly call into question whether it is time to consider expansion of our current germline testing guidelines to detect all potential patients who may benefit from this therapy.

Application for Clinical Practice

Adjuvant olaparib in high-risk patients with germline *BRCA1* or *BRCA2* mutations improves invasive and distant disease-free survival and should be considered in patients who meet the enrollment criteria of the current study. Furthermore, this highlights the importance of appropriate germline genetic testing in patients with breast cancer.

—Mahmoud Abdelsamia, MD, and Daniel Isaac, DO, MS, Department of Medicine, Michigan State University, East Lansing, MI

Financial disclosures: None.

doi:10.12788/jcom.0074

References

1. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-533. doi:10.1056/NEJMoa1706450
2. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med*. 2018;379(8):753-763. doi:10.1056/NEJMoa1802905
3. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med*. 2017;376(22):2147-2159. doi:10.1056/NEJMoa1612645

FFR-Guided or Angiography-Guided Nonculprit Lesion PCI in Patients With STEMI Without Cardiogenic Shock

Puymirat E, Cayla G, Simon T, et al. Multivessel PCI guided by FFR or Angiography for Myocardial Infarction. N Engl J Med. 2021;385(4):297-308. doi:10.1056/NEJMoa2104650

Study Overview

Objective. To determine whether fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) of nonculprit lesion in patients with ST-segment elevation myocardial infarction (STEMI) is superior to angiography-guided PCI.

Design. Multicenter randomized control trial blinded to outcome, conducted in 41 sites in France.

Setting and participants. A total of 1163 patients with STEMI and multivessel coronary disease, who had undergone successful PCI to the culprit lesion were randomized to either FFR-guided PCI or angiography-guided PCI for nonculprit lesions. Randomization was stratified according to the trial site and timing of the procedure (immediate or staged).

Main outcome measures. The primary outcome was a composite of death from any cause, nonfatal myocardial infarction (MI) or unplanned hospitalization leading to urgent revascularization at 1 year.

Main results. At 1 year, the primary outcome occurred in 32 of 586 patients (5.5%) in the FFR-guided group and in 24 of 577 (4.2%) in the angiography-guided group (hazard ratio [HR], 1.32; 95% CI, 0.78-2.23; $P = .31$). The rate of death (1.5% vs 1.7%), nonfatal MI (3.1% vs 1.7%), and

unplanned hospitalization leading to urgent revascularization (3.1% vs 1.7%) were also similar between FFR-guided and angiography-guided groups.

Conclusion. Among patients with STEMI and multivessel disease who had undergone successful PCI of the culprit vessel, an FFR-guided strategy for complete revascularization was not superior to angiography-guided strategy for reducing death, MI, or urgent revascularization at 1 year.

Commentary

Patients presenting with STEMI often have multivessel disease.[1] Recently, multiple studies have reported the benefit of nonculprit vessel revascularization in patients presenting with hemodynamically stable STEMI compared to culprit-only strategy including the most recent COMPLETE trial which showed reduction in death and MI.[2-6] However, the previous studies have variable design in evaluating the nonculprit vessel, some utilized FFR guidance, while others used angiography guidance. Whether FFR-guided PCI of nonculprit vessel can improve outcome in patients presenting STEMI remains unknown.

In the FLOWER-MI study, Puymirat et al investigated the use of FFR compared to angiography-guided nonculprit vessel PCI. A total of 1163 patients presenting with STEMI and multivessel disease who had undergone successful PCI to the culprit vessel, were randomized to either FFR guidance or angiography guidance among 41 centers in France. The authors found that after 1 year, there was no difference in composite endpoint of death, nonfatal MI or unplanned hospitalization leading to urgent revascularization in the FFR-guided group compared to angiography-guided group (5.5% vs 4.2%, HR, 1.32; 95% CI, 0.678-2.23; $P = .31$). There was also no difference in individual components of primary outcomes or secondary outcomes such as rate of stent thrombosis, any revascularization, or hospitalization.

There are a few interesting points to consider in this study. Ever since the Fractional Flow Reserve vs Angiography for Multivessel Evaluation (FAME) trial reported the lower incidence of major adverse events in routine FFR measurement during PCI compared to angiography-guided PCI, physiological assessment has become the gold standard for treatment of stable ischemic heart disease.[7] However, the results of the current FLOWER-MI trial were not consistent with the FAME trial and there are few possible reasons to consider.

First, the use of FFR in the setting of STEMI is less validated compared to stable ischemic heart disease.[8] Microvascular dysfunction during the acute phase can affect the FFR reading and the lesion severity can be underestimated.[8] Second, the rate of composite endpoint was much lower in this study compared to FAME despite using the same composite endpoint of death, nonfatal MI, and unplanned hospitalization leading to urgent revascularization. At 1 year, the incidence of primary outcome was 13.5% in the FFR-guided group compared to 18.6% in the angiography-guided group in the FAME study compared to 5.5% and 4.2% in the FLOWER-MI study, despite having a sicker population presenting with STEMI. This is likely due to improvement in the PCI techniques such as radial approach, imaging guidance, and advancement in medical therapy such as use of more potent antiplatelet therapy. With lower incidence of primary outcome, larger number of patients are needed to detect the difference in the composite outcome. Finally, the operators' visual assessment may have been calibrated to the physiologic assessment as the operators are routinely using FFR assessment which may have diminished the benefit of FFR guidance seen in the early FAME study.

Another interesting finding from this study was that although the study protocol encouraged the operators to perform the nonculprit PCI in the same setting, only 4% had nonculprit PCI in the same setting and 96% of the patients underwent a staged PCI. The advantage of performing the nonculprit PCI on the same setting is to have 1 fewer procedure for the patient. On the other hand, the disadvantage of this approach includes prolongation of the index procedure, theoretically higher risk of complication during the acute phase and vasospasm leading to overestimation of the lesion severity. A recent analysis from the COMPLETE study did not show any difference when comparing staged PCI during the index hospitalization vs after discharge.[9] The optimal timing of the staged PCI needs to be investigated in future studies.

A limitation of this study is the lower than expected incidence of clinical events decreasing the statistical power of

the study. However, there was no signal that FFR-guided PCI is better compared to the angiography-guided group. In fact, the curve started to diverge at 6 months favoring the angiography-guided group. In addition, there was no core-lab analysis for completeness of revascularization.

Applications for Clinical Practice

In patients presenting with hemodynamically stable STEMI for undergoing nonculprit vessel PCI, both FFR-guided or angiography-guided strategies can be considered.

—Shubham Kanake, BS, Taishi Hirai, MD, and Chirag Bavishi, MD, University of Missouri, Columbia, MO

Financial disclosures: None.

doi:10.12788/jcom.0075

References

1. Park DW, Clare RM, Schulte PJ, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. *JAMA*. 2014;312(19):2019-27. doi:10.1001/jama.2014.15095
2. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369(12):1115-23. doi:10.1056/NEJMoa1305520
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(10):963-72. doi:10.1016/j.jacc.2014.12.038
4. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation 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(9994):665-71. doi:10.1016/s0140-6736(15)60648-1
5. Smits PC, Abdel-Wahab M, Neumann FJ, , et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. *N Engl J Med*. 2017;376(13):1234-44. doi:10.1056/NEJMoa1701067
6. Mehta SR, Wood DA, Storey RF, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. *N Engl J Med*. 2019;381(15):1411-21. doi:10.1056/NEJMoa1907775
7. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360(3):213-24. doi:10.1056/NEJMoa0807611
8. Thim T, van der Hoeven NW, Musto C, et al. Evaluation and Management of Nonculprit Lesions in STEMI. *JACC Cardiovasc Interv*. 2020;13(10):1145-54. doi:10.1016/j.jcin.2020.02.030
9. Wood DA, Cairns JA, Wang J, et al. Timing of Staged Nonculprit Artery Revascularization in Patients With ST-Segment Elevation Myocardial Infarction: COMPLETE Trial. *J Am Coll Cardiol*. 2019;74(22):2713-23. doi:10.1016/j.jacc.2019/09.051

Preoperative Code Status Discussion in Older Adults: Are We Doing Enough?

Hadler RA, Fatuzzo M, Sahota G, Neuman MD. Perioperative Management of Do-Not-Resuscitate Orders at a Large Academic Health System. JAMA Surg. 2021;e214135. doi:10.1001/jamasurg.2021.4135

Study Overview

Objective. The objective of this study was to evaluate orders and documentation describing perioperative management of code status in adults.

Design. A retrospective case series of all adult inpatients admitted to hospitals at 1 academic health system in the US.

Setting and participants. This retrospective case series was conducted at 5 hospitals within the University of Pennsylvania Health System. Cases included all adult inpatients admitted to hospitals between March 2017 and September 2018 who had a Do-Not-Resuscitate (DNR) order placed in their medical record during admission and subsequently underwent a surgical procedure that required anesthesia care.

Main outcome measures. Medical records of included cases were manually reviewed by the authors to verify whether a DNR order was in place at the time surgical intervention was discussed with a patient. Clinical notes and DNR orders of eligible cases were reviewed to identify documentation and outcome of goals of care discussions that were conducted within 48 hours prior to the surgical procedure. Collected data included patient demographics

(age, sex, race); case characteristics (American Society of Anesthesiologists [ASA] physical status score, anesthesia type [general vs others such as regional], emergency status [emergent vs elective surgery], procedures by service [surgical including hip fracture repair, gastrostomy or jejunostomy, or exploratory laparotomy vs medical including endoscopy, bronchoscopy, or transesophageal echocardiogram]); and hospital policy for perioperative management of DNR orders (written policy encouraging discussion vs written policy plus additional initiatives, including procedure-specific DNR form). The primary outcome was the presence of a preoperative order or note documenting code status discussion or change. Data were analyzed using χ^2 and Fisher exact tests and the threshold for statistical significance was $P < .05$.

Main results. Of the 27 665 inpatient procedures identified across 5 hospitals, 444 (1.6%) cases met the inclusion criteria. Patients from these cases aged 75 (SD 13) years (95% CI, 72-77 years); 247 (56%, 95% CI, 55%-57%) were women; and 300 (68%, 95% CI, 65%-71%) were White. A total of 426 patients (96%, 95% CI, 90%-100%) had an ASA physical status score of 3 or higher and 237 (53%, 95% CI, 51%-56%) received general anesthesia. The most common procedures performed were endoscopy (148 [33%]), hip fracture repair (43 [10%]), and gastrostomy or jejunostomy (28 [6%]). Reevaluation of code status was documented in 126 cases (28%, 95% CI, 25%-31%); code status orders were changed in 20 of 126 cases (16%, 95% CI, 7%-24%); and a note was filed without a corresponding order for 106 of 126 cases (84%, 95% CI, 75%-95%). In the majority of cases (109 of 126 [87%], 95% CI, 78%-95%) in which documented discussion occurred, DNR orders were suspended. Of 126 cases in which a discussion was documented, participants of these discussions included surgeons 10% of the time (13 cases, 95% CI, 8%-13%), members of the anesthesia team 51% of the time (64 cases, 95% CI, 49%-53%), and medicine or palliative care clinicians 39% of the time (49 cases, 95% CI, 37%-41%).

The rate of documented preoperative code status discussion was higher in patients with higher ASA physical status score (35% in patients with an ASA physical status score ≥ 4 [55 of 155] vs 25% in those with an ASA physical status score ≤ 3 [71 of 289]; $P = .02$). The rates of documented preoperative code status discussion were similar by anesthesia type (29% for general anesthesia [69 of 237 cases] vs 28% [57 of 207 cases] for other modalities; $P = .70$). The hospitals involved in this study all had a written policy encouraging rediscussion of code status before surgery. However, only 1 hospital reported added measures (eg, provision of a procedure-specific DNR form) to increase documentation of preoperative code status discussions. In this specific hospital, documentation of preoperative code status discussions was higher compared to other hospitals (67% [37 of 55 cases] vs 23% [89 of 389 cases]; $P < .01$).

Conclusion. In a retrospective case series conducted at 5 hospitals within 1 academic health system in the US, fewer than 1 in 5 patients with preexisting DNR orders had a documented discussion of code status prior to undergoing surgery. Additional strategies including the development of institutional protocols that facilitate perioperative management of advance directives, identification of local champions, and patient education, should be explored as means to improve preoperative code status reevaulation per guideline recommendations.

Commentary

It is not unusual that patients with a DNR order may require and undergo surgical interventions to treat reversible conditions, prevent progression of underlying disease, or mitigate distressing symptoms such as pain. For instance, intubation, mechanical ventilation, and administration of vasoactive drugs are resuscitative measures that may be needed to safely anesthetize and sedate a patient. As such, the American College of Surgeons[1] has provided a statement on advance directives by patients with an existing DNR order to guide management. Specifically, the statement indicates that the best approach for these patients is a policy of "required reconsideration" of the existing DNR order. Required reconsideration means that "the patient or designated surrogate and the physicians who will be responsible for the patient's care should, when possible, discuss the new intraoperative and perioperative risks associated with the surgical procedure, the patient's treatment

goals, and an approach for potentially life-threatening problems consistent with the patient's values and preferences." Moreover, the required reconsideration discussion needs to occur as early as it is practical once a decision is made to have surgery because the discussion "may result in the patient agreeing to suspend the DNR order during surgery and the perioperative period, retaining the original DNR order, or modifying the DNR order." Given that surgical patients with DNR orders have significant comorbidities, many sustain postoperative complications, and nearly 1 in 4 die within 30 days of surgery, preoperative advance care planning (ACP) and code status discussions are particularly essential to delivering high quality surgical care.[2]

In the current study, Hadler et al[3] conducted a retrospective analysis to evaluate orders and documentation describing perioperative management of code status in patients with existing DNR order at an academic health system in the US. The authors reported that fewer than 20% of patients with existing DNR orders had a documented discussion of code status prior to undergoing surgery. These findings add to the notion that compliance with such guidance on required reconsideration discussion is suboptimal in perioperative care in the US.[4,5] A recently published study focused on patients aged more than 60 years undergoing high-risk oncologic or vascular surgeries similarly showed that the frequency of ACP discussions or advance directive documentations among older patients was low.[6] This growing body of evidence is highly clinically relevant in that preoperative discussion on code status is highly relevant to the care of older adults, a population group that accounts for the majority of surgeries and is most vulnerable to poor surgical outcomes. Additionally, it highlights a disconnect between the shared recognition by surgeons and patients that ACP discussion is important in perioperative care and its low implementation rates.

Unsurprisingly, Hadler et al[3] reported that added measures such as the provision of a procedure-specific DNR form led to an increase in the documentation of preoperative code status discussions in 1 of the hospitals studied. The authors suggested that strategies such as the development of institutional protocols aimed to facilitate perioperative advance directive discussions, identify local champions, and educate patients may be ways to improve preoperative code status reevaulation. The idea that institutional value and culture are key factors impacting surgeon behavior and may influence the practice of ACP discussion is not new. Thus, creative and adaptable strategies, resources, and trainings that are required by medical institutions and hospitals to support preoperative ACP discussions with patients undergoing surgeries need to be identified, validated, and implemented to optimize perioperative care in vulnerable patients.

Applications for Clinical Practice

The findings from the current study indicate that less than 20% of patients with preexisting DNR orders have a documented discussion of code status prior to undergoing surgery. Physicians and health care institutions need to identify barriers to, and implement strategies that, facilitate and optimize preoperative ACP discussions in order to provide patient-centered care in vulnerable surgical patients.

—Fred Ko, MD, MS, Icahn School of Medicine at Mount Sinai, New York, NY

Financial disclosures: None.

doi:10.12788/jcom.0076

References

1. American College of Surgeons Board of Regents. Statement on Advance Directives by Patients: "Do Not Resuscitate" in the Operating Room. American College of Surgeons. January 3, 2014. Accessed November 6, 2021. https://www.facs.org/about-acs/statements/19-advance-directives
2. Kazaure H, Roman S, Sosa JA. High mortality in surgical patients with do-not-resuscitate orders: analysis of 8256 patients. *Arch Surg*. 2011;146(8):922-928. doi:10.1001/archsurg.2011.69
3. Hadler RA, Fatuzzo M, Sahota G, Neuman MD. Perioperative Management of Do-Not-Resuscitate Orders at a Large Academic Health System. *JAMA Surg*. 2021;e214135. doi:10.1001/jamasurg.2021.4135
4. Coopmans VC, Gries CA. CRNA awareness and experience with perioperative DNR orders. *AANA J*. 2000;68(3):247-256.
5. Urman RD, Lilley EJ, Changala M, Lindvall C, Hepner DL, Bader AM. A Pilot Study to Evaluate Compliance with Guidelines for Preprocedural Reconsideration of Code Status Limitations. *J Palliat Med*. 2018;21(8):1152-1156. doi:10.1089/jpm.2017.0601
6. Kalbfell E, Kata A, Buffington AS, et al. Frequency of Preoperative Advance Care Planning for Older Adults Undergoing High-risk Surgery: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Surg*. 2021;156(7):e211521. doi:10.1001/jamasurg.2021.1521

Evaluation of Intermittent Energy Restriction and Continuous Energy Restriction on Weight Loss and Blood Pressure Control in Overweight and Obese Patients With Hypertension

He CJ, Fei YP, Zhu CY, et al. Effects of Intermittent Compared With Continuous Energy Restriction on Blood Pressure Control in Overweight and Obese Patients With Hypertension. Front Cardiovasc Med. 2021;8:750714. doi:10.3389/fcvm.2021.750714

Study Overview

Objective. To compare the effects of intermittent energy restriction (IER) with those of continuous energy restriction (CER) on blood pressure control and weight loss in overweight and obese patients with hypertension during a 6-month period.

Design. Randomized controlled trial.

Settings and participants. The trial was conducted at the Affiliated Hospital of Jiaxing University from June 1, 2020, to April 30, 2021. Chinese adults were recruited using advertisements and flyers posted in the hospital and local communities. Prior to participation in study activities, all participants gave informed consent prior to recruitment and were provided compensation in the form of a $38 voucher at 3 and 6 months for their time for participating in the study.

The main inclusion criteria were patients between the ages of 18 and 70 years, hypertension, and body mass index (BMI) ranging from 24 to 40 kg/m^2. The exclusion criteria were systolic blood pressure (SBP) ≥ 180 mmHg or diastolic blood pressure (DBP) ≥ 120 mmHg, type 1 or 2 diabetes with a history of severe hypoglycemic episodes, pregnancy or breastfeeding, usage of glucagon-like peptide 1 receptor agonists, weight loss > 5 kg within the past 3 months or previous weight loss surgery, and inability to adhere to the dietary protocol.

Of the 294 participants screened for eligibility, 205 were randomized in a 1:1 ratio to the IER group (n = 102) or the CER group (n = 103), stratified by sex and BMI (as overweight or obese). All participants were required to have a stable medication regimen and weight in the 3 months prior to enrollment and not to use weight-loss drugs or vitamin supplements for the duration of the study. Researchers and participants were not blinded to the study group assignment.

Interventions. Participants randomly assigned to the IER group followed a 5:2 eating pattern: a very-low-energy diet of 500-600 kcal for 2 days of the week along with their usual diet for the other 5 days. The 2 days of calorie restriction could be consecutive or nonconsecutive, with a minimum of 0.8 g supplemental protein per kg of body weight per day, in accordance with the 2016 Dietary Guidelines for Chinese Residents. The CER group was advised to consume 1000 kcal/day for women and 1200 kcal/day for men on a 7-day energy restriction. That is, they were prescribed a daily 25% restriction based on the general principles of a Mediterranean-type diet (30% fat, 45-50% carbohydrate, and 20-25% protein).

Both groups received dietary education from a qualified dietitian and were recommended to maintain their current daily activity levels throughout the trial. Written dietary information brochures with portion advice and sample meal plans were provided to improve compliance in each group. All participants received a digital cooking scale to weigh foods to ensure accuracy of intake and were required to keep a food diary while following the recommended recipe on 2 days/week during calorie restriction to help with adherence. No food was provided. All participants were followed up by regular outpatient visits to both cardiologists and dietitians once a month. Diet checklists, activity schedules, and weight were reviewed to assess compliance with dietary advice at each visit.

Of note, participants were encouraged to measure and record their BP twice daily, and if 2 consecutive BP readings were < 110/70 mmHg and/or accompanied by hypotensive episodes with symptoms (dizziness, nausea, headache, and fatigue), they were asked to contact the investigators directly. Antihypertensive medication changes were then made in consultation with cardiologists. In addition, a medication management protocol (ie, doses of antidiabetic medications, including insulin and sulfonylurea) was designed to avoid hypoglycemia. Medication could be reduced in the CER group based on the basal dose at the endocrinologist's discretion. In the IER group, insulin and sulfonylureas were discontinued on calorie restriction days only, and long-acting insulin was discontinued the night before the IER day. Insulin was not to be resumed until a full day's caloric intake was achieved.

Measures and analysis. The primary outcomes of this study were changes in BP and weight (measured using an automatic digital sphygmomanometer and an electronic scale), and the secondary outcomes were changes in body composition (assessed by dual-energy x-ray absorptiometry scanning), as well as glycosylated hemoglobin A_{1c} (HbA_{1c}) levels and blood lipids after 6 months. All outcome measures were recorded at baseline and at each monthly visit. Incidence rates of hypoglycemia were based on blood glucose (defined as blood glucose < 70 mg/dL) and/or symptomatic hypoglycemia (symptoms of sweating, paleness, dizziness, and confusion). Two cardiologists who were blind to the patients' diet condition measured and recorded all pertinent clinical parameters and adjudicated serious adverse events.

Data were compared using independent-samples *t*-tests or the Mann–Whitney *U* test for continuous variables, and Pearson's χ^2 test or Fisher's exact test for categorial variables as appropriate. Repeated-measures ANOVA via a linear mixed model was employed to test the effects of diet, time, and their interaction. In subgroup analyses, differential effects of the intervention on the primary outcomes were evaluated with respect to patients' level of education, domicile, and sex based on the statistical significance of the interaction term for the subgroup of interest in the multivariate model. Analyses were performed based on completers and on an intention-to-treat principle.

Main results. Among the 205 randomized participants, 118 were women and 87 were men; mean (SD) age was 50.5 (8.8) years; mean (SD) BMI was 28.7 (2.6); mean (SD) SBP was 143 (10) mmHg; and mean (SD) DBP was 91 (9) mmHg. At the end of the 6-month intervention, 173 (84.4%) completed the study (IER group: n = 88; CER group: n = 85). Both groups had similar dropout rates at 6 months (IER group: 14 participants [13.7%]; CER group: 18 participants [17.5%]; $P = .83$) and were well matched for baseline characteristics except for triglyceride levels.

In the completers analysis, both groups experienced significant reductions in weight (mean [SEM]), but there was no difference between treatment groups (–7.2 [0.6] kg in the IER group vs –7.1 [0.6] kg in the CER group; diet by time $P = .72$). Similarly, the change in SBP and DBP achieved was statistically significant over time, but there was also no difference between the dietary interventions (–8 [0.7] mmHg in the IER group vs –8 [0.6] mmHg in the CER group, diet by time $P = .68$; –6 [0.6] mmHg in the IER group vs –6 [0.5] mmHg in the CER group, diet by time $P = .53$]. Subgroup analyses of the association of the intervention with weight, SBP and DBP by sex, education, and domicile showed no significant between-group differences.

All measures of body composition decreased significantly at 6 months with both groups experiencing comparable reductions in total fat mass (–5.5 [0.6] kg in the IER group vs –4.8 [0.5] kg in the CER group, diet by time $P = .08$) and android fat mass (–1.1 [0.2] kg in the IER group vs –0.8 [0.2] kg in the CER group, diet by time $P = .16$). Of note, participants in the CER group lost significantly more total fat-free mass than did participants in the IER group (mean [SEM], –2.3 [0.2] kg vs –1.7 [0.2] kg; $P = .03$], and there was a trend toward a greater change in total fat mass in the IER group ($P = .08$). The secondary outcome of mean (SEM) HbA_{1c} (–0.2% [0.1%]) and blood lipid levels (triglyceride level, –1.0 [0.3] mmol/L; total cholesterol level, –0.9 [0.2] mmol/L; low-density lipoprotein cholesterol level, –0.9 [0.2 mmol/L; high-density lipoprotein cholesterol level, 0.7 [0.3] mmol/L] improved with weight loss ($P < .05$), with no differences between groups (diet by time $P > .05$).

The intention-to-treat analysis demonstrated that IER and CER are equally effective for weight loss and blood pressure control: both groups experienced significant reductions in weight, SBP, and DBP, but with no difference between treatment groups – mean (SEM) weight change with IER was –7.0 (0.6) kg vs –6.8 (0.6) kg with CER; the mean (SEM) SBP with IER was –7 (0.7) mmHg vs –7 (0.6) mmHg with CER; and the mean (SEM) DBP with IER was –6 (0.5) mmHg vs –5 (0.5) mmHg with CER, (diet by time $P = .62$, .39, and .41, respectively). There were favorable improvements in body composition, HbA_{1c}, and blood lipid levels, with no differences between groups.

Conclusion. A 2-day severe energy restriction with 5 days of habitual eating compared to 7 days of CER provides an acceptable alternative for BP control and weight loss in overweight and obese individuals with hypertension after 6 months. IER may offer a useful alternative strategy for this population, who find continuous weight-loss diets too difficult to maintain.

Commentary

Globally, obesity represents a major health challenge as it substantially increases the risk of diseases such as hypertension, type 2 diabetes, and coronary heart disease.[1] Lifestyle modifications, including weight loss and increased physical activity, are recommended in major guidelines as a first-step intervention in the treatment of hypertensive patients.[2] However, lifestyle and behavioral interventions aimed at reducing calorie intake through low-calorie dieting is challenging as it is dependent on individual motivation and adherence to a strict, continuous protocol. Further, CER strategies have limited effectiveness because complex and persistent hormonal, metabolic, and neurochemical adaptations defend against weight loss and promote weight regain.[3-4] IER has drawn attention in the popular media as an alternative to CER due to its feasibility and even potential for higher rates of compliance.[5]

This study adds to the literature as it is the first randomized controlled trial (to the knowledge of the authors at the time of publication) to explore 2 forms of energy restriction – CER and IER – and their impact on weight loss, BP, body composition, HbA_{1c}, and blood lipid levels in overweight and obese patients with high blood pressure. Results from this study showed that IER is as effective as, but not superior to, CER (in terms of the outcomes measures assessed). Specifically, findings highlighted that the 5:2 diet is an effective strategy and noninferior to that of daily calorie restriction for BP and weight control. In addition, both weight loss and BP reduction were greater in a subgroup of obese compared with overweight participants, which indicates that obese populations may benefit more from energy restriction. As the authors highlight, this study both aligns with and expands on current related literature.

This study has both strengths and limitations, especially with regard to the design and data analysis strategy. A key strength is the randomized controlled trial design which enables increased internal validity and decreases several sources of bias, including selection bias and confounding. In addition, it was also designed as a pragmatic trial, with the protocol reflecting efforts to replicate the real-world environment by not supplying meal replacements or food. Notably, only 9 patients could not comply with the protocol, indicating that acceptability of the diet protocol was high. However, as this was only a 6-month long study, further studies are needed to determine whether a 5:2 diet is sustainable (and effective) in the long-term compared with CER, which the authors highlight. The study was also adequately powered to detect clinically meaningful differences in weight loss and SBP, and appropriate analyses were performed on both the basis of completers and on an intention-to-treat principle. However, further studies are needed that are adequately powered to also detect clinically meaningful differences in the other measures, ie, body composition, HbA_{1c}, and blood lipid levels. Importantly, generalizability of findings from this study is limited as the study population comprises only Chinese adults, predominately middle-aged, overweight, and had mildly to moderately elevated SBP and DBP, and excluded diabetic patients. Thus, findings are not necessarily applicable to individuals with highly elevated blood pressure or poorly controlled diabetes.

Applications for Clinical Practice

Results of this study demonstrated that IER is an effective alternative diet strategy for weight loss and blood pressure control in overweight and obese patients with hypertension and is comparable to CER. This is relevant

CONTINUED ON PAGE 279

Outcomes Research in Review

CONTINUED FROM PAGE 258

for clinical practice as IER may be easier to maintain in this population compared to continuous weight-loss diets. Importantly, both types of calorie restriction require clinical oversight as medication changes and periodic monitoring of hypotensive and hypoglycemic episodes are needed. Clinicians should consider what is feasible and sustainable for their patients when recommending intermittent energy restriction.

—Katrina F. Mateo, PhD, MPH, CUNY School of Public Health, New York, NY

Financial disclosures: None.

doi:10.12788/jcom.0077

References

1. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. 2019;15(5):288-298. doi:10.1038/s41574-019-0176-8
2. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global hypertension practice guidelines. *J Hypertens*. 2020;38(6):982-1004. doi:10.1097/HJH.0000000000002453
3. Müller MJ, Enderle J, Bosy-Westphal A. Changes in Energy Expenditure with Weight Gain and Weight Loss in Humans. *Curr Obes Rep*. 2016;5(4):413-423. doi:10.1007/s13679-016-0237-4
4. Sainsbury A, Wood RE, Seimon RV, et al. Rationale for novel intermittent dieting strategies to attenuate adaptive responses to energy restriction. *Obes Rev*. 2018;19 Suppl 1:47–60. doi:10.1111/obr.12787
5. Davis CS, Clarke RE, Coulter SN, et al. Intermittent energy restriction and weight loss: a systematic review. *Eur J Clin Nutr*. 2016;70(3):292-299. doi:10.1038/ejcn.2015.195