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Mitigating the effects of COVID-19 pandemic on controlling vascular risk factors among participants in a carotid stenosis trial

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Introduction: The COVID-19 pandemic has presented challenges to managing vascular risk factors with in-person follow-up of patients with asymptomatic carotid stenosis enrolled in the CREST2 trial. CREST2 is comparing intensive medical management alone versus intensive medical management plus revascularization with endarterectomy or stenting. We performed a study to evaluate the feasibility of a home-based program for testing blood pressure (BP) and low-density lipoprotein (LDL) in CREST2. *Methods:* This study involved 45 patients at 10 sites in the CREST2 trial. The initial patients were identified by the Medical Management Core (MMC) as high-risk patients defined by stage 2 hypertension, LDL > 90 mg/dl, or both. If a patient at the site declined participation, another was substituted. All patients who agreed to participate were sent a BP monitoring device and a commercially available at-home lipid test kit that uses a self-performed finger-stick blood sample that was resulted to the patient. Training on the use of the equipment and obtaining the risk factor results was done by the study coordinator by telephone. *Results:* Ten of the 130 currently active CREST2 sites participated, 8 in the LDL portion and 5 in the BP portion (3 sites did both). Twenty-six BP devices and 23 lipid tests were sent to patients. Of the 26 patients who obtained BP readings with the devices, 9 were out of the study target and adjustments in BP medications were made in 3. Of the 23 patients sent LDL tests, 13 were able to perform the test showing 7 were out of target, leading to adjustments in lipid medications in 4. *Conclusion:* This study established the feasibility of at-home monitoring of BP and LDL in a clinical trial and identified implementation challenges prior to widespread use in the trial. (ClinicalTrials.gov number NCT02089217)

Key Words: Asymptomatic carotid stenosis—Risk factors—COVID-19—Coronavirus

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Introduction

The COVID-19 public health emergency has resulted in numerous challenges for ongoing clinical trials, including the conduct of in-person study visits to obtain biomarker data. The CREST2 trial (ClinicalTrials.gov number NCT02089217), which compares intensive medical management (IMM) to IMM plus revascularization in patients with asymptomatic high-grade atherosclerotic stenosis of the cervical internal carotid artery,[1] has also faced these challenges.[2] The IMM protocol currently requires that all patients' primary risk factors, systolic blood pressure (BP) and low-density lipoprotein (LDL), are managed by the study Medical Management Physician and coordinator. At the sites, BP is measured using a well-validated study-supplied device (Omron HEM-705) and LDL is measured at a CLIA-certified lab. As many of the CREST2 patients have vascular risk factors that put them at increased risk for severe COVID-19 infection, the ability of patients to attend study follow-up visits or obtain labs without risk of exposure is limited. Therefore, many CREST2 patients were transitioned to Phone Follow-up Visits, which allow for surveillance of study endpoints, but not rigorous monitoring of BP and LDL.[2]

Due to the ongoing impact of COVID-19 on clinical research, the FDA has issued a formal guidance document that recommends clinical trials evaluate the feasibility of alternative approaches to obtain laboratory and other biomarker data.[3] With the persistent pervasiveness of COVID-19 and the need to minimize face-to-face medical visits, we sought to assess the feasibility of a program of home-based testing of BP and LDL in the CREST2 trial. Therefore, we performed a pilot feasibility study on a sample of CREST2 subjects with the goal of implementing more comprehensive home-based testing if successful. Herein we describe our findings related to the feasibility and challenges of home-based testing of BP and LDL.

Methods

IRB and FDA approval to modify the procedure for risk factor collection in select patients were obtained prior to proceeding with study activities. All patients supplied written informed consent to participate in CREST2 and agreed to the modified procedure for risk factor collection by telephone. In order to assess the feasibility of home-based testing of BP and LDL, the CREST2 Medical Management Core (MMC) identified a sample of potentially high-risk CREST2 patients currently in follow-up who would potentially benefit from home-based risk factor testing in this pilot. Based on current follow-up risk factor data collected in the study, patients with stage 2 hypertension or LDL > 90 mg/dl were identified and deemed high-risk. High-risk patients were selected because they were felt to benefit most from additional risk factor management (i.e. medication titration) during the pandemic. Sites with the highest numbers of such patients were selected to participate in the study.

The CREST2 MMC contacted the potential sites, who then contacted the selected patients to confirm their participation by telephone. If a selected patient declined, the site was permitted to substitute another high-risk patient at that site. If no high-risk patients were available, the site selected a non-high-risk patient. This was because procurement issues required that all of the patients selected for the study had to come from the chosen sites. Procurement of the home-based testing supplies through an online vendor with direct delivery to the patient was critical to decrease exposure for the coordinator and the patient. The home-based testing equipment was selected by the MMC and paid for by the study with the MMC providing coordinators with purchasing codes to order the materials for direct delivery to the patients' homes. The BP device was a highly reliable device similar to the current study device (Omron model 3 or 5 series, approximate unit cost $60). The at-home lipid test kit was a commercially available CLIA-certified home testing kit that uses a patient-performed finger-stick blood sample[4] and includes return shipping with direct to patient resulting (Everlywell Cholesterol and Lipids test, approximate unit cost $50). The MMC also provided the sites with training materials for instructing patients on the proper use of the home-based equipment. Sites and patients participating in the COVID study were compensated at the rate of a clinic-based return visit.

The sites were responsible for ensuring equipment delivery and patient training, contacting patients to obtain the risk factor data, responding to the values (by adjusting medications, counseling, etc.), and entering the risk factor data into the clinical trial database. The case report forms were modified study-wide to allow the designation of a study-supplied BP device as an option for the BP measurement device used at the visit.

Results

Timeline and feasibility

On March 11, 2020 the World Health Organization officially characterized COVID-19 as a pandemic. FDA approval for this risk factor mitigation plan was obtained on March 30, 2020, and IRB approval was obtained on March 31, 2020. Ten of the 130 currently active CREST2 sites participated and collected data, 8 in the LDL portion and 5 in the BP portion (3 sites did both). One other site initially selected was unable to participate due to regulatory issues. Sites with the highest numbers of patients that met the criteria for high-risk were initially selected. These sites were in the following states: North Carolina, Minnesota, Kentucky, Oregon, Louisiana, South Dakota, Alabama, and Maryland. The study purchased 26 BP devices and 26 LDL tests. After ordering,

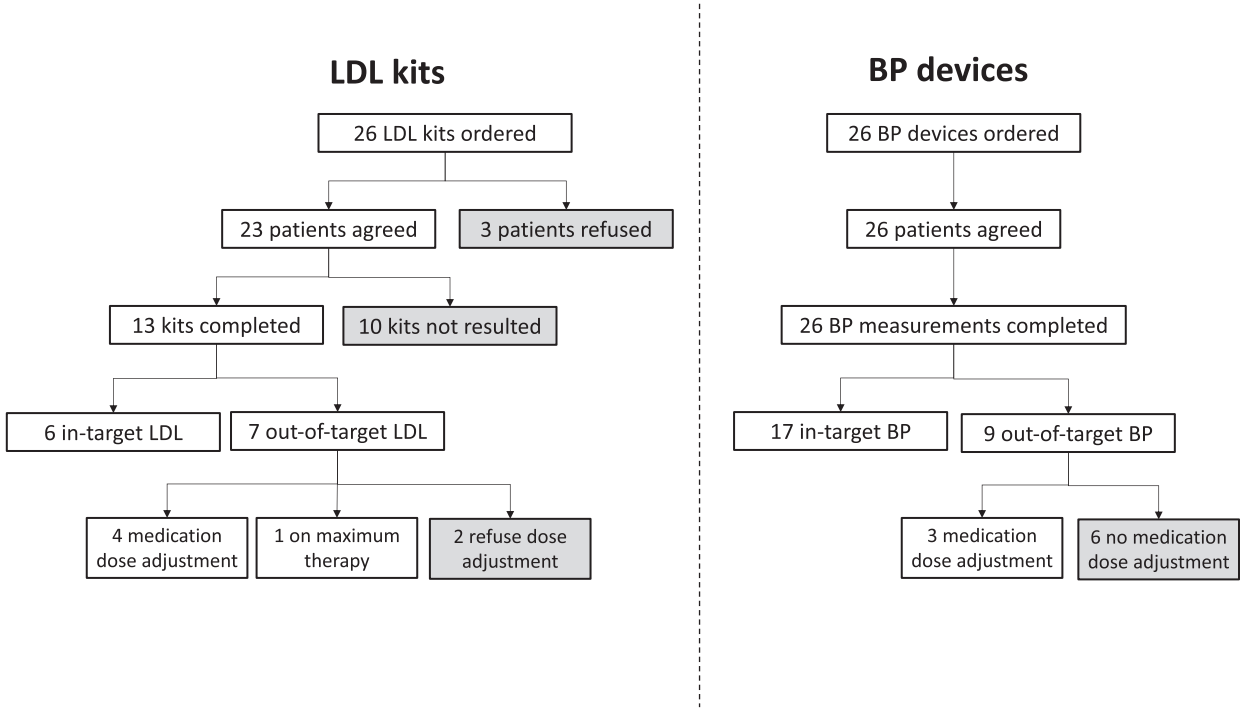

Fig. 1. *CREST2 COVID-19 risk factor testing and response to results.*

delivery, and patient training, the first BP result was obtained and entered into the database on April 17, 2020 and the first LDL result on April 21, 2020. The number of risk factor values obtained and the response of the sites to the values is shown in Fig. 1. The overall equipment cost of the feasibility study was $2865, including $1575 for BP devices and $1290 for LDL kits.

Implementation challenges and solutions

The main implementation challenge for home BP measurement identified was the short supply of automated BP devices available for purchase on-line, possibly due to supply chain issues or increased demand by the general public. Since many physician offices were performing phone or video visits, it was difficult to find a single vendor that had sufficient stock of the same BP device early in the pandemic. Several Omron models of similar quality were ultimately used. As the pandemic continues, online vendors have replenished stock and, moving forward, the supply issue is less likely to be a problem. Fortunately, because the BP devices can be reused throughout the study, repeated measurements can be obtained in those patients to make further adjustments to BP management.

The challenges for home LDL measurement were primarily related to the patients' understanding of the testing and resulting process. Most home laboratory testing kits require online kit registration with a user identification number and password and are resulted directly to patients. Patient errors in the process occurred at several steps despite training, including failure to register the kit before mailing the sample, not recording the login information resulting in inability to retrieve the result, and inability to collect an adequate finger-stick sample. In addition, a few states (e.g. New York and New Jersey) prohibit the use of home laboratory testing kits and this feasibility study was not able to be performed in those states, which included those most severely impacted by the early phase of the pandemic in the United States. However, for those who were able to complete the home LDL test, almost half were found to be in target and 4 additional patients had adjustments to their lipid-lowering medication as a result.

Additional barriers to implementation resulted from the economic effects of the pandemic on many of the CREST2 site hospitals.[2] Some study coordinators were furloughed or asked to work reduced hours, which impacted the time they could spend on this feasibility study. Coordinators working from home also had limited access to hospital phones and study records stored onsite.

Discussion

In the early phase of the COVID-19 pandemic when many states had stay-at-home orders, the CREST2 clinical trial was able to obtain risk factor values on a subset of high-risk patients at reasonable cost. The risk factor values obtained in this feasibility study resulted in changes to medical treatment of primary risk factor targets, avoiding face-to-face contact with study personnel. This feasibility

study allowed identification of implementation challenges of home-based testing that were critical to address prior to moving forward with a larger-scale implementation. Currently, the approach to risk factor mitigation in CREST2 provides all subjects undergoing follow-up video visits a study-supplied BP cuff.

Since the COVID-19 pandemic has persisted, many clinical trials that previously performed study activities in-person are assessing the feasibility of transitioning to remote assessments,[5] including video visits and remote biomarker collection. While remote monitoring of risk factors, such as BP, has been evaluated in dedicated studies designed to provide all of the necessary infrastructure and technology (e.g. wireless access, specialized apps, or devices), adding remote measures to an existing protocol that sites and patients have not previously agreed to is a new challenge. Within the field of remote clinical trial implementation, collection of biomarker data has remained a challenge, particularly when biomarkers are important outcome measures that require validation.[6] In such cases, video verification of biomarker collection is utilized to ensure proper technique and sample identification,[6] as is currently being done in CREST2. Patient difficulties with technology and video communication (e.g. inadequate knowledge or access) have been somewhat mitigated by the necessity to use these tools for clinical care and social interaction in the COVID-19 pandemic, making their use in clinical trials slightly more feasible. However, challenges related to social distancing requirements and access to wireless signal remain for many patients.

As clinical trials develop innovative solutions to the challenges of acquiring study outcome data during COVID-19, sharing these approaches (both successful and unsuccessful) and their limitations is important to improve the overall efficiency and quality of trials moving forward in this uncertain era. For example, based on our experience future studies may be advised to be proactive in purchasing home-based equipment in advance or early at the sign of a similar future public health threat, if funding permits. In the future, clinical trial strategies and resources developed during this difficult time could be used to help with recruitment and follow-up of patients whose primary barrier to trial participation is transportation for follow-up visits, such as the elderly, rural and low socioeconomic status patients.

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