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Effect of Modernized Collaborative Care for Depression on Depressive Symptoms and Cardiovascular Disease Risk Biomarkers: eIMPACT Randomized Controlled Trial

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Abstract

Although depression is a risk and prognostic factor for cardiovascular disease (CVD), clinical trials treating depression in patients with CVD have not demonstrated cardiovascular benefits. We proposed a novel explanation for the null results for CVD-related outcomes: the late timing of depression treatment in the natural history of CVD. Our objective was to determine whether successful depression treatment before, versus after, clinical CVD onset reduces CVD risk in depression. We conducted a single-center, parallel-group, assessor-blinded randomized controlled trial. Primary care patients with depression and elevated CVD risk from a safety net healthcare system ($N = 216$, $M_{\text{age}} = 59$ years, 78% female, 50% Black, 46% with income $< \$10,000/\text{year}$) were randomized to 12 months of the eIMPACT intervention (modernized collaborative care involving internet cognitive-behavioral therapy [CBT], telephonic CBT, and/or select antidepressants) or usual primary care for depression (primary care providers supported by embedded behavioral health clinicians and psychiatrists). Outcomes were depressive symptoms and CVD risk biomarkers at 12 months. Intervention participants, versus usual care participants, exhibited moderate-to-large (Hedges' $g = -0.65$, $p < 0.01$) improvements in depressive symptoms. Clinical response data yielded similar results – 43% of intervention participants, versus 17% of usual care participants, had a 50% reduction in depressive symptoms ($OR = 3.73$, 95% $CI: 1.93-7.21$, $p < 0.01$). However, no treatment group differences were observed for the CVD risk biomarkers – i.e., brachial flow-mediated dilation, high-frequency heart rate variability, interleukin-6, high-sensitivity C-reactive protein, β -thromboglobulin, and platelet factor 4 (Hedges' $gs = -0.23$ to 0.02 , $ps = 0.09$). Our modernized collaborative care intervention – which harnessed technology to maximize access and minimize resources – produced clinically meaningful improvements in depressive symptoms. However, successful depression treatment did not lower CVD risk biomarkers. Our findings indicate that depression treatment alone may not be sufficient to reduce the excess CVD risk of people with depression and that alternative approaches are needed. In addition, our effective intervention highlights the utility of eHealth interventions and centralized, remote treatment delivery in safety net clinical settings and could inform contemporary integrated care approaches.

Keywords

depression; cardiovascular disease; endothelial dysfunction; autonomic dysfunction; systemic inflammation; platelet activation; collaborative care; internet interventions; clinical trial

1. Introduction

Over 30 years of rigorous research indicates that depression is an independent risk and prognostic factor for atherosclerotic cardiovascular disease (CVD).¹ Despite this strong evidence base, few clinical trials have evaluated whether depression interventions improve CVD-related outcomes. In those trials, the expected cardiovascular benefits were generally

not observed, even though improvements in other important endpoints were detected.¹ While other explanations for the null results for CVD-related outcomes have been suggested,² we proposed that the depression interventions may have been delivered too late in the natural history of CVD,³ as nearly all prior trials involved patients with clinical CVD. Further, we hypothesized that successful depression treatment before clinical CVD onset could yield cardiovascular benefits³ because: (1) evidence suggests that depression begins to exert a cardiotoxic influence early in CVD pathogenesis;^{4, 5} (2) depression interventions may have greater antidepressive efficacy before clinical CVD onset;^{3, 6} (3) there is a growing consensus that earlier treatment of other risk factors produces greater CVD risk reductions;⁷ and (4) conventional prognostic factors may override depression effects in later CVD stages.^{8, 9}

This hypothesis was supported by our preliminary study – an 8-year follow-up³ of the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) trial.¹⁰ Among those *without* clinical CVD, primary care patients with depression randomized to collaborative care had a 48% lower risk of incident CVD events than patients randomized to usual care for depression. Among those *with* clinical CVD, there was no cardioprotective effect of the intervention. However, because our analysis was post hoc, it remains unknown if the depression-CVD risk relationship is causal and if depression treatment reduces CVD risk.¹¹

Accordingly, we conducted the eIMPACT randomized controlled trial (RCT), which compared modernized collaborative care to usual care for depression in primary care patients with depression and elevated CVD risk from a safety net healthcare system. We modernized the IMPACT trial's effective intervention¹⁰ by incorporating an established internet cognitive-behavioral therapy (CBT),¹² delivering an established manualized CBT¹³ by phone, and optimizing the antidepressant algorithm for CVD risk reduction. The primary outcome was endothelial dysfunction assessed by brachial flow-mediated dilation (FMD),^{14, 15} as FMD is impaired in depression,¹⁶ FMD is considered an index of CVD risk,¹⁷ and intervention-related FMD improvements are associated with reduced CVD incidence.^{18–20} The secondary outcomes were depressive symptoms and other CVD risk biomarkers – i.e., measures of leading candidate mechanisms (autonomic dysfunction, systemic inflammation, and platelet activation) underlying the depression-incident CVD association.^{1, 21}

2. Methods

2.1. Trial Design

The eIMPACT trial was a 24-month, phase II, single-center RCT conducted at eight primary care clinics of a safety net healthcare system (Eskenazi Health) in Indianapolis, IN from 2015–2020. Participants attended the pre-treatment visit at a clinical research center (CRC) of the Indiana Clinical and Translational Science Institute (CTSI). Staff instructed participants to fast and avoid tobacco and exercise for 8 hours before the visit. Participants provided written informed consent; completed self-report scales; had their height, weight, and blood pressure (BP) measured; and underwent a blood draw and heart rate variability (HRV) and FMD assessments. After baseline assessments, participants were

randomized 1:1, stratified by age group (50–59 years, ≥60 years) and sex (male, female), to the eIMPACT intervention or usual primary care for depression. For each stratum, a randomization sequence was computer generated using random block sizes of 2 and 4,²² and sequentially numbered opaque envelopes containing treatment assignment were prepared. Staff assigned participants to treatment groups by opening the next envelope from the appropriate stratum. Participants completed three additional assessment contacts – 6-month mid-treatment call, 12-month post-treatment visit, and 24-month follow-up call. For the mid-treatment and follow-up calls, participants were administered self-report scales. For the post-treatment visit, participants returned to the CRC to undergo the same assessments as the pre-treatment visit. Outcomes assessors were blinded to treatment assignment. Due to the nature of our intervention, participants, the intervention team, and staff running the assessment contacts (but not assessing outcomes) were not blinded. This trial was approved by Indiana University Institutional Review Board and the Eskenazi Health Research Committee. The full study protocol and statistical analysis plan are available at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02458690) (NCT02458690), and the data and statistical code that support the main findings of this study are available at NHLBI BioData Catalyst (insert dbGaP link when available).

2.2. Participants

All 216 participants were recruited using a 3-stage process, which consisted of electronic health record (EHR) searches to generate lists of potentially eligible patients, an opportunity for primary care providers (PCPs) to opt all their patients out of this study (a very rare occurrence), and phone or in-clinic screening interviews conducted by staff of Indiana University's primary care practice-based research network. Participants were screened and enrolled from August 13, 2015 to July 31, 2018. Data collection ended on July 31, 2020.

Inclusion criteria were: age ≥50 years, current depression, and elevated CVD risk. Current depression was defined as a Patient Health Questionnaire-9 (PHQ-9) score ≥10²³ and a PHQ-9 major or other depressive disorder diagnosis (which require depressed mood and/or anhedonia).²⁴ The PHQ-9 cut point of ≥10 has 88% sensitivity and 88% specificity for major depressive disorder diagnosed by clinical interview.²³ To help equate risk across participants, elevated CVD risk was defined as ≥1 (if ≥60 years) or ≥2 (if 50–59 years) of the following risk factors in the EHR in the past 5 years (diagnostic code, lab value, or medication indicating presence): hypertension, hypercholesterolemia, diabetes, or current smoking.

Exclusion criteria were: clinical CVD (diagnostic/procedural code in the EHR or self-report of myocardial infarction, coronary artery disease, cerebrovascular disease, heart failure, percutaneous coronary intervention, or coronary artery bypass graft); HIV/AIDS, chronic kidney disease, or active cancer/current cancer treatment (self-report); current pregnancy (self-report or positive test); continuous treatment for a systemic inflammatory condition in the past 3 months (nonsteroidal anti-inflammatory drugs were allowed; self-report); current use of anticoagulant medications (aspirin, lipid-lowering agents, and antihypertensive agents were allowed; self-report); severe cognitive impairment (≥3 errors on a 6-item screener²⁵); bipolar or psychotic disorder (diagnostic code in the EHR or self-report); acute risk of

suicide (determined by clinical staff); and ongoing depression treatment with a psychiatrist outside of Eskenazi Health (self-report). Patients unable to understand English were also not eligible, as our intervention was available in English only.

2.3. Interventions

2.3.1. eIMPACT Intervention—The eIMPACT intervention is a collaborative care intervention in which a multidisciplinary team delivers established depression treatments consistent with patient preference. It uses a stepped, flexible, treat-to-target approach that modernized the IMPACT intervention¹⁰ by: incorporating an internet CBT (Beating the Blues US [BtB]; Workpartners UPMC), delivering another CBT (Problem Solving Treatment in Primary Care [PST-PC]) and other psychological components (psychoeducation, behavioral activation, and antidepressant adherence support) by phone or FaceTime, and optimizing the antidepressant algorithm for CVD risk reduction. The remaining IMPACT intervention components were not altered. The intervention team consisted of a Master's-level behavioral health clinician (K.L.M.) as the depression clinical specialist (DCS), a supervising psychiatrist (J.I.N.), a primary care liaison (C.M.C.), and the participants' usual PCPs.

BtB is an efficacious internet CBT for depression and/or anxiety that is appropriate for adults with little computer experience and 5th grade reading level.^{26–28} BtB uses an interactive, multimedia format to deliver 8 weekly sessions, the structure and content of which mirror face-to-face CBT. Covered topics include challenging dysfunctional thoughts, activity scheduling, problem-solving, graded exposure, task breakdown, sleep management, and relapse prevention. Patients are encouraged to complete homework assignments between sessions. BtB sessions occurred at a location with internet access selected by participants (e.g., home or work). Those with no internet access or limited computer skills could complete sessions in the principal investigator's laboratory with the DCS available for assistance. Participants were mailed a folder containing BtB worksheets, were oriented to the program, were instructed to complete 1 session/week, and worked through the sessions on their own. The DCS provided weekly support via phone by reviewing progress/content and addressing questions/issues.

PST-PC is a manualized and efficacious CBT for depression developed for primary care.^{13, 29} The focus of the 6–8, weekly, 30-minute sessions is teaching patients the seven problem-solving steps (i.e., defining the problem, setting a realistic goal, brainstorming potential solutions, evaluating potential solutions, selecting a solution, implementing the solution, and reviewing the outcome) and helping them apply these steps to current problems contributing to their depression. In the final session, the therapist and patient also collaboratively formulate a relapse prevention plan. The DCS (certified in PST-PC) delivered sessions by phone, which is feasible and effective.³⁰ In-person sessions were allowed if they were the participant's strong preference. Participants were mailed a folder containing PST-PC worksheets that they completed in collaboration with the DCS.

The IMPACT intervention manual³¹ guidelines for managing antidepressants were followed after our psychiatrist made necessary updates to dosing/titrating. To optimize the algorithm for CVD risk reduction, the IMPACT medication list was restricted to selective serotonin

reuptake inhibitors (SSRIs), duloxetine, bupropion, and mirtazapine. These FDA-approved antidepressants are the safest from a cardiovascular perspective.^{32, 33} We prohibited the use of most serotonin-norepinephrine reuptake inhibitors (SNRIs) and all tricyclic antidepressants due to their potential adverse effects on cardiovascular parameters.^{32, 33} The intervention team made antidepressant recommendations, which the DCS communicated to participants and PCPs. PCPs wrote all prescriptions, and the intervention team and PCPs collaboratively managed pharmacotherapy.

The intervention process followed the IMPACT manual³¹ with modifications noted below. To end the pre-treatment visit, the DCS met with participants for 20 minutes over FaceTime to build rapport, review depression education materials, deliver a behavioral activation intervention,¹³ and schedule the initial visit within the next week. During the initial visit by phone, the DCS completed an assessment interview and discussed treatment options and preferences. At meetings every 2 weeks, the DCS presented cases to the intervention team, who formulated a Step 1 plan. The DCS collaborated with the PCP to implement this plan. Step 1 treatment was 2–3 months of CBT or an antidepressant, largely driven by patient preference. BtB and PST-PC were the first- and second-line CBTs, respectively; SSRIs and the other medications were the first- and second-line antidepressants, respectively. For participants on an antidepressant at entry, the dosage was adjusted, CBT was added, and/or a different antidepressant was recommended. For participants with a strong preference for CBT but with barriers to BtB delivery (e.g., no internet access), PST-PC was offered at Step 1. Our DCS followed patients for 12 months, monitoring response and staffing cases with the intervention team at least every 3 months. DCS contacts (typically 30 minutes by phone) occurred every 1–2 weeks during active treatment. In addition to delivering CBT (if prescribed), the DCS assessed depressive symptoms, maintained engagement in behavioral activation, and provided antidepressant adherence support including side effect monitoring (for those receiving antidepressants) at most contacts. For participants who achieved remission (50% PHQ-9 score reduction and <3 symptoms for 6 weeks¹⁰), the DCS developed a relapse prevention plan and followed-up every 2–4 weeks by phone. If remission was not achieved after Step 1, Step 2 treatment – i.e., augmenting Step 1 treatment with CBT or an antidepressant or switching to another CBT or antidepressant – was delivered for an additional 2–3 months. If remission was still not achieved after Step 2, Step 3 treatment was delivered, which consisted of additional CBT and/or adjustments to the antidepressant regimen and, if indicated, a phone evaluation with our psychiatrist.

2.3.2. Usual Primary Care for Depression—The comparator was modeled after that of the IMPACT trial.¹⁰ Eskenazi Health primary care clinics utilize a team care approach for behavioral health issues, with PCPs supported by embedded Master’s-level behavioral health clinicians and affiliated psychiatrists available for brief counseling and antidepressant management. To end the pre-treatment visit, participants were informed of their current depression and group assignment, were encouraged to follow-up with their usual PCP regarding their depression, and were provided a list of local mental health services. They were also reminded that all depression treatments that participants in this group receive during the study are delivered by their usual providers. Participants’ PCPs received a letter or EHR message from the trial team indicating their patient’s group assignment,

encouraging them to address their patient's depression, and providing the same list of services. This correspondence also noted that, like participants in the intervention group, there were no care restrictions. Although a PCP could have patients in both treatment groups, crossover effects were unlikely, as (a) PCPs did not have access to the intervention protocol and did not attend intervention team meetings and (b) internet and telephonic CBT was not available in the targeted clinics.

2.4. Assessments

2.4.1. Primary Outcome—The primary outcome was brachial FMD at 12 months. It was measured at the Indiana CTSI Human Vascular Imaging Core per consensus guidelines¹⁴ using a GE LOGIQe high-resolution ultrasound with a 15-MHz vascular transducer. After a 10-minute supine rest period, a BP cuff was placed on the forearm and inflated to 250 mmHg for five minutes. Brachial diameter was measured at pre-inflation and 60- and 90-seconds post-deflation using AccessPoint 2011 software (version 8.2; Freeland Systems). FMD was computed the maximum % increase in brachial diameter at 60- or 90-seconds post-deflation.

2.4.2. Secondary Outcomes—Secondary outcomes were depressive symptoms, autonomic dysfunction, systemic inflammation, and platelet activation at 12 months. As in the IMPACT trial,¹⁰ participants completed the reliable and valid Hopkins Symptom Checklist-20 (SCL-20)³⁴ to assess depressive symptoms. Total scores (mean of items responses) and a clinical response variable (50% reduction in total score) were computed.

To quantify autonomic dysfunction, we measured high-frequency heart rate variability (HF HRV), an index of parasympathetic cardiac control, per established guidelines³⁵ and as described elsewhere.³⁶ HF HRV estimates (ln of ms²/Hz) were derived by spectral analysis (bandwidth: 0.15–0.40 Hz) from 1-minute epochs of electrocardiographic data obtained during the last 5 minutes of the 10-minute supine rest period using MindWare Technologies HRV analysis software (version 3.1.2). Mean HF HRV was computed as the average of the five estimates. To control for respiration rate, participants completed a paced-breathing computer task set to 12 breaths/minute.

To quantify systemic inflammation and platelet activation, fasting blood samples obtained by CRC nurses were collected in EDTA tubes and centrifuged within 20 minutes. Plasma aliquots were frozen at –80°C until the time of assay at the Indiana University Center for Diabetes and Metabolic Diseases Translation Core. Using enzyme-linked immunosorbent assay kits according to the manufacturer's instructions, we measured levels of inflammatory markers, interleukin-6 (IL-6; R&D Systems HS600C) and high-sensitivity C-reactive protein (hsCRP; R&D Systems DCRP00), and platelet-specific release products, β -thromboglobulin (BTG; Biomatik EKU02712) and platelet factor 4 (PF4; R&D Systems DPF40). All samples were measured in duplicate. The limit of detection was 0.09 pg/mL, 0.022 ng/mL, 6.7 pg/mL, and 0.032 ng/mL for IL-6, hsCRP, BTG, and PF4, respectively.

2.4.3. Other Factors—At pre-treatment, sociodemographic factors, CVD risk factors, mental health variables, and current medications were assessed by self-report (Table 1). Medical and mental health conditions were assessed by the questions: “Have you ever been

told by a doctor or other health professional that you have [high cholesterol, hypertension or high blood pressure, diabetes, a depressive disorder, an anxiety disorder, an alcohol or drug problem]? Smoking status was assessed by a Behavioral Risk Factor Surveillance System measure.³⁷ Current psychotherapy/counseling for depression was assessed by the question: “Are you currently receiving talk therapy or counseling for depression?” Participants were instructed to bring a list of current prescription medications. Medication types – CVD prevention (lipid-lowering and antihypertensive agents), diabetes (oral/injectable hypoglycemic agents and insulin products), and antidepressants – were coded by staff. Lipid fractions were measured in duplicate using a Daytona Clinical Analyzer. Three seated BP readings separated by two minutes were obtained by a CRC nurse after five minutes of rest.³⁸ Systolic and diastolic BP (SBP and DBP) were computed as the mean of the last two readings. Body mass index (BMI) was calculated from weight and height measured by a CRC nurse using a Scale-Tronix 5002 medical scale.

At mid- and post-treatment, the DCS conducted EHR chart reviews to quantify depression treatment received as part of usual primary care for both groups. We recorded participant withdrawals as they occurred. We identified adverse events by conducting EHR searches every 6 months and administering a brief self-report questionnaire at mid-treatment, post-treatment, and follow-up to capture events occurring outside of Eskenazi Health. We identified deaths via EHR searches every 6 months, secondary contacts provided by participants, and internet searches for obituaries.

2.5. Statistical Analysis

Based on results of our pilot trial (see [NCT01605552](#)), the eIMPACT trial was powered to detect $d = 0.43$ for the effect of the eIMPACT intervention on the primary and secondary outcomes. For an independent t test with two-tailed $\alpha = 0.05$, 172 participants are needed to achieve 80% power to detect a $d = 0.43$. Using an attrition rate of 20%, we randomized 216 participants to ensure at least 172 completers.

Analyses were conducted using SAS 9.4. P values are two-tailed ($p < 0.05$ considered significant). Outcome variables exhibiting considerable skew were log transformed (HF HRV: \ln ; IL-6 and hsCRP: $\log_{10}[X_i+1]$). Untransformed values for IL-6 and hsCRP are provided in Supplemental Table 2 to facilitate comparisons with other reported data. Change scores for each outcome were computed as post-treatment minus pre-treatment level. To compare treatment groups on baseline characteristics, independent t tests and χ^2 tests were performed. To compare treatment groups on outcome variables at baseline, ANCOVA models adjusting for age group and sex were conducted with baseline levels of the outcomes as dependent variables. To characterize intervention delivery, descriptive statistics were computed for intervention process variables. To compare treatment groups on depression treatment received as part of usual care, withdrawals, adverse events, and deaths, χ^2 tests were performed.

For hypothesis-testing analyses, an intention-to-treat approach employing multiple imputation was used, in accordance with recent recommendations for RCTs when the missing completely at random (MCAR) assumption may be implausible.^{39, 40} First, to properly handle missing data (0.9–5.6% for pre-treatment outcomes and 7.4–12.0% for

post-treatment outcomes; see Table 4 *Note*), 10 multiple imputation datasets were generated from the observed data using the SAS MI procedure and the fully conditional specification method, where missing pre-treatment outcomes were imputed from regression models using age, sex, race, and treatment group, and missing post-treatment outcomes were imputed from models using pre-treatment level for the same outcome variable, age, sex, race, and treatment group. Second, to compare treatment groups on the outcomes, primary ANCOVA models adjusting for the stratification variables of age group and sex and with post-treatment outcomes as dependent variables were conducted on each imputed dataset, and results were combined using the SAS MIANALYZE procedure. A parallel set of supplemental ANCOVA models was run with outcome change scores as dependent variables. Third, secondary ANCOVA models further adjusting for baseline characteristics (education, income, and SBP) exhibiting imbalance between treatment groups ($p < 0.10$) and pre-treatment level for the outcome were conducted on each imputed dataset, and results were combined. Fourth, between-group effect sizes (Hedges' g) for each outcome were computed using the group means and standard deviations derived from multiple imputation. In addition, a χ^2 test was performed to assess for treatment group differences in the depression clinical response variable. Finally, as a sensitivity analysis, hypothesis-testing models were rerun using only the observed data (complete case analysis⁴⁰).

3. Results

3.1. Participant Flow and Characteristics

As indicated in Figure 1, 4,474 patients were contacted for screening. Of the 304 patients eligible and interested after screening, 216 (71%) were randomized. Retention was high and balanced across the treatment groups (intervention: 93%; usual care: 92%).

As shown in Table 1, our randomized sample had good representation of women and Black/African American adults, people with low incomes, and individuals with high CVD risk factor burden. The mean pre-treatment PHQ-9 score was 15.1, falling in the moderately severe depression range. There was a high prevalence of depressive disorder history and a high frequency of current antidepressant use. Treatment groups were balanced on baseline characteristics, although the intervention group had somewhat higher education and incomes and lower SBP ($ps < 0.10$).

3.2. Depression Treatment

As can be seen in Table 2, our intervention team delivered substantial depression treatment. On average, intervention participants had 21 DCS contacts, most of which were by phone. A total of 85% were prescribed CBT, with 70% prescribed internet CBT and 29% prescribed telephonic CBT. For 31%, our intervention team made an antidepressant recommendation, three quarters of which were for an SSRI. Phone evaluations with our psychiatrist were rare, and few outside referrals were made (none directly related to depression or CVD). EHR chart reviews revealed that the treatment groups received similar depression treatment as part of usual care (Table 3).

3.3. Primary Outcome: Endothelial Dysfunction

There was no intervention effect on endothelial dysfunction. The intention-to-treat analysis revealed that the treatment groups did not differ on post-treatment FMD (Table 4 and Figure 2: Panel A). Of note, FMD slightly worsened in both groups during the treatment period. Supplemental analyses examining FMD change scores (Table 4) or further adjusting for baseline education, income, SBP, and FMD (Supplemental Table 1) yielded similar results, as did sensitivity analyses examining the observed data (Supplemental Tables 2 and 3).

3.4. Secondary Outcomes: Depressive Symptoms, Autonomic Dysfunction, Systemic Inflammation, and Platelet Activation

The eIMPACT intervention significantly and meaningfully improved depressive symptoms. The intention-to-treat analysis demonstrated that the intervention group, versus the usual care group, exhibited moderate-to-large improvements in SCL-20 score at post-treatment (Table 4 and Figure 2: Panel B). This group difference was clinically meaningful – 43% of intervention participants, versus 17% of usual care participants, showed a clinical response ($\chi^2 [1, N=198] = 16.19, p < 0.01, OR = 3.73, 95\% CI: 1.93-7.21$). Comparable results were observed in supplemental analyses (Table 4 and Supplemental Table 1) and sensitivity analyses (Supplemental Tables 2 and 3).

No intervention effects were found for post-treatment measures reflecting autonomic dysfunction (HF HRV: Hedges' $g = 0.02$), systemic inflammation (IL-6: Hedges' $g = -0.15$; hsCRP: Hedges' $g = -0.22$), or platelet activation (BTG: Hedges' $g = -0.16$; PF4: Hedges' $g = -0.23$; Table 3). Nonetheless, the small, nonsignificant improvements in hsCRP and PF4 favored the intervention group. Again, supplemental analyses (Table 4 and Supplemental Table 1) and sensitivity analyses (Supplemental Tables 2 and 3) yielded similar results.

3.5. Withdrawals, Adverse Events, and Deaths

The treatment groups (intervention vs. usual care) did not differ in the frequency of withdrawals (5 vs. 1, $\chi^2 [1, N=216] = 2.82, p = 0.09$), adverse events possibly related to depression or study procedures (8 vs. 6, $\chi^2 [1, N=216] = 0.80, p = 0.37$), or deaths (5 vs. 8, $\chi^2 [1, N=216] = 0.68, p = 0.41$) through July 31, 2020. Only three adverse events were possibly related to study involvement (all mild/moderate and in the intervention group). No death was related to study involvement.

4. Discussion

We report the main results of the eIMPACT trial, the most definitive RCT to date testing whether depression treatment reduces CVD risk biomarkers among people with depression and elevated CVD risk. Our modernized collaborative care intervention, versus usual primary care for depression, produced statistically significant, moderate-to-large, and clinically meaningful improvements in depressive symptoms at 12 months. However, no group differences were observed for the primary outcome of endothelial dysfunction (FMD) and the secondary outcomes of autonomic dysfunction (HF HRV), systemic inflammation (IL-6, hsCRP), and platelet activation (BTG, PF4). Therefore, our hypothesis that successful depression treatment before clinical CVD onset yields cardiovascular benefits was not

supported. Instead, our results agree with the general absence of cardiovascular benefits found in prior depression trials in patients with clinical CVD.¹ Our findings indicate that depression treatment alone may not be sufficient to reduce the excess CVD risk in people with depression.

While our trial advances understanding of the depression-CVD risk link, there remains ambiguity about this relationship. Our null results for the CVD risk biomarkers fit with several possibilities. One possible explanation is that depression is not a causal risk factor for CVD and that a third factor is responsible for their association. However, recent compelling evidence suggests that depression may indeed be a causal CVD risk factor. Bidirectional Mendelian randomization analyses revealed that genetic predisposition to depression is causally associated with CVD risk but not vice versa.⁴¹ Furthermore, clinical trials in people with depression but no clinical CVD have observed some promising beneficial effects of depression treatment on indicators of CVD risk,^{3, 42, 43} and a recent meta-analysis found that SSRI treatment improves endothelial function.⁴⁴

There are other possible explanations for our null results for the CVD risk biomarkers. First, we may have still delivered depression treatment too late. Due to the inclusion criteria, the prevalence of CVD risk factors (and perhaps advanced subclinical atherosclerosis) was high in our sample. To yield cardiovascular benefits, it might be necessary to deliver depression interventions earlier in the natural history of CVD. Second, depression may be a distal and modest¹¹ causal risk factor for CVD. Consequently, depression treatment alone may be insufficient to meaningfully improve the putative mechanisms^{1, 21} and, ultimately, downstream CVD outcomes. A combined intervention approach in which depression and candidate biological mechanisms¹ (e.g., autonomic dysfunction and systemic inflammation) are treated concurrently might be required. Another approach worthy of evaluation is integrated cardiologic care focused on concurrent management of depression and candidate behavioral mechanisms¹ (e.g., poor diet, physical inactivity, smoking, medication nonadherence, and insomnia), as depression has been linked with poor adherence to medical recommendations to prevent CVD,⁴⁵ and insomnia is common in depression⁴⁶ and is associated with elevated inflammatory markers and incident CVD.^{47, 48} Third, only some subtypes or facets of depression may confer CVD risk, and current treatments may not adequately improve them. Accumulating evidence indicates that the atypical/immunometabolic subtype is the depression subgroup at particularly elevated CVD risk.^{49, 50} Other research suggests that somatic depressive symptoms (which often remain after treatment^{51, 52}) may be stronger predictors of CVD-related outcomes than other symptoms in people initially free of CVD.^{53, 54} These observations imply that cardiovascular benefits of depression treatment may be present only in people with the atypical/immunometabolic subtype and only if interventions improve somatic symptoms. Again, this may call for a combined intervention approach – here, integrating depression interventions with pharmacological or psychological interventions shown to be efficacious for specific somatic symptoms (e.g., appetite and sleep disturbance).

The present findings provide direction regarding the way forward in the depression-CVD risk area. In the research domain, future work seeking to determine the causal mechanisms underlying the depression-CVD risk relationship is needed to refine conceptual frameworks

and intervention targets. Additionally, future RCTs are needed in which (a) the depression subgroups at greatest CVD risk (e.g., people with the atypical/immunometabolic subtype) are enrolled and (b) optimized interventions (e.g., those concurrently targeting depression and putative mechanisms or appetite/sleep disturbance) are delivered. In addition, future RCTs should consider recruiting young and middle-aged adults with no history of clinical CVD, a group less likely to have advanced subclinical atherosclerosis. In the practice domain, it is important for clinicians engaged in CVD primary prevention to know that depression treatment alone is likely not sufficient to reduce the excess CVD risk of people with depression. Furthermore, because depression is an independent risk factor for incident CVD,^{1, 11} its presence should signal the need for frequent screening and intensified attention and support to improve management of traditional CVD risk factors.⁵⁵

The eIMPACT trial also has important implications for the design and delivery of contemporary integrated care in CVD prevention settings and elsewhere. Our trial is among the first to integrate an eHealth intervention into a collaborative care framework for depression²⁸ and is the first to do so in a safety net healthcare system where there are additional barriers (e.g., lower rates of internet access). Our depression results highlight the utility of our modernized approach, as we found that the eIMPACT intervention is feasible, acceptable, and effective. The substantial depression treatment delivered and the low intervention arm attrition support the feasibility and acceptability of our approach. Moreover, the eIMPACT intervention was found to be superior to usual primary care in the targeted clinics, which had implemented an integrated care model for mental health issues. Notably, intervention participants had 3.7 times greater odds of exhibiting a clinical response in depressive symptoms than usual care participants. Outperforming current integrated care underscores the potential added value of the innovative features of the eIMPACT intervention. These features also support broader dissemination and implementation. First, our intervention is practical for both patients and healthcare systems, given that nearly all our treatment was delivered remotely from a centralized location by one Master's-level clinician. For patients, our intervention is convenient and accessible, perhaps especially for those with logistical barriers to treatment (e.g., unreliable transportation). For healthcare systems, our intervention is efficient and resource sparing, as it harnesses technology to minimize personnel, training, and space resources. Second, given our remote, centralized treatment delivery and our use of internet CBT, the eIMPACT intervention is more scalable, easier to deliver with high fidelity, and likely more cost effective than face-to-face alternatives.²⁶

Our trial has strengths and limitations that should be considered. Concerning strengths, because this trial had pragmatic aspects (e.g., real-world setting, minimal mental health exclusions, and a flexible intervention), its results should be generalizable to routine clinical settings. Our sample also had strong representation of Black/African American adults and people with low incomes, which is uncommon in eHealth trials and enhances generalizability. Moreover, our intervention provided multiple treatment options and prioritized shared decision-making, which allowed for tailoring to participant preferences and situations. Regarding limitations, because a depressive disorder diagnosis was not required, our sample likely includes some patients with subclinical depression, which could have attenuated our depression effect sizes. However, 58% reported a depressive disorder

history at entry, and our depression effect sizes compare favorably to those for collaborative care for depression.⁵⁶ Furthermore, a recent meta-analysis determined that even subclinical depressive symptoms are associated with elevated CVD risk.¹¹ There is also room for improvement in eHealth engagement, as 41% of intervention participants prescribed internet CBT completed zero sessions. Because no device with internet access at home (49% of intervention participants) and limited computer skills were common barriers, future trials should consider loaning tablets with data plans and providing basic computer training to participants in need of them. In addition, CVD prevention medication use was high in our sample at 73%, which may have masked depression intervention effects on the CVD risk biomarkers. Finally, we may have missed a depression intervention effect on other CVD-related outcomes. Future trials should consider a comprehensive assessment approach, including candidate mechanisms, CVD risk factors, clinical outcomes, and quality of life measures. Follow-up periods longer than ours may also be needed to observe depression intervention effects on CVD-related outcomes.

5. Conclusions

Our modernized collaborative care intervention – which harnessed technology to maximize access and to minimize the needed resources – improved depressive symptoms in primary care patients with depression and elevated CVD risk. However, 12 months of successful depression treatment did not lower CVD risk as assessed by multiple CVD risk biomarkers. Our findings indicate that depression treatment alone may not be sufficient to reduce the excess CVD risk of people with depression and that alternative approaches are needed. In addition, our effective intervention could inform the design and delivery of contemporary integrated care approaches.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Our modernized depression intervention used internet and telephonic psychotherapy.
- Intervention participants exhibited meaningful improvements in depressive symptoms.
- Successful depression treatment did not reduce cardiovascular risk biomarkers.
- Depression treatment is not sufficient to lower cardiovascular risk in depression.
- Integrated care should harness technology to maximize access/minimize resources.

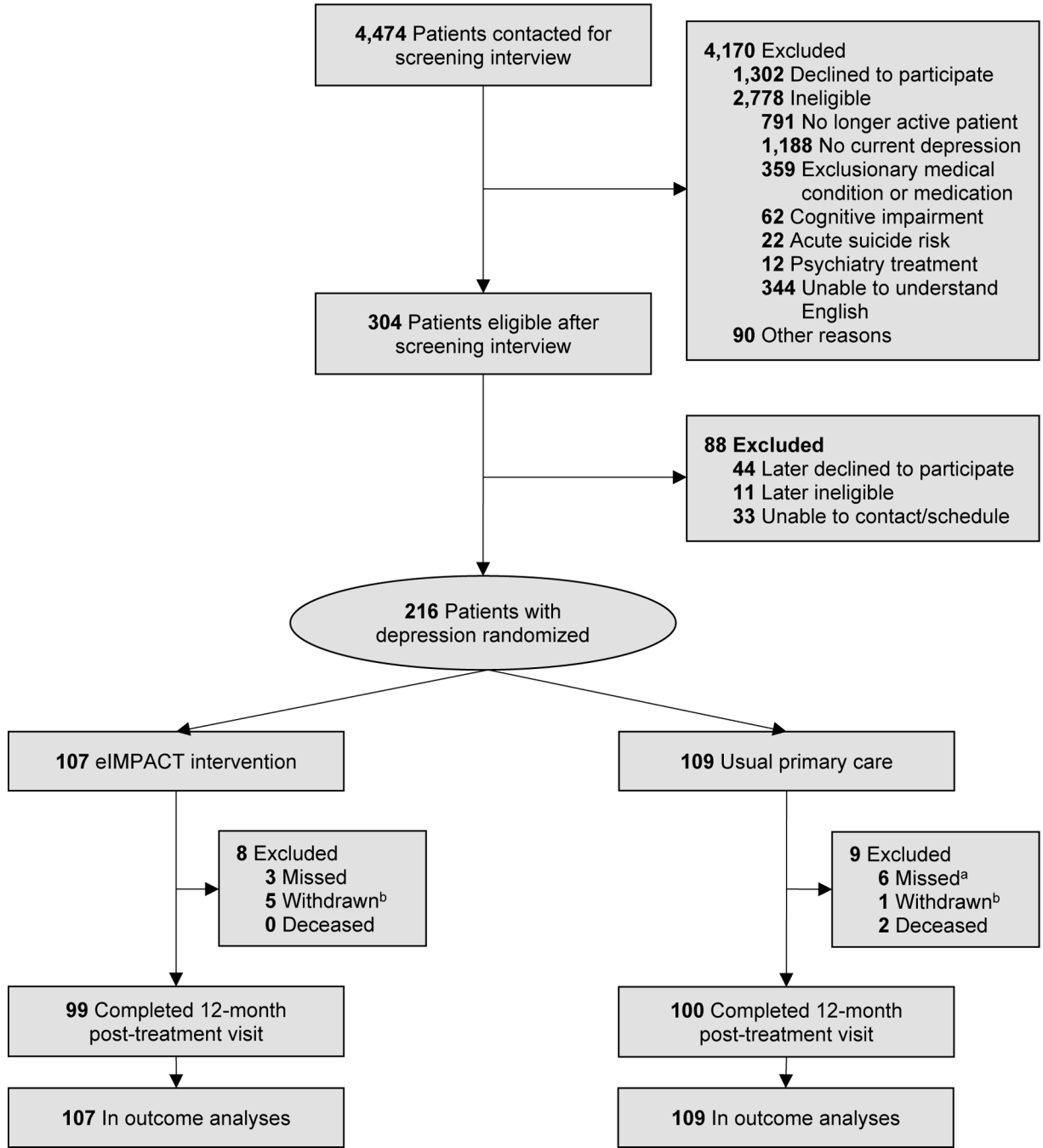


Figure 1. Flowchart of Screening, Enrollment, Randomization, and Follow-Up for the eIMPACT Trial
Note. Participants were screened and enrolled from August 13, 2015 to July 31, 2018. Data collection ended on July 31, 2020.

^aFor two of these participants, 12-month survey data were obtained.

^bFor all withdrawn by investigator (intervention: 3; usual care: 1), it was determined after randomization that the participant met an exclusion criterion.

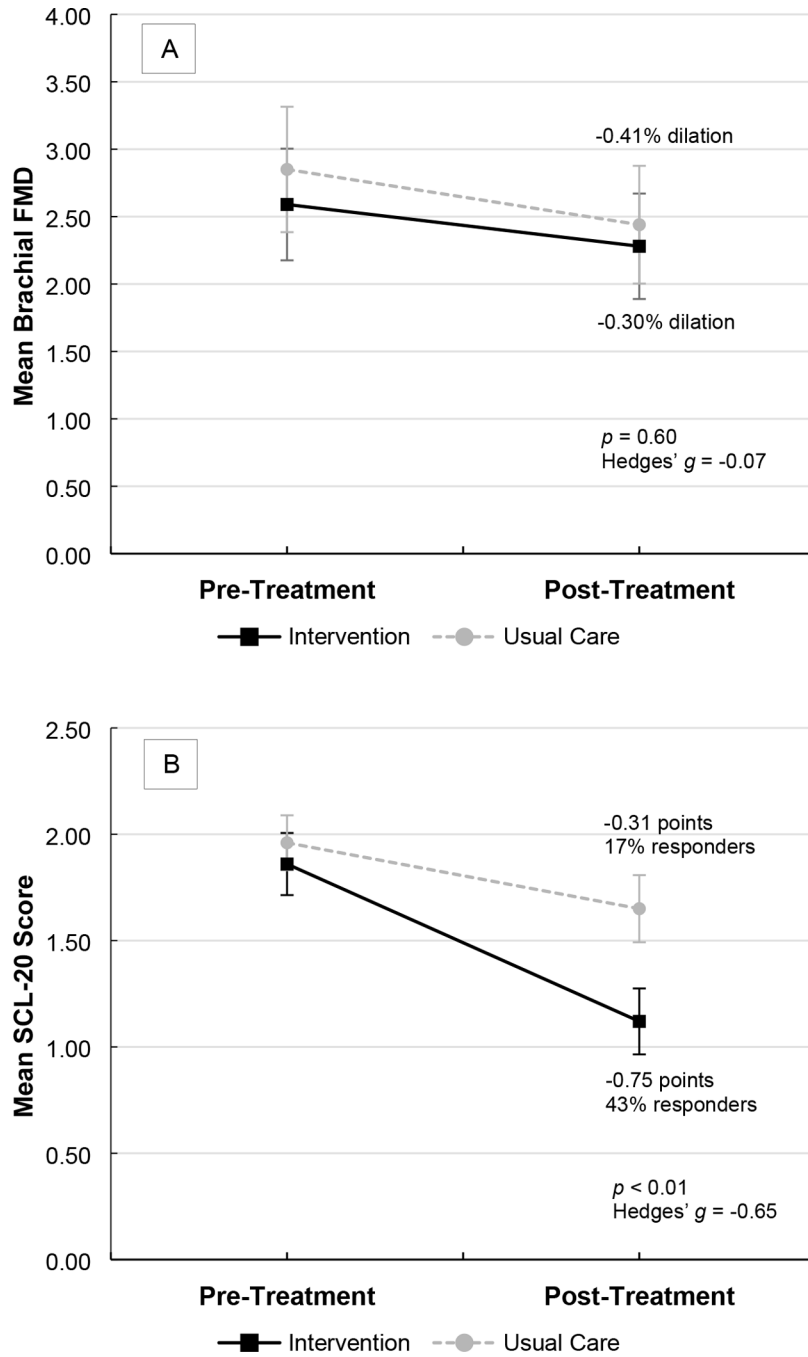


Figure 2. Mean Brachial Flow-Mediated Dilation (Endothelial Dysfunction; Panel A) and Hopkins Symptom Checklist-20 Scores (Depressive Symptoms; Panel B) at Pre-Treatment and Post-Treatment (12 Months) by Treatment Group
Note. Values are from imputed datasets. Error bars represent 95% confidence intervals. *P* values are from analysis of covariance (ANCOVA) models using multiple imputation and adjusting for the stratification variables of age group and sex. Effect sizes (Hedges' *g*) were

computed from imputed M s and SD s. Responder defined as a 50% reduction in SCL-20 score. FMD = flow-mediated dilation; SCL-20 = Hopkins Symptom Checklist-20.

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Table 1.

Baseline Characteristics of Participants in the eIMPACT Trial

	All (N = 216)	Intervention (n = 107)	Usual Care (n = 109)	p value
Sociodemographic Factors				
Age, years, <i>M</i> (<i>SD</i>)	58.7 (5.7)	58.5 (6.0)	58.9 (5.4)	0.62
Sex, <i>n</i> (%)				0.81
Female	169 (78.2)	83 (77.6)	86 (78.9)	
Male	47 (21.8)	24 (22.4)	23 (21.1)	
Race, <i>n</i> (%)				0.70 ^a
American Indian/Alaskan Native	1 (0.5)	0 (0.0)	1 (0.9)	
Asian	1(0.5)	1 (0.9)	0 (0.0)	
Black/African American	107 (49.5)	56 (52.3)	51 (46.8)	
Native Hawaiian/Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	
White	97 (44.9)	45 (42.1)	52 (47.7)	
Multi-Racial	8 (3.7)	4 (3.7)	4 (3.7)	
Other Race	2 (0.9)	1 (0.9)	1 (0.9)	
Ethnicity, <i>n</i> (%)				0.98
Hispanic or Latino/a/x	10 (4.6)	5 (4.7)	5 (4.6)	
Not Hispanic or Latino/a/x	206 (95.4)	102 (95.3)	104 (95.4)	
Education, years, <i>M</i> (<i>SD</i>)	12.8 (2.3)	13.1 (2.5)	12.6 (2.0)	0.09
Annual Household Income, <i>n</i> (%)				0.04
<\$10,000	98 (45.6)	44 (41.1)	54 (50.0)	
\$10,000-\$14,999	37 (17.2)	16 (15.0)	21 (19.4)	
\$15,000-\$24,999	45 (20.9)	21 (19.6)	24 (22.2)	
\$25,000-\$39,999	25 (11.6)	18 (16.8)	7 (6.5)	
\$40,000+	10 (4.7)	8(7.5)	2 (1.9)	
Cardiovascular Disease Risk Factors				
Hypercholesterolemia, <i>n</i> (% yes)	114 (53.0)	56 (52.3)	58 (53.7)	0.84
LDL Cholesterol, mg/dL, <i>M</i> (<i>SD</i>)	108.8 (40.9)	109.8(41.4)	107.8 (40.5)	0.72
HDL Cholesterol, mg/dL, <i>M</i> (<i>SD</i>)	48.9 (15.8)	50.5 (18.2)	47.3 (12.8)	0.14
Triglycerides, mg/dL, <i>M</i> (<i>SD</i>) ^b	141.2 (90.8)	140.0 (94.5)	142.3 (87.5)	0.72
Hypertension, <i>n</i> (% yes)	164 (76.3)	82 (76.6)	82 (75.9)	0.90
SBP, mmHg, <i>M</i> (<i>SD</i>)	135.7 (19.7)	133.0 (18.9)	138.4 (20.2)	0.04
DBP, mmHg, <i>M</i> (<i>SD</i>)	80.9 (11.8)	79.7 (11.0)	82.1 (12.5)	0.14
Diabetes, <i>n</i> (% yes)	76 (35.3)	34 (31.8)	42 (38.9)	0.28
Fasting Glucose, mg/dL, <i>M</i> (<i>SD</i>) ^b	130.9 (60.1)	130.4 (59.2)	131.5 (61.1)	0.80
Fasting Insulin, μ U/mL, <i>M</i> (<i>SD</i>) ^b	17.6 (17.3)	17.6 (20.6)	17.7 (13.3)	0.45
Body Mass Index, kg/m ² , <i>M</i> (<i>SD</i>)	33.6 (9.5)	32.7 (9.3)	34.6 (9.6)	0.14
Smoking Status, <i>n</i> (%)				0.21

	All (N = 216)	Intervention (n = 107)	Usual Care (n = 109)	p value
Never Smoker	66 (30.6)	37 (34.6)	29 (26.6)	
Former Smoker	37 (17.1)	14 (13.1)	23 (21.1)	
Current Smoker	113 (52.3)	56 (52.3)	57 (52.3)	
Mental Health Variables				
Pre-Treatment PHQ-9 Score, <i>M (SD)</i>	15.1 (5.0)	14.7 (5.2)	15.4 (4.8)	0.33
Depressive Disorder History, <i>n (% yes)</i>	125 (58.1)	64 (59.8)	61 (56.5)	0.62
Anxiety Disorder History, <i>n (% yes)</i>	101 (47.0)	48 (44.9)	53 (49.1)	0.54
Alcohol or Drug Problem History, <i>n (% yes)</i>	33 (15.4)	18 (16.8)	15 (14.0)	0.57
Current Psychotherapy/Counseling for Depression, <i>n (% yes)</i>	35 (16.3)	20 (18.9)	15 (13.8)	0.31
Current Medication Use				
CVD Prevention Medication, <i>n (% yes)</i>	155(73.1)	74 (71.8)	81 (74.3)	0.69
Diabetes Medication, <i>n (% yes)</i>	65(30.7)	27 (26.2)	38 (34.9)	0.17
Antidepressant Medication, <i>n (% yes)</i>	124 (58.5)	63 (61.2)	61 (56.0)	0.44

Note. Values are from the observed dataset. All variables had complete data except (*n*): education (215), income (215), hypercholesterolemia (215), LDL cholesterol (214), HDL cholesterol (214), triglycerides (214), hypertension(215), diabetes (215), fasting glucose (214), fasting insulin (214), depressive disorder (215), anxiety disorder (215), alcohol or drug problem (214), current psychotherapy/counseling for depression (215), CVD prevention medication (212), diabetes medication (212), and antidepressant medication (212). *P* values are from independent samples *t* tests for continuous variables and χ^2 tests for categorical variables comparing the intervention and usual care groups. LDL = low-density lipoprotein; HDL = high-density lipoprotein; SBP = systolic blood pressure. DBP = diastolic blood pressure. PHQ-9 = Patient Health Questionnaire-9.

^aDue to some low cell counts, race was recoded into a 3-level variable (Black/African American, White, other race) prior to conducting the χ^2 test.

^bFor triglycerides, fasting glucose, and fasting insulin, untransformed values are shown. To normalize their distributions, these variables were log₁₀-transformed prior to conducting *t* tests.

Table 2.

Depression Treatment Delivered as part of the eIMPACT Intervention During the 12-Month Treatment Period

Intervention Process Variable	Value
Number of Depression Clinical Specialist Contacts per Participant, $M(SD)$	20.8 (9.1)
Cognitive-Behavioral Therapy (CBT) Prescribed, n (%)	91 (85.0)
Internet CBT (BtB) Prescribed, n (%)	75 (70.1)
Number of BtB Sessions Completed (possible range: 0–8) ^a , $M(SD)$	2.6 (3.0)
Telephonic CBT (PST-PC) Prescribed, n (%)	31 (29.0)
Number of PST-PC Sessions Completed (possible range: 0–6/8), $M(SD)$	4.5 (3.1)
Antidepressant Medication Recommended, n (%)	33 (30.8)
Selective Serotonin Reuptake Inhibitor (SSRI), n (%)	25 (23.4)
Duloxetine, n (%)	3 (2.8)
Bupropion, n (%)	2 (1.9)
Mirtazapine, n (%)	3 (2.8)
Phone Evaluation with Intervention Team Psychiatrist Completed, n (%)	3 (2.8)
Outside Referral Made ^b , n (%)	15 (14.0)

Note. $n = 107$. 95% of participants received a first-line intervention (68% BtB, 13% PST-PC, 14% antidepressant medication), 32% a second-line intervention (2% BtB, 14% PST-PC, 16% antidepressant medication), and 3% a third-line intervention (0% BtB, 2% PST-PC, 1% antidepressant medication). BtB = Beating the Blues; PST-PC = Problem Solving Treatment in Primary Care.

^aThirty-one (41%) of intervention participants prescribed internet CBT completed zero BtB sessions. When there was not early BtB engagement or when there were BtB access issues (49% did not have a computer/tablet with internet access at home), our intervention team moved to another treatment option (e.g., telephonic CBT). For the 44 (59%) intervention participants who completed at least one BtB session, the mean number of BtB sessions was markedly higher at 4.4 ($SD = 2.8$).

^b12 participants had 1 referral, 2 participants had 2 referrals, and 1 participant had 3 referrals for a total of 19 referrals (8 to a medical social worker for basics needs/resources; 8 to the patient's primary care provider or embedded behavioral health clinician for health issues unrelated to depression or cardiovascular disease; 3 to other programs [palliative care, substance use treatment, health and wellness groups]).

Table 3.

Depression Treatment Received as part of Usual Primary Care in the Targeted Clinics During the 12-Month Treatment Period

	Intervention ^a (n = 107)	Usual Care (n = 109)	p value
Depression Treatment			
Started New Psychotherapy/Counseling for Depression, n (%)	7 (6.5)	14(12.8)	0.12
Started New Antidepressant Medication or Had Dosage Adjusted, n (%)	33 (30.8)	40 (36.7)	0.36
Seen by a Provider with Psychiatry Specialty, n (%) ^b	14 (13.1)	21 (19.3)	0.22

Note. Values are from the observed dataset. All variables had complete data. P values are from χ^2 tests comparing the intervention and usual care groups.

^aIncludes only treatments not initiated by our intervention team

^bIncludes both psychiatrists and psychiatric and mental health clinical nurse specialists

Table 4.

Results for Primary and Secondary Outcomes of the eIMPACT Trial: Intention-to-Treat Analyses using Multiple Imputation Adjusted for Age Group and Sex

	All (N = 216) M (SD)	Intervention (n = 107) M (SD)	Usual Care (n = 109) M (SD)	p value
Brachial Flow-Mediated Dilation (% dilation)				
Pre-Treatment FMD	2.72 (2.31)	2.59 (2.16)	2.85(2.45)	0.42
Post-Treatment FMD ^a	---	2.28 (2.04)	2.44 (2.29)	0.60
Pre-to-Post Change in FMD ^b	---	-0.30 (2.25)	-0.41 (2.90)	0.78
Depressive Symptoms (possible range of SCL-20: 0.00–4.00)				
Pre-Treatment SCL-20	1.91 (0.72)	1.86 (0.76)	1.96 (0.68)	0.30
Post-Treatment SCL-20 ^c	---	1.12 (0.80)	1.65 (0.83)	< 0.01
Pre-to-Post Change in SCL-20 ^b	---	-0.75 (0.78)	-0.31 (0.66)	< 0.01
High-Frequency Heart Rate Variability (ln of ms ² /Hz)				
Pre-Treatment HF HRV	5.22 (1.71)	5.29 (1.72)	5.15 (1.66)	0.49
Post-Treatment HF HRV ^c	---	5.39 (1.85)	5.35 (1.78)	0.81
Pre-to-Post Change in HF HRV ^b	---	0.10 (1.73)	0.20 (1.66)	0.68
Interleukin-6 (log ₁₀ of pg/mL)				
Pre-Treatment IL-6	0.73 (0.27)	0.71 (0.28)	0.75 (0.27)	0.22
Post-Treatment IL-6 ^c	---	0.73 (0.26)	0.77 (0.27)	0.20
Pre-to-Post Change in IL-6 ^b	---	0.02 (0.16)	0.02 (0.21)	1.00
High-Sensitivity C-Reactive Protein (log ₁₀ of mg/L)				
Pre-Treatment hsCRP	0.69 (0.40)	0.67 (0.40)	0.71 (0.40)	0.38
Post-Treatment hsCRP ^c	---	0.65 (0.40)	0.74 (0.41)	0.09
Pre-to-Post Change in hsCRP ^b	---	-0.02 (0.29)	0.03 (0.30)	0.27
β-thromboglobulin (ng/mL)				
Pre-Treatment BTG	204(113)	194 (118)	213 (108)	0.22
Post-Treatment BTG ^c	---	185 (125)	205 (118)	0.23
Pre-to-Post Change in BTG ^b	---	-9 (135)	-8 (123)	0.94
Platelet Factor 4 (ng/mL)				
Pre-Treatment PF4	4165 (2094)	4038 (2047)	4290 (2133)	0.37
Post-Treatment PF4 ^c	---	3842 (2011)	4351 (2341)	0.09
Pre-to-Post Change in PF4 ^b	---	-196 (2230)	61 (2373)	0.43

Note. Values are from imputed datasets. Post-treatment and pre-to-post change values are not shown for all participants (both groups combined), as it is differential change between groups that is of interest. Pre-treatment values for all participants are shown to further characterize the sample. Observed *ns* for each outcome were (pre-treatment; post-treatment; pre-to-post change): FMD (212, 195, 194), SCL-20 (214, 200, 198), HF HRV (204, 190, 179), IL-6 (214, 195, 194), hsCRP (214, 196, 195), BTG (214, 195, 194), and PF4 (214, 195, 194). *P* values are from analysis of covariance (ANCOVA) models using multiple imputation and adjusting for the stratification variables of age group and sex. FMD = flow-mediated dilation; SCL-20 = Hopkins Symptom Checklist-20; HF HRV = high-frequency heart rate variability; IL-6 = interleukin-6; hsCRP = high-sensitivity C-reactive protein; BTG = β -thromboglobulin; PF4 = platelet factor 4.

^a Primary outcome

^b Pre-to-post change values were computed as: post-treatment value - pre-treatment value.

^c Secondary outcomes

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