Left Ventricular Function Recovery After Coronary Revascularization and Medical Therapy: A Systematic Review and Meta-Analysis [version 1; peer review: awaiting peer review]

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Abstract

Background: The prevalence of coronary artery disease (CAD) with reduced left ventricular ejection fraction (LVEF) is rising, but the optimal treatment remains unclear. The present study aims to investigate the impact of revascularization (coronary artery bypass grafting (CABG), or percutaneous coronary intervention (PCI)) and medical therapy (MT) on LVEF recovery in patients with CAD and LVEF ≤ 40%.

Methods: All clinical studies which reported LVEF in patients with CAD and LVEF ≤ 40% undergoing either revascularization or MT were included. A systematic literature search up to May 11, 2017 was performed on MEDLINE, EMBASE and the Cochrane Library in Ovid. Studies were assessed for eligibility and data were extracted by independent reviewers in duplicate with disagreements resolved by a third reviewer. Bias assessment was performed using the Newcastle-Ottawa Scale. Random effect meta-analysis was performed on included studies. The primary outcome was change in LVEF after intervention as compared to baseline.

Results: 83 cohort studies with a total of 7,157 patients were included. We observed a statistically significant increase in LVEF following
revascularization with CABG (MD 7.76; 95% CI: 6.81 to 8.70; p<0.00001; \( I^2 = 99\% \)) and PCI (MD 6.70; 95% CI: 4.71 to 8.70; p<0.00001; \( I^2 = 94\% \)) but not after MT (MD 4.06; 95% CI: -2.12 to 10.24; p=0.20; \( I^2 = 98\% \)).

**Conclusion:** In patients with CAD and LVEF \( \leq 40\% \), revascularization leads to LVEF recovery as compared to MT. There is continued need for RCT level evidence to enable optimization of treatment selection in this difficult population.

**Keywords**
Coronary artery disease; Left ventricular ejection fraction; coronary artery bypass grafting; per-cutaneous coronary intervention; medical therapy
Introduction

The prevalence of heart failure is rising, and ischemic cardiomyopathy is currently the most common cause.\textsuperscript{1,2} Ischemic cardiomyopathy is commonly defined as left ventricular (LV) ejection fraction (EF) of 40% or less in the context of coronary artery disease (CAD) as evidenced by angiographic diagnosis, a history of myocardial infarction, or prior revascularization. There is evidence that patients with recovered EF, either by natural history or in response to therapy,\textsuperscript{3} have distinctly better 3-year survival and fewer cardiovascular and HF-related hospitalizations.\textsuperscript{4} However, LVEF recovery has not been the primary subject of investigation in randomized clinical trials (RCTs).\textsuperscript{5,6}

The Surgical Treatment for Ischemic Heart Failure Extension Study (STICHES) demonstrated at a decade of follow-up, that CABG plus standard medical therapy (MT) for ischemic cardiomyopathy resulted in lower rates of all-cause mortality and hospitalization than those who received MT alone.\textsuperscript{6} However, LVEF recovery was not specifically studied. Indeed, the vast majority of revascularization trials have excluded patients with reduced LVEF. In the ARTS, MASS II, SoS, CARDia, SYNTAX and FREEDOM trials, the mean LVEF before intervention was between 57-67%.\textsuperscript{7-12}

We conducted a systematic review of the literature and analyzed all available evidence to date from both randomized and observational studies evaluating the impact of CABG, percutaneous coronary intervention (PCI), and MT on LVEF recovery in patients with ischemic cardiomyopathy.

Methods

Data sources and search strategy

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for conducting systematic reviews and meta-analyses in healthcare interventions.\textsuperscript{13} A literature search strategy was created by a medical librarian (SV) using a combination of keywords and subject headings relating to heart failure, revascularization and reduced ejection fraction,\textsuperscript{14} and was peer reviewed by another according to the PRESS guideline.\textsuperscript{15} The MEDLINE line search strategy is shown in Supplemental Table 1 in the data availability section. We systematically searched MEDLINE, EMBASE and the Cochrane Library in Ovid from inception until May 11\textsuperscript{th}, 2017. We also searched the reference list of landmark papers for additional relevant studies. The review protocol was registered in PROSPERO (CRD42017069849).

Selection criteria and outcomes measures

This study was designed to examine the degree of change in LVEF after CABG, PCI and MT in adult patients with CAD and LVEF < 40%. All full text, randomized, and comparative or single arm observational studies published in the English language were eligible for inclusion. Editorial letters, conference presentations, or non-original studies were excluded. We also excluded studies without a documented LVEF prior to intervention, of patients with non-ischemic cardiomyopathy, a history of cardiac resynchronization therapy or previous revascularization procedure, underwent CABG with concomitant valvular procedure, LV remodeling or ventricular assist device surgery, received stem cell therapy or intracoronary medications. Our outcome of interest was the difference in LVEF after intervention as compared to baseline. For patients with multiple LVEF measurements, the last value reported was used for analysis.

Data abstraction and quality assessment

Two independent reviewers (G.E.W. & T.X.V.) assessed each reference against eligibility criteria, and a third reviewer (J.M.C.N.) resolved conflicts. The same process applied when extracting data into pre-specified forms. Bias assessment was performed using the Newcastle-Ottawa Scale.\textsuperscript{16} We performed sensitivity analyses to account for emerging biases.

Statistical analysis

Random effects meta-analysis was undertaken using Review Manager version 5.3 (Cochrane Collaboration). Mean differences were used to pool continuous outcomes. Weighted mean differences were calculated using the inverse variance method. For studies in which mean and standard deviation were not provided, we estimated them using the median and range, as described previously.\textsuperscript{17} We reported heterogeneity as low ($I^2 = 0\%$ to $25\%$), moderate ($I^2 = 26\%$ to $50\%$), and high ($I^2 > 50\%$).\textsuperscript{18} We also conducted subgroup analyses according to the year of publication, timing of follow-up, baseline LVEF and the presence of viability testing. Furthermore, we tested the interaction between baseline LVEF and timing of follow-up. All results were reported as pooled weighted results with 95% confidence interval (CI), with statistical significance defined as a two-tailed p-value of less than 0.05.

Results

Study selection and patient characteristics

Our literature searches identified a total of 5992 references. The PRISMA flow chart is illustrated in Figure 1. After title and abstract screening, 5063 studies were excluded, leaving 640 studies for full text screening. Detailed review of these
articles led to the exclusion of 557 studies, leaving 83 studies including 6 double-arm and 77 single-arm studies (69 on CABG; 4 on PCI; 4 on MT) available for data extraction (Figure 1). The characteristics of the included studies were summarized in Supplemental Table 2 in the data availability section. Baseline patient characteristics are shown in Supplemental Table 3. Of a total of 7,157 patients, 6,061 underwent CABG, 747 underwent PCI, and 349 received MT. Myocardial viability testing was performed in 58% (48/83) of the studies. Of these included studies, 73 were rated as poor, 9 as fair and 1 as good quality using the New-Castle Ottawa Scale (Supplemental Table 4 in the data availability section).

LVEF recovery after CABG, PCI, or MT

Table 1 summarizes the mean difference (MD) in LVEF following different therapeutic approaches in patients with ischemic cardiomyopathy. The MD was calculated as LVEF_{after} – LVEF_{before} intervention. Figure 2 shows the forest plot of LVEF change in CABG, PCI and MT groups. Seventy-five studies reported changes in LVEF following CABG in 6,061 patients. There was a statistically significant increase in LVEF following CABG (MD 7.76; 95% CI: 6.81 to 8.70; PCI = percutaneous coronary intervention.

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Therapy</td>
<td>7</td>
<td>349</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>4.06 [-2.12, 10.24]</td>
</tr>
<tr>
<td>PCI</td>
<td>6</td>
<td>747</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>6.70 [4.71, 8.70]</td>
</tr>
<tr>
<td>CABG</td>
<td>75</td>
<td>6061</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.76 [6.81, 8.70]</td>
</tr>
</tbody>
</table>

*PCI = percutaneous coronary intervention.
*CABG = coronary artery bypass grafting.
‡IV = inverse variance.
§CI = confidence interval.
Figure 2. Forest plot of LVEF change in CABG, PCI and MT groups.
Six studies reported LVEF recovery following PCI in 747 patients. A statistically significant increase in LVEF was found following PCI (MD 6.70; 95% CI: 4.71 to 8.70; p < 0.0001; \( I^2 = 94\% \)). Seven studies reported LVEF after MT in 349 patients. There was no statistically significant change in LVEF following MT (MD 4.06; 95% CI: -2.12 to 10.24; p = 0.20; \( I^2 = 98\% \)).

**Sensitivity analyses**

We conducted several post-hoc subgroup analyses to account for the heterogeneity of the included CABG studies. Subgroup analyses were not feasible for PCI and MT, given the limited number of articles available.

**By publication date**

The included CABG studies ranged between 1980-2017. We stratified these studies as before 2000, 2000-2010 and after 2010 to account for improvements in surgical techniques and perioperative care over time. Overall, the MD in LVEF decreased over time while remaining statistically significant (Table 2).

**By timing of follow-up**

We stratified the CABG studies by the time period during which follow-up assessment of LV function was performed (immediately postoperatively, at 0-3 months, 3-6 months, 6-12 months and > 1 year) (Table 3). The magnitude of LVEF improvement was greatest during the first 3 months of follow-up. No obvious LVEF recovery trends were observed during the follow-up period.

**Table 2. Mean difference in LVEF following CABG, by year of publication (before 2000, 2000-2010, and after 2010).**

<table>
<thead>
<tr>
<th>Year of Publication</th>
<th>Studies</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 2000</td>
<td>22</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>9.36 [6.74, 11.99]</td>
</tr>
<tr>
<td>2000 – 2010</td>
<td>42</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.30 [6.02, 8.57]</td>
</tr>
<tr>
<td>After 2010</td>
<td>12</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>6.47 [4.00, 8.93]</td>
</tr>
</tbody>
</table>

*IV = inverse variance.
†CI = confidence interval.

**Table 3. Mean difference in LVEF following CABG over different timings of follow-up.**

<table>
<thead>
<tr>
<th>Timing of Follow-up</th>
<th>Studies</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Postop</td>
<td>8</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.09 [4.48, 9.69]</td>
</tr>
<tr>
<td>0 – 3 Months</td>
<td>19</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>8.51 [6.08, 10.93]</td>
</tr>
<tr>
<td>3 – 6 Months</td>
<td>14</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.68 [5.07, 10.29]</td>
</tr>
<tr>
<td>6 – 12 Months</td>
<td>24</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.59 [6.05, 9.13]</td>
</tr>
<tr>
<td>Beyond 1 Year</td>
<td>20</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.41 [4.77, 10.04]</td>
</tr>
</tbody>
</table>

*IV = inverse variance.
†CI = confidence interval.

**Table 4. Mean difference in LVEF following CABG with a baseline LVEF less than 30% vs. \( \geq 30\% \).**

<table>
<thead>
<tr>
<th>Baseline LVEF</th>
<th>Studies</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30%</td>
<td>51</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>8.41 [7.19, 9.63]</td>
</tr>
<tr>
<td>( \geq 30% )</td>
<td>25</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>5.92 [4.56, 7.29]</td>
</tr>
</tbody>
</table>

*IV = inverse variance.
†CI = confidence interval.
By baseline LVEF

We stratified the studies by baseline LVEF of < 30% and ≥ 30% (Table 4) and observed a numerically higher increase in LVEF in patients whose baseline function was < 30% (MD 8.41; 95% CI: 7.19 to 9.63; p < 0.00001; I² = 99%) as compared to those whose baseline LVEF was ≥ 30% (MD 5.92; 95% CI: 4.56 to 7.29; p < 0.00001; I² = 98%).

By baseline LVEF And timing of follow-up

In the immediate postoperative period, we observed a numerically higher magnitude of LVEF improvement in patients whose baseline function were ≥ 30% (MD 7.22; 95% CI: 1.33 to 13.11; p < 0.00001; I² = 99%) vs. MD 7.01; 95% CI: 3.59 to 10.43; p < 0.00001; I² = 100%). However, at other intervals of follow-up, those with a baseline LVEF of < 30% showed greater improvement in LVEF (Table 5).

By the presence of baseline viability testing

We stratified the CABG studies based on whether or not viability testing was performed (Table 6). A numerically greater magnitude of improvement in LVEF was observed in the absence of viability testing (MD 10.21; 95% CI: 8.42 to 12.00; p < 0.00001; I² = 99%) vs. MD 6.42; 95% CI: 5.25 to 7.59; p < 0.00001; I² = 98%).

Discussion

The current meta-analysis contributes to the literature by comprehensively examining the extent of LVEF recovery following revascularization and MT in patients with CAD and reduced LVEF. We observed an improvement in LVEF after revascularization by CABG or PCI but not with MT alone, and that CABG was associated with a numerically greater magnitude of LVEF improvement as compared to PCI and MT.

Table 5. Mean difference in LVEF following CABG as analyzed by baseline LVEF (less than 30% vs. ≥ 30%) and time out from surgery.

<table>
<thead>
<tr>
<th>Time of Follow-up</th>
<th>Studies</th>
<th>Statistical Method</th>
<th>Effect estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Postop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 30% LVEF ≥ 30%</td>
<td>5, 3</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.01 [3.59, 10.43]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.22 [1.33, 13.11]</td>
</tr>
<tr>
<td>0 – 3 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 30% LVEF ≥ 30%</td>
<td>14, 5</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>8.74 [5.75, 11.73]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.52 [3.97, 11.07]</td>
</tr>
<tr>
<td>3 – 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 30% LVEF ≥ 30%</td>
<td>15, 6</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>9.35 [6.75, 11.95]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>4.38 [1.02, 7.75]</td>
</tr>
<tr>
<td>6 – 12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 30% LVEF ≥ 30%</td>
<td>10, 9</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>7.04 [4.55, 9.54]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>6.60 [3.75, 9.46]</td>
</tr>
<tr>
<td>Beyond 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF &lt; 30% LVEF ≥ 30%</td>
<td>13, 7</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>9.26 [6.67, 12.84]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>4.08 [2.14, 6.02]</td>
</tr>
</tbody>
</table>

*LVEF = left ventricular ejection fraction.
†IV = inverse variance.
‡CI = confidence interval.

Table 6. Mean difference in LVEF following CABG with and without pre-operative myocardial viability testing.

Abbreviations: IV = inverse variance; CI = confidence interval.

<table>
<thead>
<tr>
<th>Viability Test</th>
<th>Studies</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Viability Test</td>
<td>51</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>6.42 [5.25, 7.59]</td>
</tr>
<tr>
<td>Without Viability Test</td>
<td>26</td>
<td>Mean Difference (IV, Random, 95% CI)</td>
<td>10.21 [8.42, 12.00]</td>
</tr>
</tbody>
</table>
We demonstrated that revascularization in the setting of CAD and severely reduced LVEF resulted in some degree of LVEF recovery. This observation could be physiologically explained by the restoration of blood flow to malperfused myocardium, which cannot be achieved with MT alone.19 Nonetheless, guideline-directed MT is associated with survival benefit in patients with CAD and reduced LVEF20–24 and should be prescribed in this patient group for that reason.25

The improvement in LVEF was numerically highest in patients who underwent CABG. This observation could be attributed to more frequent complete revascularization with CABG, as well as a higher likelihood of long-term patency of CABG grafts as compared to stents.26 Several trials have noted a greater need for repeat revascularization after PCI as compared to CABG, as well as a higher rate of adverse cardiovascular events; all of which may negate the left ventricular recovery process.27–30 In contrast, the creation of an epicardial conduit bypasses the culprit lesion and additional vulnerable plaques, reduces the likelihood of future cardiac events, and mechanistically optimizes LVEF recovery.31 This is especially important in the setting of ischemic cardiomyopathy, where the burden of coronary lesions is diffuse and anatomically complex; making complete revascularization and graft longevity more feasible with CABG.32,33

One must also consider the alternate explanation that studies of CABG and/or PCI may be confounded by selection bias, whereby patients who were deemed more likely to derive long-term benefits from revascularization were preferentially selected for these procedures over MT. This highlights the need for a randomized clinical trial to directly compare revascularization vs. MT, to determine the long-term efficacy of each strategy in terms of LVEF recovery.

A greater degree of LVEF recovery was observed following CABG in patients without preoperative viability testing. It is important to recognize that viability testing is not routinely performed in all patients with ischemic heart disease and it would usually be done in patients with less certainty of recovery. In the context of ischemic cardiomyopathy, the loss of LV contractile function occurs as a consequence of myocardial necrosis, scarring, stunning, or myocardial hibernation. Myocardial stunning results from brief ischemic insults and manifests as a reversible reduction in contractile function after flow is restored, whereas hibernating myocardium refers to viable but non-functioning myocardium that likely results from down-regulation of ventricular function thought to occur after repetitive ischemia and stunning. Perfusion is often observed to be reduced which may also be a down-regulation.34 Traditionally, both stunned and hibernating myocardium are regarded as important functional reservoirs with the potential to recover after restoration of blood flow by revascularization.35,36 It is this rationale that has driven the investigation of viability testing to predict the extent of LVEF recovery after revascularization.36–38 Interestingly, a recent study found no association between the amount of hibernating myocardium and LVEF recovery following CABG.39 The authors posit that chronic, severe reduction in coronary flow may reduce the likelihood of LVEF recovery even after restoration of flow. In addition, it is recognized the hibernating myocardium may take several months to a year to recover, and the long-term benefits of revascularization in the context of hibernating myocardium may be attributed to a reduction in arrhythmia, independent of LVEF recovery.

A secondary analysis of STICH trial data revealed that CABG had outcome benefit in the presence of proven myocardial viability, however there was no interaction between viability and treatment modality (CABG vs. MT) for the outcome of mortality.19 Therefore no conclusion could be drawn regarding the utility of viability testing, and its prognostic relevance remains uncertain.40 Alternatively, studies such as PARR2, showed a trend towards less cardiac death, myocardial infarction or cardiac rehospitalization with viability directed therapy in post-hoc analysis of patients whose treatment adhered to viability imaging recommendations40,41; as well as at experienced centers under a team based approach.42 Our observed lack of LVEF recovery in patients who underwent viability testing may in part be explained by the more prevalent use of this test in cases where treatment decision-making is difficult. In addition, the lack of clear viability cut-off values to guide revascularization decisions poses further limitations on this strategy.

In addition to potential survival benefit, LVEF recovery may also be associated with improved quality of life after CABG. Future revascularization trials could be designed to assess the impact of revascularization versus MT on LVEF recovery, as well as to explore the relationship between LVEF recovery and patient-oriented outcomes such as quality of life and disability-free survival.43

Limitations
The data available for the meta-analysis was derived solely from observational studies, as no RCTs met the inclusion criteria. In addition, large variations in patient demographics, regional differences in revascularization versus MT practices and outcomes, and the lack of standardization in the timing of follow-up LVEF assessments, as well as heterogeneity in LVEF assessment modality, likely contributed to the high degree of heterogeneity observed in the analysis. Lastly, the lack of comparative studies precluded comparative meta-analysis.
Conclusions
In this meta-analysis of studies of patients with CAD and LVEF ≤ 40%, revascularization by PCI or CABG was associated with a greater magnitude of LVEF recovery as compared to MT. There is continued need for RCT level evidence to elucidate the comparative effectiveness of revascularization versus medical therapy and to determine the clinical significance of LVEF recovery in this high-risk patient group.

Data availability
Open Science Framework. Left ventricular function recovery after coronary revascularization and medical therapy: a systematic review and meta-Analysis. DOI: https://doi.org/10.17605/OSF.IO/HCPT5.44

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

References


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