Comparing the effectiveness of revascularization interventions with medical therapy in patients with ischemic cardiomyopathy: A systematic review and meta-analysis

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Abstract

Background: Determining the effectiveness of cardiovascular interventions plays an important role in reimbursement decisions, health care pricing, and providing clinical guidance on the use of existing clinical technologies. This study aimed to review and analyze the effectiveness of revascularization interventions (CABG and PCI) compared to medical therapy in patients with ischemic cardiomyopathy.

Methods: Different databases were searched up to December 2017. The articles were selected based on inclusion and exclusion criteria. Quality of all studies was evaluated by Jadad score and relevant checklists. The I² test was used to test heterogeneity. Also, to integrate the results of similar studies, meta-analysis was done using STATA software.

Results: A total of 18 studies were included. Based on the random effects model, the overall results of comparing the effectiveness of revascularization interventions with medical therapy were as follow: 38.94 [95% CI: 26.95-50.94, p<0.001, I² = 99.6%, p<0.001], 75.31, [95% CI: 74.06-76.57, p<0.001, I² = 88.8, p<0.001], and 75.76 [95% CI: 71.99-79.53, p<0.001, I² = 99.2, p<0.001] for cardiac mortality rate, quality of life, and 5-year survival, respectively. Also, in patient satisfaction index, revascularization interventions were shown to be more effective than medical therapy.

Conclusion: This study showed that revascularization interventions in all studied indices were more effective than medical therapy. Also, between revascularization interventions, PCI was more effective in cardiovascular mortality and 5-year survival than CABG in terms of quality of life. Moreover, CABG was more effective than PCI. In patient satisfaction index, the results of the 2 included studies were contradictory.

Keywords: Effectiveness, Revascularization, Medical therapy, Ischemic cardiomyopathy

Conflicts of Interest: None declared
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Introduction

Ischemic cardiomyopathy is generally defined as left ventricular dysfunction due to severe coronary artery disease (CAD), myocardial infarction, or ongoing ischemic injury (hibernating myocardium) (4).

Despite major advances in cardiovascular therapy, cardiovascular disease remains the primary cause of death and disability in the industrialized world. Unfortunately, improved survival after acute myocardial infarction (MI) has been associated with an increased incidence of ischemic cardiomyopathy and heart failure. Patients with ischemic cardiomyopathy, defined as impaired left ventricular (LV), have high mortality rates and an impaired
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There are several methods for treating and controlling ischemic cardiomyopathy in different health systems in the world: (A) medical therapy (MT) which uses anticoagulants, such as thrombolytic, beta blocker, calcium blocker, antiarrhythmic, nitrates, diuretics, antiplatelet, and lipid regulating drugs; (B) percutaneous coronary intervention (PCI) that includes piercing the skin to access the femoral artery by a catheter, catheter-guided balloon to narrow or block the coronary artery, inflating the balloon, and dilating coronary stenting to prevent reblockage; and (C) coronary artery bypass graft (CABG) that includes a bypass with saphenous vein or arterial graft pieces of breast through open narrowed or blocked coronary stenosis in place. This is a surgical technique that involves opening the chest and the tight and closed coronary artery and is usually done using a vein or artery from other parts of the body (9-10).

The advantages of the surgical technique include angina relief in 60% to 90% of patients in the first year, a significant reduction in mortality due to cardiovascular disease when combined with drug therapy, and a reduction in revascularization after 1 year. However, its disadvantages are high costs-in particular hospital care costs- and an increase in myocardial infarction rate compared to drug therapy (13).

To date, no systematic reviews have been made on this topic. Medical treatment for coronary disease has advanced dramatically in recent years and produced prognostic benefits in the context of properly designed, randomized, controlled trials. Surgical techniques have also advanced, however, it is difficult to ensure that they have truly reduced mortality rate, as such comparisons are retrospective rather than concurrent. Even if the proportionate benefits from surgery were to increase, the falling mortality with optimal medical therapy would reduce the absolute benefits of surgery over medical treatment. Thus, surgical interventions seem to become outdated, and thus their relevance to modern medical practice must be questioned (16-17). A clinical trial study compared drug therapy with surgery in patients with ischemic heart disease and found no significant evidence on the benefit of these 2 therapies in reducing mortality and morbidity (10).

Performing systematic review studies and determining the effectiveness of cardiovascular interventions play an important role in reimbursement decisions, health care pricing, providing clinical guidance on the use of existing clinical technologies, strategic purchasing of interventions, providing targeted health care, and producing scientific evidence for policy-making and, ultimately, the optimal allocation of financial resources of the health sector to cardiovascular diseases (10, 20). Thus, the aim of this study was to review and compare the effectiveness of revascularization interventions (CABG and PCI) and medical therapy in patients with ischemic cardiomyopathy.

**Review of the literature**

**Protocol and registration**

This systematic review protocol was registered in PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42018079889) and published in Medicine (2018) 97:10(e9958).

**Study characteristics**

Data were extracted and presented according to PRISMA (providing innovative service models and assessment) criteria (22).

This systematic review included observational (case report, case series, cross sectional, case-control, cohort, etc.) and interventional (quasi-experimental studies, randomized controlled trials, etc.) studies in English and Persian language and examined the effectiveness of revascularization and medical therapy interventions in patients with ischemic cardiomyopathy. Animal studies were not considered.

**Participants**

This systematic review targeted studies conducted on ischemic cardiomyopathy patients with ejection fraction <35% who underwent percutaneous coronary intervention, surgery, or medical treatment.

**Report characteristics**

Only studies that had abstracts in English and those studies whose full-texts were available were selected. No limitation was considered for date of acceptance or publication. Also, only articles that were published or in press were considered.

**Information sources**

Our sources of information included electronic databases, trial registries, and different types of grey literature. An electronic search was performed in PubMed, Cochrane library, Scopus, Web of Science, EMBASE, Tufts Medical Center Cost-Effectiveness Analysis Registry, and NHS Economic Evaluations Database up to 12/30/2017. To identify appropriate key words, in addition to MESH terms, popular and commonly-used phrases stated in the related literature were used. For example, the search strategy in PubMed database was as follows: 1) Percutaneous coronary intervention [MeSH Terms] 2) Coronary artery bypass [MeSH Terms] 3) CABG [Title/Abstract] 4) Drug therapy [MeSH Terms] 5) Medical therapy [Title/Abstract] 6) Medical treatment [Title/Abstract] 7) Cardiomyopathies [MeSH Terms] 8) Cardiomyopathy [Title/Abstract] 9) Ischemia [Title/Abstract] 10) 1 OR 2 OR 3 11) 4 OR 5 OR 6 12) 7 OR 8 OR 9 13) 10 AND 11 AND 12

First, the search strategy was developed and completed in PubMed, then; a modified strategy was applied to other databases. Other sources were searched to identify related grey literature. ProQuest was searched for dissertations. Meeting abstracts were searched through SCOPUS and Web of Science. Also, reference lists of included studies...
were searched.

**Selection process**

Two authors independently performed the primary article screening. First, they reviewed the titles and abstracts of the articles independently. Then, the selected articles were categorized into 2 groups: relevant and irrelevant. Articles categorized as irrelevant by both reviewers were eliminated from the study. Then, each reviewer reviewed the full-text of the remaining articles and made a list. Then, the 2 lists were compared and nonconformities were discussed. In case of a disagreement, the entire team made the final decision.

**Data management**

Data were extracted from papers and entered into data sheets independently by 2 reviewers. These 2 sheets and their differences were checked by a third reviewer. Any potential difference of opinion among reviewers was discussed by the team members.

**Data extraction**

The following information was extracted from each article: article ID; author; publication year; study design; sample size; and our final outcomes, including heart mortality rate, survival rate, quality of life, and patient satisfaction (utility) rate. Heart mortality rate was the number of deaths during a particular period of time among patients with ischemic cardiomyopathy (26). The 5-year survival rate is the percentage of people who lived at least 5 years after being diagnosed with a certain disease (26, 28). Quality of life is the degree to which an individual is healthy, comfortable, and able to participate in or enjoy life events (29-31). Patient satisfaction is an important and commonly used indicator for measuring the quality of health care, which affects clinical outcomes, patient retention, and medical malpractice claims (33).

**Quality assessment**

Studies on quality of life were evaluated by the Jadad score, with a score between 0 and 5 based on randomization, blindness, a decrease in the number of samples during the study, and relevant checklists (34-35). To test heterogeneity, the I$^2$ test was used, and as there was heterogeneity or lack of studies, the random effects method was used. Percentages of around 25% (I$^2$ = 25), 50% (I$^2$ = 50), and 75% (I$^2$ = 75) were recognized as low, medium, and high heterogeneity, respectively (36). The funnel plot was used to detect publication bias in studies included in the meta-analysis, but there was no publication bias, as the distribution of studies was symmetric.

**Data synthesis**

To integrate the results of studies with similar results, meta-analysis was done using STATA software. Also, the results of the studies were analyzed based on the ES relevant outcome. Significance level was set at p<0.05 (37).

**Results**

Fig. 1. Flow diagram showing the process of study selection
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Table 1. The main characteristics studies included

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>Country/city</th>
<th>MT</th>
<th>CABG</th>
<th>PCI</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harindra C (1)</td>
<td>2011</td>
<td>Cohort</td>
<td>Canada</td>
<td>75</td>
<td>70</td>
<td>73</td>
<td>39131</td>
<td></td>
</tr>
<tr>
<td>Akira Marui (2)</td>
<td>2016</td>
<td>RCT</td>
<td>Japan</td>
<td>49.3</td>
<td>40.5</td>
<td>1212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Francesco Nudi (3)</td>
<td>2017</td>
<td>Observational</td>
<td>Italy</td>
<td>80</td>
<td>20</td>
<td>20</td>
<td>3786</td>
<td></td>
</tr>
<tr>
<td>Eric J. Velazquez (5)</td>
<td>2011</td>
<td>Cohort</td>
<td>North Carolina</td>
<td>43</td>
<td>29</td>
<td>36</td>
<td>1369</td>
<td></td>
</tr>
<tr>
<td>William E. Boden (8)</td>
<td>2007</td>
<td>RCT</td>
<td>New York</td>
<td>8.3</td>
<td>7.6</td>
<td>2287</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peter Carson (11)</td>
<td>2013</td>
<td>RCT</td>
<td>USA</td>
<td>31.4</td>
<td>26.6</td>
<td>1212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sahil Khera (12)</td>
<td>2017</td>
<td>RCT</td>
<td>New York</td>
<td>58</td>
<td>47</td>
<td>1212</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelle M (14)</td>
<td>2002</td>
<td>RCT</td>
<td>Canada</td>
<td>12.5</td>
<td>9.8</td>
<td>983</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Heart mortality | Terence Lin (7) | 2010 | RCT | Loma Linda | 3 | 6 | 1369 | p<0.001 |
|Survival| Daniel B. Mark (25) | 2014 | RCT | North Carolina | 74 | 77 | 1212 | df= 7 |
| QoL| Michelle M. Graham (27) | 2006 | RCT | Canada | 75.1 | 77.4 | 76 | 2940 | I²=88.8%
| and utility| Michelle M. Graham (27) | 2006 | RCT | Brazil | 70.8 | 75.2 | 76 | 579 | p<0.001 | df= 17 |

In this review, 2913 records were retrieved from electronic databases and manual searches. Search and study selection procedures are summarized in the PRISMA flow-diagram (Fig. 1). After removing duplicate articles, 2864 full-texts were assessed for eligibility. A total of 49 records were reviewed for full-text articles, of which 18 were included in the final analysis. Of the included studies, 23 compared PCI with CABG intervention or effects of one of them, and 8 studies did not contain sufficient information to extract related data.

All the included studies were published between 1970 and 2017. A total of 108 008 patients were included in the meta-analysis. All the patients included in the meta-analysis had ischemic cardiomyopathy. PCI arm included 39 012, CABG arm 24 439, and medical therapy arm 44 577 ischemic cardiomyopathy patients. The mean age of the participants was 66.09 years, and average proportions of patient characteristics showed that 77.1% of the participants were male. All 18 studies were coded as having low risk of bias within all categories.

Because of the great heterogeneity of the studies, the random-effects model and sensitivity analyses approach were selected and 3 studies (Terence Lin (7), William E. Boden (8) and Michelle M (14)) were excluded. Also, the impact of removing each of the studies was evaluated in the summary results but the results did not change. In this meta-analysis, both χ² based Q-statistic test and I² test were considered to assess heterogeneity across studies, and P-value less than or equal to 0.05 was considered significant. I² is a description of the variation across studies that is due to heterogeneity instead of chance.

Mortality rate in ischemic cardiomyopathy patients who underwent CABG was 34.46 [95% CI: 23.45-45.82, p<0.001, I²= 98.1%, p=0.001]. This index in the PCI intervention was [26.79]95% CI: 12.92-40.66, p<0.001, I²= 99.1%, p<0.001, I²= 99.6%, p<0.001] and it was 49.87 [95% CI: 27.78-71.97, p<0.001, I²= 99.6%, p<0.001] for MT. The overall result for this outcome was 38.94 [95% CI: 26.95-50.94, p<0.001, I²= 99.6%, p<0.001].

In the context of comparing revascularization interventions with medical therapy in quality of life, we concluded that this index was 76.71 [95% CI: 75.22-78.72, p=0.001, I²= 56%, p= 0.1] for CABG. Also, in the PCI intervention, this index was equal to 76 [95% CI: 75.51-76.49, p=0.00, I²= 99.1%, p=0.001, I²= 99.2%] and it was 73.18 [95% CI: 71.99-79.53, p<0.001, I²= 74.4, p = 0.02] for MT. The overall result for QoL (Quality of life) was 75.31 [95% CI: 74.06-76.57, p<0.001, I²= 88.8, p=0.001] (Table 1, Fig. 2).

In patient satisfaction and utility of therapeutic interventions, after searching for studies, we eventually came to 2 articles: Michelle M. Graham et al reported that patient satisfaction was 86.6%, 88.6%, and 87.4% for MT, CABG, and PCI, respectively. Moreover, Sara Michelly et al concluded that this index was 75.5%, 78%, and 80.9% for MT, CABG, and PCI, respectively.

According to Table 1 and Figure 4, the 5-year survival rate for PCI was 85.18 [95% CI: 81.63-88.72, p=0.001, I²= 99.4%, p=0.001]. Also, this rate was 79.35 [95% CI: 68.76-89.95, p<0.001, I²= 97.5, p<0.001] for CABG and it was 65.93 [95% CI: 54.27-77.59, p<0.001, I²= 99.6%, p<0.001] for MT. Also, the overall result for 5-year survival was 75.76 [95% CI: 71.99-79.53, p<0.001, I²= 99.2, p<0.001].
Discussion

To our knowledge, this study was the first comprehensive systematic review and meta-analysis to compare the effectiveness of revascularization interventions and medical therapy in patients with ischemic cardiomyopathy. Ultimately, 18 studies were included and effectiveness indicators, such as cardiac death rate, 5-year survival, and quality of life, were analyzed and patient satisfaction results were reported. In studies included in quantitative synthesis (meta-analysis), 2 examined effectiveness indicators, including cardiac mortality and survival (1, 5), and 2 studies done on quality of life examined the utility and

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<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harindra C</td>
<td>88.00 (87.40, 88.50)</td>
<td>5.00</td>
</tr>
<tr>
<td>Christopher M</td>
<td>37.00 (34.50, 39.50)</td>
<td>4.90</td>
</tr>
<tr>
<td>Jacques Claude</td>
<td>38.00 (38.40, 48.80)</td>
<td>3.66</td>
</tr>
<tr>
<td>Sandra Weiss</td>
<td>87.80 (85.70, 89.60)</td>
<td>4.94</td>
</tr>
<tr>
<td>Vijay Raja</td>
<td>61.00 (50.20, 70.20)</td>
<td>3.70</td>
</tr>
<tr>
<td>William E. Boden</td>
<td>87.00 (84.90, 88.80)</td>
<td>4.94</td>
</tr>
<tr>
<td>Bimal R. Shah</td>
<td>47.00 (41.20, 52.80)</td>
<td>4.47</td>
</tr>
<tr>
<td>Deborah H</td>
<td>53.00 (46.00, 60.00)</td>
<td>4.27</td>
</tr>
<tr>
<td>Michelle M</td>
<td>91.00 (88.20, 93.10)</td>
<td>4.90</td>
</tr>
<tr>
<td>Subtotal (I-squared = 99.6%, p = 0.000)</td>
<td>65.03 (54.27, 77.59)</td>
<td>40.78</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harindra C</td>
<td>92.00 (91.30, 92.50)</td>
<td>5.00</td>
</tr>
<tr>
<td>Christopher M</td>
<td>61.00 (55.60, 66.20)</td>
<td>4.55</td>
</tr>
<tr>
<td>Jacques Claude</td>
<td>79.00 (69.00, 86.40)</td>
<td>3.95</td>
</tr>
<tr>
<td>Bimal R. Shah</td>
<td>73.00 (64.90, 80.10)</td>
<td>4.16</td>
</tr>
<tr>
<td>Deborah H</td>
<td>75.00 (69.10, 80.30)</td>
<td>4.51</td>
</tr>
<tr>
<td>Michelle M</td>
<td>95.00 (89.40, 97.80)</td>
<td>4.71</td>
</tr>
<tr>
<td>Subtotal (I-squared = 97.5%, p = 0.000)</td>
<td>79.95 (78.76, 89.95)</td>
<td>26.88</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
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</tr>
<tr>
<td>Harindra C</td>
<td>92.00 (91.50, 92.50)</td>
<td>5.00</td>
</tr>
<tr>
<td>Sandra Weiss</td>
<td>88.30 (80.20, 95.00)</td>
<td>4.94</td>
</tr>
<tr>
<td>Vijay Raja</td>
<td>69.00 (59.90, 77.50)</td>
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<td>William E. Boden</td>
<td>90.00 (88.10, 91.66)</td>
<td>4.95</td>
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<td>Bimal R. Shah</td>
<td>73.00 (64.90, 80.10)</td>
<td>4.16</td>
</tr>
<tr>
<td>Deborah H</td>
<td>75.00 (69.19, 80.38)</td>
<td>4.51</td>
</tr>
<tr>
<td>Michelle M</td>
<td>93.00 (89.50, 95.70)</td>
<td>4.84</td>
</tr>
<tr>
<td>Subtotal (I-squared = 94.0%, p = 0.000)</td>
<td>85.18 (81.63, 88.72)</td>
<td>32.33</td>
</tr>
<tr>
<td>Overall (I-squared = 99.2%, p = 0.000)</td>
<td>75.76 (71.99, 79.53)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Fig. 4. The Forest plot of 5-year survival in PCI, CABG, and medical therapy in ischemic cardiomyopathy

Revascularization interventions in ischemic cardiomyopathy patients are more effective than medical therapy in preventing cardiac mortality. Also, cardiac mortality rate in PCI was lower than CABG intervention and, as a result, PCI was more effective than CABG. Pursani et al, in a systematic review and meta-analysis of 12 randomized trials, compared PCI and MT in 7182 stable ischemic heart disease patients and found a strong trend for lower mortality with PCI (38). Schömig et al reported similar trends from 17 trials of PCI versus OMT in 7513 stable ischemic heart transplant recipients with coronary allograft vasculopathy (40). They found that PCI was associated with a significant reduction in all-cause mortality (39). Luc et al reported that compared to patients who had PCI, those who underwent CABG had a higher early mortality and overall mortality, but there was no difference in cardiac-related mortality in heart transplant recipients with coronary allograft vasculopathy (40).

The 5-year survival rate in revascularization interventions is greater than medical therapy. Also, this rate is different between revascularization interventions and is more in PCI intervention than CABG. A previous network meta-analysis comparing percutaneous coronary intervention with medical treatment was limited to the inclusion of early generation paclitaxel eluting stents and sirolimus eluting stents and observed no benefit in medical treatment in terms of survival (41). In another study, long-term survival was not significantly different between PCI and CABG among patients in whom coronary revascularization was clinically indicated, and both procedures were technically feasible for these patients (42). Thus, despite this similarity in long-term survival, several distinct differences between these alternative coronary revascularization procedures may affect the choice of procedure. The most important finding of this analysis was that several revascularization techniques, such as coronary artery bypass grafting and percutaneous coronary intervention, were found to be associated with improved survival compared to an initial strategy of medical therapy alone among patients with ischemic cardiomyopathy.

PCI and CABG had improved QoL. Both were significantly better than medical therapy but did not differ from each other. These findings were consistent with those of Blankenship et al (43) who concluded that PCI decreases angina and the need for anti-anginal medications and increases exercise capacity and QoL, compared to baseline status and medical therapy without PCI (Jokinen et al) (44). However, these authors examined only PCI and only CABG, respectively. A discussion exists in the literature regarding the instruments used in QoL research. In this study, all studies used valid and reliable measures. However, most of them used generic rather than disease specific measures. As there has been no agreed upon definition of QoL, results produced by various measurements may vary significantly because each instrument may include mutual as well as different domains, depending on the

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theoretical framework used by the authors.

Results of this study indicated that PCI and CABG, as initial treatments, were associated with higher utility and patient satisfaction compared to MT. Also, between the revascularization interventions, results of the 2 included studies were different and contradictory with regards to patient satisfaction. The overall results of this study are not directly comparable with those of previous studies because we applied this research tool in a study that compared 3 therapeutic strategies simultaneously. Hlatky MA et al reported that utility was more favorable among CABG patients for the first year, which was different from our results, although the values became similar thereafter (45).

Conclusion

This study showed that revascularization interventions in all indices are more effective than medical therapy. Also, between revascularization interventions, PCI in cardiovascular mortality and 5-year survival were more effective than CABG. Also, in terms of quality of life, CABG was more effective than PCI. However, with regards to patient satisfaction index, the results of the 2 included studies were different contradictory. Thus, both CABG and PCI are reasonable options for patients with ischemic cardiomyopathy. Current evidence dictates that despite advances in CABG, patients with ischemic cardiomyopathy are better served with PCI intervention.

Limitations

As with any meta-analysis, the conclusions drawn from such data are subject to the limitations of the original studies. Similarly, due to the lack of patient level data, we could not account for different follow-up times and for censoring or drop-outs by performing any meaningful survival analysis.

Acknowledgments

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Conflict of interests

The authors declare that they have no competing interests.

References

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