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Long-term outcomes after revascularization and medical therapy in premature coronary artery disease for cost-effectiveness study: A systematic review protocol

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Abstract:

BACKGROUND: The long-term outcomes are important concepts for cost-effectiveness analysis in patients with premature coronary artery disease after revascularization (coronary artery bypass grafting [CABG] and percutaneous coronary intervention [PCI]) and medical therapy (MT). The finding of this study will be used to calculate the events probabilities for cost-effectiveness study.

METHODS AND ANALYSIS: This systematic review will use studies in which patients age must be 18–60 years in eligible studies that obtained from PubMed, Web of Science, Scopus, and Embase. We will assess the long-term outcomes after CABG, PCI, and MT by random-effects meta-analysis and effects will be shown by risk ratio. We will ascertain the probabilities of adverse events during certain periods and then outcomes will compare separately based on specific characteristics.

CONCLUSION: This study will provide information related to outcomes of CABG, PCI, and MT in patients with premature coronary artery disease. Doing this systematic review is valuable from clinically and economically aspects such as cost-effectiveness and cost-utility analysis.

Keywords:

Cost-effectiveness, premature coronary artery disease, revascularization

Introduction

Undoubtedly, patients with coronary artery disease (CAD) benefit from coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), and MT.^[1-5] These common treatments, which are often invasive, have increased in many countries, such as the United States, even among young people.^[6] Despite the fact that patients PCAD undergoing invasive treatment and medical therapy have fewer fatal and nonfatal events, there is no convincing reason why this is insignificant because the survival of the

younger generation is very important which is directly related to the adverse long-term events.^[7] Many studies have reported limited research accomplished on the effects of treatments in patients with PCAD and in these few studies, the report of the consequences is scattered.^[8-10] At the same time, suitable systematic reviews were conducted on the outcomes of CAD after CABG, PCI, and MT, However, none of them exactly address the details of long-term outcomes among the young patients.^[11-14]

Determining the probabilities of long-term adverse events after CABG, PCI, and MT

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in patients with PCAD is part of the effectiveness and effectiveness is part of the cost-effectiveness, and the cost-effectiveness is the most common method of the health economic evaluation.^[15,16] Thus, outcomes, especially long-term adverse events, are closely related to life expectancy, the time horizon, and the Markov model in the health economic evaluations.^[17-20] The Markov model, as the most common model of health economics, consists of health state cycles, which plays a categorical role in determining the cost-effectiveness of therapeutic interventions.^[16,19-23] Therefore, determining effectiveness is a very sensitive issue that all factors should be considered to get more precise results in choosing and making cost-effectiveness decisions.^[16,21,24-28] Many demographic, clinical, and risk factors are effective factors on long-term outcomes that have been considered in various studies, in the meantime, a special characteristic such as age is most decisive.^[26,29-32]

In one of the most relevant meta-analyses ever performed on long-term adverse events of CAD patients, 28% of the samples were under 55-year-old. About 10% and 8% of patients who underwent CABG and PCI died, respectively.^[1] In another of the most relevant meta-analysis studies, selected studies have different designs. In this Bayesian cross-design and network meta-analysis from the 12 studies that compared CABG with PCI, 4 and 8 were randomized controlled trial (RCT) and observational, respectively, and from the 7 studies that compared CABG with MT, 2 and 5 were RCT and observational, respectively.^[11] Using this type of meta-analysis, it was found that CABG's 1-year mortality rate did not differ much from PCI in randomized clinical trials (odds ratio [OR], 0.99; 95% Bayesian credible interval, 0.67–1.43).^[11]

PCI may be a better option for young patients than CABG, but among diabetics, regardless of age, CABG may be a better option.^[1,10] Therefore, in addition to determining the probability of long-term events after common therapeutic interventions in PCAD, there is another issue: What is the result of comparing adverse events based on specific characteristics? The primary goal of our study is to determine the probabilities of events in PCAD after CABG, PCI, and MT. The secondary goal of the study is to compare each treatment intervention with the same treatment based on at least two specific clinical characteristics or specific risk factors. Therefore, this goal represents a wider range of current effectiveness and cost-effectiveness that is usable in future studies. The results of such a study will be used for determining the probabilities of cardiac adverse events for placement in the Markov model for cost-effectiveness study.

Materials and Methods

Study design and setting

Since limited studies have been published on the long-term outcomes of CABG, PCI, and MT in patients with PCAD, all three types of original studies including observational, cohort, and randomized trial will be considered. In other words, it is not obligatory to have a control group in the eligible studies. Other publications will be excluded, such as the case reported, abstracts, and epidemiological. The sample size and duration of the follow-up periods of publications should not be less than 100 cases and 6 months, respectively.

Year of publication: Only studies published in 2005 and after (to reduce time bias) will be included because we consider new results.

Language: Only English and Persian language studies will be included.

Assessment of methodological quality and risk of bias of included studies: Methodological quality of eligible studies will be assessed using the criteria of the SIGN checklist (<https://www.sign.ac.uk/checklists-and-notes.html>). We will try to avoid the impact of quality rates on the polling results of studies, and we will only mention the differences in studies from this perspective in the discussion section. If the methodological explanations of the study are not sufficient, we will have difficulty in prioritizing the quality of the studies. For this purpose, the corresponding author will be contacted. If a convincing methodological answer or information is not obtained, the unclear quality situation is assigned to a related study. With the help of independent out-of-team raters, the risk of bias will be assessed in eligible studies. If the results are not much different from ours, we will report the results together with their help. However, if there are many differences, we will resolve the differences through a third rater.

Assessment of heterogeneity: To evaluate the heterogeneity between the studies, it will be tried to use appropriate tests such as the standard Chi-square test and Higgins I2 statistics. The Chi-square standard test will be used to evaluate the asymmetry based on specific clinical features, and the Higgins A2 statistic will be used to evaluate the overall inefficiency of the studies. The lower the I2 from 50% to zero, the more homogeneous the studies will be, otherwise, the studies will be more heterogeneous. We will also calculate the interactions between risk factors and outcomes using a random-effects meta-analysis (95% confidence interval for OR, relative risk, or Hazard ratio).

Data synthesis and evaluation of risk factors: Since studies can have different researchers, different

times, and different designs, we avoid fixed-effect meta-analysis as much as possible because the probability of bias increases significantly.^[11] Initially, events are determined after receiving each of the three therapeutic interventions (Cabg, Pci, And MT) over specific time of periods. This is done by general adjustment of effective factors including patients' clinical manifestations, risk factors, and study characteristics (study time, year of publication, sample size, study design, etc.). The adjustment and weighting of these items is based on the "Sensitivity analysis" section. If no study is found which compared at least two specific treatment interventions, the network meta-analysis will be used to compare these. If patients in some studies have a number of specific characteristics, the outcomes of a therapeutic intervention are compared based on the specific characteristics of the patients. These comparisons will be shown by forest Plot. For example, it may be from five observational studies founded that examined PCI outcomes, three studies are related to diabetic patients and two studies are related to ST-elevation myocardial infarction (STEMI) patients. In this case, we will show a comparison of PCI outcomes among diabetic and STEMI patients with forest plot. Differences between therapeutic interventions after adjustment of effective factors and the differences between specific characteristics will be reported using confidence intervals or *t* and *P* values.

Sensitivity analyses: Before the general calculation of outcomes separately for each of the treatments, to measure the components affecting the outcomes, univariate sensitivity analysis and probabilistic sensitivity analysis will be performed. In a one-way sensitivity analysis, the effect of the amount of change of a component (e.g., STEMI) on the amount of one of the adverse events is measured.

This process is performed for other required components (such as risk factors and clinical manifestations). As a small change in the component leads to a large change in the event, it is said that the event is sensitive to the component, otherwise, the results are resistant to the modified component. Furthermore, the results of the unilateral definitive sensitivity analysis are plotted in the form of a Tornado diagram.^[33,34]

Subgroup analyses: Main groups are type of treatments (CABG, PCI, and MT) and subgroups are based on the following:

- Special clinical manifestation: STEMI/UNSTEMI, stable/unstable angina, multivessel/two-vessel/single-vessel disease, heart failure, and left ventricular systolic dysfunction are the special clinical manifestation

- PCAD with special risk factors: PCAD with special risk factors included family history, current smoker, diabetes mellitus, hypertension, and hyperlipidemia
- Other characteristics: Other characteristics included ethnicity and nationality.

Our point from "special" is the existence of 100% frequency in patients. In other words, subgroups will be 100% frequency in one of the characteristics.

Narrative synthesis: If the narrative synthesis is required, a predeveloped narrative synthesis method will be used.^[35] For example, the number of studies may be low or there may be a problem with the heterogeneity of the results, which makes it difficult to pooling of quantitative data. In this method, a number of techniques are used to discover the relationships between studies. The studies are then weighted according to different methods to be used in the final polling. In one of the methods, studies are weighted according to four criteria (trustworthiness, appropriateness, relevance, and overall weight). Low, medium, and high grades are assigned to each of the criteria in each study. Due to the severity of the defect in quantitative data, inconsistencies, and the process of performing the work, the most appropriate way to display the results and methods will be applied.

Assessment of meta-bias: The bias in meta-analysis can be detected by funnel plot and Egger statistical test.^[36] The higher the funnel plot asymmetry is equal to the higher of the meta-analysis bias.

Sources of funnel plot asymmetry (that is bias in meta-analysis) may be due to the following:

- Selection bias: Publication bias; Probability of identifying relevant trials for metaanalysis is also influenced by their results. Location biases; Location biases included English language bias, citation bias, and multiple publication bias.

True heterogeneity: Size of the effect differs according to the study size: intensity of intervention and differences in underlying risk.

Data irregularities:

- Poor methodological design of small studies
- inadequate analysis.

Fraud:

- Artfactual
- Choice of effect measure
- Chance.

Confidence in cumulative evidence: Using grading quality of evidence and strength of recommendations (GRADE), the strength of systematic review results will be judged.^[37,38]

Amendments: Depending on the type and volume of studies found, we may need corrections. We will try to improve the scope of the information provided by the systematic review to eliminate it. Therefore, in case of possible corrections, a list of all corrective cases will be mentioned in the study method.

Study participants and sampling

Studies with the following cases' conditions will be considered for inclusion:

- The minimum and maximum age of patients should be 18 and 60 years, respectively (because this age range is related to premature CAD)^[2,5]
- Patients who undergoing at least one the CABG, PCI, and MT treatment
- Patients were followed for at least 6 months
- In addition to three types of foreside treatments, comparison groups can be based on other characteristics (gender, age, risk factors, clinical manifestations, etc.)
- Patients did not undergo other treatments (eg., pacemakers and valve surgery).

Types of interventions, exposures, and risk factors: At least one of three types of CABG, PCI, and MT therapy should be included in the study [Figures 1 and 2]. There are no restrictions about risk factors, clinical manifestations and demographic and baseline characteristics. In addition, patients with special characteristics (100% feature in all samples) will also be considered. In this manner, the difference between specific characteristics will be obvious in each treatment.

Outcomes: All-cause death, cardiac death, myocardial infraction (MI), stroke, and re-revascularization included in our outcomes [Figures 1 and 2]. These will be our long-term adverse events that at least two of them must have been reported in the study, no secondary outcomes have been considered.

Data collection tool and technique

PubMed, Embase, Medline, and Web of Science are our information sources. If the number of studies found is not sufficient, will be searched using the other information sources. All search restrictions will be observed including medical interventions, auto commands, study designs, and adaptation of search engine data database strategies. Studies that have examined only hospital outcomes (short-term outcomes) will be excluded.

Search strategy: Search keywords will consist of three parts (The strategy search table is shown in Additional file 1)

- CAD, coronary heart disease, and arteriosclerosis
- Revascularization, CABG, PCI, and medical treatment (MT)
- Long-term outcomes (adverse events): All-cause deaths, cardiac death, MI, and stroke.

Health information experts to set up search strategies will combine all keywords. The title of each category may be considered a keyword component.

Selection of studies and data management: Reading the study titles and abstracts will be managed using the EndNote X8 software. The two reviewers will check the titles and abstracts independently. After identifying and eliminating of duplicate studies in this software, two reviewers will divide them into two related and unrelated groups. Then, in addition to two independent readers, separately, one of the authors will also select appropriate relevant studies to extract their full text.

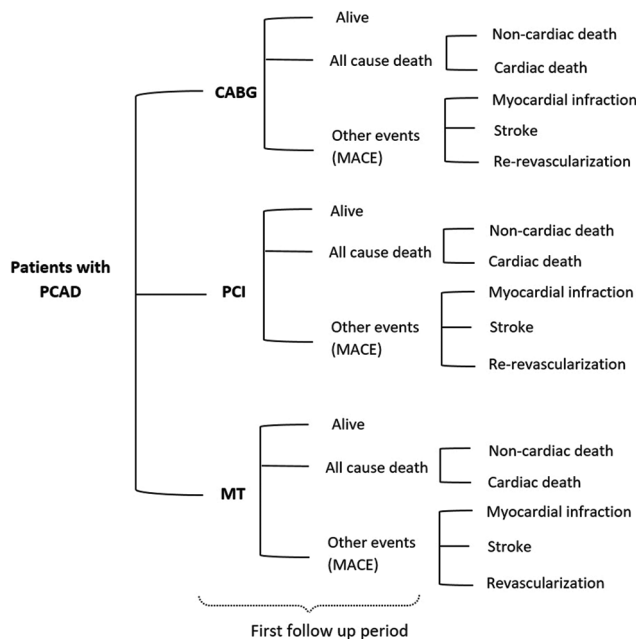


Figure 1: Decision tree of patients with PCAD

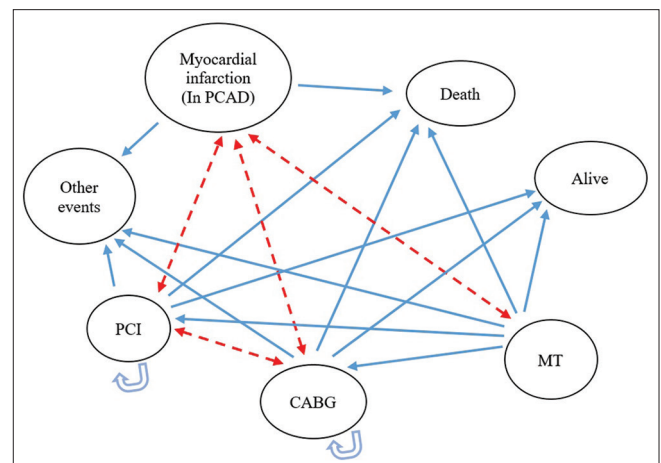


Figure 2: Markov model of patients with PCAD after follow-up

Then, the team of authors will review the full text of all three persons for the final selection (extracting of eligible studies).

Data extraction: We will report all information about long-term events, history of events, patient characteristics, patient risk factors, and study features in an initial form. This will be done by two independent authors. Then, the data mining form is compared by other team members. Then, the form of these two authors will be compared by other team members. Finally, given the amount of data available, each data set will be selected separately for the final analysis in a separate form. For example, if we have a very small percentage of stroke history data (for example, a maximum of 10%) of their studies, we will not consider these data for final analysis. A separate form will be the final data extraction form, which originates from the original data extraction form. The corresponding author may be contacted because of the lack of data transparency. For example, smoking, which is a risk factor, can be reported in three different ways and each of these ways may overlap:

- Smoking in the present
- Smoking in the past
- Smoking in the present and past.

If the time of this risk factor is not clear or the exact definition is not available in the study, the corresponding author will be contacted. In another example, there may be overlap in a repeat revascularization event because this event can consist of at least two of the following:

- CABG
- PCI
- Target-lesion revascularization
- Target-vessel revascularization.

Therefore, the corresponding author may be contacted to clarify such data.

Dealing with missing data: There may be a brief reference to some of the essential data in the publication or it may not be available at all. The most important of these data are long-term outcomes. Long-term outcomes may be reported collectively, that is, they may not be reported separately, or they may be displayed in the form of Kaplan–Meier charts without many crude data. In this case, the corresponding author will be contacted to obtain the outcomes separately for each case or crude frequency.

Ethical consideration

The Ethics Committee of Iran University of Medical Sciences approved the research protocol (Approval ID: IR. IUMS. REC.1397.1363). The protocol of this systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) on July 8, 2020 (registration number CRD42020189837), and as

much as possible, this protocol was written using the framework defined in the "PRISMA-P" checklist.^[33]

Discussion

The results of such a study are important in two aspects: from the clinical aspect, so far, no review has examined this issue in premature heart patients specifically and from the economical aspect, to determine the cost-effectiveness of three therapeutic interventions (CABG, PCI, and MT) using economic assessment models such as the Markov model; we need information on the probability of events (transition probability between different health conditions) for each of the interventions over a period. Therefore, this systematic review will provide an important segment of the effectiveness information of an economic evaluation study.

The most relevant and closest meta-analyses ever conducted on this subject are Hlatky and Bittle studies.^[1,11] All selected studies in Hlatky study are randomized trials; there is no mention of noninvasive treatment; it has not been reported adverse events separately; and there is no table of overall clinical outcomes for the young age range, which is most important. Almost all of these deficiencies are present in the Bittle study, except that the Bittle meta-analysis has a greater variety of studies (RCT, observational, and matched cohort).

The primary goal of our study is to determine the probabilities of events in PCAD after CABG, PCI, and MT. The secondary goal of the study is to compare each treatment intervention with the same treatment based on at least two specific clinical characteristics or specific risk factors. Therefore, this goal represents a wider range of current effectiveness and cost-effectiveness that is usable in future studies. The results of such a study will be used for determining the probabilities of cardiac adverse events for placement in the Markov model.

Ethics approval and consent to participate

This study was evaluated by the Research Ethics Committee of Iran University of Medical Sciences; Approval ID was IR. IUMS. REC.1397.1363; Approval date: 2019-02-24.

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Conflicts of interest

There are no conflicts of interest.

References

- Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: A collaborative analysis of individual patient data from ten randomised trials. *Lancet* 2009;373:1190-7.
- Maleki M, Alizadehasl A, Haghjoo M. ST-segment elevation myocardial infarction. In: *Practical Cardiology*. Ch. 19. Philadelphia, PA: Elsevier; 2017. p. 311-28.
- Mäkikallio T, Holm NR, Lindsay M, Spence MS, Erglis A, Menown IB, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): A prospective, randomised, open-label, non-inferiority trial. *Lancet* 2016;388:2743-52.
- Patterson T, McConkey HZ, Ahmed-Jushuf F, Moschonas K, Nguyen H, Karamasis GV, et al. Long-term outcomes following heart team revascularization recommendations in complex coronary artery disease. *J Am Heart Assoc* 2019;8:e011279.
- Witberg G, Leviner D, Sharon A, Boulus Y, Sharoni E, Vaknin-Assa H, et al. CABG is associated with improved long term outcomes compared to PCI in patients with premature coronary artery disease. *Eur Heart J* 2016;37:475.
- Khera S, Kolte D, Gupta T, Subramanian KS, Khanna N, Aronow WS, et al. Temporal trends and sex differences in revascularization and outcomes of ST-segment elevation myocardial infarction in younger adults in the United States. *J Am Coll Cardiol* 2015;66:1961-72.
- Petrie MC, Jhund PS, She L, Adlbrecht C, Doenst T, Panza JA, et al. Ten-year outcomes after coronary artery bypass grafting according to age in patients with heart failure and left ventricular systolic dysfunction: An analysis of the extended follow-Up of the STICH trial (Surgical Treatment for Ischemic Heart Failure). *Circulation* 2016;134:1314-24.
- Dalén M, Ivert T, Holzmann MJ, Sartipy U. Coronary artery bypass grafting in patients 50 years or younger: A swedish nationwide cohort study. *Circulation* 2015;131:1748-54.
- Azar FE, Solhi M, Darabi F, Rohban A, Abolfathi M, Nejhadadgar N. Effect of educational intervention based on PRECEDE-PROCEED model combined with self-management theory on self-care behaviors in type 2 diabetic patients. *Diabetes Metab Syndr*. 2018;12 (6):1075-8.
- Sattar N, Rawshani A, Franzén S, Rawshani A, Svensson AM, Rosengren A, et al. Age at diagnosis of Type 2 diabetes mellitus and associations with cardiovascular and mortality risks. *Circulation* 2019;139:2228-37.
- Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SL, American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation* 2013;127:2177-85.
- Deb S, Wijeyesundera HC, Ko DT, Tsubota H, Hill S, Fremes SE. Coronary artery bypass graft surgery vs percutaneous interventions in coronary revascularization: A systematic review. *JAMA* 2013;310:2086-95.
- Fulcher J, Mihaylova B, O'Connell R, Emberson J, Blackwell L, Reith C, et al. Efficacy and safety of statin therapy in older people: A meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;393:407-15.
- Simoons ML, Windecker S. Controversies in cardiovascular medicine: Chronic stable coronary artery disease: Drugs vs. revascularization. *Eur Heart J* 2010;31:530-41.
- Kirchberger I, Meisinger C, Seidl H, Wende R, Kuch B, Holle R. Nurse-based case management for aged patients with myocardial infarction: Study protocol of a randomized controlled trial. *BMC Geriatr* 2010;10:29.
- Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;11:1-160, iii-iv.
- Fearon WF, Bornschein B, Tonino PA, Gothe RM, Bruyne BD, Pijls NH, et al. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation* 2010;122:2545-50.
- Gillespie P, Murphy E, Smith SM, Cupples ME, Byrne M, Murphy AW. Long-term cost effectiveness of cardiac secondary prevention in primary care in the Republic of Ireland and Northern Ireland. *Eur J Health Econ* 2017;18:321-35.
- Kourlaba G, Gourzoulidis G, Andrikopoulos G, Tsioufifis K, Beletsi A, Maniadakis N. Economic evaluation of trimetazidine in the management of chronic stable angina in Greece. *BMC Health Serv Res* 2016;16:520.
- Trapero-Bertran M, Muñoz C, Coyle K, Coyle D, Lester-George A, Leidl R, et al. Cost-effectiveness of alternative smoking cessation scenarios in Spain: Results from the EQUIPTMOD. *Addiction* 2018;113 Suppl 1:65-75.
- Clement FM, Ghali WA, Rinfret S, Manns BJ, APPROACH Investigators. Economic evaluation of increasing population rates of cardiac catheterization. *BMC Health Serv Res* 2011;11:324.
- Foglia E, Bonfanti P, Rizzardini G, Bonizzoni E, Restelli U, Ricci E, et al. Cost-utility analysis of lopinavir/ritonavir versus atazanavir+ritonavir administered as first-line therapy for the treatment of HIV infection in Italy: From randomised trial to real world. *PLoS One* 2013;8:e57777.
- Lamotte M, Annemans L, Evers T, Kubin M. A multi-country economic evaluation of low-dose aspirin in the primary prevention of cardiovascular disease. *Pharmacoeconomics* 2006;24:155-69.
- Ennis S, Lobley G, Worrall S, Powell R, Kimani PK, Khan AJ, et al. Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): Study protocol for a randomised controlled trial and economic evaluation. *BMJ Open* 2018;8:e019748.
- Gorenoi V, Schönermark MP, Hagen A. CT coronary angiography vs. invasive coronary angiography in CHD. *GMS Health Technol Assess* 2012;8:Doc02.
- Oldridge N, Taylor RS. Cost-effectiveness of exercise therapy in patients with coronary heart disease, chronic heart failure and associated risk factors: A systematic review of economic evaluations of randomized clinical trials. *Eur J Prev Cardiol* 2020;27:1045-55.
- Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA, APPROACH Investigators. Economic evaluation of sirolimus-eluting stents. *CMAJ* 2005;172:345-51.
- Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: A systematic review and economic evaluation. *Health Technol Assess* 2008;12:iii, ix-x, 1-86.
- McEwan P, Bennett H, Ward T, Bergenheim K. Refitting of the UKPDS 68 risk equations to contemporary routine clinical practice data in the UK. *Pharmacoeconomics* 2015;33:149-61.
- Murphy S, Raisanen L, Moore G, Edwards RT, Linck P, Williams N, et al. A pragmatic randomised controlled trial of the Welsh National Exercise Referral Scheme: Protocol for trial and integrated economic and process evaluation. *BMC Public Health* 2010;10:352.
- Robertson C, Archibald D, Avenell A, Douglas F, Hoddinott P, van Teijlingen E, et al. Systematic reviews of and integrated report on the quantitative, qualitative and economic evidence base

- for the management of obesity in men. *Health Technol Assess* 2014;18:v-vi, xxiii-xxix, 1-424.
32. Sharma P, Boyers D, Boachie C, Stewart F, Miedzybrodzka Z, Simpson W, *et al.* Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia: A systematic review and economic evaluation. *Health Technol Assess* 2012;16:1-266.
 33. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
 34. Jeffrey A, Iyengar S GJ. Sensitivity analysis and diagnostics. *Res Synth Methods* 2009;417:316-33.
 35. Ferdosi M, Vatankhah S, Khalesi N, Ebadi Fard Azar F, Ayoobian A. Designing a referral system management model for direct treatment in social security organization. *Journal Mil Med.* 2012;14 (2):129-35.
 36. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997;315:629-34.
 37. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, *et al.* Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res* 2004;4:38.
 38. Azar FE, Asiabar AS. Does leadership effectiveness correlates with leadership styles in healthcare executives of Iran University of Medical Sciences. *Med J Islam Repub Iran.* 2015;29:166.