The Effects of Geography on Outcomes of Routine Early Versus Selective Late Revascularization Strategy in the Treatment of Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction: A Meta-Analysis of Transatlantic Randomized Controlled Trials

Hafeez Ul Hassan Virka, d, Kevin Bryan Loa, Chayakrit Krittanawongb, Faisal Inayata, Usman Sarwarc, Ali Raza Ghanc, Christian Witzkea, Sean Janzerd, Jon C. Georgea, Gregg Pressmana, Behnam Bozorgniaa, Saurav Chatterjeec, Vincent M. Figueredoa

Abstract

Background: The optimal timing of revascularization in unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) remains uncertain. We compared routine early revascularization (REV) versus selective late revascularization (SLR) strategies and divergence in the approach of cardiologists in the United States and Europe.

Methods: Seventeen randomized controlled trials (RCTs) (15,812 patients) were extracted from PubMed, Cochrane Library, EMBASE and Web of Science databases. The data were pooled using the Der Simonian and Laird random-effect models and expressed as pooled risk ratios (RR) with 95% confidence intervals (95% CIs).

Results: Overall, there was no difference in all-cause mortality (RR: 1.01, 95% CI: 0.95 - 1.08, P = 0.7), myocardial infarction (MI) (RR: 0.98, 95% CI: 0.79 - 1.22, P = 0.85) or coronary artery bypass grafting (CABG) (RR: 1.33, 95% CI: 0.92 - 1.91, P = 0.12) between REV and SLR strategy. There were trends of decreased incidence of MI in REV, 13.3% (1,029/7,704) vs. 15.1% (1,108/7,314) in SLR (P = 0.007), and rate of CABG was higher in REV, 4.9% (140/2,831) vs. 3.7% (105/2,819) in SLR (P = 0.031). There were trends of lower all-cause mortality in the combined US/international trials in both REV 8.4% (390/4,624) vs. 22.8% (908/3,975) (P < 0.001) and SLR 8% (359/4,421) vs. 24% (910/3,808) (P < 0.001) compared to the European trials. There were also trends of lower rates of MI in the European trials in the REV group 20% (623/3,080) vs. 25% (712/2,893) in SLR (P = 0.001) and higher rates of CABG in REV 8.3% (96/1,144) vs. 5.7% (67/1,165) in SLR (P = 0.02); however, there were no significant effects in the pooled RR ratios even after subgroup analysis between US/international trials and European trials.

Conclusions: Despite having contemporary differences in the management approach towards UA/NSTEMI patients, no significant differences in trends were observed with REV strategy in US/international trials vs. European trials.

Keywords: Unstable angina; Non-ST-segment elevation myocardial infarction; Routine early revascularization; Selective late revascularization

Introduction

Routine early revascularization (REV)/early invasive strategy versus selective late revascularization (SLR)/ischemia-guided strategy are generally used to manage patients with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) [1, 2]. However, superiority of either approach is still under debate with numerous studies and meta-analyses published over the last decade with different outcomes, limitations and clinical implications. Even the guidelines differ in their recommendations, with the European guidelines leaning towards REV and the AHA/ACC guidelines inclining towards both REV and SLR based on the appropriate patient population [1, 2]. So far, the most recent Cochrane meta-analysis published in 2016 showed appreciable risk reduction in refractory angina, myocardial infarction (MI) and re-hospitalization but no difference in all-cause mortality and death or nonfatal MI at 6 - 12 months with REV therapy [3]. However, over the past 2 years, results of long-term (10 - 15 year) follow-up of
trials evaluating REV vs. SLR strategies have been published shedding light on potentially valuable long-term clinical outcomes. A close look and analysis of these trials together with previous results are particularly warranted. In addition, majority of these trials comparing these two strategies have been done either in Europe or the US/multicenter international trials. To date, no specific analysis has been done as to the effect of geographical location together with its implied differences in guideline-directed management.

Methods

Search strategy

We conducted a comprehensive search of five databases with human studies in any language from inception to June 2018. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, and Scopus. No language restriction was imposed, and only human studies were considered. The search strategy was designed and conducted by investigators. Controlled vocabulary, supplemented with keywords, was used to search for relevant studies. Search terms used were: “invasive strategy”, “routine invasive strategy”, “selective invasive strategy”, “non-ST-segment elevation myocardial infarction”, “unstable angina” and “acute coronary syndrome”.

Study selection

Studies were included in this meta-analysis if they satisfied the following criteria: 1) The study design was prospective, randomized controlled trials (RCTs) comparing REV versus SLR strategy for UA/NSTEMI; 2) Studies providing desired outcomes, particularly revascularization, death and bleeding. We excluded reviews, editorials, non-human studies and studies without sufficient data. In addition, we excluded studies which included patients with NSTEMI, but not with desired outcomes. Studies of ST-segment elevation myocardial infarction and stable angina were also excluded.

Data extraction

Two authors (H.V. and C.K.) independently carried out data extraction using a standard extraction form. We extracted the following information from each study: authors, year of publication, study name, study location, years of follow-up, sample size (number of participants and incident cases), diagnostic criteria, participants’ characteristics (age, gender and body mass index), length of follow-up, cardiovascular mortality, all-cause mortality, revascularization, and bleeding.

Quality assessment

Two authors (C.K. and H.V.) independently assessed the risk of bias for each study by using the modified Newcastle-Ottawa Scale (NOS). We resolved disagreements by discussion or by involving the co-authors to adjudicate and establish consensus. The quality of studies was no longer individually numerically quantified as all studies included were randomized controlled trials.

Statistical analysis

We extracted or calculated relative risks (RR) and 95% confidence intervals (CI) from the included studies. For studies reporting odds ratios (ORs) or hazard ratios (HRs), as cardiovascular events were rare (<1%), HRs and ORs asymptotically approach RRs, and they were treated as RRs in the analysis. We converted RR to log transformed RR (logRR) and pooled the logOR from all the included studies using the DerSimonian and Laird random-effects method with the estimate of heterogeneity from the Mantel-Haenszel model. Exploratory random-effect meta-regression analyses were conducted to assess the influence of study characteristics (geographical location and type of study design) on study results. We also conducted subgroup analyses stratified according to the geographic location (region and country). The performances of subgroup-specific and statistical test of interactions among subgroups were assessed. Heterogeneity between the studies was evaluated using I², in which > 50% suggests substantial heterogeneity. Due to a limited number of studies included in each analysis and/or substantial heterogeneity, we could not evaluate potential publication bias. All statistical analyses were performed with Review Manager (RevMan) (computer program) (Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), and test of proportions was performed using SPSS by IBM Build 1.0.0.903. All tests were two-sided with a significance level of 0.05. The meta-analysis has been reported in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE).

Results

Seventeen trials were included with a total of 15,812 patients. Out of 11 trials (7,783 patients) which were conducted in Europe, 3,975 patients were randomized to REV strategy and 3,808 patients were randomized to SLR strategy. Out of six trials (8,029 patients) which were conducted in the US/multicenter international trials, 4,112 patients were randomized into REV and 3,917 patients were randomized into SLR strategy. Average age of the patients included was 64.7 years (66 years in European and 61 years in US/international trials); 68% of patients were male. Average follow-up period of European and US/international trials was 43 months and 18.4 months, respectively. Baseline characteristics of European and the US/international trials are mentioned in Table 1 [4-20]. Similarly, outcome characteristics of European and US/international trials are summarized in Table 2 [4-20].

Overall, there was no difference in all-cause mortality (RR: 1.01, 95% CI: 0.95 - 1.08, P = 0.7), MI (RR: 0.98, 95%
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CI: 0.79 - 1.22, P = 0.85) or coronary artery bypass grafting (CABG) (RR: 1.33, 95% CI: 0.92 - 1.91, P = 0.12) between REV and SLR strategy (Figs. 1-3). There was however trend towards decreased incidence of MI in REV, 13.3% (1,029/7,704) vs. 15.1% (1,108/7,314) in SLR (P = 0.007) based on test of proportions analysis. In contrast, rate of CABG was higher in REV, 4.9% (140/2,831) vs. 3.7% (105/2,819) in SLR (P = 0.031). All of these trends however did not translate into significant effects based on the pooled risk ratios in the results of the meta-analysis (Figs. 2, 3).

In the US/international trials, incidence of all-cause mortality in the REV group was lower than that in the European trials (8.4% vs. 22.8%), whereas incidence of MI and rates of CABG were similar in REV and SLR groups in the US/international trials. A potential explanation is that the US/international trials generally had shorter follow-up of about 1 year except for Table 1. Baseline Characteristics of European and North American Trials [4-20]

| Authors | Follow-up | Patients in REV group | Patients in SLR group | Age (yrs) | Male (%) | Diabetes mellitus (%) | Hypertension (%) |
|---------|-----------|-----------------------|-----------------------|-----------|----------|-----------------------|------------------|
| European trials | | | | | | | |
| FRISC-II [4] | Wallentin et al (2016) | 15 years | 1,222 | 1,235 | 66 | 72 | 13 | 30 |
| RITA-3 [5] | Henderson et al (2015) | 10.6 years | 895 | 915 | 63 | 61 | 15 | 35 |
| ITALIAN ELDERLY ACS [15] | Savonitti et al (2012) | 12 months | 154 | 159 | 81.8 | 49 | 38 | 92 |
| ICTUS [6] | Hoedemacker et al (2017) | 10 years | 604 | 596 | 62 | 74 | 14 | 37 |
| ISAR COOL [16] | Neumann et al (2003) | 1 month | 203 | 207 | 70 | 66 | 26.1 | 85.5 |
| LIPSIA NSTEMI [11] | Thiele et al (2011) | 6 months | 400 | 200 | 69 | 68 | 41 | 82 |
| OPTIMA [19] | Riezebos et al (2009) | 6 months | 73 | 69 | 63 | 51 | 19 | 53 |
| TRUCS [10] | Michalis et al (2000) | 12 months | 76 | 72 | 62 | 76 | 29 | 54 |
| VINO [20] | Spacek et al (2002) | 6 months | 64 | 67 | 65.7 | 50 | 30 | 60 |
| ABOARD [12] | Montalescot et al (2009) | 1 month | 175 | 177 | 65 | 72.6 | 21.7 | 65.7 |
| ELISA [13] | van’t Hof et al (2003) | 1 month | 109 | 111 | 63 | 72 | 15 | 45 |
| North American trials | | | | | | | |
| MATE [7] | McCullough et al (1998) | 21 months | 111 | 90 | 57 | 77 | 11 | - |
| OASIS 5 [9] | Swahn et al (2009) | 24 months | 92 | 92 | 68.2 | 74 | 14 | 62 |
| TACTUS TIMI 18 [17] | Cannon et al (2001) | 6 months | 1,114 | 1,106 | 60 | 65 | 28 | - |
| TIMACS [14] | Mehta et al (2009) | 6 months | 1,593 | 1,438 | 65 | 63.2 | 26.5 | - |
| TIMI IIIB [18] | Anderson et al (1995) | 12 months | 740 | 733 | - | 66 | - | - |
| VANQUISH [8] | Boden et al (1998) | 23 months | 462 | 458 | 62 | 97 | 24.9 | 56.7 |

REV: routine early revascularization; SLR: selective late revascularization.

Discussion

We report an up-to-date meta-analysis comparing REV vs. SLR strategies opted for the treatment of UA/NSTEMI across the Atlantic. First, there was no difference in all-cause mortality rate of CABG and MI between REV and SLR strategy (Figs. 1-3). There was however trend towards decreased incidence of MI in REV, 13.3% (1,029/7,704) vs. 15.1% (1,108/7,314) in SLR (P = 0.007) based on test of proportions analysis. In contrast, rate of CABG was higher in REV, 4.9% (140/2,831) vs. 3.7% (105/2,819) in SLR (P = 0.031). All of these trends however did not translate into significant effects based on the pooled risk ratios in the results of the meta-analysis (Figs. 2, 3).

In the US/international trials, incidence of all-cause mortality is much lower in REV group (8.4% vs. 22.8%) vs. European trials (Fig. 1); and in SLR group (P = 0.001) based on test of proportions analysis. However, this did not translate into significant changes in effects based on the pooled RR ratios in the meta-analysis even after subgroup analysis between US/international and European trials (P = 0.42, Fig. 3).

In US/international trials, incidence of all-cause mortality in the REV group was lower than that in the European trials (8.4% vs. 22.8%), whereas incidence of MI and rates of CABG were similar in REV and SLR groups in the US/international trials. A potential explanation is that the US/international trials generally had shorter follow-up of about 1 year except for...
### Table 2. Outcome Characteristics of European and North American Trials [4-20]

| Group                     | Index hospital revascularization (%) | Total revascularized patients (%) | Total deaths (%) | Cardiac deaths (%) | Repeat MI during follow-up (%) | Rehospitalization due to ischemic heart disease (%) | CABG(%) |
|---------------------------|--------------------------------------|----------------------------------|------------------|--------------------|--------------------------------|-----------------------------------------------------|---------|
| **European trials**       |                                      |                                  |                  |                    |                                |                                                     |         |
| FRISC [4]                 | REV 76                               | 82                               | 38.7             | 14.3               | 37.2                           | -                                                   | -       |
|                           | SLR 14                               | 58                               | 39               | 16                 | 45                             | -                                                   | -       |
| RITA-3 [5]                | REV 55                               | 61                               | 25.1             | 15.1               | -                              | -                                                   | 21      |
|                           | SLR 10                               | 38                               | 25.4             | 16.1               | -                              | -                                                   | 4       |
| ITALIAN ELDERLY ACS [15]  | REV 56                               | 58                               | 12.3             | 10.4               | 7.1                            | 16                                                  | 7       |
|                           | SLR 23                               | 31                               | 13.8             | 10.7               | 10.7                           | 21                                                  | 2.5     |
| ICTUS [6]                 | REV -                                | 83                               | 26.7             | 17.6               | 18.9                           | -                                                   | -       |
|                           | SLR -                                | 61                               | 23.7             | 15.2               | 14.9                           | -                                                   | -       |
| ISAR COOL [16]            | REV 78.3                             | -                                | 0                | -                  | 6                              | -                                                   | 7.9     |
|                           | SLR 72                               | -                                | 1.4              | -                  | 10.1                           | -                                                   | 7.7     |
| LIPSIA NSTEMI [11]        | REV 84                               | -                                | 5.2              | -                  | 2.2                            | 28                                                  | 10      |
|                           | SLR 70                               | -                                | 6.5              | -                  | 1                              | 9                                                   | 13      |
| OPTIMA [19]               | REV -                                | 100                              | 1                | -                  | 3                              | 18                                                  | -       |
|                           | SLR -                                | 99                               | 0                | -                  | 4                              | 14                                                  | -       |
| TRUCS [10]                | REV 78                               | 100                              | 3.9              | -                  | 3.9                            | 13                                                  | 33      |
|                           | SLR 38                               | 61                               | 12.5             | -                  | 4.2                            | 17                                                  | 18      |
| VINO [20]                 | REV -                                | 73                               | 3.1              | -                  | 3.1                            | 2                                                   | 35      |
|                           | SLR -                                | 39                               | 13.4             | -                  | 14.9                           | 2                                                   | 30      |
| ABOARD [12]               | REV -                                | 80.1                             | 2.9              | -                  | 9.1                            | 12                                                  | 11      |
|                           | SLR -                                | 69.5                             | 1.1              | -                  | 4.5                            | 18.6                                                | 11.3    |
| ELISA [13]                | REV 61                               | -                                | 3                | -                  | 7                              | -                                                   | 14      |
|                           | SLR 58                               | -                                | 5                | -                  | 6                              | -                                                   | 19      |
| **North American trials (Canada/US)** |                                      |                                  |                  |                    |                                |                                                     |         |
| MATE [7]                  | REV 58                               | 72                               | 11               | -                  | 6                              | 23                                                  | 18      |
|                           | SLR 37                               | 60                               | 6                | -                  | 2                              | 22                                                  | 11      |
| OASIS 5 [9]               | REV 57.7                             | 64                               | 8.8              | -                  | 12.9                           | -                                                   | 16      |
|                           | SLR 30.4                             | 51                               | 2.2              | -                  | 13.3                           | -                                                   | 12      |
| TACTUS TIMI 18 [17]       | REV 51                               | 64                               | 3.3              | -                  | 4.8                            | 11                                                  | 22      |
|                           | SLR 36                               | 45                               | 3.5              | -                  | 6.9                            | 13.7                                                | 16      |
| TIMACS [14]               | REV 74.4                             | 93.1                             | 4.8              | -                  | 4.8                            | 1                                                   | 14.8    |
|                           | SLR 68.7                             | 77.2                             | 5.9              | -                  | 5.7                            | 3.3                                                  | 13.6    |
| TIMI IIIB [18]            | REV 6                                | 64                               | 8.8              | -                  | 16.3                           | 26                                                  | 30      |
|                           | SLR 19                               | 58                               | 9.9              | -                  | 15.4                           | 33                                                  | 30      |
| VANQUISH [8]              | REV 44                               | -                                | 17.3             | -                  | 15.6                           | -                                                   | 20      |
|                           | SLR 33                               | -                                | 13               | -                  | 17.4                           | -                                                   | 19      |
the MATE [7], VANQWISH [8] and OASIS-5 [9] trials which were up to 20 months, while the European trials had 10 to 15 years follow-up, garnering more mortality data. REV strategy had a trend of lower incidence of MI in European trials, in contrast to US/international trials where an increased incidence of MI was observed. An explanation for this was the significant heterogeneity in the US/international studies in terms of MI with the MATE trial skewing the results as it included subjects with ST-elevation MI in the analysis [7], and we were unable to extract or differentiate the date pertaining to only NSTEMI patients for this study, thus another explanation for the heterogeneity. In US/international trials, rate of CABG was comparable between both groups, whereas in European trials, rate of CABG was higher in the REV group. However, there was significant heterogeneity as the results are being skewed by the TRUCS study [10] wherein the investigators intentionally randomized patients to onsite balloon angioplasty plus emergency airlift for bypass surgery versus conservative medical treatment; thus, the higher rates of CABG. After exclusion of all these studies which skew the data, the likelihood of difference is small.

In looking for geographical differences in outcomes in REV versus SLR, we had to look at potential studies conducted in the US/international and Europe, including some old studies done before 2000, as some of them had the latest long-term follow-up data available for further analysis. However, the pitfall to this is that these studies may no longer be representative of contemporary standards of medical practice as a lot of progress has happened over the past 10 years. Some of the data derived is also limited by the natural differences in methodology such as the duration of follow-up, with most studies with 1 year or less follow-up duration, but several studies with 10 years or longer follow-up. As of now there is a mounting need to conduct more studies, this time incorporating most of the advances in guideline directed medical therapy including statins, newer antiplatelet agents as well as the highly sensitive troponin assays [21] and other new biomarkers. This is to help classify patients at a higher risk for which the evidence for benefit for REV was the highest based on the previous studies [22, 23]. In a different light, as some of the studies like the ICTUS [6] and LIPSIA-NSTEMI [11] trials involving only patients with positive troponin levels labeling them as higher risk showed no difference between REV and SLR strategies, therefore a better method of risk factor assessment and risk stratification which includes other variables is needed. There is a possibility that the previous trials did not fully capture the higher risk groups hence the ambiguous results; as recorded mortality rates have been lower compared to the large multinational registry GRACE cohort with mortality rates approaching about 12% at 6 months after discharge [24]. Another important limitation in interpretation is the differences in the timing of the invasive procedures. The ABOARD [12], ELISA [13] and TIMACs [14] trials tend-
ed to employ the invasive strategy earlier from as early as 70 min for the ABOARD trial to less than 24 h in the ELISA [13] and TIMACS [14] trials, while the delayed invasive group got it within 48 - 72 h. In comparison, in the old trials ICTUS

Figure 2. Rate of myocardial infarction (MI) after index hospitalization in routine early revascularization (REV) versus selective late revascularization (SLR) in randomized controlled trials conducted in Europe and the United States. Boxes represent the weight/effect size for each study; the diamonds reflect the pooled combined effect from the meta-analysis.

Figure 3. Rate of coronary artery bypass grafting (CABG) in routine early revascularization (REV) versus selective late revascularization (SLR) in randomized controlled trials conducted in Europe and the United States. Boxes represent the weight/effect size for each study; the diamonds reflect the pooled combined effect from the meta-analysis.
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Adherence to guideline-directed therapy yielded further benefit is that advances in medical care in general, including the use of newer drug-eluting stents, newer antiplatelet agents, more adherence to guideline-directed therapy yielded further benefit for those in the SLR group closing the gap of benefit between the two groups. This includes the trend towards the use of better newer antiplatelet agents [29, 30], statins in the setting of ACS [31], the preferential use of radial approach for interventions [32], the now available second-generation drug-eluting stents [33], all of which contributed to an overall increase in favorable outcomes in management of acute cardiac ischemic events. This is evidenced by one study wherein an analysis of the GRACE cohort done on the trends between 1999 to 2006 revealed an increase in the use of beta blockers by 10%, statins by 40%, thienopyridines by over 50% while both angiography and percutaneous coronary intervention (PCI) rates increased by approximately 20% as well among NSTEMI and UA patients [34]. Consequently, this translated to a decrease in cardiogenic shock, heart failure, MI and death from discharge to the 6 months follow-up [34].

The findings of this meta-analysis should be interpreted with caution as the studies clumped together have high heterogeneity, specifically by the differences in follow-up. The studies with longer-term follow-up periods of 10 - 15 years like the FRISC-II [4], RITA-3 [5] and ICTUS [6] tend to have higher odds of mortality compared to the ones with shorter follow-up [12-14, 16-18, 34].

Conclusions

There was no statistical difference in all-cause mortality, MI or CABG in REV versus SLR strategy, even after analyzing trials across the Atlantic separately. Interestingly, trends of decreased all-cause mortality in REV were observed in US trials when compared to European trials. Furthermore, trends of decreased rate of MI and increased rate of CABG were observed in REV vs. SLR, likely driven by the results from European trials, which showed similar trends, whereas US/international trials showed comparable rates of MI and CABG. Still there is significant heterogeneity between studies and these findings should be interpreted with caution. Newer studies are warranted to reflect contemporary practice.

Conflict of Interest

The authors declare that they do not have any conflict of interest.

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Author Contributions

All authors participated to review. All authors were involved in writing and revising the article prior to submission.
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