Research Article

Non-Culprit Revascularization Timing in (N)STE-ACS: A Patient Preference Report

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Abstract

Objectives: To elucidate the preference of (non)ST-Segment Elevation Acute Coronary Syndrome ((N)STE-ACS) patients with Multivessel Disease (MVD), with regard to the timing of Non-Culprit Lesion (NCL) treatment by Percutaneous Coronary Intervention (PCI). Methods: At the end of 2020, a survey was sent to 442 patients who received PCI for (N)STE-ACS between December 2018 and October 2020 at Radboudumc, Nijmegen, the Netherlands. The primary outcome was patient preference for the timing of NCL revascularization, being during index PCI, during index admission, or as an outpatient procedure. The secondary outcomes consisted of peri-procedural complaints and symptoms of ischemia, namely chest pain and dyspnoea, during exercise and at rest. Secondly, effects on mental well-being were assessed. All symptoms were graded on a 5-point scale to allow for a quantitative comparison. Finally, unplanned visits with cardiac symptoms were scored. Results: Of the 442 invited patients, 265 (60%) responded of whom 197 (45%) were included and 68 (15%) were excluded. Overall, the majority of patients (69%) preferred direct complete revascularization. Non-invasive imaging-guided PCI was chosen by 23% of patients. Interestingly, MVD patients (n=98) who underwent a single PCI procedure consulted the physician with cardiac complaints less frequently than patients who underwent multiple procedures (21.4% vs. 53.6%, p=0.001) and had lower chest pain scores (1.36±0.62 vs. 1.95±1.07, p=0.001). Conclusion: Complete revascularization of all non-culprit lesions during index PCI was the preferred treatment and was associated with reduced chest pain severity and fewer consultations for cardiac symptoms.

Keywords: Acute coronary syndrome; Decision making, Shared; Percutaneous coronary intervention

Abbreviations: ACC: American College of Cardiology; CMR: Cardiac Magnetic Resonance imaging; COMPLETE: Complete Revascularization with Multivessel PCI for Myocardial Infarction; iMODERN: iFR Guided Multi-vessel Revascularization During Percutaneous Coronary Intervention for Acute Myocardial Infarction; MACCE: Major Adverse Cardiovascular and Cerebral Events; MI: Myocardial Infarction; MVD: Multivessel Disease; NCL: Non-culprit Lesion; (N)STE-ACS: Non-ST-segment Elevation Acute Coronary Syndrome; NSTEMI: Non-ST-Segment Elevation Myocardial Infarction; OR: Odds Ratio; PCI: Percutaneous Coronary Intervention; SLIM: FFR-driven Complete Revascularization Versus Usual Care in NSTEMI Patients and Multivessel Disease; SMILE: Single-Staged Compared With Multi-Staged PCI in Multivessel NSTEMI Patients; STEMI: ST-Segment Elevation Myocardial Infarction
Introduction

Roughly 50% of (non)-ST-Segment Elevation Acute Coronary Syndrome ((N)STE-ACS) patients have Multivessel Disease (MVD) [1], defined by one or more Non-Culprit Lesions (NCLs). If left untreated, MVD confers a higher risk of cardiovascular mortality and recurrent Myocardial Infarction (MI) [2,3]. Complete treatment of NCLs may be beneficial to the patient partly as a consequence of protection against unstable plaque disease [4]. Secondly, direct complete reperfusion was associated with smaller infarct size in a non-randomized sub study of the CVLPRIT trial [5].

According to the American College of Cardiology (ACC) guidelines[1], four different treatment options can be used interchangeably for NCLs in ST-Segment Elevation Myocardial Infarction (STEMI) patients: Direct complete revascularization through Percutaneous Coronary Intervention (PCI) during the emergency cardiac catheterization, staged PCI of the remaining NCLs during the index admission, staged PCI of the remaining NCLs during outpatient follow-up or non-invasive functional imaging-guided outpatient PCI. In STEMI, the COMPLETE trial demonstrated superior clinical outcomes with complete versus culprit-only revascularisation [3]. In non-STEMI (NSTEMI), the guidelines recommend to consider complete revascularization [6], based on observational data [7]. The SLIM study is an ongoing randomized clinical trial that compares complete treatment of significant lesions versus culprit-lesion only PCI, followed by staged NCL PCI within 6 weeks, if deemed necessary by the heart team [8].

Regarding the timing of revascularisation of NCLs, the COMPLETE trial showed no difference in outcomes between a direct and deferred strategy, although the trial did not randomize patients to this regard and the optimal treatment timing remains unclear to date [3]. This is currently under investigation in the iMODERN trial [9] for STEMI. For NSTEMI patients, the SMILE trial randomized 584 NSTEMI patients towards complete single treatment of all lesions versus staged treatment of all lesions and found that single-stage complete reperfusion reduces Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) [10].

In the era of shared decision making, physicians increasingly consider the patient’s preference to achieve a personalised treatment regimen [11]. In the absence of a clear benefit of the different options for NCL PCI timing, patient preference constitutes an important argument when choosing for an NCL treatment strategy. We set out to evaluate patient preference for NCL PCI timing and the effects, both physical and mental, of different treatment strategies in this regional survey.

Methods

Study Design

This cross-sectional online survey was conducted between November 11th 2020 and December 14th 2020, using Castor EDC. Informed consent was waived by the Medical Ethics Committee Arnhem/Nijmegen, The Netherlands (protocol number 2021-8286). The target population was identified by consecutive screening of (N)STE-ACS patients who underwent PCI between December 22nd 2018 and October 14th 2020, at Radboud UMC, Nijmegen, The Netherlands. The inclusion criteria were PCI for an (N)STE-ACS within the last 2 years and patients with and without MVD were included. Exclusion criteria were inability or unwillingness to complete the online questionnaire, and inability to speak Dutch.

The primary outcome was patient preference for the timing of NCL revascularization, being direct revascularisation during the index procedure, staged revascularisation during index admission, staged deferred revascularisation after discharge, and imaging-guided complete treatment after discharge. Patients were asked how many PCI procedures they had undergone to assess the secondary outcomes, being the physical and mental effects of one or several PCI procedures. Additionally, unplanned visits to the general practitioner or emergency room were documented. In total, 442 eligible patients received an e-mail with the rationale of this study and a link to the questionnaire, in Dutch. After 4 weeks, survey responses were collected anonymously and stored electronically.

Patient Preference Survey

This questionnaire was developed at the Vrije Universiteit Medical Center (VUMc) in a collaboration of PhD fellows, consultant cardiologists and the patient board. The questions focus on three important factors that constitute patient preference: Firstly, physical and mental complaints were assessed, following the index hospital admission. Secondly, the treatment preference for MVD was evaluated. To allow for a quantitative comparison of subjective symptoms, physical complaints after the first procedure were quantified with a grading scale ranging from 1, meaning no symptoms, to 5, indicating severe symptoms. Patients were asked about angina and shortness of breath, both exertional and at rest. The mental aspects of the administered treatment were assessed with an identical grading scale and involved anxiety before the procedure, anxiety during the procedure and emotional burden of the procedure, both for the first and second procedure. Overall patient preference was assessed through serial questions about the desired treatment of MVD, hypothetical preference for the treatment of MVD if complete revascularization of non-culprit vessels would confer a higher risk of adverse outcomes,
and questions about experienced or hypothetical reassurance if a non-invasive Cardiac Magnetic Resonance imaging (CMR)-guided approach would have been used, using a score range from 1 (entirely unassured) to 5 (extremely reassured). Reassurance from CMR results was dichotomized with a score range 1-2 meaning unassured, and scores ≥3 indicating sufficient reassurance. Patients who did not have MVD were asked to formulate a hypothetical answer as if they had MVD. The questionnaire can be found in Appendix A.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS (version 26). Continuous variables were expressed as mean±Standard Deviation (SD) and dichotomous variables as a number with percentage. The Chi Square test was performed for comparison of dichotomous variables. Fisher’s Exact Test was used when less than 5 patients were present per group. For the comparison of means of normally distributed continuous variables, the independent Student’s T-test was used. For non-normally distributed variables, the Wilcoxon signed-rank test was performed.

Results

Baseline Characteristics

A total of 442 invitations were sent. These were answered by 265 patients (60%), of which 197 respondents (45%) matched the inclusion criteria and completed the survey. Exclusion criteria applied to 68 respondents (15%): Of these patients, 30 patients (7%) indicated that they did not undergo a PCI procedure, 26 patients (6%) underwent PCI for another reason than an (N)STE-ACS, and 12 patients (3%) did not complete the questionnaire. In 5 cases (2%), patients did not know how many PCI procedures had been performed. These patients were included in the overall analysis for patient preference, but are not classified in one of the two treatment groups, being one or multiple PCI procedures.

Table 1 shows the demographics of the study population. The mean age was 65±10 years and 149 (76%) respondents were men. A single PCI procedure was performed in 103 respondents (52%) and 89 respondents (45%) underwent two procedures. MVD was reported by 100 respondents (51%). These patients were mainly present in the group that underwent multiple procedures (63% vs 41%, P=0.002).

| Characteristics               | All patients (n=197) | One PCI procedure (n=103) | Multiple PCI procedures (n=89) | P-value |
|-------------------------------|---------------------|---------------------------|-------------------------------|---------|
| Age – mean (SD), y            | 65.4 (10.0)         | 65.1 (10.4)               | 65.5 (9.4)                    | 0.776   |
| Gender (male) – n (%)         | 149 (75.6)          | 79 (76.7)                 | 68 (76.4)                     | 0.962   |
| (N)STE-ACS                    | 197 (100)           | 103 (100)                 | 89 (100)                      |         |
| Multi Vessel Disease (MVD) – n (%) | 100 (50.8)     | 42 (40.8)                 | 56 (62.9)                     | 0.002   |
| Additional imaging – n (%)    | 104 (52.8)          | 49 (47.6)                 | 53 (59.6)                     | 0.097   |
| CMR-scan                      | 35 (17.8)           | 14 (13.6)                 | 21 (23.6)                     |         |
| Echocardiography              | 48 (24.4)           | 26 (25.2)                 | 21 (23.6)                     |         |
| Nuclear scan (SPECT)          | 5 (2.5)             | 1 (1.0)                   | 4 (4.5)                       |         |
| Unknown scan type             | 15 (7.6)            | 8 (7.8)                   | 7 (7.9)                       |         |

Table 1: (N)STE-ACS: (non)ST-Segment Elevation Acute Coronary Syndrome; MVD: Multivessel Disease; CMR: Cardiac Magnetic Resonance imaging; SPECT: Single Photon Emission Computed Tomography.
Overall Patient Preference

Overall, 69% of patients opted for direct complete revascularization in a single procedure. This was followed by non-invasive imaging-guided PCI, chosen by 23%. Both second PCI during index admission and second PCI during outpatient follow-up were chosen by 4%. The administered treatment did not significantly influence the patient’s preference with regard to non-culprit revascularization timing (p=0.721), see Figure 1 and Table 2. Furthermore, the implementation of non-invasive ischemia detection to establish the indication for PCI would leave 151 (76.6%) of our patients sufficiently reassured.

![Overall patient preference](image)

**Figure 1:** Pie charts of patient preference. The top chart shows overall patient preference for treatment regimen of non-culprit lesions. The lower 2 pie charts show patient preference according to treatment groups, being one or multiple PCI procedures. PCI: Percutaneous Coronary Intervention.

| Hypothetical preference treatment MVD | All patients (n=197) | One PCI procedure (n=103) | Multiple PCI procedures (n=89) | P-value |
|--------------------------------------|----------------------|--------------------------|-------------------------------|---------|
| Complete revascularization during index PCI – n (%) | 137 (69.5) | 74 (71.8) | 59 (66.3) | 0.721 |
| PCI at a later time during hospitalization – n (%) | 8 (4.1) | 3 (2.9) | 5 (5.6) | 0.779 |
| PCI during a day admission – n (%) | 7 (3.6) | 3 (2.9) | 4 (4.5) | |
| Imaging-guided PCI – n (%) | 45 (22.8) | 23 (22.3) | 21 (23.6) | |

| Hypothetical preference treatment MVD if there are risks involved | All patients (n=197) | One PCI procedure (n=103) | Multiple PCI procedures (n=89) | P-value |
|---------------------------------------------------------------|----------------------|--------------------------|-------------------------------|---------|
| Complete PCI during hospitalization – n (%) | 63 (32.0) | 35 (34) | 27 (30.3) | 0.025 |
| PCI at a later time during hospitalization – n (%) | 43 (21.8) | 19 (18.4) | 22 (24.7) | |
| PCI during a day admission – n (%) | 20 (10.2) | 11 (10.7) | 9 (10.1) | |
| Imaging-guided PCI – n (%) | 71 (36.0) | 38 (36.9) | 31 (34.8) | |
| Anxiety recurrence infarction – n (%) | 57 (28.9) | 22 (21.4) | 32 (36.0) | |
| Reassurance from imaging – n (%) | 151 (76.6) | 90 (87.4) | 57 (64.0) | |

**Table 2:** MVD: Multivessel Disease; PCI: Percutaneous Coronary Intervention.
When asked to hypothesize that additional risks were involved through complete NCL treatment during the index procedure, patient preference changed significantly (p<0.0001 for all groups). Whereas 32% of patients still preferred direct complete revascularization, 36% now chose for non-invasive imaging-guided PCI, 22% for second PCI during index admission, and 10% for second PCI during outpatient follow-up.

Symptoms in MVD Patients

In a sub selection of patients with MVD who underwent one or two PCI procedures and recalled how many procedures they underwent (n=98), the group that received one revascularization procedure was characterized by a lower chest pain score at rest and during exercise after initial hospital discharge (1.36±0.62 vs. 1.95±1.07, p=0.001). For dyspnea at rest or during exercise, no significant difference was demonstrated between patients with one PCI procedure and patients who underwent two PCI procedures (respectively p=0.866 and p=0.852), as shown in Table 3.

|                                | One PCI procedure (n=42) | Multiple PCI procedures (n=56) | P-value |
|--------------------------------|--------------------------|-------------------------------|---------|
| **Physical**                   |                          |                               |         |
| Chest pain at rest after hospitalization – mean (SD) | 1.21 (0.68) | 1.80 (0.96) | 0.001 |
| Chest pain during exercise after hospitalization – mean (SD) | 1.36 (0.62) | 1.95 (1.07) | 0.001 |
| Dyspnea at rest after hospitalization – mean (SD) | 1.86 (1.00) | 1.82 (1.06) | 0.866 |
| Dyspnea during exercise after hospitalization – mean (SD) | 2.12 (1.11) | 2.16 (1.06) | 0.852 |
| Pain wrist / groin during PCI – mean (SD) | 1.50 (0.63) | 1.75 (0.97) | 0.129 |
| Unplanned hospital visits – n (%) | 9 (21.4) | 30 (53.6) | 0.001 |
| Physical burden – mean (SD) | 1.76 (0.91) | 1.95 (0.96) | 0.338 |
| **Mental**                     |                          |                               |         |
| Anxiety before procedure – mean (SD) | 1.67 (0.87) | 2.20 (1.26) | 0.016 |
| Anxiety during procedure – mean (SD) | 1.64 (0.91) | 2.00 (1.11) | 0.092 |
| Emotional strain – mean (SD) | 1.88 (0.86) | 2.16 (1.06) | 0.165 |
| **Overall satisfaction**       |                          |                               |         |
| Hypothetical preference treatment MVD – mean (SD) | 0.90 (1.34) | 0.89 (1.29) | 0.965 |
| Anxiety recurrence infarction, n (%) | 7 (16.7) | 21 (37.5) | 0.024 |

Table 3: PCI: Percutaneous Coronary Intervention; MVD: Multivessel Disease.

On the other hand, MVD patients who underwent two PCI procedures were more likely to have an unplanned consultation with cardiac symptoms (Odds ratio (OR)=4.2, 95% Confidence Interval (CI) 1.7-10.4). Finally, patients with one PCI procedure were less afraid of recurrent MI after the initial hospital admission than patients who underwent multiple PCI procedures (16.7% vs. 37.5% anxiety for recurrent MI, p=0.024).

Procedural Effects of the First and Second PCI Procedure

Of the 89 patients who received two PCI procedures, 70 (78%) completed the questions about the first and the second procedure. These respondents indicated no significant differences between the first PCI procedure and the second procedure regarding pain at the access site (score 1.70±0.98 for the first procedure vs. 1.60±0.86, p=0.376) nor in pain duration (21 days for both...
procedures). Overall physical burden was similar between groups (1.90±0.95 vs. 1.84±0.39, p=0.388). Accordingly, this applied to anxiety before the procedure (1.96±1.11, p=0.108) and anxiety during the procedure (1.77±1.01 vs. 1.71±0.95, p=0.457).

Discussion

This study aims to define the preference of (N)STE-ACS patients for the timing of NCL treatment and it is the first survey to do so. The main finding is that in our region, the preferred treatment timing of NCLs in (N)STE-ACS patients is direct complete revascularization. If, hypothetically, risks were involved with direct complete treatment of NCLs, the preference would veer towards imaging-guided deferred PCI and second PCI during index hospital admission. Nevertheless, a significant proportion would still prefer direct complete revascularization.

While the factors underlying patient preference are plethoric, it is known that ACS patients discharged after receiving PCI face increased levels of anxiety, in part due to a higher perceived risk of recurrent heart complaints [12,13]. In this study, we demonstrate that patients who are discharged and aware of having residual NCLs may experience additional stress until a second PCI procedure has been performed or until hemodynamic significance of these lesions has been ruled out non-invasively, because patients who underwent multiple procedures were more anxious of a recurrent MI but could generally be reassured through the implementation of non-invasive ischemia detection. Alternatively, the preference for direct complete revascularization may owe to the practical advantages of one hospital admission over a possible outpatient visit to acquire the CMR scan and a day admission for the second procedure.

Possible Advantages of Acute Complete PCI in Multivessel Disease

MVD patients who underwent a single PCI procedure had a lower chest pain score at rest and during exercise after index admission. Secondly, they were significantly less likely to visit the hospital unplanned because of ischemic symptoms. These findings suggest that in this group of patients, direct complete revascularization is superior to multiple procedures. It is also conceivable that direct treatment of NCLs offers physiological advantages in the form of improved myocardial perfusion in coronary territories that are adjacent to the infarct region, needing to compensate for the infarcted myocardium that has become dysfunctional [14]. Better coronary perfusion may specifically reduce symptoms of radiating chest pain [15], as is indicated by the results of this survey. On the other hand, the mere knowledge of having residual NCLs may lead to more pronounced anginal symptoms and more unplanned hospital visits [16]. McCann et al. [17] showed that complete treatment comes at the cost of a slightly increased risk of peri-procedural MI. However, complete reperfusion does not alter infarct size[17], unless it is performed during the index PCI. Then, complete treatment of lesions is associated with reduced infarct size and lower incidence of no re-flow, as opposed to staged, in-hospital complete treatment [5]. This is important, as CMR-defined infarct size and no-reflow are both strong prognosticators that predict all-cause mortality [18,19]. In line with these results, the SMILE trial 10 has shown that direct NCL treatment in NSTEMI patients reduces MACCE. Consequently, patient preference is less important in this population as the primary concern is to administer optimal treatment. Finally cardiac rehabilitation, consisting of supervised exercise training and psychological support, is paramount after (N)STEMI [20] but it is often postponed until complete reperfusion has been achieved. Direct treatment of NCLs may help to reduce the delay between hospital discharge and initiation of cardiac rehab.

Why Would One Choose for Staged Revascularization?

Staged complete revascularization remains the most widely used treatment strategy for ACS patients with MVD. However, the treatment guidelines for STEMI and NSTEMI offer no specific advice regarding the timing of NCL PCI[1, 6]. Arguments for a staged approach are primarily logistical by nature, as the interventionalist may be on a busy day schedule or needs to perform several emergency procedures at night on short notice. Secondly, the CULPRIT SHOCK trial [21] discourages direct complete revascularization in hemodynamically compromised patients, as this increases the risk of mortality and renal insufficiency. Finally, it is known that ACS triggers inflammation [22], which may precipitate coagulation. As such, an ACS is univariately associated with stent thrombosis, as compared to non-ACS indications for PCI (Hazard Ratio 3.79, 95% CI 2.26-6.33) [23].

A Second PCI Procedure is as burdening as the first

Reported pain scores did not differ between the first and second procedure in the subgroup that answered the questions for both procedures. On the contrary, the physical and mental effects of the second PCI procedure were similar to the effects of the first procedure. This suggests that if a second PCI procedure is indicated, the physical complaints following the second procedure will not exceed the complaints as experienced during the first procedure. However, the cumulative exposure to several PCI procedures naturally imposes an incremental risk of bleeding at the entry site.

Limitations

The single-centre non-randomized nature of this study impedes generalization of these results for a wider population, especially as the Radboudumc is a tertiary referral center where patients frequently participate in clinical trials or receive physiology-guided PCI. Regarding our secondary outcomes, the retrospective design likely resulted in a remembrance bias, e.g. that patients...
who underwent multiple procedures had a clearer recollection of their anginal symptoms. Secondly, the anonymization hindered retrospective patient dossier searching, meaning that it was impossible to verify whether patients had STEMI or NSTEMI, to which different treatment guidelines apply. Furthermore, patients without MVD were included too and these patients were asked to hypothesize that there were NCLs. As the patient was relied upon to report MVD, some counter-intuitive results were obtained, with respondents indicating that they did not have MVD, but underwent multiple PCI procedures nonetheless. We speculate that these patients underwent a cardiac catheterization to measure stenosis severity, showing that PCI was not necessary. Finally, despite the effort to design the survey as understandable as possible without losing information content, some participants may not have fully understood the questions. This is contradicted by the high response rate that indicates that patients understood the questions and could complete the survey without difficulties. In order to gain a better perspective on the preference of all patients, this study should be repeated prospectively in a larger group of patients from multiple regional centres.

Conclusion

The majority of patients in our region favors direct complete treatment of all NCLs, followed by a non-invasive imaging-guided strategy. In this cohort, (N)STE-ACS patients who underwent a single PCI procedure indicated less severe chest pain and a lower incidence of unplanned hospital visits.

What’s New?

- Patients with a myocardial infarction who have multivessel disease prefer direct complete revascularization over an in-hospital second procedure or an outpatient deferred regimen;
- If direct complete revascularization turns out to be inferior to a staged approach, the majority of patients prefers an outpatient, imaging guided treatment strategy;
- In this cohort, patients with multivessel disease who underwent one angioplasty procedure had fewer unplanned consultations with cardiac complaints and a lower chest pain score than patients who underwent multiple procedures.

Statement of Ethics

Informed consent was waived by the Medical Ethics Committee Arnhem/Nijmegen, The Netherlands as the questionnaire was minimally burdensome for participants (protocol number 2021-8286).

Author Contributions

The primary author CWHB was primarily responsible for the drafting of the manuscript and the collection and interpretation of relevant sources. GTMG was responsible for data collection and revising the manuscript. PD, MHW, TJFtC, CC, RMyV, HG, and SCHvdO have all read the manuscript and provided critical revisions. RN (senior author) and NvR were co-responsible for drafting the manuscript and interpreting the used literature.

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