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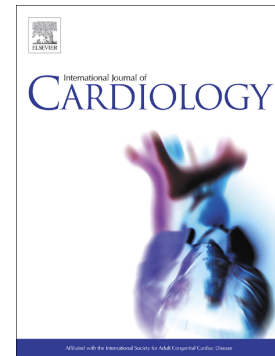
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Unreported exclusion and sampling bias in interpretation of randomized controlled trials in patients with STEMI

Short title: Screening and sampling bias in randomized trials

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Short title : Sampling bias in a randomized trial of STEMI

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Abstract:

Aims: To assess the impact of sampling bias due to reported as well as unreported exclusion of the target population in a multi-center randomized controlled trial (RCT) of ST-elevation myocardial infarction (STEMI).

Methods and Results: We compared clinical characteristics and mortality between participants in the DANAMI-3 trial to contemporary non-participants with STEMI using unselected registries. A total of 179 DANAMI-3 participants (8%) and 617 contemporary non-participants (22%) had died (Log-Rank: $P < 0.001$) after a median follow-up of 1333 days (range: 1-2021 days). In an unadjusted cox regression model all groups of non-participants had a higher hazard ratio to predict mortality compared to participants: eligible excluded ($n=144$) (hazard ratio: 3.41 (95%CI: (2.69-4.32)), ineligible excluded ($n=472$) (hazard ratio: 3.42 (95%CI: (2.44-4.80)), eligible non-screened ($n=154$) (hazard ratio: 3.37 (95%CI: (2.36-4.82)), ineligible non-screened ($n=154$) (hazard ratio: 6.48 (95%CI: (4.77-8.80)).

Conclusion: Sampling bias had occurred due to both reported and unreported exclusion of eligible patients and the difference in mortality between participants and non-participants could not be explained only by the trial exclusion criteria. Thus, screening logs may not be suited to address the risks of sampling bias.

Keywords: Sampling bias, screening logs, randomized controlled trials, ST-elevation myocardial infarction, external validity

1. Introduction

In randomized controlled trials determinants of external validity are rarely reported [1]. Patients with high risk characteristics are often excluded due to predefined exclusion criteria which can lead to major differences between participants and non-participants [2;3]. The requirement for informed consent and issues related to timing and the complexity of clinical trial protocols could also result in missed inclusion of the per-protocol desired study population (target population). Sampling bias can be introduced by resistance to participate by eligible patients, practical challenges and violation of the pre-defined eligibility criteria resulting in differences in characteristics between participants and non-participants related to risk of i.e. cardiovascular outcomes [4]. In recently published RCTs with patients with STEMI reasons for exclusion of patients are usually reported only from the screening logs to describe the selection of study participants and the risk of sampling bias. However, screening rates as well as characteristics and prognosis for the non-screened target population are rarely accounted for in the trial screening log.

Previous studies have investigated external validity in RCTs of acute myocardial infarction [5-7]. However, most studies have compared trial participants to non-participants from selected registries or to the excluded patients from the trial screening log only. The issue of sampling bias due to unreported screening and exclusion of eligible patients with STEMI has, to our knowledge, not been addressed. In this study we assessed the external validity in a national multi-centre RCT of STEMI with all-comers design conducted in Denmark [8-10]. We compared participants in the “The Third Danish Study of Optimal Acute Treatment of Patients with ST-segment elevation Myocardial Infarction” (DANAMI-3) trial to contemporary non-participants. We evaluated the impact of trial exclusion criteria as well as the impact of sampling bias from both reported exclusion in the trial screening log and unreported exclusion of eligible patients with STEMI using unselected national registry data.

2. Methods:

2.1 Patients and databases

Since 2002 reperfusion with primary percutaneous coronary intervention (pPCI) has been standard of care for patients with STEMI in Denmark and each pPCI procedure has been recorded in the two Danish Heart registries (the Eastern and Western Danish Heart Registry). The registries were designed for safety, administrative and research purposes and contain baseline and procedural information about every single consecutive pPCI for patients with STEMI. The DANAMI-3- trial was an investigator-initiated all-comers national multicenter, randomized controlled trial with endpoint design and with participation from all four pPCI-centres in Denmark [9]. The inclusion started March 21st 2011 to February 2nd 2014 in the top including study site. The study population in the present study constitutes all patients admitted with STEMI in Denmark during the DANAMI-3 inclusion period in the top participating study site. All patients in this study were identified through the heart registries and the DANAMI-3 screening log. In the top including study site the aim was to formally screen all consecutive patients with STEMI for study eligibility during the inclusion period. The decision to enrol a patient was made by the pPCI-operator before the pPCI procedure and variables related to treatment specifics were reported and stored immediately after completion of the pPCI regardless of study participation by an on-site study nurse. The inclusion criteria for DANAMI-3 were >18 years, acute onset of chest pain with ≤ 12 hours and ST-segment elevation in the ECG. The exclusion criteria were suspected pregnancy, intolerance to aspirin or P2Y₁₂-receptor antagonists, inability to provide signed consent, cardiogenic shock, unconsciousness, indication for CABG, stent thrombosis or coagulopathy. Reasons for exclusion from DANAMI-3 were recorded in the trial screening log. Information about existing comorbidity (ICD-10-classifications) was obtained from the Danish National Patient Registry using a unique 10-digit civil person registration number assigned at birth or at registration within the Danish Centralized Civil Registration System. For all patients,

information on vital status and causes of death were obtained for all patients from the Danish Centralized Civil Registry and the Cause of Death Registry also using the civil person registration number. Patients without Danish civil person registration number (e.g. tourists) were excluded from analysis due to missing data on vital status and comorbidities in the national registries.

For the main analysis the comparative groups were patients >18 years treated with pPCI and presenting with STEMI <12 hours after symptom onset in the DANAMI-3 inclusion period who 1) participated in DANAMI-3 (participants), 2) did not participate in DANAMI-3 and who were recorded in the trial screening log (excluded) and 3) did not participate and were not recorded in the trial screening log (non-screened). To assess the impact of the exclusion criteria and the issue of sampling bias we also compared participants to 1) eligible non-participants (non-participants without exclusion criteria) 2) ineligible non-participants (non-participants with exclusion criteria). Participants were also compared to 1) eligible excluded (excluded patients without exclusion criteria), 2) ineligible excluded (excluded with exclusion criteria), 3) eligible non-screened (non-screened without exclusion criteria) and finally 4) ineligible non-screened (non-screened with exclusion criteria).

Characteristics and endpoints

Differences in baseline clinical characteristics which are known to be associated with higher risk and procedure-related variables which could be associated with sampling bias were assessed between the comparative groups from the top including study site. We compared differences in demographics, cardiovascular risk factors, and known predictors of mortality including clinical presentation at admission [11] and comorbidity present at the time of the pPCI [12;13]. Cancer included all ICD10 cancer classifications with or without metastasis. All cardiac rhythms except sinus rhythm, first degree atrium-ventricular block, bundle branch block, ventricular fibrillation and ventricular tachycardia (VF/VT) were categorized as a cardiac arrhythmia present at time of admission. The

cardiac arrhythmias VF/VT were assessed separately and included patients with at least one documented episode of VF/VT prior to admission where unconsciousness was not recorded in the patient records. Unconsciousness included unconscious patients with return of spontaneous circulation following documented VF/VT. All patients with VF/VT were assessed manually in local electronic patient files to assess if they were unconscious at the time of admission. Heart failure was classified as comorbidity if the condition was known prior to the PCI-procedure. Information about all base-line characteristics was available for all patients in the heart registries. All the non-screened patients from the top including study site were assessed manually for exclusion criteria in the local electronic patient records and the STEMI diagnosis was confirmed. The patients were followed until death, emigration or the termination date of this study (September 31st 2016). Mortality was reported during the entire follow-up period, at 30-days and from 30 days to the end of follow-up. The National Board of Health (case file no 3-3013-1227/1/Reference SABN) and the Danish Data Protection Agency (case file no. 30-1286, 03727) gave its permission to cross-check data from electronic patient files at the pPCI centers and from public registries.

2.3 Data-analysis and statistical considerations

Categorical variables were presented as numbers and percentages and compared using the Chi² or Fisher's exact tests. Continuous variables were evaluated for normal distribution by visual assessment of histograms and compared by means \pm SD using one-way independent ANOVA or by median (25-75 interquartile range) Kruskal-Wallis test as appropriate. Post-hoc adjustment for multiple comparisons was performed in one-way Anova and Kruskal-Wallis test using Tukey-Kramer correction. . .Comparison of event free survival between participants and non-participants was performed visually by Kaplan-Meier curves and statistically by the Log-rank test. All-cause mortality was used as an endpoint to explore the difference in total risk over time between all groups and is a robust parameter due to completeness of data and no risk of misclassification. Cox proportional

hazard models were used to calculate the unadjusted hazard ratios along with 95% confidence intervals between participants and four groups of non-participants. The model was assessed for proportionality of hazards and interactions. Missing data was handled with x20 multiple imputations by chained equations [14] as the data was not missing completely at random. Variables with missing data less than 15% were imputed and variables with more than 15% of cases were excluded from analysis. SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

3. Results:

During the DANAMI-3-study period a total of 5061 patients >18 years with STEMI and symptom duration <12 hours were admitted and treated with pPCI in Denmark in the four participating study sites (figure 1). A total of 2206 (43%) of these patients were included in DANAMI-3 and the inclusion rates varied from 5%-63% between the four participating study sites. At the top including study site (centre 1) a total of 1601 patients (64%) were included in the trial (73% of the overall study population) and 605 (24%) patients were excluded for reasons listed in the trial screening log (figure 1). A total of 308 patients (12%) were not screened for eligibility/not recorded in the trial screening log at the top including study site. Following retrospective manual assessment, DANAMI-3 eligibility of the non-screened patients was listed and 154 (6%) patients in this group did not have exclusion criteria (figure 1). After randomization 27 patients dropped out before discharge from hospital due to withdrawal of consent and they were categorized as participants in this analysis. Of the excluded patients 144 (5%) did not, after thorough studying of hospital charts, have any per-protocol defined exclusion criteria but were excluded due to participation in other studies, short life expectancy, logistic reasons (two or more STEMI requiring acute treatment at the same time), expected poor patient compliance or comorbidity. Unconsciousness/cardiogenic shock (30%), inability to sign informed consent due to communicational or cognitive issues (28%) and refusal (16%) were the most

frequent reason for per-protocol exclusion. The ethics committee did not permit collection of reasons for refusal by patients.

3.1 Baseline characteristics

In table 1 (e-component 1) all clinical characteristics at were compared between participants, excluded and non-screened patients from the top including study site. DANAMI-3-participants were younger, had fewer risk factors (except for smoking status) and less frequently comorbidities. The clinical presentation by participants at admission was also significantly different than the two other groups and the participants had shorter duration from symptom onset to first wire and were treated more often during office hours. The excluded had similar characteristics compared to the non-screened patients except for cardiac arrhythmias, systolic blood pressure, cardiogenic shock and stent thrombosis (P for all <0.001) and were less frequently treated during off-hours ($P<0.001$) and has less language and communicational issues ($P<0.001$). A total of 131 of the non-screened patients did not have an exclusion criterion and were not screened for unknown reasons (figure 1). For these patients 54% were available for formal screening during weekdays in day time (8 a.m - 4 p.m) compared to 32 % of the participants (data not shown).

3.3 Mortality

All-cause mortality was used as an endpoint to explore the difference in the combined clinical longitudinal risk between the groups. For all patients with STEMI treated with pPCI in Denmark during the DANAMI-3 inclusion period a total of 478 patients (9.8%) died after 1 year follow-up and 796 patients (16%) after a median follow-up of 1333 days (range: 1-2021 days). At the top including study site the recorded screening rate was 88% and mortality was significantly lower among the participants (9%) compared to the excluded patients (27%) and the non-screened (34%) (Log-Rank:

$p < 0.001$) after a median follow up of 1377 days (range: 1-2021) (figure 2). The difference in mortality was also significantly lower from 1-30 days among participants (2%) compared to excluded (13%) and non-screened (22%) (Log-Rank: $p < 0.001$) and also from 30 days to the end of follow-up for participants (7%) compared to excluded (16%) and non-screened (16%) (Log-Rank: $p < 0.001$). After 5 days there was no significant difference in mortality between excluded (18%) and non-screened (19%) (Log-Rank: $p = 0.65$). Participant had lower mortality (9%) compared to eligible non-participants (30%) and ineligible non-participants (28%) (Log-Rank: $p < 0.001$) (figure 3). There was no difference in mortality between eligible non-participants and ineligible non-participants. Participants had a lower hazard ratio for mortality (9%) compared to both eligible excluded (26%) and ineligible excluded (27%) patients as well as compared to eligible non-screened (27%) and ineligible non-screened patients (42%) (Log-Rank for all $P < 0.001$) (table 2).

4 Discussion

In this study we were able to compare participants in a RCT of STEMI with contemporary excluded and non-screened patients from the top inclusion study site through unselected registries. The two main findings were: 1) Non-screened had similar characteristics and all-cause mortality compared to the excluded patients and thus unreported screening and exclusion of the target population had occurred. 2) Participants had a lower mortality rate compared to eligible excluded and eligible non-screened and may therefore not be representative to the entire target population without exclusion criteria.

RCTs are the gold standard to test efficacy and safety in evidence based medicine, and the results from a well-executed RCT with strong internal validity and without sampling bias can be extrapolated to the extent of the trial protocol. However, it is commonly acknowledged that patients included in

RCTs have a better prognosis than patients not included in RCTs of acute coronary syndromes [5;6] including RCTs with all-comers design [2;3]. It is also acknowledged that patients with exclusion criteria represent patients with higher risk and have a worse prognosis than patients without exclusion criteria [5]. In addition, sampling bias can be a source of poor external validity because eligible patients who are screened for study inclusion, but not randomized, have a worse prognosis compared to participants [15].

The results from this study consisted with previous results that sampling bias can occur due to exclusion of eligible patients recorded in the screening logs. We also suggested that the full extent of sampling bias cannot be assessed using screening logs because not all screening and exclusion of eligible patients is recorded in screening logs. As a result of investigator incentives a great proportion of patients in the non-screened group were probably bypassed from the DANAMI-3 screening log and these patients constituted a source of sampling bias. Comparison of mortality between participants and both eligible and ineligible non-participants supports the findings that exclusion of eligible patients and sampling bias had occurred and that the differences between participants and non-participants could not be only due to exclusion criteria (figure 3). If screened patients are not recorded in the trial screening log it is difficult to assess the representativity of the trial participants in the absence of unselected registry data. The Danish heart registries, The National Cardiovascular Data Registry [16] and the SCAAR registry [17] are examples of databases, which contain unselected routinely collected clinical data according to European data standards for clinical care in cardiology [18]. Such registries represent important infrastructures for reporting important determinants of external validity in RCTs.

We showed that participants had a different baseline profile compared to patients who were excluded from the trial as well as patients who were not screened in the top including study site. Both short-term and long-term mortality was lower among participants and this finding consisted with the lower

average of predicted risk and long-term mortality predictors in the excluded and non-screened.. In DANAMI-3 the effect of the intervention did not show any beneficial effect on mortality. Thus, the difference between participants and non-participants could not be due to treatment effects. We also recognize performance bias to be a potential factor for the difference between the groups. Unfortunately, we were not able to explore this parameter

Reasons for unreported exclusion of eligible patients are difficult to address and are most likely multifactorial. In this study 50% (154 patients) of the non-screened had an exclusion criterion. However, 44% (131 patients) of the non-screened did not have an exclusion criterion and were not recorded in the screening log for unknown reasons. We were not able to show any statistically significant correlation between non-screening for unknown reasons and any of the examined parameters. Importantly, non-screening would not have been expected to result in sampling bias if non-screening was due to random circumstances. Based on the results from this study the results from DANAMI-3 in the top including study site could not be extrapolated to patients with exclusion criteria (26%) because they showed different prognosis compared to participants. In addition, the results could not be extrapolated to eligible non-participants (12%) and extrapolation of results may be limited to patients with similar characteristics as participants. The present inclusion rate of 43% in the DANAMI-3 from the Danish population with STEMI is only comparable to one other contemporary RCT of STEMI patients treated with pPCI [19] because most RCTs do not report inclusion rates at all. The recorded screening rate of 88% in the top including study site was more difficult to compare to other studies because formal screening of the target population could potentially be defined in different ways. The protocol in DANAMI-3 stated that only the top including study site was committed to record all consecutive patients from the target population in the trial screening log during the inclusion period. Reporting of screening rates as well as characteristics,

eligibility and clinical course for the non-screened patients (or a random sample of this group) is important to evaluate the relative size of the sample and extend of sampling bias.

The ability of RCTs to represent a true population with STEMI patients is potentially hampered by several issues as shown in this study. First, protocolled exclusion criteria are applied due to ethical- or safety considerations from the investigators or ethics committees. Secondly, patients with STEMI represent a group of critically ill patients and immediate informed consent is difficult to obtain from a large proportion of the most critically ill patients. Third, screening in the acute setting of STEMI must be done by research personal available, which can be sparse during off hours and acute lifesaving treatment must not be delayed. Failure to obtain informed consent prior to study inclusion has been a concern for external validity in previous RCTs of acute myocardial infarction [2] and at least one contemporary study had ethical approval to obtain what was labelled “delayed informed consent” after study inclusion which is a way to improve inclusion rates [7]. In the DANAMI-3 study 149 (24%) of the excluded and 105 (32%) of the non-screened were unconscious after out of hospital cardiac arrest or presented with cardiogenic shock and these characteristics are also known predictors of mortality. The failure to include the most critically ill patients may compromise the ability of a RCT with STEMI patients to assess short term effectiveness of a new treatment. Proxy consent of trial inclusion for the most critically ill patients could potentially help to overcome this issue. Failure to include the chronically ill patients could also compromise external validity and long term effectiveness assessment. The long term clinical course for the participants was consistent with the lower prevalence of risk factors and comorbidities, which are known predictors of mortality.

4.1 Limitations:

This study is largely based on data based on data from a single centre. In addition, we were not able to assess the impact of all exclusion criteria because information about refusal and intolerance to aspirin or P2Y₁₂-receptor antagonists were not available for all patients.

5. Conclusion

In a national multicenter all-comers randomized controlled trial of STEMI patients treated with pPCI, the participants had a lower mortality rate than contemporary patients who did not participate. Sampling bias occurred due to both reported and unreported exclusion of eligible patients and the difference in mortality between participants and non-participants could not be explained only by the trial exclusion criteria. Thus, sampling bias may represent a caveat when performing randomized all-comers STEMI studies and screening logs are potentially not suited to address this bias in RCTs.

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Table and figure legends

Table 2

Hazard ratios according to screening status and eligibility

Unadjusted cox-regression analysis of the relationship between all-cause mortality and DANAMI-3 screening status in the top including study site.

Figure 1

Patient selection

Flow of patients and selection of DANAMI-3-participants. pPCI=Primary percutaneous coronary intervention

Figure 2

Mortality according to screening status

Kaplan-Meier curves for event-free survival for DANAMI3 participants, excluded and non-screened in the top including study site.

Figure 3

Mortality according to DANAMI-3 eligibility

Kaplan-Meier curves for event-free survival for DANAMI3 participants, eligible non-participants and ineligible non-participants in the top including study site.

Table 2

	n	Hazard Ratio	(95% CI)	P
Participants	1564	1		
Excluded- eligible	144	3.41	(2.69-4.32)	<0.001
Excluded- ineligible	488	3.42	(2.44-4.80)	<0.001
Non-screened- eligible	154	3.37	(2.36-4.82)	<0.001
Non-screened- ineligible	154	6.48	(4.77-8.80)	<0.001

Highlights

- Participants in the DANAMI-3 trial were not representative to the background population with STEMI
- Participants in the DANAMI-3 trial were not representative to the per protocol target population
- Sampling bias and unreported screening had occurred
-
- Screening logs may not be suitable for addressing issues of external validity

In all four participating study sites a total of 5061 consecutive patients >18 years with STEMI and chest pain <12 hours underwent pPCI during the DANAMI-3 inclusion period.
Center 1: n=2514 (top including study site)
Remaining participating centers: n=2547

Patients who did not participate:
Remaining participating centers: n=1942

Patients who did not participate:
Center 1: n=913

Excluded (DANAMI-3 screening log):

605 patients were screened and excluded:

472 patients had at least one exclusion criteria :

(Ineligible excluded)

- 82 had stent thrombosis at admission
- 149 were unconscious or had cardiogenic shock at admission
- 15 had haemorrhagic diathesis or known coagulopathy
- 1 had suspected pregnancy
- 82 refused to participate
- 142 excluded due to communicational or cognitive issues

17 patients had more than 1 exclusion criteria

27 patients were excluded after randomization:

- 27: Angiographic reasons

144 Patients did not have an exclusion criteria:

(Eligible excluded)

- ❖ 43 participated in another study (and no other exclusion criteria)
- ❖ 101 were excluded due to other reason (i.e logistic reasons, expectations of poor patient compliance, comorbidity or short life expectancy)

2206 patients with STEMI participated in DANAMI-3
Center 1: n=1601
(Participants)

Remaning participating centers: n=605

Non- Screened:

308 patients were not recorded in the DANAMI-3 screening log:

154 patients had at least one exclusion criteria :

(Ineligible non-screened)

- 25 had stent thrombosis at admission
- 105 were unconscious or had cardiogenic shock at admission
- 21 due to communicational or cognitive issues
- 3 PCI not possible (and no CABG)

154 Patients did not have an exclusion criteria:

(Eligible non-screened)

- ❖ 23 participated in another study (and no other exclusion criteria)
- ❖ 131: unknown reasons:

Figure 1

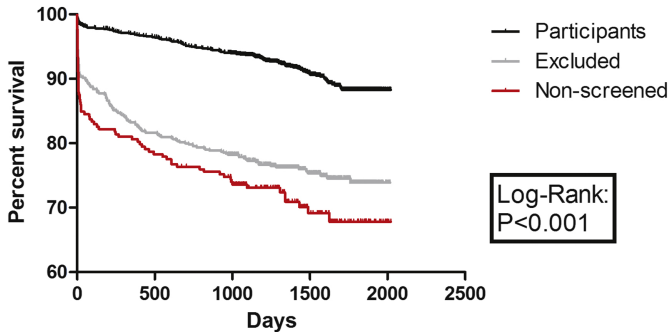


Figure 2

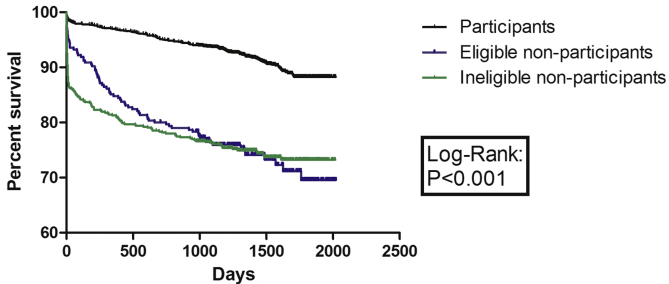


Figure 3