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ORIGINAL PAPER

Impact of recruitment and retention on all-cause mortality in a large all-comers randomised controlled trial: insights from the GLOBAL LEADERS trial

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Abstract

Objective Recruitment and retention in trials may bias the results and subsequently complicate their interpretation and validity. The aim of this study is to evaluate the impact of recruitment and retention on all-cause mortality in a large all-comers trial.

Methods The recruitment rate in each investigating center of the GLOBAL LEADERS trial was assessed and the 130 centers were subdivided into low and high recruiters according to the median, with all-cause mortality then compared between the two groups. Vital status was obtained from public records in patients with incomplete follow-up.

Results The trial randomized 15,991 (7.86%) of 203,483 eligible patients with percutaneous coronary intervention during the recruitment period, of whom 15,267 (95.47%) completed follow-up, 23 (0.14%) patients withdrew consent and formally requested to be deleted from the database; 183 (1.14%) withdrew consent but only objected to future data collection; 303 (1.89%) discontinued the study; and 215 (1.34%) were lost to follow-up. Vital status was finally obtained in all but 31 patients (99.81%). Patients from low recruiters had a significantly lower all-cause mortality than high ones (2.26% vs. 3.24%; hazard ratio: 0.69; 95% confidence interval: 0.55–0.87; $p=0.002$). There was a significant difference in all-cause mortality among the incomplete follow-up groups (log-rank $p<0.001$) with a significantly higher mortality in the 183 patients who withdrew consent than those who completed follow-up (7.38% vs. 2.99%, $p=0.002$).

Conclusions Recruitment and retention significantly impacted all-cause mortality. Search for vital status through public domains is of paramount importance in the interpretation and validity of large clinical trials.

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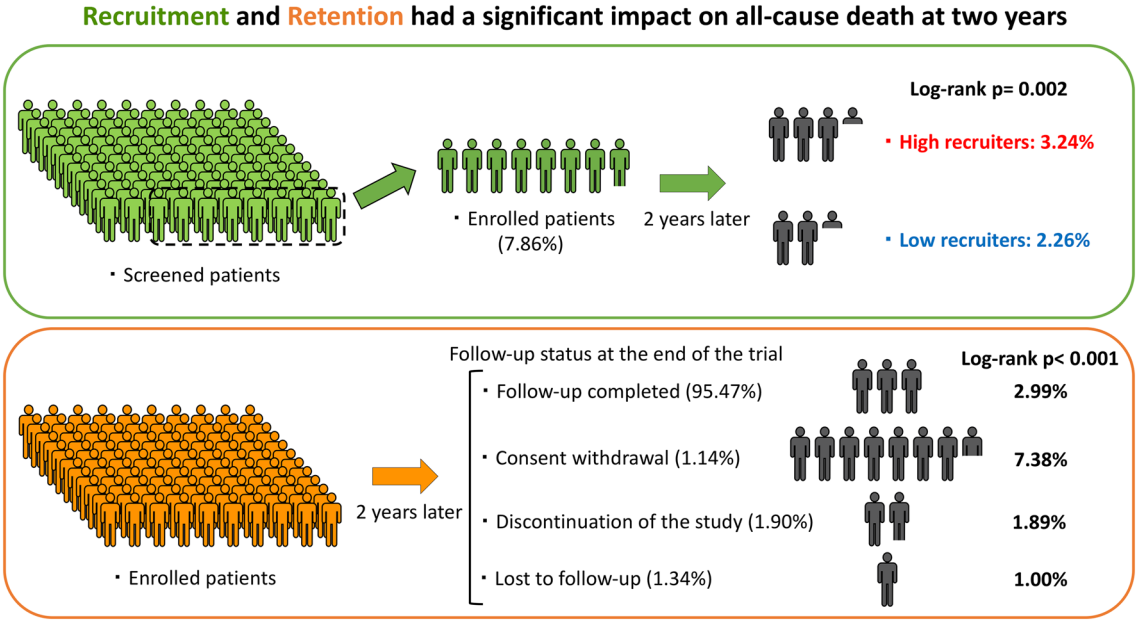
Graphic abstract



Keywords All-cause mortality · All-comers · Recruitment · Retention · Randomised controlled trial

Introduction

Randomized controlled trials (RCT) have long been considered as the gold standard to evaluate the clinical safety and efficacy of therapeutic interventions due to the control of bias. However, recruitment and retention of trial participants is a common issue in the conduct of trials. Indeed, 84–98% of screened patients were not recruited in RCTs with the strict inclusion and exclusion criteria [1] and participants are a selected group of patients who may not be representative of the vast majority of those encountered in daily practice [2]. To address this issue of selection bias and to improve the generalizability of RCT results, the term "all-comers" was first introduced in the LEADERS trial [3]. Since then, the all-comers design has become popular in the design of contemporary cardiovascular RCTs, because it allows enrolment of a population which is more reflective of routine practice. To date, there have been at least three studies analyzing all-comers concept, demonstrating recruitment of only approximately half of the screened population and significant differences in baseline characteristics and subsequently in all-cause mortality between participants and non-participants [4, 5]. However, reasons for non-inclusion of the all-comers population have not been fully investigated [6].

"Dropouts" from trials can also introduce bias in results, particularly if the patient characteristics and reasons for missing follow-up are associated with the study drug or clinical outcomes of interest [7–10]. In this regard, rigorous trial design and implementation have been a key for trial interpretation and validity in clinical research and practice as well as for regulatory decision making [11]. In addition, clear and detailed reporting of the participant flow diagram according to the consolidated standards of reporting trials (CONSORT) statement is of paramount importance [12]. Since the introduction of the CONSORT statement, adherence to this guidance has improved the rate of reporting complete data [10]. Nevertheless, to our best knowledge, no previous study in the literature performed outcome assessment in patients who did not complete follow-up. We therefore sought to evaluate the impact of recruitment and retention on all-cause mortality in a large "all-comers" RCT.

Methods

Study patients

The GLOBAL LEADERS trial is a prospective, multicenter, open-label, all-comers, RCT (NCT01813435). Details of the trial protocol and design have been published previously [13, 14]. In summary, patients undergoing percutaneous coronary intervention (PCI) treated by default with

Biolimus A9-eluting stents (BioMatrix, Biosensors Europe) were randomized in a 1:1 ratio to receive either: (i) the experimental strategy (one-month course of dual antiplatelet therapy (DAPT) followed by 23-month ticagrelor monotherapy), or (ii) the reference regimen (standard 12-month DAPT followed by 12-month aspirin monotherapy). Randomization was stratified by center and clinical presentation [stable coronary artery disease (CAD) or acute coronary syndrome (ACS)]. The trial had an "all-comers" design, so that any coronary syndrome [stable CAD, unstable angina (UA), Non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI)] as well as any type of coronary anatomical lesions were included, and the number and length of implanted stents were unrestricted.

Due to a lack of a screening log, investigators were retrospectively asked about the total number of patients who underwent PCI during the exact period of recruitment for the given center. With the numerator (number of randomized patients in the center) and the denominator (total number of treated patients with PCI during the recruitment period), we were able to calculate the proportion of patients randomized in each participating center. Subsequently, a survey was sent to all the investigators to determine the potential reasons for non-inclusion of the all-comers population (Online Material 1 and Online Table 1). The 130 participating centers were then subdivided into two groups (low and high recruiters) according to whether their recruitment rate was above or below the median value.

The trial was approved by the institutional review board at each investigating center. The study followed the ethical principles of the Declaration of Helsinki. All the participants provided written informed consent at the time of participation in the trial.

Study proceedings and endpoint

Patients were followed for 2 years after discharge. The protocol requested a total of six hospital visits (at 1, 3, 6, 12, 18, and 24 months) to obtain trial medication and to assess the major adverse events and adherence to medical treatment. Complete follow-up was defined as patients who completed the study follow-up over 2 years, whereas incomplete follow-up included: (i) consent withdrawal with formal request for complete deletion of their data from the database; (ii) consent withdrawal with objection to future data collection; (iii) discontinuation of the study without objection to further data collection; (iv) lost to follow-up. These four categories of incomplete follow-up were pre-specified and included in the electronic case report form (eCRF) of the trial, and have been used in other recent studies [15]. If patients did not show up at a study visit, the protocol mandated all possible efforts to be made to trace the patients. These patients were contacted by telephone. Family, general practitioners, and referring cardiologists were contacted if necessary, and finally the survival data was sought through public domains. records (national, provincial, and municipal registries). However, information on causes of death were not always available in these public domains. Therefore, we decided to study all-cause mortality as a single robust endpoint without need for adjudication.

Statistical analysis

Continuous variables were presented as mean ± standard deviations (SD) or median and interquartile range (IQR) depending on distribution, compared with Student's *t* tests or Mann–Whitney *U* test, respectively. Categorical variables were presented as numbers and percentages (%), compared with Chi square or Fisher's exact test as appropriate.

Kaplan–Meier curves were generated to estimate the cumulative incidence of all-cause mortality during follow-up. The log-rank test was applied to compare a risk for all-cause mortality at 2 years between groups. A Cox proportional hazard model was used to evaluate a risk for all-cause mortality with 95% confidence intervals (CI), and then adjusted hazard ratio (HR) is obtained for the baseline characteristics. In addition, we performed a meta-regression analysis to evaluate the relationship between the recruitment rate in each center and all-cause mortality at 2 years, taking into account the number of patients recruited in each center.

We also perform a sensitivity analysis on the assumptions with best- or worst-case scenarios in order to investigate whether patients with unknown vital status endanger the result of all-cause mortality in the trial.

A two-sided p value of < 0.05 was considered significant for all tests. All statistical analyses were conducted using R version 3.4.2 (R Foundation, Vienna, Austria) and the meta-regression model was fitted with metafor package.

Results

Study population

During the recruitment period, 203,483 patients underwent PCI in the investigating centers, with 15,991 (mean; 7.86%, median; 6.68%) patients being recruited into the trial (Fig. 1). Among them, 15,267 (95.47%) completed 2-year follow-up, 23 (0.14%) patients withdrew consent with formal request for complete deletion of their data, 183 (1.14%) withdrew consent with objection to future data collection, 304 (1.90%) discontinued the study; and 214 (1.34%) were lost to follow-up. Vital status was not obtained in 31 patients (0.19%); search for survival data was not attempted in those 23 patients with consent withdrawal; and the remaining eight

patients were permanently missing for survival information (Fig. 1).

Reasons for non-inclusion into the trial

Our survey aiming at determining potential reasons for the overall low recruitment rate of the trial had a response rate of 99.2% (129 of 130 centers; the single center which did not respond recruited only nine patients into the trial). The major reasons for non-inclusion were: the travel/expense burden for patients [Number of centers (Ncenters) = 83/129, 64.3%]; exclusion criteria such as need for oral anticoagulant therapy (Ncenters = 79/129, 61.2%); and participation of the investigator's center in other competing PCI trials (Ncenters = 75/129, 58.1%) (Table 1).

Baseline characteristics and all-cause mortality according to recruitment rate

Baseline characteristics between low and high recruiters are presented in Table 2. Patients from low recruiters were younger, and more likely to be male than those in the high recruiters. Patients in this latter group were also less likely to have hypercholesterolemia whilst they had significantly higher rates of current smoking, impaired renal function, peripheral vascular disease, and previous stroke ($p < 0.05$, for each). In terms of clinical presentation, low recruiters recruited less patients with ACS as compared to high recruiters (49.4% vs. 39.5%, $p < 0.001$), especially with STEMI (15.6% vs. 5.5%, $p < 0.001$).

Patients from low recruiters had a significantly lower mortality as compared with high recruiters (2.26% vs. 3.24%, unadjusted HR: 0.69; 95% CI: 0.55–0.87; $p = 0.002$) (Fig. 2). This significant between-group difference was no longer observed when adjusted for the baseline characteristics ($p = 0.079$).

Meta-regression analysis showed the logarithmic correlation ($y = 0.56*\log(x) + 1.09$, $p < 0.001$) between the recruitment rate in each center and all-cause mortality at 2 years taking into account the number of patients recruited in each center (Fig. 3).

Baseline characteristics and all-cause mortality according to each follow-up status

Baseline characteristics according to each type of follow-up status are summarized in Table 3. Patients who withdrew consent with objection to future data collection were older, more likely to be female, more commonly received the experimental treatment, and had a higher prevalence of previous PCI. Patients with discontinuation of the study

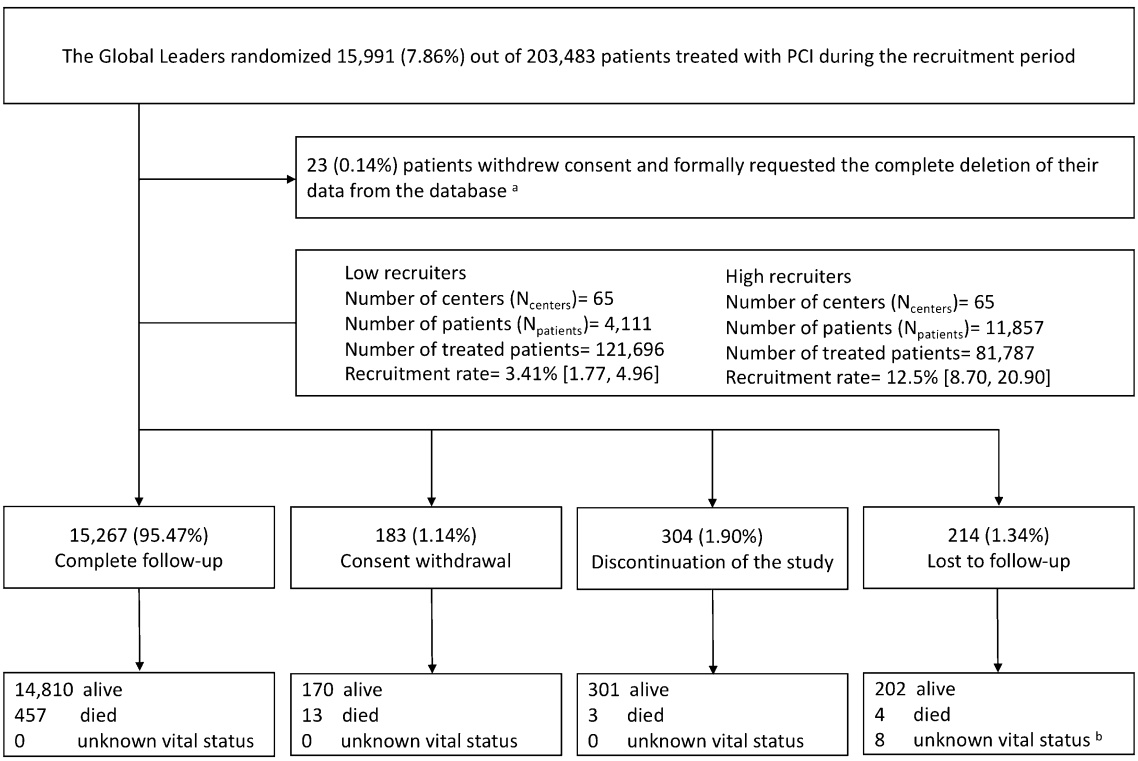


Fig. 1 Participant flow diagram of the present study. [a]Randomization allocation is the only remaining information available in the database. [b]Four patients were in the experimental group and the others were in the reference group

Table 1 Major reasons for non-inclusion of all-comers patients according to our survey with a response rate of 99.2% (129/130)

Total number of interventional cardiologists at each center	6.7 ± 2.8
The number of interventional cardiologists involved in the trial	5.1 ± 2.4
The number of interventional cardiologists actually recruiting their patients	4.4 ± 2.4
Reasons for non-inclusion of all-comers population	
1. Travel hurdles/expenses for the patients	83/129 (64.3)
2. One of the exclusion criteria (need for oral anticoagulation therapy)	79/129 (61.2)
3. Other competing PCI trials	75/129 (58.1)
4. Ad hoc PCI without informed consent prior to the procedure	59/129 (45.7)
5. Patients' refusal to participate in the trial	44/129 (34.1)
6. Pharmacological complexity of the trial	43/129 (33.3)
7. One of the exclusion criteria (inability to provide informed consent)	33/129 (25.6)
8. One of the exclusion criteria (planned surgery within 12 months of PCI)	24/129 (18.6)
9. Availability of the correct size of the BioMatrix™ family DES on the shelf	21/129 (16.3)
10. One of the exclusion criteria (known previous major bleeding)	15/129 (11.6)

Data are presented as means ± standard deviations or frequency (%)

had a higher prevalence of COPD. Patients with lost to follow-up had a higher prevalence of previous MI and were more frequently current smoker ($p < 0.05$ for each).

Two-year all-cause mortality was significantly different according to the follow-up status (Log-rank $p < 0.001$): 183 patients with consent withdrawal had a significantly higher mortality, as compared with the complete follow-up group (7.38% vs. 2.99%; unadjusted HR: 2.40; 95% CI: 1.38–4.17; $p = 0.002$). This significant difference was no longer observed when adjusted for the baseline characteristics ($p = 0.074$) (Fig. 4).

Would patients with unknown vital status endanger the result of all-cause mortality in the trial (a sensitivity analysis)?

The rate of all-cause mortality in the experimental arm in the trial was 2.81% (224/7976) vs. 3.17% (253/7984) in the reference arm ($p = 0.182$). A total of 31 (0.19%) patients were missing for vital status at the end of the trial (16 patients were in the experimental arm and 15 patients were in the reference arm). In the "best-case scenario" assuming that death occurs only in the reference arm ($n = 15$), all-cause mortality would be 2.80% (224/7992) in the experimental arm vs. 3.35% (268/7999) in the reference arm ($p = 0.045$, based on Chi square test). In the "worst-case scenario" on the assumption that death occurs only in the experimental arm ($n = 16$), all-cause mortality would be 3.00% (240/7992) in the experimental arm vs. 3.16% (253/7999) in the reference arm ($p = 0.559$, based on Chi square test).

Discussion

The main findings of the present analysis can be summarized as follows:

1. The GLOBAL LEADERS trial recruited 15,991 patients (mean: 7.86%, median: 6.68%) of an all-comers population. During the follow-up period, 15,267 (95.47%) completed two-year follow-up, while 724 (4.53%) did not. Vital status was not obtained in 31 (0.19%) patients.
2. Patients from lower recruiters had a more benign clinical risk profile and less acute indications for PCI and subsequently had a lower unadjusted mortality, when compared with those from high recruiters.
3. Among patients with incomplete follow-up, there were significant differences in baseline characteristics and subsequently in all-cause mortality at 2 years: patients who withdrew consent had a significantly higher mortality, as compared to the complete follow-up group.
4. The sensitivity analysis illustrates the instability of outcome assessment even when dealing with a large number of participants and a substantial mortality.

Theoretically, all-comers RCTs are designed to mimic real-world practice. Since the introduction of the term "all-comers" in the LEADERS trial [3], the all-comers design has become popular in the design of contemporary cardiovascular RCTs. According to previous "all-comers" RCTs, a recruitment rate of almost 50% was attainable in single-centre studies [4, 5], whereas rates in multi-centre all-comers trials ranged from 15.2% to 53.8% (Online Table 2). Disappointingly, the GLOBAL LEADERS trial only recruited 7.86% of the potential target population.

Table 2 Baseline clinical characteristics between low versus high recruiters

	Low recruiters ($n=4111$)	High recruiters ($n=11,857$)	p value
Randomized treatment			
Experimental strategy	50.0 (2054/4111)	50.0 (5926/11,857)	0.986
Reference strategy	50.0 (2057/4111)	50.0 (5931/11,857)	
Age (year)	63.8 ± 10.0	64.8 ± 10.4	< 0.001
Sex			0.005
Male	78.4 (3221/4111)	76.2 (9033/11,857)	
Female	21.6 (890/4111)	23.8 (2824/11,857)	
Body mass index (kg/m^2)	28.5 ± 4.8	28.1 ± 4.5	< 0.001
Diabetes	26.1 (1074/4111)	25.0 (2964/11,846)	0.161
Insulin-dependent diabetes mellitus	8.4 (344/4109)	7.4 (879/11,812)	0.054
Hypertension	74.7 (3066/4103)	73.2 (8649/11,811)	0.061
Hypercholesterolemia	72.1 (2924/4055)	68.7 (7844/11,410)	< 0.001
Current smoker	23.2 (952/4111)	27.1 (3217/11,857)	< 0.001
Peripheral vascular disease	5.4 (222/4095)	6.7 (783/11,727)	0.005
Chronic obstructive pulmonary disease	5.1 (208/4102)	5.2 (613/11,794)	0.752
Previous bleeding	0.4 (17/4110)	0.7 (81/11,837)	0.056
Impaired renal function[a]	12.5 (507/4071)	14.1 (1664/11,812)	0.009
Previous stroke	2.0 (84/4105)	2.8 (337/11,840)	0.006
Previous myocardial infarction	23.6 (964/4090)	23.2 (2746/11,832)	0.637
Previous percutaneous coronary intervention	32.3 (1328/4107)	32.9 (3893/11,847)	0.536
Previous coronary artery bypass grafting	6.1 (252/4107)	5.8 (691/11,848)	0.477
Clinical presentation			< 0.001
Stable coronary artery disease	60.5 (2486/4111)	50.6 (5995/11,857)	
Acute coronary syndrome	39.5 (1625/4111)	49.4 (5862/11,857)	
Overall			< 0.001
Unstable angina	9.0 (372/4111)	13.9 (1650/11,857)	
Non-ST segment elevation myocardial infarction	25.0 (1026/4111)	19.8 (2347/11,857)	
ST segment elevation myocardial infarction	5.5 (227/4111)	15.7 (1865/11,857)	

Data are presented as mean ± standard deviation or percentage (number)

TIMI Thrombolysis in myocardial infarction

[a]Estimated glomerular filtration rate of creatinine clearance of < 60 mL/min per 1.73 m^2 based on the modification of diet in renal disease formula

Reasons for non-inclusion of all-comers population

There were many reasons for non-inclusion of the target population and therefore not fulfilling the trial's design aspiration. The study protocol mandated a total of six clinic visits after hospital discharge [13], which made it difficult for patients especially older ones from geographically distant areas to comply with this scheme of hospital visits, and therefore rather than incomplete follow-up, these patients were not recruited.

A major difference in the inclusion and exclusion criteria between the GLOBAL LEADERS trial and previous all-comers RCTs listed in Online Table 2, which compared the safety and efficacy of new drug-eluting stents without any pharmacological component listed, is that the need for oral anticoagulant therapy was not usually an exclusion criterion except for the BIO-RESORT trial [16]. There has been an increasing number of patients who need long-term treatment with oral anticoagulants and approximately 20–30% of these patients have coronary artery disease that requires PCI [17, 18]. Furthermore, the current European Society of Cardiology guideline recommends combining dual or single antiplatelet therapy with anticoagulants for a shorter period taking into account the ischemic and bleeding risk [19]. In the GLOBAL LEADERS trial, the reference arm mandated 12-month DAPT and oral anticoagulation was one of the exclusion criteria, which prevented investigators from recruiting these patients into the trial.

An uncited reason is that all the interventional cardiologists in a centre did not recruit their patients as a united team of operators committed to contribute to the trial. This is evidenced by the difference between the mean number

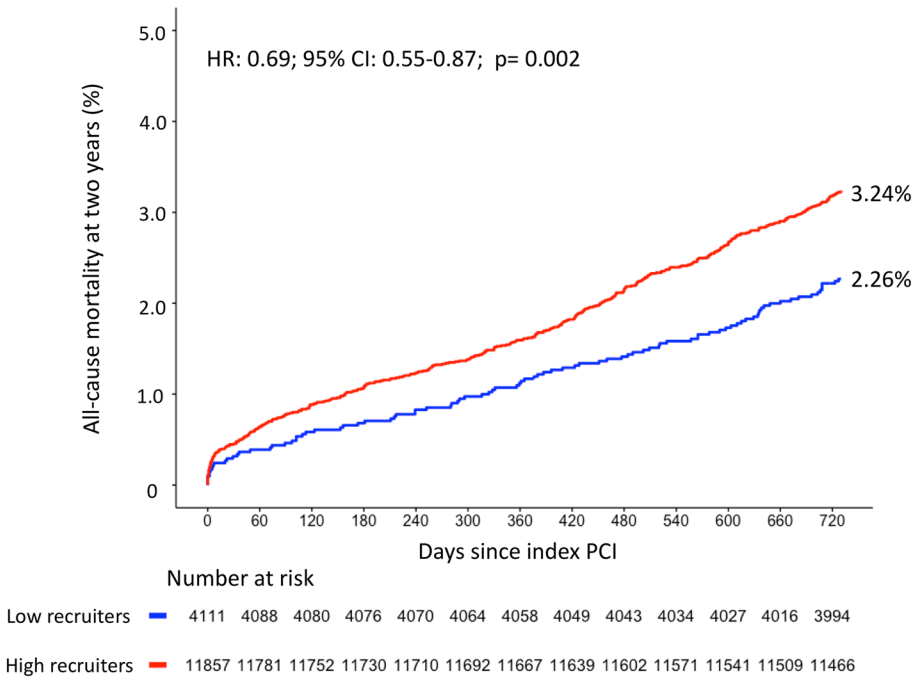


Fig. 2 All-cause mortality up to 2 years between the low versus high recruiters

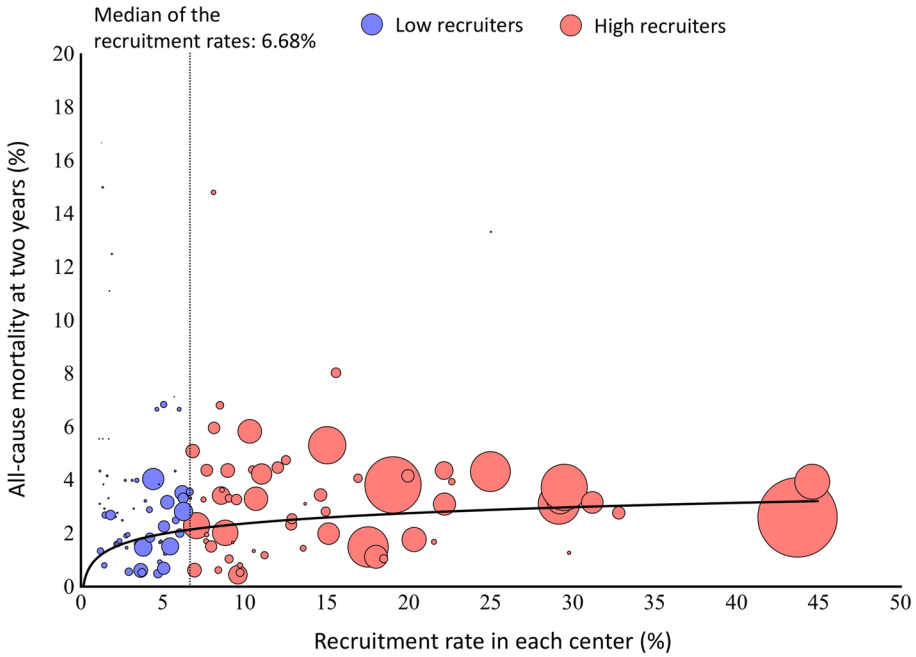


Fig. 3 The logarithmic correlation between recruitment rate and all-cause mortality at 2 years based on a meta-regression model. The size of each bubble represents the number of patients recruited in each center. Pink color represents above median of the overall recruitment rate whereas blue color represents below the median rate. *CI* confidence interval, *HR* hazard ratio, *PCI* percutaneous coronary intervention

of operators in the investigators' center (6.7 ± 2.8) and the number actually recruiting to the study (4.4 ± 2.4) (Table 1), suggesting that other competing trials or unwillingness to contribute may have played a role.

Another issue for the recruitment might be the duration of recruitment. Online Figure 1 shows that the longer the recruitment period, the poorer the observed recruitment rate, which was possibly due to "research fatigue". Therefore, in order to maximize the all-comers concept, future all-comers trials may be restricted to a fixed time period in a center so that a high rate of recruitment can be achieved [3].

Impact of recruitment rate on all-cause mortality

The overall low recruitment rate of the trial raised the question as to whether there was a selection bias. Indeed, we observed a lower proportion of patients with ACS, especially STEMI in the low recruiters (Table 2). Apparently, the

Table 3 Baseline characteristics according to each type of follow-up status

	Complete follow-up ($n=15,267$)	Withdrawal consent ($n=183$)	Discontinuation of the study ($n=304$)	Lost to follow-up ($n=214$)	p value[a]
Randomized treatment					< 0.001
Experimental strategy	49.8 (7600/15,267)	58.5 (107/183)	57.9 (176/304)	45.3 (97/214)	
Reference strategy	50.2 (7667/15,267)	41.5 (76/183)	42.1 (128/304)	54.7 (117/214)	
Age (year)	64.5 ± 10.2	68.1 ± 10.9	67.9 ± 11.2	57.8 ± 11.0	< 0.001
Sex					0.002
Male	76.9 (11,747/15,267)	67.8 (124/183)	71.1 (216/304)	78.0 (167/214)	
Female	23.1 (3520/15,267)	32.2 (59/183)	28.9 (88/304)	22.0 (47/214)	
Body mass index (kg/m^2)	28.2 ± 4.6	27.9 ± 4.7	27.8 ± 4.7	28.4 ± 5.0	0.381
Diabetes	25.3 (3857/15,256)	25.1 (46/183)	26.6 (81/304)	25.2 (54/214)	0.961
Insulin-dependent diabetes mellitus	7.6 (1158/15,220)	6.0 (11/183)	11.2 (34/304)	9.3 (20/214)	0.074
Hypertension	73.6 (11,204/15,217)	71.4 (130/182)	76.8 (232/302)	70.0 (149/213)	0.318
Hypercholesterolemia	69.7 (10,305/14,786)	68.2 (120/176)	66.9 (198/296)	70.0 (145/207)	0.736
Current smoker	25.9 (3952/15,267)	23.5 (43/183)	24.0 (73/304)	47.2 (101/214)	< 0.001
Peripheral vascular disease	6.3 (959/15,126)	8.3 (15/180)	5.0 (15/302)	7.5 (16/214)	0.454
Chronic obstructive pulmonary disease	5.0 (765/15,198)	7.1 (13/182)	9.9 (30/302)	6.1 (13/214)	0.001
Previous bleeding	0.6 (91/15,248)	1.1 (2/182)	1.0 (3/303)	0.9 (2/214)	0.607
Impaired renal function	13.6 (2058/15,187)	16.5 (30/182)	18.2 (55/302)	13.2 (28/212)	0.081
Previous stroke	2.6 (396/15,247)	2.8 (5/181)	4.6 (14/303)	2.8 (6/214)	0.190
Previous myocardial infarction	23.1 (3521/15,225)	27.1 (49/181)	24.5 (74/302)	30.8 (66/214)	0.033
Previous percutaneous coronary intervention	32.5 (4959/15,255)	39.0 (71/182)	36.0 (109/303)	38.3 (82/214)	0.044
Previous coronary artery bypass grafting	5.9 (900/15,256)	6.0 (11/182)	6.3 (19/303)	6.1 (13/214)	0.993
Clinical presentation					0.565
Stable coronary artery disease	53.1 (8106/15,267)	57.9 (106/183)	52.3 (159/304)	51.4 (110/214)	
Acute coronary syndrome	46.9 (7161/15,267)	42.1 (77/183)	47.7 (145/304)	48.6 (104/214)	
Overall					0.242
Unstable angina	12.8 (1951/15,267)	8.2 (15/183)	12.8 (39/304)	7.9 (17/214)	
Non-ST segment elevation myocardial infarction	21.0 (3210/15,267)	23.0 (42/183)	22.0 (67/304)	25.2 (54/214)	
ST segment elevation myocardial infarction	13.1 (2000/15,267)	10.9 (20/183)	12.8 (39/304)	15.4 (33/214)	

Data are presented as mean ± standard deviation or percentage (number)

Data on 23 patients with consent withdrawal is not presented due to formal request for the deletion of their data from the database

TIMI Thrombolysis in myocardial infarction

[a]Comparison among the four groups

logistics of recruitment into the trial could also have played a role, since informed consent and randomization could not always be achieved especially in emergent situations outside working hours. A potential method of solving this issue is using a delayed consent post procedure as demonstrated in the HEAT PPCI trial where only four patients refused to participate [20, 21]. However, the legal and ethical implication of a patient randomized without informed consent dying during the index procedure remains an important trial concern.

The inability of an all-comers design to represent the vast majority of patients by excluding those at higher risk, may explain the trial's lower than expected rate of all-cause mortality. If the trial had been event driven, recruitment of a low risk population would not have been an issue.

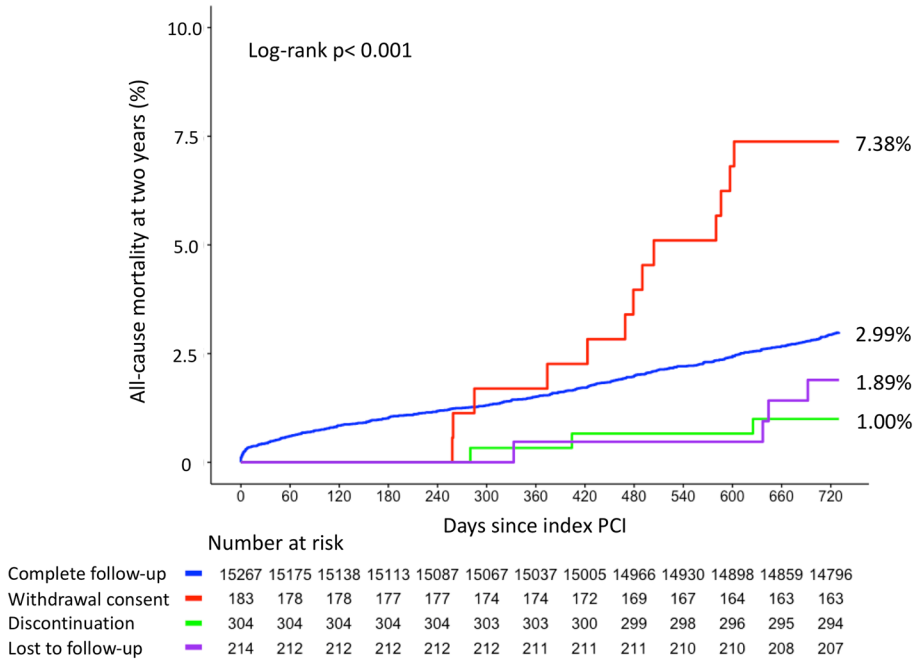


Fig. 4 All-cause mortality up to 2 years according to each type of follow-up status at the end of study

Impact of retention on all-cause mortality

Even if the recruitment of an all-comers population is more feasible than a trial with restrictive inclusion and exclusion criteria, there is still an issue of missing data, which is commonly encountered in the conduct of clinical trials, and may pose a threat to the interpretation and validity of trial results. The topic of missing data received attention in the ATLAS ACS 2–TIMI 51 Trial, which randomised a total of 15,226 patients, however, 2402 (15.5%) patients prematurely discontinued the study drug, of whom 1294 (8.3%) patients withdrew consent. Vital status was not available in 1117 (7.2%) patients who withdrew consent [11]. It is often reported that the potential bias is not significant if the proportion of missing data is < 20% and that the bias is minimal if the proportion < 5% [7], however, this 5-and-20 rule of thumb has been questioned and the proportion of 5% may potentially have an important impact when trials have low event rates [22], as demonstrated in the present sensitivity analysis.

Guidance for future large "all-comers" trials

In light of these observations that recruitment and retention significantly impacted on all-cause mortality, future PCI trials should realize that the term "all-comers" represents not only trials with broad inclusion criteria encompassing all four ischemic syndromes (stable CAD, UA, NSTEMI, and STEMI) with all kinds of lesions (no limitation on the number, type, location, and length of lesions and number of treated vessels), unrestricted use of stents (number and length) and minimum exclusion criteria, but also implies consecutive recruitment, suggesting that a united team of investigators should focus on a single trial in a limited predefined time period without any major competing studies. Only if randomized trials fulfil and document these *sine qua nons*, then the label "all-comers" may be used. Otherwise the term should be abandoned and the cherry-picking selection of patients will be resurrected. Ultimately, trial results will be less generalizable and lose their external validity as seen in classical RCTs.

Even if the recruitment of an "all-comers" targeted population is more feasible, careful attention to minimizing missing data and maximizing patient retention needs to be paid in the conduct of trials, since missing data have limited the ability to draw inferences from trials and the only optimal approach to address is to prevent it. To this end, investigators should make all possible efforts to contact dropouts to obtain data on treatments and outcomes, and official relationship with national, provincial, and municipal registries and easy access to certificates of death should be established. If a kind of "post-mortem privacy" is implemented in the national laws in the near future, quality and accuracy of large epidemiologic studies with medical intervention may be endangered.

Limitations

This analysis needs to be interpreted in light of the following limitations. First, this sub-study was not pre-specified in the GLOBAL LEADERS trial. The number of screened patients

who were not enrolled was not prospectively captured, neither was the frequency of individual exclusion criteria that precluded the participation of all screened patients. Therefore, we retrospectively collected from the investigators the data on the number of patients treated with PCI during the recruitment period, as well as the investigator's reasons for not including every patient. Second, the protocol did not prospectively record reasons for dropouts from the trial, which did not allow us to assess the causality between the study drug and incomplete follow-up.

Conclusions

The present study in a large "all-comers" RCT demonstrated that recruitment and retention significantly impacted all-cause mortality at 2 years. Trials with the "all-comers" label should comply with strict conditions to prevent jeopardizing their validity. Search for vital status through public domains is of paramount importance in the interpretation and validity of large clinical trials that aim at detecting any treatment effect on all-cause mortality.

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Compliance with ethical standards

Conflict of interest Dr. Liebetrau reports personal fees from Astra Zeneca, outside the submitted work. Dr. Hamm reports personal fees from AstraZeneca, outside the submitted work. Dr. Steg reports Grants and personal fees from Bayer/Janssen, Grants and personal fees from Merck, Grants and personal fees from Sanofi, Grants and personal fees from Amarin, personal fees from Amgen, personal fees from Bristol Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Pfizer, personal fees from Novartis, personal fees from Regeneron, personal fees from Lilly, personal fees from AstraZeneca, Grants and personal fees from Servier, outside the submitted work. Dr. Valgimigli reports Grants and personal fees from Abbott, personal fees from Chiesi, personal fees from Bayer, personal fees from Daiichi Sankyo, personal fees from Amgen, Grants and personal fees from Terumo, personal fees from Alvimedica, Grants from Medicure, Grants and personal fees from Astrazeneca, personal fees from Biosensors, outside the submitted work. Dr. Vranckx has received personal fees from AstraZeneca and the Medicines Company during the conduct of the study and personal fees from Bayer Health Care, Terumo, and Daiichi-Sankyo outside the submitted work. Dr. Windecker reports Grants from Amgen, Grants from Abbott, Grants from Boston Scientific, Grants from Biotronik, Grants from Bayer, Grants from Medtronic, Grants from Edwards Lifesciences, Grants from St Jude, Grants from Terumo, outside the submitted work. Dr. Serruys reports personal fees from Abbott Laboratories, personal fees from Biosensors, personal fees from Medtronic, personal fees from Micel Technologies, personal fees from Sinomedical Sciences Technology, personal fees from Stentys, personal fees from Svelte Medical Systems, personal fees from Philips/Volcano, personal fees from Xeltis, personal fees from StentIt and personal fees from HeartFlow outside the submitted work. All other authors declare no competing interests.

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