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Consecutive or selectively included high bleeding risk patients in the MASTER DAPT screening log and trial

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ABSTRACT (223 words)

Aims. Screening logs have the potential to appraise the actual prevalence and distribution of predefined patient subsets, avoiding selection biases, which are inevitably and potentially present in randomised trials and real-world registries, respectively. We aimed to assess the prevalence of high bleeding risk (HBR) characteristics in the real world and the external validity of the MASTER DAPT trial.

Methods and results. All consecutive patients who underwent percutaneous coronary intervention (PCI) for at least two consecutive weeks across 65 sites participating in the trial were entered into a screening log. Of 2,847 consecutive patients, 1,098 (38.6%) were HBR and 109 (9.9%) consented for trial participation. PRECISE-DAPT score ≥ 25 was the most frequent HBR feature, followed by advanced age, use of oral anticoagulation (OAC) and anaemia. Compared with consecutive HBR patients, consenting patients were older (≥ 75 years: 69% *versus* 62%, absolute standardized difference [SD] 0.16), more frequently male (78% *versus* 71%, absolute SD 0.18), had higher use of OAC (38% *versus* 20%, absolute SD 0.39), treatment with steroids or nonsteroidal anti-inflammatory drugs (10% *versus* 5%, SD 0.16), and prior cerebrovascular events (10% *versus* 6%, absolute SD 0.18) but lower PRECISE DAPT score ≥ 25 (54% *versus* 66%, absolute SD 0.24).

Conclusions. The HBR criteria distribution differed between consecutive versus selectively included HBR patients, suggesting the existence of selection biases in the trial population.

Trial Registration: ClinicalTrials.gov number, NCT03023020.

KEYWORDS: high bleeding risk; antiplatelet therapy; dual antiplatelet therapy; percutaneous coronary intervention.

INTRODUCTION

Patients at high bleeding risk (HBR) represents a variable, yet not negligible, proportion of subjects undergoing percutaneous coronary intervention (PCI) in clinical practice [1–5], and have been historically under-represented in PCI trials [6].

The Academic Research Consortium for HBR (ARC-HBR) proposed by consensus a set of clinical and laboratory criteria for the identification of patients at HBR [7], which underwent extensive validation in European and Asian cohorts [1–3,8,9], and, with the aim of further standardizing trial-specific features in HBR patients, a consensus document to guide trial design and conduct [10].

Despite these initiatives, it remains largely unknown if HBR patients who are offered and accept trial participation are truly representative of unselected HBR patients encountered in practice. Registries complement randomised trials by informing on the HBR criteria distribution in practice, but multicentre registries frequently fail to include all consecutive patients across the entire spectrum of participating sites. Tools such as screening logs, capturing individual HBR features among truly consecutive patients, included or not included in the trial, have the greatest potential to assess whether selection bias occurs in patient enrolment.

The *Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated versus Standard DAPT Regimen* (MASTER DAPT) trial is the largest clinical trial investigating an abbreviated dual antiplatelet therapy (DAPT) compared with a longer DAPT regimen in unselected patients at HBR after drug-eluting stent (DES) implantation, featuring broad inclusion and minimal exclusion criteria [11–14]. We report here a prespecified analysis from the MASTER DAPT screening log and trial, investigating the prevalence and distribution of HBR criteria in consecutive or selectively included PCI patients in the trial.

METHODS

MASTER DAPT design and population

The MASTER DAPT trial is an investigator-initiated, multicenter, randomized, open- label, noninferiority trial with sequential superiority testing in a large cohort of HBR patients who underwent PCI with implantation of a biodegradable polymer-coated Ultimaster (*Terumo Corporation, Tokyo, Japan*) sirolimus-eluting stent [11–14]. The trial was performed at 140 sites in 30 countries across Europe, South America, the Middle East, Asia, and Australia. The trial was approved by the institutional review board at each participating site, and all patients gave written informed consent. The study design and main results of this trial were previously published [11,12,15]. Briefly, patients at HBR were considered to be candidates for participation in the trial if they had undergone PCI of all planned coronary artery stenoses with Ultimaster stent implantation for acute or chronic coronary syndromes and remained event-free (including a new acute coronary syndrome, symptomatic restenosis, stent thrombosis, stroke, or any revascularization resulting in the prolonged use of DAPT) at 1 month after the index procedure. Key exclusion criteria were minimal and restricted to implantation of a stent other than the Ultimaster stent within 6 months before the index procedure, implantation of a bioresorbable scaffold at any time before the index procedure, and treatment for in-stent restenosis or stent thrombosis. Patients were deemed HBR if at least one of the following criteria applied: any oral anticoagulation (OAC) therapy for at least 12 months, recent (<12 months) non-access site bleeding episode(s) that required medical attention, previous bleeding episode(s) that required hospitalization if the underlying cause had not been definitively treated, advanced age (≥75 years), systemic conditions associated with an increased bleeding risk (eg, hematologic disorders or any known coagulation disorder associated with increased bleeding risk), documented anaemia (defined as repeated haemoglobin levels <11 g/dL or transfusion within 4 weeks before randomization), need for chronic treatment with steroids or nonsteroidal anti-inflammatory drugs (NSAIDs), diagnosed malignancy (other than skin), stroke at any time or

transient ischemic attack in the previous 6 months, or predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score ≥ 25 [16].

Screening log sub-study

All participating sites in the trial were invited to participate in the screening-log sub-study, which collected fully anonymized data on HBR features and study eligibility of all consecutive PCI patients for at least 14 consecutive days. Sixty-five sites participated for a median duration of 14 days (interquartile range 14 to 14) and provided data on age, gender, estimated glomerular filtration rate (eGFR), prior bleeding, PRECISE DAPT score and each qualifying HBR feature. Patient outcomes were not collected, unless for those who ultimately participated into the trial. The screening log sub-study was an integral part of the main trial and institutional review boards of the participating sites approved the study and required written informed consent only for those accepting trial participation.

Study populations

All consecutive patients at participating sites who underwent PCI during the screening phase were entered into the screening log (screening log population) and were stratified into those with or without HBR features. Consecutive HBR patients in the screening log were further analysed based on i) whether they were consented for trial participation during the screening log phase, ii) study eligibility, according to the fulfilment of all inclusion and exclusion criteria and compared with all patients who were consented at participating sites during the entire duration of the study.

Statistical analysis

Collected log data were analysed to assess the number of patients screened versus enrolled in the trial. In addition, differences between consented and non-consented patients and eligibility differences among those who did not consent were analysed. Mean differences with 95% confidence interval (CI) and absolute standardized differences (SD) were generated to compare differences among groups. Absolute SD is the difference in the mean of a variable between two groups divided by an estimate of the standard deviation of that variable. An absolute SD of less than 0.10 denotes a negligible difference between the two groups [17]. The analyses were done using Stata release 16.1 (StataCorp LLC, College Station, Texas).

RESULTS

A total of 2,847 consecutive patients who underwent PCI across 65 sites, during a median of 14 days, were entered in the screening log, including 1,749 (61.4%) non-HBR and 1,098 (38.6%) HBR patients, of whom 109 (9.9%) consented for trial participation (**Figure 1**). Of the 989 HBR patients in the log who were not consented, 275 (27.8%) were and 714 (72.2%) were not eligible. The majority (69%) of non-eligible patients met at least one exclusion criterion, largely related to implantation of stents other than Ultimaster. The treating physician not involved in the study in the study (33%) and logistical issues (31%) were the two most frequent reasons for not including eligible patients (**Table S1**). Of the overall 5,208 consented patients in the trial across 140 sites, 3,374 (64.8%) patients were recruited from the 65 sites participating into the screening log.

The frequency distribution of the HBR criteria in the screening log population is shown in the **Figure 2**. High PRECISE-DAPT score was the most frequent (25.3%) HBR feature, followed by advanced age (23.6%), OAC (7.8%), anaemia (5.8%), known active malignancy (2.4%) and prior bleeding or chronic use of non-steroidal anti-inflammatory drug (NSAIDs) or steroids (both at

2.0%). Systemic conditions associated with increased bleeding risk was the least frequent HBR feature (0.7%).

High bleeding risk features in consecutive and selectively included patients in the trial

Table 1 shows the characteristics of HBR and non-HBR patients and differences among consecutive patients (screening log) versus those who consented for trial participation. HBR features of consented patients in the sites participating in the screening log were entirely representative of all consented patients (**Table 1**). Study eligibility did not affect HBR criteria distribution among consented versus non-consented patients (**Figure 1** and **Table S2**).

Consecutive HBR patients were younger (75.1 ± 9.1 *versus* 76.2 ± 8.3 years), had lower eGFR (66.5 ± 29.4 *versus* 70.5 ± 24.5 ml/min/1.73 m2) and higher PRECISE-DAPT score (29.3 ± 11.5 *versus* 26.8 ± 11.1) compared with non-consented HBR patients. The proportion of patients with clinical indication for OAC treatment was almost half (20% *versus* 38%) in consecutive compared with consented HBR patients (mean difference: -17.3%; 95% CI: -20.2% to -14.5%; absolute SD: 0.39). Likewise, the proportion of older (≥ 75 years) patients (62% *versus* 69%), need for chronic treatment with steroids/NSAIDs (5% *versus* 10%) or previous stroke/TIA (6% *versus* 10%) was lower in consecutive HBR patients (absolute SD: 0.16, 0.16 and 0.18, respectively). Conversely, the proportion of patients with PRECISE DAPT score ≥ 25 was higher in consecutive compared with consented HBR patients (66% *versus* 54%; mean difference: 11.7%; 95% CI: 8.4% to 15.0%; absolute SD: 0.24). The remaining HBR characteristics were reasonably balanced between the groups (SD below 0.10).

The comparison of consented versus non-consented HBR patients provided consistent findings and revealed, in addition, that also anaemia (9% *versus* 16%; mean difference: -6.7%; 95% CI: -12.6% to -0.8%; absolute SD: 0.20) and female patients (22% *versus* 30%; mean difference: 7.8%; 95%

CI: -0.5% to 16.1%; absolute SD: 0.18) were less represented in consented versus non-consented HBR patients in the screening log (**Table 1**).

DISCUSSION

To the best of our knowledge, this is the first analysis investigating the external validity and generalizability of a trial including HBR-PCI patients in relation to consecutive patients (screening log) who were treated at recruiting sites (**Graphical abstract**). The main findings of this analysis can be summarized as follows:

1. Among consecutive PCI patients, PRECISE-DAPT score ≥ 25 was the most frequent HBR feature, followed by advanced age. The use of OAC and anaemia were the third and fourth most frequent HBR features.
2. The remaining HBR features were much less represented with a single-digit prevalence.
3. The HBR criteria distribution differed between consecutive and consented HBR PCI patients; clinical indication for OAC and age, while, to less extent, the need for chronic treatment with steroids or NSAIDs and prior cerebrovascular events were all more prevalent in the MASTER DAPT trial population compared with consecutive HBR PCI patients. Conversely, PRECISE DAPT score ≥ 25, anaemia and female patients were under-represented in consented compared with consecutive patients.

Clinical trials apply inclusion and exclusion criteria to target a defined study population which is expected to derive most benefit from the intervention(s) under evaluation. Even in a study potentially addressing an all comer pre-defined population (e.g., all PCI patients), a minority of patients is offered study participation largely, but not limited to, the complex process of obtaining informed consent and patient commitment for any given trial during routine patient care [18].

In order to understand the external validity of trial results, maintaining an accurate record of patients considered for RCT participation is a recommendation in Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. However, reviews of published RCT results have shown that trials consistently fail to record participant flow accurately, particularly before informed consent and randomisation [19,20], undermining the appraisal of the generalizability of trial results. In the MASTER DAPT trial, to comply with the recent SEAR (Screened, Eligible, Approached, Randomised) framework [21], we implemented a comprehensive screening log sub-study capturing key information for consecutive PCI patients. To ensure that all participating sites captured *all* consecutive PCI patients, we purposely limited this activity to a reasonably short time period. This allowed us to gather unique information on HBR criteria distribution in a truly consecutive PCI population and to compare it with consented patients in the study both during the screening log phase as well as during the entire duration of the study across participating sites. This is particularly relevant for HBR trials, which usually target an heterogenous population defined by different clinical or biochemical criteria.

Almost 40% of consecutive patients were at HBR in the MASTER DAPT screening log. This prevalence is consistent with that observed in all-comer registries in the USA, Europe and East Asia, which has been reported varying between 34% and 45% [1–3,8,9]. In the present study, nearly 10% of consecutive HBR patients were consented and that the vast majority of non-consenting patients were deemed not eligible for participation.

We observed a differential HBR criteria distribution in consecutive compared with selectively included HBR patients in the trial. Importantly, no discernible impact of trial eligibility on HBR criteria distribution was observed. This reflects the limited exclusion criteria set by the trial, largely related to the use of stents other than Ultimaster.

The trial population was enriched primarily by indication for treatment with OAC, followed by advanced age, prior CVA and need for chronic treatment with steroids or NSAIDs. Conversely, the

trial population was primarily diluted with respect to PRECISE DAPT score ≥ 25. Consented patients had roughly twice higher prevalence of OAC compared with consecutive HBR PCI patients. These observations support the concept that HBR patients are included in trials preferably by means of readily detectable HBR characteristics (i.e. age, chronic medications such as OAC or steroids or NSAIDs, knowledge of prior cerebrovascular events) and less likely based on patient laboratory data (such as haemoglobin) or through the computation of scores (e.g. PRECISE DAPT), which in fact, would allow the identification of the highest number of HBR patients in practice. The preferential use of some HBR criteria over the others for trial participation, is also consistent with prior HBR trials, in which the proportion of patients with indication for treatment with OAC was around 40% [22–25].

Whether this reflects a differential perception of the bleeding risk associated with some HBR criteria or the readiness in the identification of some HBR criteria over the others remains to be elucidated. Yet, our results may suggest that screening for HBR features in practice may prioritize the presence of some criteria over others and this should be interpreted taking into account that multiple prior validation studies have shown that all of them seem to adequately identify HBR patients [1–3,8,9].

While not formally an HBR criterion [26], our study confirmed the presence of a selection bias in trial participation with respect to sex. In comparison with consecutive HBR patients, the trial population was slightly enriched with male as opposed to female patients, with an absolute standardised difference of 0.18. While this difference attenuated itself when the comparison was restricted to eligible patients, yet it remained above 0.10. This observation reinforces the notion that there are barriers to women's entry into studies that contribute to their being even less represented than in clinical practice.

Study limitations

Some limitations of this study should be considered. First, half of the involved sites in the MASTER DAPT trial participated to the screening log with a limited time window (14 days). Adhesion for participation was on a voluntary basis and not at random, to maximize the probability that all consecutive PCI patients were entered into the screening log among participating sites. Second, screening log data included only age, gender, eGFR and the qualifying HBR characteristics; other medical treatments and clinical outcomes were not available for screened patients. Third, not all ARC-HBR criteria were present in our analysis, as not all of them have been implemented in the HBR definition for the trial which antedated the release of these criteria.

CONCLUSIONS

This sub-analysis from the MASTER DAPT screening log and trial shows that the consented population was consistently primarily enriched by indication for treatment with OAC and advanced age, and, to a lesser extent, by prior CVA and need for chronic treatment with steroids or NSAIDs, and diluted with respect to PRECISE DAPT ≥ 25 and anaemia. While not formally an HBR criterion, we also found a negative selection bias towards females' participation in the study. Further research should investigate whether this reflects the readiness of HBR criteria in routine care and the existing barriers for a less biased HBR population in future trials.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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FIGURE LEGENDS

Graphical abstract. Differences in HBR characteristics between all consented patients (* in sites participating in the screening log) and consecutive HBR patients. *Abbreviations: OAC, oral anticoagulation; NSAIDs, non-steroidal anti-inflammatory drugs; TIA, transient ischemic attack; CVA, cerebrovascular accident.*

Figure 1. Screening log flowchart. The lower panel shows absolute standardized difference (SD) between consented and non-consented high bleeding risk (HBR) patients (*left*) and between consented HBR versus eligible non-consented HBR (*right*) patients. Dark yellow/green indicates positive SD; light green/yellow indicates negative SD. *Abbreviations: eGFR, estimated glomerular filtration rate; OAC, oral anticoagulation; Hb, haemoglobin; NSAIDs, non-steroidal anti-inflammatory drug; TIA, transient ischemic attack.* *Other than skin.

Figure 2. Distribution of the high bleeding risk (HBR) criteria in the all-comer PCI population. *Abbreviations: OAC, oral anticoagulation; CVA, cerebrovascular accident; NSAIDs, non-steroidal anti-inflammatory drugs.*

TABLES

Table 1. High bleeding risk (HBR) criteria of patients who consented and did not consent for the MASTER DAPT trial during the screening log periods and during the trial. *Abbreviations: eGFR, estimated glomerular filtration rate; OAC, oral anticoagulation; Hb, haemoglobin; NSAIDs, non-steroidal anti-inflammatory drug; SD, standardized difference; TIA, transient ischemic attack.*

	Screening log					**MASTER DAPT trial**		**Absolute SD [Mean difference; 95% CI]**	
	All patients (N = 2847)	Non-HBR patients (N = 1749)	HBR patients (N = 1098)	Consented HBR patients (N = 109)	Non-consented HBR patients (N = 989)	All consented patients in the trial (N = 5208)	Consented patients in the trial at log sites (N = 3374)	HBR patients in the screening log vs consented patients in the trial at log sites	Consented versus non-consented HBR patients in the screening log
Age (years)	65.8 ± 11.9	59.9 ± 9.4	75.1 ± 9.1	76.5 ± 7.8	75.0 ± 9.3	76.3 ± 8.7	76.2 ± 8.3	0.125 [-1.09; -1.67 to -0.51]	-0.180 [1.54; -0.27 to 3.35]
Sex (Male)	2215 (78%)	1436 (82%)	779 (71%)	85 (78%)	694 (70%)	3592 (69%)	2324 (69%)	-0.045 [2.1%; -1.0% to 5.2%]	-0.179 [7.8%; -0.5% to 16.1%]
eGFR	83.9 ± 56.6	95.0 ± 66.2	66.5 ± 29.4	65.3 ± 26.5	66.6 ± 29.7	70.5 ± 24.3	70.5 ± 24.5	0.150 [-4.04; -5.80 to -2.29]	0.047 [-1.33; -7.15 to 4.48]
Prior Bleeding	65/2843 (2%)	0 (0%)	65 (6%)	7 (6%)	58 (6%)	371 (7%)	215 (6%)	0.019 [-0.4%; -2.1% to 1.2%]	-0.023 [0.6%; -4.3% to 5.4%]
PRECISE DAPT score	19.3 ± 11.7	12.8 ± 5.8	29.3 ± 11.5	27.9 ± 11.6	29.5 ± 11.5	27.1 ± 11.2	26.8 ± 11.1	-0.220 [-0.1%; -0.3% to 0.1%]	0.138 [0.1%; -0.1% to 0.3%]
HBR patients	1098 (39%)								
Clinical indication for OAC treatment for at least 12 months	221 (8%)		221/1092 (20%)	42 (39%)	179/983 (18%)	1959 (38%)	1268 (38%)	0.390 [-17.3%; -20.2% to -14.5%]	-0.461 [20.3%; 10.9% to 29.8%]
Recent (<12 months) non-access site bleeding episode which required medical attention	25 (1%)		25/1090 (2%)	3 (3%)	22/981 (2%)	166 (3%)	88 (3%)	0.020 [-0.3%; -1.4% to 0.7%]	-0.033 [0.5%; -2.7% to 3.7%]
Previous bleeding episode(s) which required hospitalization	25 (1%)		25/1092 (2%)	4 (4%)	21/983 (2%)	211 (4%)	129 (4%)	0.089 [-1.5%; -2.6% to -0.4%]	-0.091 [1.5%; -2.1% to 5.2%]
Age ≥ 75 years	673 (24%)		673/1092 (62%)	82 (75%)	591/983 (60%)	3627 (70%)	2341 (69%)	0.164 [-7.8%; -11.0% to -4.5%]	-0.327 [15.1%; 6.4% to 23.8%]

Systemic conditions associated with increased bleeding risk	21 (1%)		21/1091 (2%)	2 (2%)	19/982 (2%)	104 (2%)	72 (2%)	0.015 [-0.2%; -1.2% to 0.7%]	0.007 [-0.1%; -2.8% to 2.6%]
Documented anaemia defined as repeated Hb levels <11 g/dl	166 (6%)		166/1091 (15%)	10 (9%)	156/982 (16%)	614 (12%)	411 (12%)	-0.088 [3.0%; 0.6% to 5.4%]	0.203 [-6.7%; -12.6% to -0.8%]
Need for chronic treatment with steroids or NSAIDs	58 (2%)		58/1092 (5%)	10 (9%)	48/983 (5%)	489 (9%)	324 (10%)	0.164 [-4.3%; -6.0% to -2.6%]	-0.168 [4.3%; -1.3% to 9.9%]
Diagnosed malignancy (other than skin) considered at high bleeding risk	68 (2%)		68/1091 (6%)	9 (8%)	59/982 (6%)	341 (7%)	247 (7%)	0.043 [-1.1%; -2.8% to 0.6%]	-0.087 [2.2%; -3.1% to 7.6%]
Stroke at any time, or TIA in the previous 6 months	61 (2%)		61/1091 (6%)	9 (8%)	52/982 (5%)	549 (11%)	352 (10%)	0.179 [-4.8%; -6.6% to -3.1%]	-0.118 [3.0%; -2.4% to 8.3%]
PRECISE DAPT score ≥25	719 (25%)		719/1091 (66%)	64 (59%)	655/982 (67%)	2876 (55%)	1828 (54%)	-0.241 [11.7%; 8.4% to 15.0%]	0.165 [-8.0%; -17.7% to 1.7%]
Mean number of HBR criteria fulfilled	0.7 ± 1.1		1.9 ± 1.0	2.2 ± 1.1	1.8 ± 1.0	2.1 ± 1.1	2.1 ± 1.1		