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LETTER TO THE EDITOR

Methodological Considerations on the Design of the DCB-DCS Registry

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Dear Editor,

I read with great interest the design and rationale paper by Kahraman et al.[1] describing the drug-coated balloons-drug-coated stents (DCB-DCS) study, a 17-center national registry designed to provide real-world data on the use of DCBs across five clinical scenarios: *de novo* lesions, small-vessel disease, in-stent restenosis (ISR), bifurcation lesions, and chronic total occlusion (CTO). The pragmatic, all-comer design and inclusion of multiple DCB platforms make this one of the most comprehensive DCB datasets planned to date, and the authors are to be commended for this effort.

First, the primary endpoint is reported inconsistently. The abstract and Table 1 identify procedural success as the primary endpoint, whereas the "Clinical Endpoints" section defines 12-month target lesion failure—comprising cardiac death, target-vessel myocardial infarction, or clinically driven target lesion revascularization—as the primary endpoint and procedural success as a secondary endpoint.[1] The investigators should specify a single primary endpoint and ensure consistency across the abstract, tables, registry protocol, and statistical analysis plan.

Second, I would like to raise a methodological concern regarding the follow-up strategy. As stated in the manuscript, routine angiographic follow-up will not be mandated, and angiographic endpoints, including late lumen loss, will be assessed only in patients undergoing clinically indicated repeat angiography.[1] Although this approach is reasonable for a pragmatic registry, it introduces the potential for ascertainment (verification) bias, which may be particularly consequential in a study explicitly designed to compare outcomes across five heterogeneous clinical scenarios. This concern is supported by the existing literature. Commentary on the ReACT trial notes that abandoning routine surveillance angiography may leave silent restenosis undetected, with clinical consequences that may become apparent only years later.[2] Similarly, a recent meta-analysis of randomized trials found that routine stress testing after percutaneous coronary intervention detects significantly more target lesion revascularization than symptom-driven follow-up alone, without a corresponding difference in mortality or myocardial infarction, suggesting that a meaningful proportion of restenosis remains clinically silent with symptom-driven surveillance.[3]

The ischemic burden required to produce symptoms, patient perception of cardiovascular risk, and operator threshold for repeat angiography may vary across the 17 participating centers. If the intensity of surveillance differs by clinical scenario or center, the reported rates of target lesion failure, revascularization, and late lumen loss may partly reflect differences in referral practices rather than underlying restenosis biology. Such variation could therefore confound the scenario-based comparisons that are central to the aims of the registry.

I suggest two pragmatic safeguards. First, a harmonized, prespecified definition of "clinically indicated" repeat angiography (e.g., recurrent angina, positive non-invasive testing, or ischemic electrocardiographic changes) should be applied uniformly across centers, consistent with the standardized endpoint approach of the Drug-Coated Balloon Academic Research Consortium.[4] Second, a limited, protocol-mandated non-invasive functional assessment at a fixed time point in a random subsample from each clinical scenario could help estimate the prevalence of silent restenosis and quantify the resulting ascertainment bias. At a minimum, the investigators should report, by clinical scenario and center, the proportion of patients who undergo any follow-up angiography and compare baseline characteristics between patients who do and do not undergo angiographic follow-up. This would allow the extent of referral bias to be evaluated rather than assumed to be absent. Although these measures would involve trade-offs with respect to registry feasibility, scenario-based comparison is a stated aim of DCB-DCS; therefore, addressing this issue prospectively, rather than treating it solely as a post-hoc limitation, would strengthen the interpretability of the study findings.

Third, the title refers to short- and long-term outcomes; however, the planned follow-up is limited to 1, 6, and 12 months, whereas the study flow diagram describes these periods as short- and mid-term follow-up.[1] Unless follow-up beyond 12 months is planned, the term "long-

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term" may overstate the temporal scope of the registry and should be revised accordingly.

Fourth, the registry combines markedly different clinical and anatomical scenarios, including acute coronary syndromes, bifurcation lesions, CTOs, ISR, and *de novo* coronary disease.[1] Pooling these groups may obscure clinically meaningful differences in patient characteristics, lesion complexity, treatment strategy, and outcomes. Accordingly, predefined subgroup definitions, interaction testing, and scenario-specific outcome reporting should be specified before database lock. The same concern applies to indirect comparisons between paclitaxel- and sirolimus-coated balloons, as device selection is operator-driven and may be substantially confounded by lesion characteristics, institutional preference, and treatment period. Available consensus statements likewise recommend that DCB outcomes be interpreted according to the treated lesion and clinical indication rather than treating DCB therapy as a single homogeneous treatment category.[4-6]

The DCB-DCS registry has the potential to provide valuable national real-world evidence regarding the use and outcomes of DCB therapy across a broad range of clinical scenarios. Resolving these methodological and reporting issues before completion of enrollment would substantially strengthen the scientific validity, transparency, and clinical relevance of the final results.

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