Author’s response to reviews

Title: Do ultrathin strut bare-metal stents with passive coating improve efficacy in large coronary arteries? Insights from the randomized, multicenter BASKET-PROVE trials

Authors:
Kim Wadt Hansen (kim.wadt.hansen@regionh.dk)
Raban Jeger (Raban.Jeger@usb.ch)
Rikke Sørensen (Rikke.Soerensen@regionh.dk)
Christoph Kaiser (Christoph.Kaiser@usb.ch)
Matthias Pfisterer (matthias.pfisterer@bluewin.ch)
Tor Biering-Sørensen (tor.biering@gmail.com)
Louise Bjerking (louise_bjerking@hotmail.com)
Søren Galatius (galatius@dadlnet.dk)

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Author’s response to reviews:
Dr. Isuru Ranasinghe Friday, June 21, 2019
Associate Editor
BMC Cardiovascular Disorders

Invitation from Editors to re-submit BCAR-D-18-00826 “Do ultrathin strut bare-metal stents with passive coating improve efficacy in large coronary arteries? Insights from the randomized, multicenter BASKET-PROVE trials”

Dear Associate Editor, Isuru Ranasinghe

Thank you for your positive reply and relevant comments from the reviewers. We have carefully prepared answers to the comments and critique points raised by the reviewers and editors. We
kindly request the editor to consider this revised manuscript for publication in BMC Cardiovascular Disorders. We have thoroughly answered all comments made by the reviewers and complied with almost all suggestions. Below we have enclosed our responses in a point by point manner. We hope you find our revision and changes to the manuscript satisfactory.

On behalf of all the authors, sincerely

Kim Wadt Hansen, MD PhD, and Søren Galatius, DMSc.

In the following the reviewer’s comments are formatted in Italic, black color and numbered (reviewer’s comments) followed by our reply in normal, green color characters (our replies to the reviewer’s comments). Changes made to the manuscript are marked by red color text for newly added text (inserted text) and blue, strikethrough for removed text from the manuscript (removed text). Line numbers have been added to the manuscript to make revision easy.

Our General Comments:

We thank the reviewers for the kind words, valuable input and for taking the time to review our manuscript. We would like to comment on an issue raised by both reviewers, that is the role of BMS in this era as compared to DES. This is of course is a very comprehensive topic. In brief, the new ESC/EACTS 2018 Guidelines on Revascularization give the routine use of DES over BMS regardless of situation a class IA recommendation (2). The retirement of BMS has also been discussed in opinion papers and expert analyses expert analyses (https://www.acc.org/latest-in-cardiology/articles/2016/10/20/10/47/there-are-no-current-indications-to-use-a-bare-metal-stent-pro#.XQy806ob1Gs.email and https://www.acc.org/latest-in-cardiology/articles/2016/10/20/10/47/there-are-no-current-indications-to-use-a-bare-metal-stent-con#.XQ0qpgAgJ6s.email) stating that current evidence does not support BMS use in patients with large coronary vessels, STEMI, advanced age, elective non-cardiac surgery (DAPT duration), and anticoagulation therapy; patient subsets in which BMS were considered indicated (1). Yet, several recently published reports suggest a relatively high use of BMS. The PRISM PCI registry reported a percentage of BMS selection ranging from 9% to 29% depending on study site from 2009 through 2011. Between operator variability was even more pronounced at 5-45%. Interestingly, markers of bleeding such as lower hemoglobin, prior bleeding, chronic use of warfarin, atrial fibrillation, and planned surgery predicted a higher use of BMS suggesting that PCI operators attempt to balance the risk of restenosis and the risk of prolonged DAPT (3). A study by Qintar et al. also reported that patients tend to accept the risk of repeat
revascularization easier than the risk of bleeding associated with DAPT of long duration(4). Another US-based study from the Nationwide Inpatient Sample between 2006 and 2011 reported increased use of BMS from 10% in 2006 to 30% in 2008 followed by a subsequent decrease stabilizing around 25% in 2011; similar significant between sites variability in use of BMS was observed(5). We were unable to identify more recent reports on the use of BMS.

Overall, despite very recently published guidelines recommending the use of DES only, available literature suggest a use of BMS of approximately 20% with pronounced between site- and operator-variability. Although, we would expect the contemporary use of BMS to be somewhat lower than observed in the above studies, we deem that there is insufficient data to suggest that BMS are not still being used in patients with CAD.

Comments from the Reviewers:

Reviewer #1:

Reviewer #1 Comment #1:

The article is well written: Overall, it was well structured. I would like to see more elaboration in the discussion. I believe a detailed explanation of why the complexity of procedures was higher in one arm compared to other is useful.

Our Comment #1:

We discussed this discrepancy in complexity of procedures in the author group very early in the process. Basically, there were some slight differences in key cardiac risk factors between the two trials, i.e. arterial hypertension, diabetes mellitus, and current smoking were significantly more prevalent while lower age, prior MI, and STEMI were less prevalent in the BASKET-PROVE II trial. We hypothesize that these differences are due to either changes in referral patterns or the replacement of study sites between the two trials. Both factors may have changed the overall composition of the patient population eligible for inclusion. We have added the paragraph below to the manuscript.

DISCUSSION AND LIMITATIONS, page 12, line 9, inserted text:

Patient and procedural characteristics. Observed discrepancies in patient- and procedure-related characteristics were quite surprising provided that in- and exclusion criteria in the BASKET-
PROVE trials were almost identical. Notably, the overall complexity of procedures in the SCC-BMS group was lower despite a higher prevalence of several cardiac risk factors compared to the UC-BMS group. Two important aspects of the BASKET-PROVE trials should be noted: (1) only six of the 11 study sites from the indigenous BASKET-PROVE trial went on to participate in the BASKET-PROVE II trial, and (2) the two trials were conducted 3 years apart. These factors may have changed the composition of potentially eligible patients in terms of patient- and procedure-related characteristics.

Reviewer #1 Comment #2:
I would have liked to see the investigators' take on why TVR was lower even though the procedure complexity was higher in the thicker strut stents.

Our Comment #2:
We provided a thorough elaboration of the associations between stent design and rates of TVR in the DISCUSSION section under the subheading Pathophysiological considerations. Our hypothesis, based on our findings and available literature, is that the silicon-carbide coating of the PRO-Kinetic stent, given its physical and biochemical capabilities, remains the most likely cause of increased symptomatic restenosis rates as compared to the uncoated, thicker-strut Vision stent. Established predictors (in multivariable regression models) of restenosis following stent implantation include patient-related factors (age, sex, smoking, hypertension, diabetes mellitus, and acute coronary syndromes) and procedure-related factors (LAD involvement, number of diseased vessels, bifurcational lesions, ostial lesions, number of deployed stents, stent diameter, and stent length). Of note, our analysis accounted for all but one (ostial lesions) of these factors.

Reviewer #1 Comment #3:
I would have also liked an elaboration on the role of bare metal stents in this era.

Our Comment #3:
Please refer to the Our General Comments section.
Reviewer #2:

Reviewer #2 Comment #1:

In this post-hoc analysis authors explored the BASKET-PROVE trials to evaluate the efficacy of a newer generation ultrathin strut silicon-carbide coated cobalt-chromium (CoCr) BMS (SCC-BMS) as compared to an older thin-strut uncoated CoCr BMS (UC-BMS) in patients presenting with coronary artery disease requiring stenting of large vessels (≥3.0mm). Authors found higher risk for clinically driven TVR in the SCC-BMS group compared to the UC-BMS group. No difference was observed in mortality, stent thrombosis, non-fatal MI. Overall the manuscript is well written. The statistical analysis is sound and appropriate.

Here are some suggestions to improve the manuscript.

- The study timeframe and interventions are both outdate and not contemporary, which is the biggest limitation of that analysis. The limitations section should be expanded to comment on the non-contemporary time frame of the study which by itself might not yield similar results in contemporary practice (using more imaging guided PCI/FFR-OCT).

Our Comment #:1

This is an important point made by the reviewer. We fully acknowledge that these are non-contemporary results. We have added the following sentence to the manuscript:

DISCUSSION AND LIMITATIONS, page 15, line 15, inserted text:

Finally, the BASKET-PROVE trials do not necessarily reflect contemporary practice as the latest trial ended 7 years ago.

Reviewer #2 Comment #2:

- The use of DES is standard practice as stated earlier in the introduction by authors. Hence, comparing 2 types of BMS might be considered by some as low-yield. Authors should expand more in introduction on contemporary remaining indications of using BMS, to rationalize the need for such analysis.
Our Comment #2:

This is of course an important point, which we addressed thoroughly in the Our General Comments section. As stated the 2018 ESC/EACTS Guidelines on Revascularization state that DES over BMS is always recommended. Any remaining indications is a topic of debate, which we deem too comprehensive for our introduction section. It is important to state that this manuscript was drafted prior to the publication of the revised guidelines. However, available literature suggests an ongoing use of BMS justifying the need for continuous data on this subject.

Reviewer #2 Comment #3:

-The difference in time interval between the BASKET PROVE 1 and 2 trials (4 years) is a major limitation. Since the study is comparing 2 arms which are reflecting possible different practices (4 years spanning many different clinical trials and guideline changes). This should be clarified in the limitations section.

Our Comment #3:

This is an important issue raised by the reviewer, which we of course will add to the manuscript. It is important to add that 77% of all patients were enrolled at sites participating in both BASKET PROVE trials. Furthermore, the two study protocols were almost identical apart from one exclusion criteria (a history of stroke/TIA), two of the three stent arms, and the use of a prasugrel-based DAPT strategy in BASKET PROVE II. Overall, any contribution of potential differences in practice are deemed minor. We have added the following sentence to the study limitations section:

DISCUSSION AND LIMITATIONS, page 15, line 12, inserted text:

The BASKET PROVE trials were conducted 3 years apart meaning that we cannot rule out bias induced by potential changes in practice; however, the fact that the two study protocols were almost identical and 77% of patients were enrolled at study sites participating in both trials limits the magnitude of such bias.

Reviewer #2 Comment #4:
The Pro-kinetic stent, evaluated in this study, has received FDA approval after results of a prospective study BIO-HELIX-1. Authors might comment on the BIO-Helix study and the contrasting results compared to their analysis.

Our Comment #4:

We thank the Reviewer for pointing out the BIOHELIX-I study, which is relevant to our analysis due to its choice the PRO-Kinetic Energy stent system. However, the BIOHELIX-I study differ from ours in several important aspects: (1) patients with myocardial infarction were excluded from the BIOHELIX-I study. In comparison, patients with acute coronary syndrome constituted almost two-thirds of our study population. (2) The BIOHELIX-I study was non-randomized and hence did not include a comparator group. These vital differences make a direct comparison of the findings implausible. However, we acknowledge the relevance of mentioning this study due to its contemporary nature and consequences in terms of FDA approval. We have added the following paragraph to the manuscript.

DISCUSSION AND LIMITATIONS, page 12, line 17, inserted text:

Recent results of the BIOHELIX-I prospective study demonstrated 9-month rates of ischaemia-driven TVR of 7.26% in patients with stable or unstable CAD(18). As patients with myocardial infarction were excluded, these results are not directly relatable to our study.

Reviewer #2 Comment #5:

- The double helix design of the PRO-kinetic stent is supposed to improve deliverability into challenging lesions. If authors are able to conduct subgroup/ sensitivity analysis exploring comparative outcomes according to lesions type (bifunctional/ CTO/ calcified lesion) would add to the value of this manuscript. This might identify proper clinical scenarios/ subsets that might benefit from this stent.

Our Comment #5:

We fully agree with the Reviewer that additional subgroup analyses would be of potential clinical value. However, we did not conduct such analyses for two reasons: (1) The number of events in the mentioned subgroups, i.e. CTO, bifurcational lesions, etc. is very low (see table below) with hardly enough events to conduct a meaningful univariable analysis. Furthermore, our findings are derived post-hoc from a subset of the BASKET-PROVE I and II trials.
Performing a subgroup analysis on such data increases the risk of type II errors and thus spurious findings. Hence, we chose to defer from such analyses.

Target-vessel revascularization at 24 months, by selected procedural characteristics

<table>
<thead>
<tr>
<th>Chronic total occlusion</th>
<th>SCC-BMS</th>
<th>UC-BMS</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/26 (3.8%)</td>
<td>3/39 (7.7%)</td>
<td>0.48 (0.01-6.44)</td>
<td>0.64</td>
<td></td>
</tr>
</tbody>
</table>

| Bifurcational lesion    | 11/45 (24.4%) | 6/68 (8.8%) | 3.31 (1.01-11.90) | 0.031   |

CI = confidence interval; OR = odds ratio; SCC-BMS = silicon-carbide coated bare-metal stent; UC-BMS = uncoated bare-metal stent.

ORs and P-values were calculated using Fisher’s exact test (univariable method).

Additional Corrections:

RESULTS, page 10, line 6, deleted text:

Prior MI,

RESULTS, page 10, line 7, inserted text:

, while prior MI and a clinical presentation with STEMI were less frequent

References:


