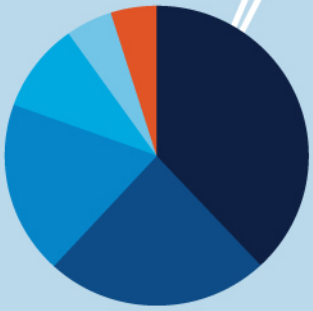

UNPARALLELED, REAL-WORLD DATA

Research on real-world patients from the Medtronic GSR showed that renal denervation (RDN) **achieved clinically meaningful, statistically significant blood pressure reductions.**[1]

REVIEW THE STUDY

[1] Mahfoud F, Mancia G, Schmieder R, et al. Three-year safety and efficacy in the Global Symplicity Registry: Impact of anti-hypertensive medication burden on blood pressure reduction. Presented at PCR e-course 2020.

Medtronic
Further, Together

Received: 25 September 2019 | Revised: 14 November 2019 | Accepted: 19 November 2019

DOI: 10.1002/ccd.28632

ORIGINAL STUDIES

WILEY

Duration of dual antiplatelet therapy in elective drug-coated balloon angioplasty

Natasha H. Corballis MBBS, MRCP[1,2] | Upul Wickramarachchi MBBS, MRCP[1] | Vassilios S. Vassiliou MA, MBBS, PhD, FESC, FACC, FRCP Edin[1,2] | Simon C. Eccleshall MBChB, MRCP, MD[1]

[1]Department of Cardiology, Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich, UK

[2]Norwich Medical School, University of East Anglia, Bob Champion Research and Education, Norwich, UK

Correspondence
Vassilios S. Vassiliou, Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich NR4 7UQ, UK.
Email: v.vassiliou@uea.ac.uk

Funding information
Norfolk Heart Trust

Abstract

Objectives: We sought to answer whether 1-month duration of dual antiplatelet therapy (DAPT) is safe after elective drug-coated balloon only (DCB) angioplasty.

Background: The duration of DAPT after elective DCB was called into question after the ESC Focused DAPT Update of 2017. Until then, a 1-month duration of DAPT was considered safe by national consensus groups (German, Italian, and Chinese) supported by data from prospective worldwide registries.

The ESC Guidelines recommended a 6-month duration of DAPT based on evidence from in-stent restenosis randomized controlled trials only.

Methods: Retrospective, real-world population, single-center analysis conducted from January 1, 2012 to March 31, 2017 in a high-volume, tertiary PCI center. Consecutive patients receiving 1-month duration of DAPT after elective DCB angioplasty were included. We identified a primary composite outcome of cardiac death, myocardial infarction and target lesion revascularization at 6-months.

Results: A total of 303 patients (78.5% male) with mean age of 67 ± 12.5 were included. This incorporated 86.1% de novo lesions and 56.5% nonsmall (≥3 mm diameter) coronary arteries treated. There were no reported outcomes of lesion thrombosis, target vessel MI, target lesion revascularization or cardiac death at 6-months. There were two (0.6%) nontarget vessel MIs and one (0.3%) noncardiac death.

Conclusion: One-month duration of DAPT appears safe after elective DCB-only angioplasty, highlighting this strategy for patients at high-risk of bleeding. These results also show favorable clinical outcomes for de novo coronary artery disease and nonsmall coronary arteries treated with DCB-only angioplasty. A 1-month duration of DAPT appears a safe and attractive option.

KEYWORDS

coronary intervention, drug-coated balloon, dual antiplatelet therapy, PCI

1 | INTRODUCTION

A lot of interest has been generated lately about the use and safety of DCB angioplasty focused mainly on peripheral intervention.[1–4] However, the use of drug-coated balloons (DCB) for coronary intervention has also been steadily increasing over the last few years and as more studies report encouraging results,[5,6] DCB-only angioplasty for coronary disease is expected to increase further. Original

recommendations for DCB use came from the German Consensus Group[7,8] which also addressed the duration of dual antiplatelet therapy following DCB; stating that 4 weeks of dual antiplatelet therapy (DAPT) with aspirin and clopidogrel were deemed appropriate in patients with stable coronary disease with monotherapy life-long thereafter. The evidence for this came from small to moderate randomized controlled studies and large prospective worldwide registries. This was followed by the Italian Society of Interventional Cardiology[9] and the Chinese Expert Group,[10] both supporting the German recommendation of 1-month DAPT for stable coronary disease.

However, The European Society of Cardiology (ESC) Focused Update on DAPT 2017 took a different view and advocated a 6-month duration of DAPT in DCB angioplasty.[11] This recommendation was supported by circumstantial evidence from three randomized control trials comparing DCB with drug eluting stents (DES) for in-stent restenosis only, while no DCB studies in de novo coronary intervention were included. In these three studies, the duration of DAPT varied from 3 to 12 months.[12–14] In RIBS-IV DAPT of a 3-month duration was given in the DCB arm, PEPCAD China ISR gave a 12-month duration of DAPT and ISAR-DESIRE-3 gave a 6-month minimum duration of DAPT. Of significance, is that bleeding events were not addressed in any of these three studies.

Following the publication of the ESC Focused Update 2017, there has been data from two important studies in de novo coronary disease. Firstly, the Basket-Small 2 was a randomized control trial comparing DCB with DES for small vessel de novo coronary disease and gave a 1-month duration of DAPT to the DCB arm in all patients with stable coronary disease.[5] Secondly, Debut, a randomized trial comparing BMS to DCB in patients with high bleeding risk, also gave a 1-month duration of DAPT for DCB angioplasty; thus suggesting that a full 6-month course of DAPT might not be necessarily required when a DCB-only approach is used.[4]

Although DCB angioplasty holds a class 1 recommendation by the ESC for in-stent restenosis angioplasty, there is now increasing evidence supporting the use of DCB for de novo coronary disease.[5] As this use is projected to expand further, we felt it was important to interrogate our existing DCB registry, a dedicated registry at the Norfolk and Norwich University Hospital including all patients who receive DCB-only angioplasty, to identify if a shorter 1-month DAPT is safe in routine clinical practice. This is, to our knowledge, the first study using a real-world population to specifically answer the question regarding the safety of 1-month DAPT in DCB-only angioplasty.

2 | MATERIALS AND METHODS

We retrospectively identified all patients from our local registry from January 3, 2012 to March 31, 2017 who had undergone elective DCB-only angioplasty for stable coronary artery disease and received 1-month DAPT. Institutional approval was obtained from Norfolk and Norwich University Hospital, UK and in line with other research of retrospective nature, the need for patient consent was waived.

We included both de novo lesions and in-stent restenosis (ISR) lesions. Clinical outcomes were obtained through electronic clinical records and up-to-date mortality data was obtained from the Demographic Batch Service Bureau of the Health and Social Care Information Centre, a National database where all deaths are recorded. All patients who had a concomitant use of oral anticoagulant were excluded, as were those who underwent a staged procedure following acute coronary syndrome, with a premandated 12-month duration of DAPT.

We defined a 6-month device-oriented primary composite end-point of cardiovascular death, myocardial infarction (not clearly attributed to a nontarget vessel) and target lesion revascularization (clinically driven) in keeping with the ARC-2 recommendation for device outcome reporting.[15] We chose the 6-month cutoff point following the ESC guidelines recommended cessation period for DAPT, as after this time monotherapy would have continued with the ESC guidelines also.

Myocardial infarction was defined as presence of chest pain or ischemic ECG changes with a rise in cardiac enzyme troponin and with no other vessel clearly identified as the culprit vessel.

Cardiac death was defined in accordance with the 2017 Consensus Report on Cardiovascular and Stroke Endpoint Definitions for Clinical Trials[16] and included:

1. death resulting from an acute myocardial infarction (AMI),
2. sudden cardiac death,
3. death due to heart failure (HF),
4. death due to stroke,
5. death due to cardiovascular (CV) procedures, and
6. death due to CV hemorrhage.

Secondary outcomes included: noncardiac death, lesion thrombosis, and nontarget vessel myocardial infarction.

Lesion thrombosis was defined as acute (<1 day), subacute (1–30 days), and late (>30 days) and defined in parallel to the ARC guidelines on Stent Thrombosis.[17]

All procedural elements were at the discretion of the operators with practice based on guidelines for DCB angioplasty as previously reviewed.[18] All adverse events were independently adjudicated.

3 | RESULTS

3.1 | Patient characteristics

A total of 303 patients were identified with 361 lesions treated with DCB-only PCI electively for coronary disease and who received DAPT for 1 month only. The cohort included mainly male patients (78.5%), with a mean age of 67 ± 12.5 with 39.6% having had prior PCI, 9.6% having had prior CABG and other risk factors as outlined in Table 1. These findings are in keeping with contemporaneous stable angina studies.[12–14]

Following 1-month DAPT, all patients continued with aspirin monotherapy thereafter. Some 96.4% received aspirin and clopidogrel

TABLE 1 Patient characteristics

Patient characteristics	*n* (%) (where *n* = 303)
Age—mean (SD)	67 ± 12.5
Male	238 (78.5)
Previous MI	69 (22.8)
Previous PCI	120 (39.6)
Previous CABG	29 (9.6)
Hypertension	196 (64.7)
Dyslipidaemia	108 (35.6)
Family history of IHD	95 (31.4)
Diabetes	58 (19.1)
Smoking	
Current smoker	72 (23.8)
Ex-smoker	91 (30.0)
Nonsmoker	140 (46.2)

Abbreviations: CABG, coronary artery bypass graft; IHD, ischemic heart disease; PCI, percutaneous intervention.

for 1 month, 2.2% received aspirin and ticagrelor, and 1.4% received aspirin and prasugrel. The use of ticagrelor or prasugrel was only due to previously documented intolerance to clopidogrel.

3.2 | Lesion and procedural characteristics

Of 361 lesions treated, 86.1% were de novo lesions, the remaining 13.9% being in-stent restenosis lesions. The majority of lesions treated were left anterior descending artery (48.2%), 24.1% circumflex, 23% right coronary artery, 3.6% left main stem, and 1.1% vein grafts. The DCBs used as follows: 143 (39.6%) were SeQuent Please (B Braun Melsungen AG, Germany), 186 (51.5%) were SeQuent Please NEO (B Braun Melsungen AG, Germany), 31 (8.6%) were IN.PACT Falcon (Medtronic, Inc., Santa Rosa, CA) and 1 (0.3%) were DIOR (Eurocor GmbH, Germany). Lesion complexity was assessed using The American College of Cardiology/ American Heart Association (ACC/AHA) Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures classification system,[19] and is summarized in Table 2.

Some 43.5% of lesions were small vessels (with DCB diameter of <3 mm used) while 56.5% were large vessel with DCB diameter ≥3 mm.

3.3 | Clinical outcomes

Follow-up at 6 months was 100% with patient outcomes shown in Table 3. There were no reported occurrences of lesion thrombosis, target lesion MI or cardiac death at 6 months. There were no TLRs at 6-months. There was 1 (0.3%) death at 50 days due to end stage renal failure. There were 2 (0.6%) nontarget vessel MIs, one at 49 days and one at 156 days. On both follow-up angiograms, the target lesion result was acceptable.

TABLE 2 Lesion characteristics

Lesion characteristics	*N* (%) (where *n* = 361)
De novo lesions	310 (85.9)
Vessel treated	
LMS	13 (3.6)
LAD	174 (48.2)
Cx	87 (24.1)
RCA	83 (23.0)
SVG	4 (1.1)
Lesion classification	
Type A	0
Type B1	56 (15.5)
Type B2	131 (36.3)
Type C	174 (48.2)
GP IIb IIIa inhibitor use (% yes)	12 (3.3)
Lesion <3 mm diameter	157 (43.5)
Lesion ≥3 mm diameter	204 (56.5)

Abbreviations: Cx, circumflex artery; GP IIb IIIa inhibitor, glycoprotein IIb IIIa inhibitor; LAD, left anterior descending artery; LMS, left main stem artery; RCA, right coronary artery; SVG, saphenous vein graft.

TABLE 3 Clinical outcomes

Primary outcome	*n* = 361 (%)
MACE	0
Treated lesion revascularization	0
MI (not attributed to nontarget vessel)	0
Cardiac death	0
Secondary outcomes	0
Noncardiac death	1 (0.3%)
Nontarget vessel MI	2 (0.6%)
Lesion thrombosis	0

Abbreviation: MI, myocardial infarction.

4 | DISCUSSION

DCB angioplasty currently holds a class Ia recommendation for its use in ISR in accordance with the current ESC Guidelines,[11] although there is increasing evidence to support its use for de novo coronary disease.[4,5] With this use of DCB angioplasty predicted to increase, it is important to determine a safe duration for DAPT for elective procedures, a gap in the literature inadvertently highlighted by the ESC Focused Update on DAPT. Although recommending a 6-month duration of DAPT, the evidence studied to reach this decision was only from ISR RCTs and did not incorporate any de novo DCB literature, while previous Consensus Groups and National Societies had recommended a 1-month duration of DAPT for DCB angioplasty in stable coronary disease. A recent literature search and subgroup analysis presented by Kleber et al.[20] reviewing all published RCTs and registries including de novo coronary disease suggested a 1-month

duration of dual antiplatelet therapy after DCB angioplasty was safe. This has been furthermore consolidated with recent RCTs which gave a 1-month duration of DAPT for stable CAD.[4,5]

We sought to answer whether a 1-month duration of DAPT for stable coronary disease is safe. We conducted a retrospective analysis, using a real-world population, incorporating 361 lesions in 303 patients, of which 85.9% were de novo lesions. We found that 1-month DAPT duration was safe with regard to lesion thrombosis, target lesion MI, TLR and cardiac death, with zero adverse outcomes at 6 months. This extends the evidence from current trials to include de novo coronary anatomy, and importantly, also incorporates data on nonsmall coronary vessels (as 56.5% in our cohort were ≥3 mm), which to this point was an evidence-free area. As such, our results are expanding on the previous work by Kleber et al.,[20] and the Basket-Small RCT.[5]

Of note, our clinical outcomes are reporting significantly lower rates of MACE than other real-life registry data.[21] Several potential explanations for the difference in outcome include a shorter clinical end-point (6-month versus 9-month), smaller numbers, increased operator skill in a single-center doing a large volume of DCB-only angioplasty and improved technique for DCB delivery. These improved clinical outcomes may be an indicator that due to improved technique and operator skill with DCB techniques, clinical outcomes with DCB-only angioplasty are better than initially reported in registry data.

We acknowledge that bleeding rates after successful PCI are independently associated with a higher morbidity and mortality rate,[22] and a shorter duration of DAPT has been shown to be beneficial in risk reduction in those with higher bleeding risk in prospective registry studies.[23,24] We believe that our data provides compelling evidence that can potentially extend the role of DCB angioplasty to those patients at high bleeding risk by enabling a shorter but safer 1-month DAPT.

5 | LIMITATIONS

Our study consists of only a small number of ISR lesions and subsequently our conclusions on that subgroup are less robust and a separate analysis with larger numbers may be warranted given the duration of DAPT in current RCT evidence ranges from 3 to 12 months.

In addition, selection bias and confounding errors are inherent limitations of a retrospective, single-center analysis. However, to limit this, we included all consecutive patients in our registry with a catchment area of over 1 million people. Furthermore, our patient demographics are similar to other contemporaneous DES studies in the UK[12–14] indicating that significant selection bias was unlikely. Finally, as we undertake more than 40% of our PCI with a DCB-only approach, we feel this would have minimized bias.

6 | CONCLUSION

A 1-month only duration of DAPT following elective DCB-only angioplasty appears safe, specifically for de novo coronary disease, in both small and nonsmall vessel disease and is the first report of real-world data on this topic. Our data further supports the use of DCB-only angioplasty for all subgroups, with zero adverse device-related outcomes across all specified end-points at 6 months, bringing into question the advice from the recent ESC guidance update.[11]

DISCLOSURE OF INTERESTS

Dr. Natasha Corballis has no conflicts of interests to declare. Dr. Vassilios Vassiliou reports research funding from Norfolk Heart Trust, UK. Dr. Simon Eccleshall received speaker fees and acts as a consultant for B Braun. Dr. Upul Wickramarachchi was previously (within the last 2 years) funded by the Research Capability Fund from the Norfolk and Norwich University Hospital and an unrestricted research grant for investigator-initiated research by B Braun, Melsungen AG, Germany.

ORCID

Natasha H. Corballis https://orcid.org/0000-0002-6837-5787
Vassilios S. Vassiliou https://orcid.org/0000-0002-4005-7752

REFERENCES

1. Secemsky EA, Kundi H, Weinberg I, et al. Association of survival with femoropopliteal artery revascularization with drug-coated devices. JAMA Cardiol. 2019;4:332-340. https://doi.org/10.1001/jamacardio.2019.0325.
2. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2018;7(24):e011245. https://doi.org/10.1161/JAHA.118.011245.
3. Anantha-Narayanan M, Shah SM, Jelani QUA, et al. Drug-coated balloon versus plain old balloon angioplasty in femoropopliteal disease: an updated meta-analysis of randomized controlled trials. Catheter Cardiovasc Interv. 2019;94(1):139-148. https://doi.org/10.1002/ccd.28176.
4. Rissanen TT, Uskela S, Eränen J, et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. Lancet. 2019;394(10194):P230-239. https://doi.org/10.1016/S0140-6736(19)31126-2.
5. Jeger RV, Farah A, Ohlow M-A, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. Lancet (London, England). 2018;392(10150):849-856. https://doi.org/10.1016/S0140-6736(18)31719-7.
6. Vos NS, Fagel ND, Amoroso G, et al. Paclitaxel-coated balloon angioplasty versus drug-eluting stent in acute myocardial infarction. JACC Cardiovasc Interv. 2019;4408:1691-1699. https://doi.org/10.1016/j.jcin.2019.04.016.
7. Kleber F, Mathey D, Rittger H, Scheller B. German drug-eluting balloon consensus group. How to use the drug-eluting balloon: recommendations by the German consensus group. EuroIntervention. 2011;7(K):K125-K128. https://doi.org/10.4244/EIJV7SKA21.
8. Kleber F, Rittger H, Bonaventura K, Al E. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from consensus group. Clin Res Cardiol. 2013;102(11):785-797.
9. Cortese B, Berti S, Biondi-Zoccai G, et al. Drug-coated balloon treatment of coronary artery disease: a position paper of the Italian Society of Interventional Cardiology. Catheter Cardiovasc Interv. 2014;83(3):427-435. https://doi.org/10.1002/ccd.25149.

10. Chen Y, Wang J, Liu B, et al. China expert consensus on clinical application of the drug coated balloon. Cardiol Plus. 2016;1:41-48.
11. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur Heart J. 2018;39(3):213-260. https://doi.org/10.1093/eurheartj/ehx419.
12. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents. J Am Coll Cardiol. 2015;66(1):23-33. https://doi.org/10.1016/j.jacc.2015.04.063.
13. Xu B, Gao R, an W, et al. A prospective, multicenter, randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis: results from the PEPCAD China ISR trial. JACC Cardiovasc Interv. 2014;7:204-211. https://doi.org/10.1016/j.jcin.2013.08.011.
14. Byrne RA, Neumann F-J, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet. 2013;381(9865):461-467. https://doi.org/10.1016/S0140-6736(12)61964-3.
15. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. Circulation. 2018;137(24):2635-2650. https://doi.org/10.1161/CIRCULATIONAHA.117.029289.
16. Hicks KA, James Hung HM, Mahaffey KW, et al. *Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials*. Behalf of the Standardized Data Collection for Cardiovascular Trials Initiative. TASK FORCE MEMBERS.
17. Cutlip DE, Windecker S, Mehran R, et al. Clinial end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115:2344-2351.
18. Wickramarachchi U, Eccleshall S. Drug-coated balloon-only angioplasty for native coronary disease instead of stents. Interv Cardiol Rev. 2016;11(2):110-115. https://doi.org/10.15420/icr.2016:17:3.
19. Theuerle J, Yudi MB, Farouque O, et al. Utility of the ACC/AHA lesion classification as a predictor of procedural, 30-day and 12-month outcomes in the contemporary percutaneous coronary intervention era. Catheter Cardiovasc Interv. 2017;92:E227-E234. https://doi.org/10.1002/ccd.27411.
20. Kleber F, Scheller B, Ong P, et al. TCT-776 duration of dual antiplatelet therapy after drug-coated balloon implantation. J Am Coll Cardiol. 2018;72(13):B309-B310. https://doi.org/10.1016/j.jacc.2018.08.2006.
21. Wöhrle J, Zadura M, Möbius-Winkler S, et al. SeQuent please world wide registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. J Am Coll Cardiol. 2012;60(18):1733-1738. https://doi.org/10.1016/J.JACC.2012.07.040.
22. Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient outcomes (PLATO) trial. Eur Heart J. 2011;32(23):2933-2944. https://doi.org/10.1093/eurheartj/ehr422.
23. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet (London, England). 2017;389(10073):1025-1034. https://doi.org/10.1016/S0140-6736(17)30397-5.
24. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome (TRACER) randomized trial. Eur Heart J. 2016;38(11):ehw525. https://doi.org/10.1093/eurheartj/ehw525.

How to cite this article: Corballis NH, Wickramarachchi U, Vassiliou VS, Eccleshall SC. Duration of dual antiplatelet therapy in elective drug-coated balloon angioplasty. *Catheter Cardiovasc Interv*. 2019;1–5. https://doi.org/10.1002/ccd.28632