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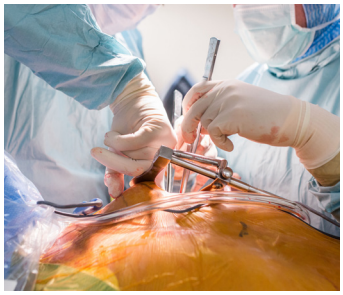

Near-infrared spectroscopy in perioperative management p21

De-escalation of antiplatelet therapy p 24

Hypertension treatment and risk of orthostatic hypertension p 26

Spectroscopy in perioperative medicine

ORIGINAL RESEARCH Assessor blinded, single centre, randomised controlled trial

Care guided by tissue oxygenation and haemodynamic monitoring in off-pump coronary artery bypass grafting (Bottomline-CS)

Han J, Zhai W, Wu Z, et al

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Find this at doi: 10.1136/bmj-2024-082104

Study question Does perioperative management aimed at maintaining multisite tissue oxygen saturation, guided by near-infrared spectroscopy and haemodynamic monitoring, reduce postoperative complications in off-pump coronary artery bypass grafting?

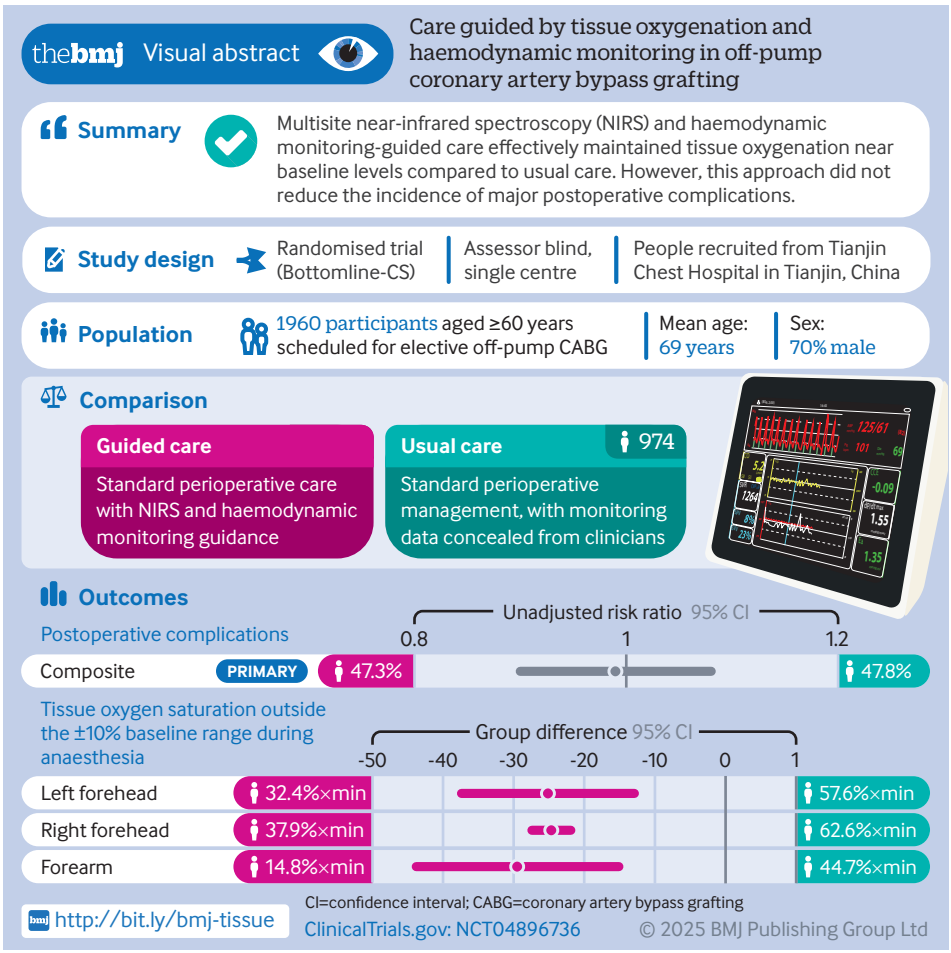
Methods In this assessor blind, single centre, randomised trial at a tertiary teaching hospital in China, participants aged 60 years or older undergoing elective off-pump coronary artery bypass grafting were included. The intervention group received care aimed at maintaining tissue oxygen saturation within 10% higher or lower than preoperative baseline values using near-infrared spectroscopy and haemodynamic monitoring in addition to usual care, while the control group received usual care alone. The primary outcome was a composite of 30 day postoperative complications of cerebral, cardiac, respiratory, renal, infectious, and mortality outcomes.

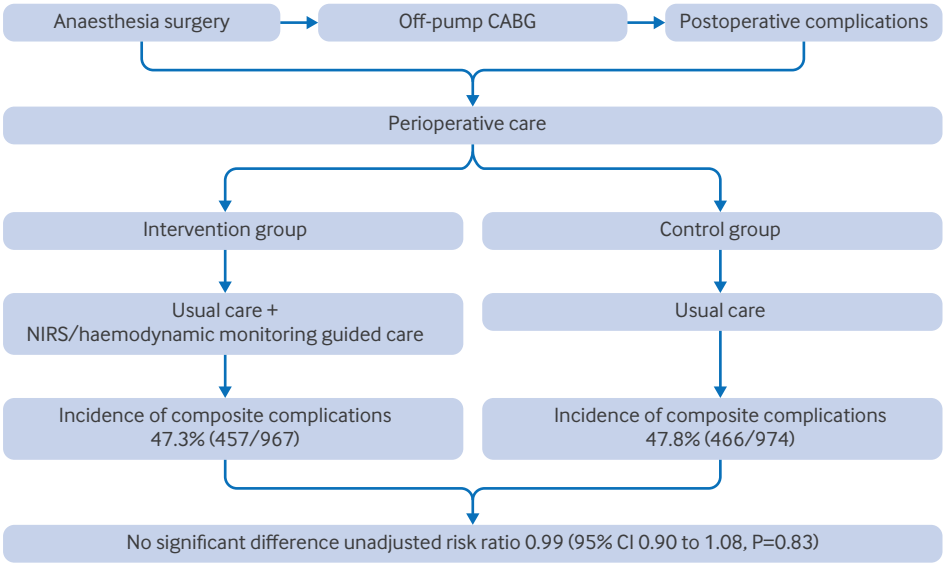
Study answer and limitations 1960 participants were randomly assigned to groups and 1941 (967 guided care and 974 usual care) met the analysis criteria. No significant difference was observed in the primary composite outcome between the groups (47.3% (457/967) v 47.8% (466/974); unadjusted risk ratio 0.99 (95% CI 0.90 to 1.08), P=0.83). The guided care group showed significantly better maintained intraoperative tissue oxygenation but that did not reduce complications. During anaesthesia, the area under the curve for tissue oxygen saturation measurements outside the plus and minus 10% baseline range was significantly smaller with guided care than only usual care: left forehead 32.4 versus 57.6 (%×min, P<0.001), right forehead 37.9 versus 62.6 (P<0.001), and forearm 14.8 versus 44.7 (P<0.001). The study was conducted in a single centre, limiting generalisability, and relied on a composite outcome, which may overemphasise less severe complications.

What this study adds Care guided by near-infrared spectroscopy and haemodynamic monitoring effectively maintained intraoperative tissue oxygenation but did not reduce major complications after off-pump coronary artery bypass grafting.

Funding, competing interests, and data sharing The Tianjin Science and Technology Project and the Tianjin Key Laboratory of Cardiovascular Emergency and Critical Care funded this study. The authors declare no competing interests. Anonymised patient data can be made available on request with ethical approval.

Trial registration ClinicalTrials.gov NCT04896736.





Overview of the Bottomline-CS trial design and the primary outcome results. CABG=coronary artery bypass grafting; CI=confidence interval; NIRS=near-infrared spectroscopy

COMMENTARY

Near-infrared spectroscopy (NIRS), originally described in 1977, entered clinical practice as a non-invasive method to assess regional tissue oxygenation.[1] This monitoring technique was initially used in high risk surgeries to measure cerebral oxygenation in real time. After encouraging results that linked intraoperative NIRS guided, goal directed treatment to improved neurological outcomes in cardiac surgery, NIRS use quickly expanded.[2-4] This increased use has sparked the development of multiple competing clinically approved NIRS monitoring systems, highlighting the substantial market interest in this technology.[5]

What do the study findings mean?

Despite the widespread use of NIRS, negative findings from subsequent trials have raised concerns about whether NIRS monitoring truly improves outcomes.[6-8] These concerns have prompted a debate regarding the surgical populations who might benefit from NIRS and the best practices for its use.[9] In a linked research paper (doi:10.1136/bmj-2024-082104), Han and colleagues present noteworthy findings from the Bottomline-CS trial, which examined whether perioperative care guided by cerebral and peripheral tissue oximetry enhanced clinical outcomes in patients undergoing off-pump coronary artery bypass graft surgery (CABG).[10] This trial is remarkable in multiple ways. It is by far the largest randomised controlled trial to study this question in surgeries associated with

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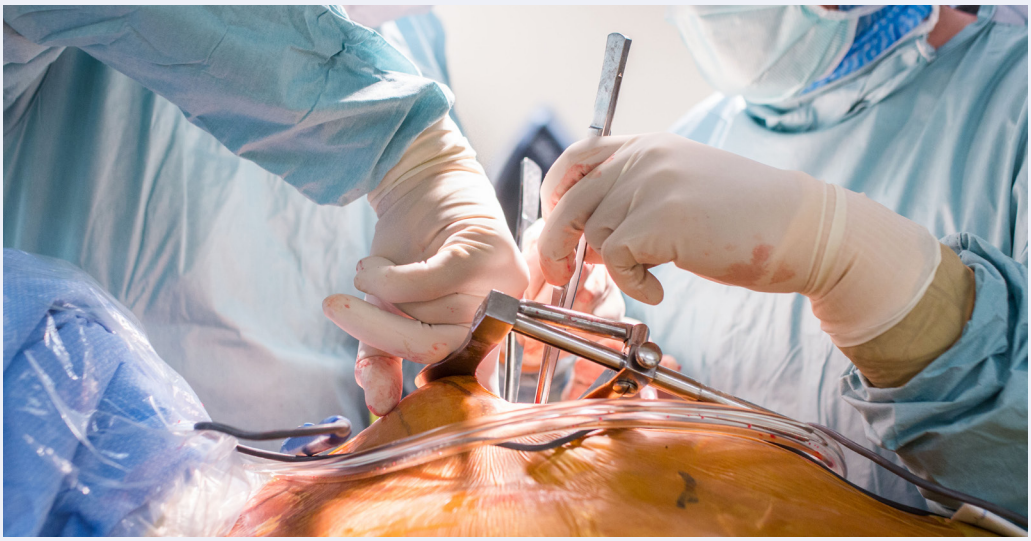

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substantial haemodynamic fluctuations.[11 12] NIRS was also paired with continuous haemodynamic monitoring to obtain estimates of cardiac output, stroke volume, and systemic vascular resistance, which were used to guide treatment. While a pragmatic design was adopted to approximate the real world use of NIRS where anaesthesiologists make individualised care decisions, a goal directed diagnostic and interventional framework was provided to keep tissue oxygenation within +/−10% of presurgical values. Finally, the trial randomised 1960 patients with sufficient power to detect a clinically relevant difference in the incidence of a meaningful composite outcome capturing one or more serious complications at 30 days. Considering the size and design of the Bottomline-CS trial, the authors' major conclusion is consequential. The findings indicate that the routine use of NIRS during off-pump CABG and similar types of surgery does not reduce the incidence of common postoperative complications, a conclusion well supported by the data.

Every trial has limitations. As a single centre study, results of the Bottomline-CS trial might not generalise to other practice settings. The use of a composite outcome, a commonly used technique for comprehensively capturing postoperative complications with sufficient statistical power, can highlight more frequent but less severe complications. In this context, it is notable that the 95% confidence intervals of the reported risk ratios were quite narrow for several neurological, cardiac, pulmonary, renal, and infectious complications captured by the composite outcome. The study groups did not differ significantly in any specific complication, and narrow confidence intervals suggest that negative findings are more likely to be true than falsely negative. However, for complications associated with wider confidence intervals, including some infectious complications, subsequent studies are required before making such conclusions.

Current clinical implementation [of NIRS] might not yield benefit in most perioperative settings

Further research needed

Notably, the Bottomline-CS trial does not address whether the routine use of NIRS in clinical conditions with no or faint pulsatile flow reduces postoperative complications. Although off-pump CABG surgery is an excellent clinical model for studying NIRS in a scenario with haemodynamic instabilities, the majority of CABG and other cardiac surgeries involve the use of cardiopulmonary bypass.[13] During cardiopulmonary bypass, circulatory flow is non-pulsatile, rendering standard monitors inadequate to assess oxygenation and perfusion in real time. In this scenario, NIRS might be particularly useful for the early detection of catastrophic equipment failures or bypass cannula malposition, allowing for quick intervention and prevention of irreversible end organ damage.[14 15] NIRS guided, goal directed treatment might also prove advantageous during prolonged periods of non-pulsatile flow and improve clinical outcomes.[11] Furthermore, NIRS could enhance the detection and management of differential hypoxia syndrome or extremity ischaemia associated with non-pulsatile flow. Patients undergoing long term extracorporeal membrane oxygenation are a relevant example.[16] Examining the potential benefits of NIRS in these clinical settings is an essential next step.

Limitations of NIRS

Finally, current NIRS monitoring techniques are limited. Although the most common use of NIRS is for monitoring cerebral oxygenation, most devices only monitor frontal brain regions. They do not provide information about regional oxygenation in other brain areas, which can differ, especially in patients with cerebrovascular disease. This limitation has led to criticism that current NIRS monitoring techniques have a considerable event rate of false negatives where patients with normal NIRS-derived oxygenation values have, in fact, experienced cerebral ischemia.[17] Multichannel NIRS arrays that offer better representation of the entire brain are a common tool in neuropsychology and have made an appearance in neurocritical care.[18] It seems appropriate to assess the usefulness of these devices in the perioperative setting.

NIRS remains a powerful tool to assess regional oxygenation, but its current clinical implementation might not yield benefit in most perioperative settings. However, cardiac surgery and monitoring of patients on mechanical circulatory support are areas where NIRS could be valuable. A nuanced approach to its clinical use is needed, along with further trials to evaluate its use in specific patient populations and to investigate the clinical usefulness of next-generation systems.

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DAPT strategies after drug coated balloon angioplasty

ORIGINAL RESEARCH Multicentre, randomised, open label, assessor blind, non-inferiority trial

Stepwise dual antiplatelet therapy de-escalation in patients after drug coated balloon angioplasty

Gao C, Bin Zhu B, Fan Ouyang F, et al

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Study question Could a less intense antiplatelet regimen be used for people treated with drug coated balloons?

Methods Between 27 November 2021 and 21 January 2023, this open label, investigator initiated, randomised, non-inferiority trial (RECAGEFREE II) recruited people from 41 sites in China with acute coronary syndrome who have been treated by drug coated balloon exclusively. Participants were randomly assigned (1:1) to stepwise dual antiplatelet therapy (DAPT) de-escalation consisting of aspirin plus ticagrelor for one month, followed by five months of ticagrelor monotherapy, and then six months of aspirin monotherapy or to standard DAPT of aspirin plus ticagrelor for 12 months. The primary endpoint was non-inferiority for net adverse clinical events (all cause death, stroke, myocardial infarction, revascularisation, and Bleeding Academic Research Consortium type 3 or 5 bleeding). Non-inferiority was tested with the margin of absolute difference of 3.2%.

Study answer and limitations 1948 participants were included and randomly assigned to one of the two groups (975 in the stepwise group and 973 in the standard DAPT group). At 12 months, the primary endpoint occurred in 87 (8.9%) participants in the stepwise de-escalation group and 84 (8.6%) in the standard group (difference 0.36%; upper boundary of the one sided 95% confidence interval 2.47%; $P_{non\text{-}inferiority}$=0.013), showing non-inferiority. However, this study was only conducted in China with an East Asian population and three quarters of participants were men, so extrapolation of these results to other groups warrants further investigation.

COMMENTARY A step forward in de-escalating treatment

The evolution of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) has been shaped by the continuous challenge of balancing ischaemic protection with bleeding risk. While prolonged DAPT confers thrombotic risk reduction, it invariably increases bleeding complications, which are themselves associated with adverse prognostic implications.[1] This dilemma has prompted the exploration of de-escalation strategies—gradual tapering of antiplatelet intensity or duration—as a means of optimising patient outcomes. Currently, the concept of DAPT de-escalation refers to the strategy of discontinuing aspirin after a short period of dual antiplatelet therapy after PCI, leaving patients on monotherapy with a potent P2Y12 inhibitor—typically ticagrelor, as supported by available evidence.[2-4] The rationale behind this approach is to maximise ischaemic protection during the initial months after PCI, when the thrombotic risk is highest, while simultaneously mitigating the bleeding risk, which remains relatively constant and is directly associated with DAPT duration.[5] In a previous meta-analysis from our group, DAPT de-escalation was indeed associated with a significant reduction of bleeding events in patients with acute coronary

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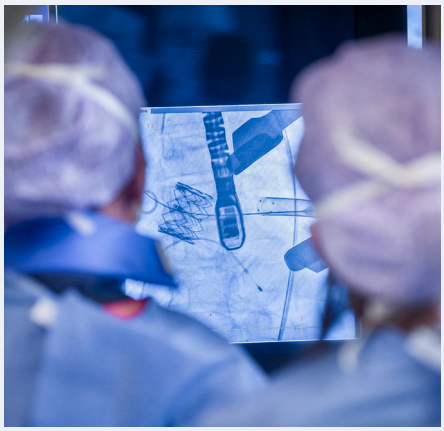

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The study provides a compelling rationale for refining current antiplatelet strategies

syndrome compared with five alternative standard DAPT strategies, while not increasing the risk of ischaemic events, even rare ones, such as stent thrombosis.[6]

Cardiovascular research has struggled over the past decade to develop accurate scores to precisely estimate the trade-off between ischaemic and bleeding risks, even by means of artificial intelligence.[7-9] However, most existing scores prioritise clinical and demographic factors while minimally incorporating procedural data. Notably, patients undergoing drug coated balloon (DCB) treatment—where an angioplasty balloon coated with an antiproliferative drug (eg, paclitaxel or sirolimus) is inflated to deliver drug treatment directly to the arterial wall without leaving a permanent metal scaffold—are not sufficiently represented in the datasets from which these risk models were derived, leaving a substantial gap in evidence based decision making for this subgroup.

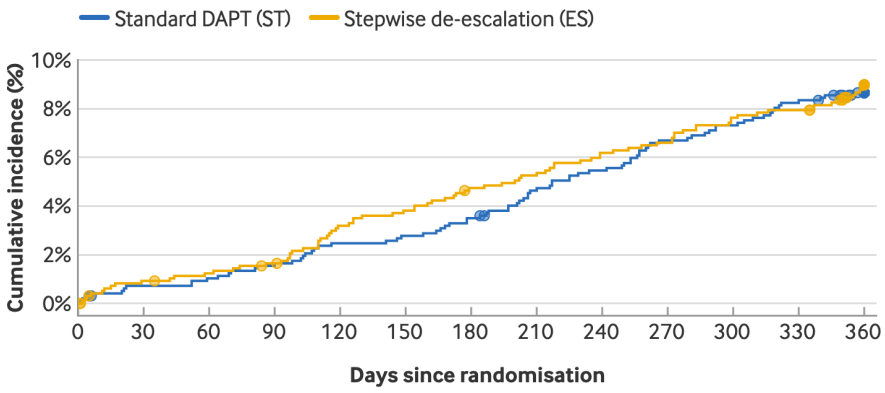
Advantages of DCBs

Concurrently, the paradigm of PCI has been reshaped by the growing adoption of DCB, an appealing alternative to conventional stenting, particularly for challenging lesion subsets such as in-stent restenosis (re-narrowing within a previously placed stent), small vessel disease (typically vessels <2.5 mm in diameter, that are associated with increased thrombotic risk), and bifurcations (branch points in the coronary arteries). In these scenarios, conventional stenting might necessitate multiple overlapping stents or complex two-stent techniques (eg, double-kissing crush, culotte stenting), which not only increase procedural complexity and metal burden but also correlate with poorer PCI outcomes. By delivering antiproliferative drug treatment without leaving a permanent scaffold, DCB might help avoid or reduce the need for these complex stenting strategies.[10] The absence of a permanent metallic scaffold, polymer, or long term antiproliferative drug exposure theoretically allows for a more lenient DAPT regimen.[11] However, this concept remains speculative. DCB angioplasty avoids the long term drawbacks of stents—such as chronic inflammation around the metal struts, neoatherosclerosis, stent thrombosis, and the potential for future

What this study adds REC-CAGEFREE II investigated a tailored antiplatelet strategy for people treated with drug coated balloon. In people with acute coronary syndrome who received drug-coated balloon angioplasty exclusively, one month DAPT followed by five months of ticagrelor monotherapy was non-inferior and could be a viable alternative option to treatment with the standard 12 months DAPT.

Funding, competing interests, and data sharing
This trial was sponsored by Xijing Hospital. The study received unrestricted grant support from Yinyi Biotech, who manufactures paclitaxel coated balloons but has no antiplatelet medication products. Authors' competing interests can be found on bmj.com and data sharing is available on request.

Studyregistration ClinicalTrials.gov, NCT04971356.



Kaplan-Meier curve of the primary outcome at 12 months. The primary outcome was a composite of all cause death, stroke, myocardial infarction, revascularisation, and Bleeding Academic Research Consortium type 3 or 5 bleeding at 12 months after randomisation assessed in the intention-to-treat population. DAPT=dual antiplatelet therapy. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/22156733/

re-intervention challenges. However, it leaves the atherosclerotic and inflamed endothelium vulnerable to procedural trauma, residual dissections, and drug induced endothelial dysfunction, thereby necessitating a tailored antithrombotic approach. Yet, the optimal DAPT strategy after DCB remains an unresolved clinical question.

The REC-CAGEFREE II trial provides useful evidence addressing this knowledge gap.[12] This multicentre, open label, assessor blind, non-inferiority trial enrolled 1948 patients across 14 hospitals in China with acute coronary syndrome who underwent PCI with paclitaxel coated balloons. Patients were randomised to a stepwise DAPT de-escalation regimen (aspirin plus ticagrelor for one month, followed by ticagrelor monotherapy for five months, then aspirin monotherapy for six months) or standard DAPT for 12 months with aspirin and ticagrelor. The primary endpoint, a composite of all cause death, stroke, myocardial infarction, revascularisation, and major bleeding, occurred at comparable rates in both groups (8.9% *v* 8.6%), establishing non-inferiority. Moreover, stepwise de-escalation conferred a significant reduction in major bleeding.

The study had several strengths. Firstly, its exclusive focus on patients with acute coronary syndrome—who inherently have a heightened thrombotic risk—provides a stringent test of de-escalation safety.[13] Secondly, the trial reflects contemporary real world indications for DCB treatment, encompassing small vessels, in-stent restenosis, and bifurcations, which are complex anatomical settings that theoretically require longer DAPT.[14] Additionally, the study leveraged a sophisticated array of secondary endpoint analyses, including hierarchical testing and sensitivity analyses. Notably, the findings were consistent across several lesion settings (ie, de novo lesions *v* in-stent restenosis) and in subgroups at high ischaemic risk. Nevertheless, the study's limitations warrant careful consideration. Furthermore, the benefits of de-escalation seem to be contingent on potent P2Y12 inhibition, as shown by the higher incidence of the patient-oriented composite outcome in the intention-to-treat cohort than in the per protocol cohort. The intention-to-treat cohort did include a broader group of patients who were treated with clopidogrel instead of ticagrelor owing to side effects. Furthermore, the cohort was predominantly East Asian, raising questions regarding applicability to other ethnic groups with varying bleeding and thrombotic propensities. Another important consideration is that while reducing bleeding risk is crucial, DAPT confers systemic ischaemic protection beyond the procedural setting. The role of DAPT in mitigating non-target vessel events and overall thrombotic burden cannot be overlooked,[15] so, while de-escalation strategies are attractive, they should be selectively applied to patients at high bleeding risk rather than universally implemented.

Clinical implications

Despite these caveats, REC-CAGEFREE II marks a step forward, translating the theoretical benefits of DCB treatment into actionable clinical practice. By demonstrating the feasibility of structured DAPT de-escalation in patients with acute coronary syndrome undergoing DCB angioplasty, the study provides a compelling rationale for refining current antiplatelet strategies.

Engaging with the perspectives of patients is paramount in shaping treatment paradigms. After reviewing the study findings summarised in this article, the patients and volunteers' association of Amici del Cuore (Friends of the Heart) in Turin, Italy, emphasised the importance of striking a delicate equilibrium—reducing bleeding risk while preserving ischaemic protection. The group consistently expressed a preference for regimens that mitigate medication burden and adverse effects, without compromising safety. Their insights underscore the real world relevance of individualised DAPT strategies, particularly for those who prioritise bleeding avoidance over theoretical ischaemic risk.

As the field of PCI continues to advance, REC-CAGEFREE II is a poignant reminder that, in some instances, letting go of intensive therapy does not translate into a compromise in care. Rather, it represents a step towards a more refined, risk adjusted approach—where less may indeed be more.

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Effects of intensive blood pressure treatment on orthostatic hypertension

Juraschek SP, Hu JR, Cluett JL, et al

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Study question What is the effect of more intensive antihypertensive drug treatment on orthostatic hypertension?

Methods This systematic review and individual participant data meta-analysis used MEDLINE, Embase, and Cochrane CENTRAL databases through 13 November 2023. Prespecified study inclusion criteria were ≥500 adults, age 18 years and older with hypertension or elevated blood pressure (population); randomised trials of more intensive blood pressure treatment (a lower blood pressure goal or active agent) with a duration of at least six months (intervention); less intensive blood pressure treatment (a higher blood pressure goal or placebo) (control); and measured standing blood pressure (outcome). The primary outcome was orthostatic hypertension, defined as an increase in systolic blood pressure ≥20 mm Hg or diastolic blood pressure ≥10 mm Hg after changing from sitting to standing. Two investigators independently abstracted articles. Individual participant data from nine trials identified during this systematic review were appended together as a single dataset.

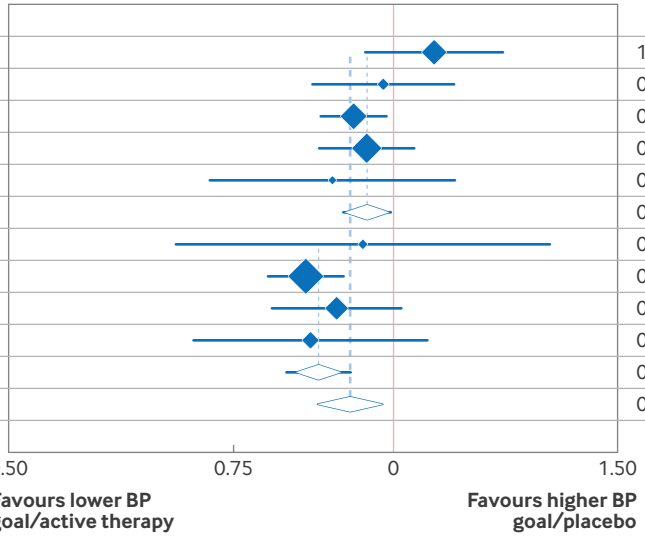
Study answer and limitations Of 31 124 participants with 315 497 standing blood pressure assessments, 17% had orthostatic hypertension. The risk of orthostatic hypertension was lower with more intensive blood pressure treatment than with less intensive blood pressure treatment (odds ratio 0.93, 95% confidence interval 0.90 to 0.96). Limitations include study heterogeneity, generalisability to clinical practice, and absence of supine-to-standing protocols.

What this study adds In this pooled cohort of adults with elevated blood pressure or hypertension, orthostatic hypertension was common and more intensive blood pressure treatment modestly reduced the occurrence of orthostatic hypertension. These findings suggest that approaches generally used for seated hypertension may also prevent hypertension on standing.

Funding, competing interests, and data sharing
The study received support from the National Institutes of Health/National Heart, Lung, and Blood Institute. The authors have no competing interests to declare. Data are available through public repositories.

Study registration Prospero CRD42020153753 (original proposal).

Trial	No of patients	No of visits	Odds ratio (95% CI)	P value
AASK	1090	48 764	1.08 (0.95 to 1.22)	0.25
ACCORD BP	4196	7162	0.98 (0.87 to 1.12)	0.79
SPRINT	9221	51 225	0.93 (0.88 to 0.99)	0.02
SPS3	2968	58 511	0.95 (0.87 to 1.04)	0.27
UKPDS	1072	2629	0.90 (0.72 to 1.12)	0.33
Trials comparing BP goals (n=5)	18 547	168 291	0.95 (0.92 to 0.99)	0.03
HYVET	2404	4732	0.95 (0.68 to 1.33)	0.75
SHEP	4681	89 346	0.85 (0.80 to 0.91)	<0.001
SYST-EUR	4595	39 329	0.90 (0.80 to 1.01)	0.08
TOMHS	897	13 799	0.86 (0.70 to 1.07)	0.17
Placebo controlled trials (n=4)	12 577	147 206	0.87 (0.83 to 0.93)	<0.001
All trials (n=9)	31 124	315 497	0.93 (0.90 to 0.96)	<0.001



Effects of blood pressure (BP) treatment (either lower blood pressure treatment goal or active therapy *v* higher blood pressure treatment goal or placebo) on occurrence of orthostatic hypertension at visit level, using generalised estimating equations to account for clustering by participant. Pooled effects are organised according to five blood pressure treatment goal trials and four placebo controlled trials and overall. Size of each point estimate and pooled effect is weighted by number of follow-up visits with orthostatic hypertension assessments. I^2=38.0% (determined on basis of two stage meta-analysis, used to assess trial heterogeneity). CI=confidence interval