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Effect of Calcium-Channel Blocker Therapy on Radial Artery Grafts After Coronary Bypass Surgery

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ABSTRACT

BACKGROUND Few studies have evaluated the effect of chronic calcium-channel blocker therapy (CCB) on the angiographic and clinical outcome of radial artery (RA) grafts used for coronary bypass surgery.

OBJECTIVES The purpose of this study was to evaluate if CCB influences midterm clinical and angiographic outcomes of RA grafts.

METHODS Patient-level data of 6 angiographic randomized trials evaluating RA graft status at midterm follow-up were joined in this observational analysis. Cox regression and propensity score methods were used to evaluate the effect of CCB on the incidence of a composite of major adverse cardiac events (MACE) (death, myocardial infarction, and repeat revascularization) and graft occlusion.

RESULTS The study population included 732 patients (502 on CCB). The median clinical follow-up was 60 months. The cumulative incidence of MACE at 36, 72, and 108 months was 3.7% vs. 9.3%, 13.4% vs. 17.6%, and 16.8% vs. 20.5% in the CCB and no CCB groups, respectively (log-rank $p = 0.003$). Protocol-driven angiographic follow-up was available in 243 patients in the CCB group and 200 in the no CCB group. The median angiographic follow-up was 55 months. The cumulative incidence of RA occlusion at 36, 72, and 108 months was 0.9% vs. 8.6%, 9.6% vs. 21.4%, and 14.3% vs. 38.9% in the CCB and no CCB groups, respectively (log-rank $p < 0.001$). After controlling for known confounding, CCB therapy was found to be consistently associated with a significantly lower risk of MACE (multivariate Cox hazard ratio: 0.52; 95% confidence interval: 0.31 to 0.89; $p = 0.02$) and RA graft occlusion (multivariate Cox hazard ratio: 0.20; 95% confidence interval: 0.08 to 0.49; $p < 0.001$).

CONCLUSIONS In patients with RA grafts CCB is associated with significantly better midterm clinical and angiographic RA outcomes. (J Am Coll Cardiol 2019;73:2299–306) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass

CCB = chronic calcium-channel blocker therapy

CI = confidence intervals

HR = hazard ratios

IQR = interquartile range

RA = radial artery

RADIAL = Radial Artery Database International Alliance

RCTs = randomized trials

The RADIAL (Radial Artery Database International ALliance) project is a combined patient-level dataset including 6 randomized trials (RCTs) that have compared the radial artery (RA) with other conduits at midterm follow-up. In a recent publication from the RADIAL database, we have shown for the first time using randomized data that the use of the RA as the second conduit for coronary artery bypass (CABG) is associated with a significant reduction in the risk of midterm cardiac events compared with the use of the saphenous vein (1).

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Although in recent years, the use of the RA has been very limited among the surgical community, the publication of the results of the primary analysis of RADIAL and the consequent Class I indication in the 2018 ESC/EACTS guidelines (2) are likely to elicit renewed interest for the artery and the issues related to its use for CABG. One of the most important unsolved questions is the role of chronic calcium-channel blocker therapy (CCB) for CABG patients who received 1 or more RA grafts.

In fact, due to the thick muscular wall of the RA and of the concerns of graft spasm, CCB is traditionally prescribed postoperatively for CABG RA patients (3). This practice, however, is weakly supported by the published data.

Only few studies to date have evaluated the effect of CCB on the angiographic and clinical outcome of RA grafts, and in most cases, the results have been neutral (4). One major problem is that, due to the high patency rate and excellent clinical outcome of the RA, a very large sample size is required to detect even moderate differences in angiographic and clinical outcomes. All of the published series were very likely largely underpowered for this purpose.

CCB is associated with non-negligible side effects and costs (5). Also, due to its hypotensive effect, the use of CCB may preclude the use of other evidence-based therapy such as beta-blockers or angiotensin-converting enzyme inhibitors. For these reasons, the evaluation of CCB efficacy in patients with RA grafts is of major relevance for the patients and the cardiovascular community.

Our primary study objective was to assess whether CCB use after RA CABG affects the midterm clinical and angiographic outcomes and address the described power limitations by pooling individual patient data from multiple RCTs in this post-hoc analysis.

METHODS

DATASET. The RADIAL initiative was created in March 2015 with the aim to combine datasets from trials on the RA to facilitate meta-analytic studies. Details of the projects have previously been published (1). The list of the RADIAL investigators can be found in Online Table 1.

In the present study, we analyzed individual patient-level data from all patients who received the RA in the published RCTs comparing the long-term (≥2 years) outcomes of the RA and other conduits. The 6 RCTs included are: the Radial Artery Patency and Clinical Outcomes (groups 1 and 2), the RAPS (Radial Artery Patency Study), Radial Artery Versus Saphenous Vein Patency Study, Petrovic, Stand-in-Y, and Yoo trials (6–11). Postoperative CCB was recommended per protocol in each of the individual trials, with differences in the type of drug used and the duration of the treatment (Online Table 2).

The RA was used on the second most important coronary target vessel in all trials except for RAPS. In RAPS, within-patient randomization was used and patients with 3-vessel disease were randomized to receive both a saphenous vein and an RA graft randomly allocated to the right or the circumflex coronary artery. For this reason, in RAPS the RA was used on either the second or third most important target coronary vessel. To minimize confounders, data from RAPS were not used for the main analysis, but were included in a sensitivity analysis on RA graft occlusion.

OUTCOMES. The primary outcome was a composite of major adverse cardiac events (MACE) (death, myocardial infarction, and repeat revascularization) at maximum follow-up. The secondary outcome was RA graft occlusion at maximum follow-up. Patency rate was graded according to Fitzgibbon classification (12). Grades A and B were considered patent and grade O occluded. Individual components of the primary composite outcome were also analyzed individually.

STATISTICAL ANALYSIS. Continuous variables were tested for normality and were reported as mean ± SD or median (interquartile range [IQR]), and the 2 groups (CCB and no CCB) were compared using the Student's *t*-test or Wilcoxon-Mann-Whitney. Baseline categorical variables were reported as counts and percentages and compared with the chi-square test. Time-to-event outcomes were reported as a cumulative incidence using Kaplan-Meier estimates, and the 2 groups were compared using the log-rank test. For the primary composite endpoint of death, myocardial

TABLE 1 Pre-Operative and Intraoperative Characteristics of the Patients

	CCB (n = 502)	No CCB (n = 230)	p Value
Age, yrs	62.28 ± 9.01	70.18 ± 8.44	<0.001
Female	96 (19.1)	84 (36.5)	<0.001
Diabetes	120 (23.9)	70 (30.4)	0.075
Prior MI	156 (31.1)	83 (36.1)	0.209
Elective admission	434 (86.5)	195 (84.8)	0.625
Renal insufficiency	30 (6.0)	21 (9.1)	0.162
LVEF <0.35	11 (2.2)	18 (7.8)	0.001
Target vessel RCA	386 (76.9)	128 (55.7)	<0.001
Number of grafts	3.20 ± 0.73	3.28 ± 1.48	0.288
OPCABG	38 (7.6)	0 (0.0)	<0.001
Proximal anastomosis on AA	461 (91.8)	221 (96.1)	0.050
First author/trial (ref. #)			
Petrovic et al. (9)	100 (19.9)	0 (0.0)	
RAPCO (6)	257 (51.2)	51 (22.2)	
RSVP (8)	82 (16.3)	0 (0.0)	
Stand-in-Y (10)	28 (5.6)	179 (77.8)	
Song et al. (11)	35 (7.0)	0 (0.0)	

Values are mean ± SD or n (%).

AA = ascending aorta; CCB = chronic calcium-channel blocker therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OPCABG = off pump coronary bypass; RAPCO = Radial Artery Patency and Clinical Outcomes trial; RCA = right coronary artery; RSVP = Radial Artery Versus Saphenous Vein Patency Study.

infarction, and repeat revascularization and for RA graft occlusion, cumulative incidences were graphically presented using Kaplan-Meier estimates (survival and survminer R package). To account for differences in baseline characteristics between patients who received CCB and those who did not, several adjustment methods were used for the computation of treatment effect estimates on primary endpoints. Treatment effect was initially calculated using univariate and multivariable Cox models forcing all baseline characteristics with further stratification by individual trials. Covariates included in the Cox models were: CCB, age, sex, diabetes, previous myocardial infarction, surgical priority, renal insufficiency, target vessel, location of RA proximal anastomosis, and off-pump surgery. Treatment effect was reported as hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazard assumptions were verified using the Schoenfeld residuals. Furthermore, propensity score methods including inverse propensity score weighting and propensity score stratification were used to adjust for confounding (Online Appendix, Online Figures 1 and 2, Online Tables 3 to 5) (13). The effect of individual CCB classes (amlodipine and diltiazem) was also tested using univariate and multivariate Cox regression. Finally, we investigated whether CCB therapy duration influenced the incidence of primary outcomes (MACE and graft occlusion) by forcing CCB therapy duration (as linear or spline terms) in a Cox regression model (patients who did not receive CCB therapy included as CCB duration = 0). Nonlinearity between CCB therapy duration and incidence of endpoint of interest was tested using the analysis of variance test and the model with highest X^2 and lowest degree of freedom was selected (restricted cubic spline 2 knots). R version 3.1.2 (2014-10-31) (R Foundation, Vienna, Austria) was used for all statistical analysis.

RESULTS

The study population included 732 patients (502 treated with CCB). Protocol-driven angiographic follow-up was available in 243 patients in the CCB group and 200 in the no CCB group. Details of the baseline and intraoperative characteristics of patients of the 2 groups are given in Table 1. Median clinical follow-up was 60 months (IQR: 39 to

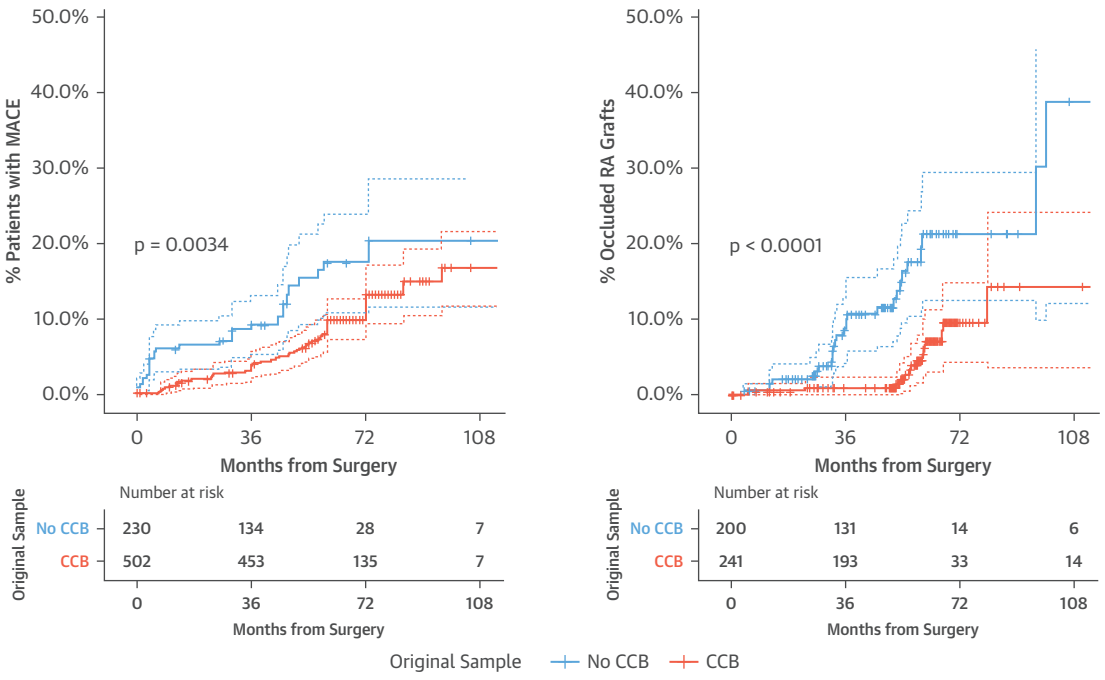
TABLE 2 Kaplan-Meier Estimates of the Primary and Secondary Outcomes*

Group	Months of Follow-Up	MACE	Graft Occlusion	Death	Myocardial Infarction	Repeat Revascularization
CCB (n = 502)						
	36	3.7 (2.0-5.4)	0.9 (0.0-2.2)	2.1 (0.8-3.4)	0.2 (0.0-0.6)	1.5 (0.4-2.5)
	72	13.4 (9.5-17.8)	9.6 (4.2-14.9)	7.5 (4.5-10.5)	2.0 (0.7-3.3)	4.8 (2.8-6.8)
	108	16.8 (11.8-21.7)	14.3 (4.0-24.7)	9.3 (5.5-13.1)	2.4 (0.9-3.8)	5.5 (3.3-7.7)
No CCB (n = 230)						
	36	9.3 (5.4-13.2)	8.6 (4.2-12.9)	5.3 (2.0-8.5)	3.1 (0.8-5.3)	3.1 (0.8-5.4)
	72	17.6 (11.0-24.1)	21.4 (13.0-29.8)	8.2 (3.7-12.8)	4.2 (1.1-7.2)	7.5 (2.8-12.2)
	108	20.5 (12-29)	38.9 (16.5-61.2)	11.5 (3.8-19.2)	4.2 (1.1-7.2)	7.5 (2.8-12.2)
Univariate Cox p value		0.003	<0.001	0.09	0.02	0.13

Values are Kaplan-Meier estimates (95% confidence interval) unless otherwise indicated. *Angiography available in 243 patients in the chronic calcium-channel blocker therapy group and in 200 patients in the no chronic calcium-channel blocker therapy group.

CCB = chronic calcium-channel blocker therapy; MACE = major adverse cardiac events.

FIGURE 1 Cumulative Incidence of MACE and RA Graft Occlusion in the 2 Groups



(Left) MACE; **(right)** RA graft occlusion. CCB = chronic calcium-channel blockers therapy; MACE = major adverse cardiac events; RA = radial artery.

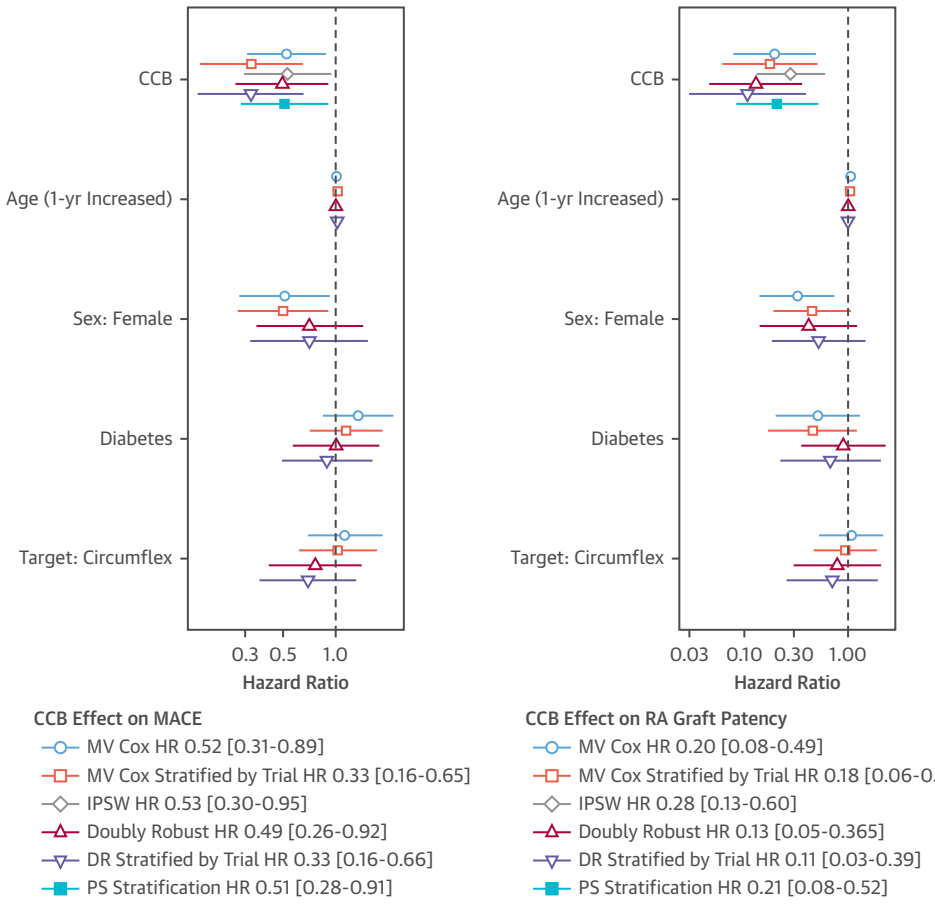
66 months) and median angiographic follow-up was 55 months (IQR: 31 to 65 months). The main clinical outcomes are summarized in Table 2. The cumulative incidence of MACE at 36, 72, and 108 months was 3.7% vs. 9.3%, 13.4% vs. 17.6%, and 16.8% vs. 20.5% in the CCB and no CCB groups, respectively (log-rank p = 0.003) (Figure 1 left). The cumulative incidence of RA occlusion at 36, 72, and 108 years was 0.9% vs. 8.6%, 9.6% vs. 21.4%, and 14.3% vs. 38.9% in the CCB and no CCB groups, respectively (log-rank p < 0.001) (Figure 1 right). After controlling for confounding with several methods (Table 3, Figure 2), CCB therapy was found to be consistently associated with a significantly lower risk of MACE (multivariate Cox HR: 0.52 [95% CI: 0.31 to 0.89]; p = 0.02) and RA graft occlusion (multivariate Cox HR: 0.20 [95% CI: 0.08 to 0.49]; p < 0.001). When classes of CCB were analyzed separately, we found that both diltiazem (multivariate Cox HR: 0.29 [95% CI: 0.11 to 0.73]; p = 0.008) and amlodipine (multivariate Cox HR: 0.42 [95% CI: 0.23 to 0.76]; p = 0.005) were associated with a lower risk of MACE when compared with no-CCB (Central Illustration, left). Among patients undergoing angiographic follow-up, we found that both diltiazem (multivariate Cox HR: 0.20 [95% CI: 0.07 to 0.51]; p < 0.001) and amlodipine (multivariate Cox HR: 30 [95% CI: 0.12 to 0.74]; p = 0.009) were associated with a lower risk of RA graft occlusion when compared with no CCB (Central Illustration, right). Finally, we found that CCB therapy duration was

TABLE 3 Treatment Effect Estimations

Outcome	Model	HR (95%CI)	p Value
MACE			
	Unadjusted	0.52 (0.33–0.81)	0.004
	MV Cox	0.52 (0.31–0.89)	0.02
	MV Cox stratified by trial	0.33 (0.16–0.65)	0.002
	IPSW Cox	0.53 (0.30–0.95)	0.03
	Doubly robust	0.49 (0.26–0.92)	0.03
	Doubly robust stratified by trial	0.33 (0.16–0.66)	0.002
	PS stratification	0.51 (0.28–0.91)	0.02
RA graft occlusion			
	Unadjusted	0.28 (0.14–0.54)	<0.001
	MV Cox	0.20 (0.08–0.49)	<0.001
	MV Cox stratified by trial	0.18 (0.06–0.51)	0.001
	IPSW Cox	0.28 (0.13–0.60)	0.001
	Doubly robust	0.13 (0.05–0.36)	<0.001
	Doubly robust stratified by trial	0.11 (0.03–0.39)	<0.001
	PS stratification	0.21 (0.08–0.52)	<0.001

HR = hazard ratio; IPSW = inverse propensity score weighting; MACE = major adverse cardiac events; MV = multivariate; PS = propensity score; RA = radial artery.

FIGURE 2 Forest Plot of Treatment Effect on MACE and RA Graft Occlusion



(Left) MACE; **(right)** RA graft occlusion. DR = doubly robust; HR = hazard ratio; IPSW = inverse propensity score weighting; MV = multivariate; PS = propensity score; other abbreviations as in Figure 1.

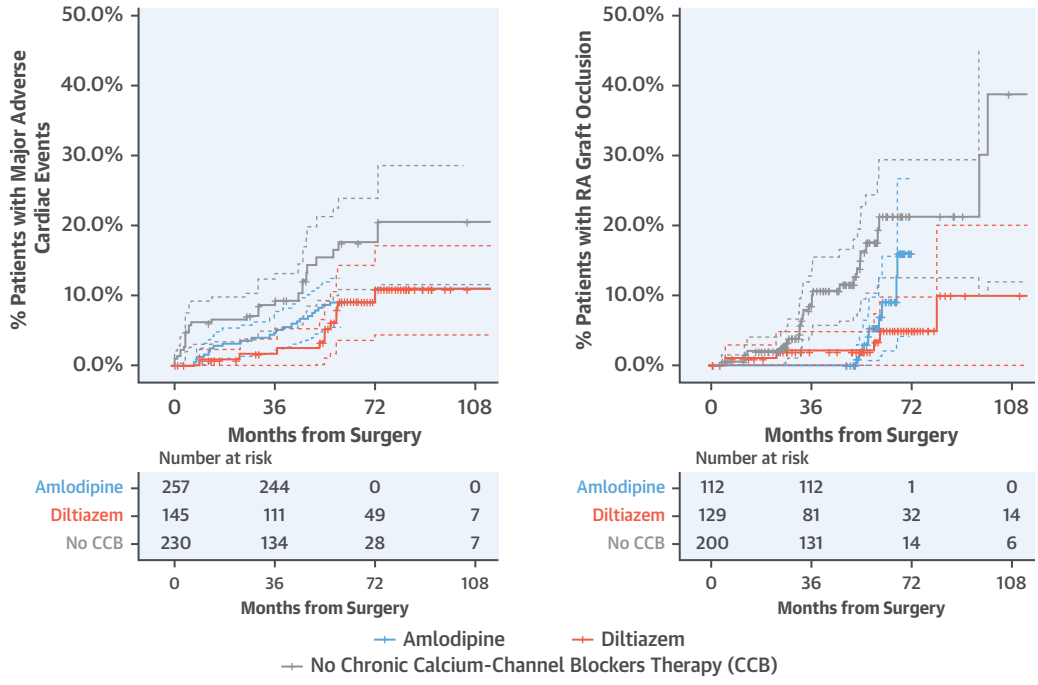
associated with the risk of MACE ($p < 0.001$) (Figure 3, left) and graft failure ($p = 0.03$) (Figure 3, right). Specifically, we found that CCB therapy for 1 year was associated with a greater reduction in MACE than a shorter duration of CCB treatment ($p < 0.001$). A benefit of a longer duration of CCB therapy was not demonstrated ($p = 0.08$), although the numbers of patients on prolonged CCB therapy was small. A similar relationship was found between CCB therapy duration and the risk of graft occlusion, with a significant reduction in graft occlusion for CCB therapy lasting 1 year compared with a shorter period ($p = 0.006$), but a further trend could not be demonstrated with longer treatment ($p = 1$). The sensitivity angiographic analysis including RAPS confirmed the robustness of the primary analysis (Online Tables 6 to 9).

DISCUSSION

In this patient-level pooled analysis of 6 RCTs on the midterm clinical and angiographic outcomes of RA graft, we found that the use of CCB was associated with a significantly lower risk of MACE and higher RA patency rate. We also found that duration of CCB for at least 1 year was associated with a reduction of clinical events and graft occlusion compared with shorter treatment and that diltiazem and amlodipine were associated with a similar protective effect.

Among all the conduits used for CABG, the RA is the only muscular artery. Histological studies have shown that the thickness of the muscular component of the RA is almost twice that of the internal thoracic artery (14). This thick muscular media is the anatomic

CENTRAL ILLUSTRATION **Calcium-Channel Blockers for Radial Artery Grafts**



Gaudino, M. et al. J Am Coll Cardiol. 2019;73(18):2299-306.

Cumulative incidence of major adverse cardiac events **(left)** and radial artery graft occlusion **(right)** according to calcium-channel blocker classes received. RA = radial artery.

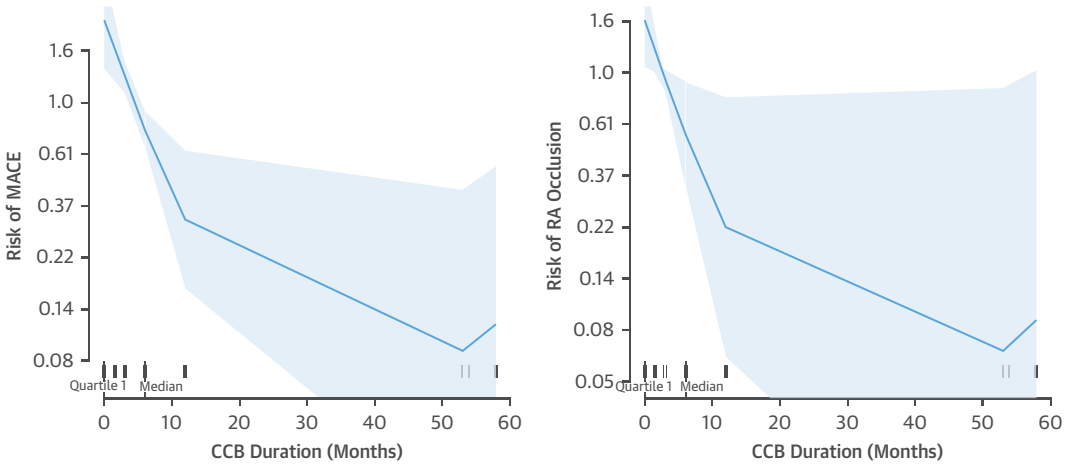
explanation of the well-known hyper-reactivity of RA rings reported in pharmacological studies. Chardigny et al. (15) in a classic organ bath experiment have shown that the spastic response of the RA to norepinephrine, serotonin, and thromboxane A2 is significantly higher than that of any other conduit used for CABG.

Those peculiar morpho-functional features of the RA and the consequent concerns of postoperative RA spasm are the reasons behind the empiric use of CCB in patients with RA grafts.

It must be noted that in the years after implantation in the coronary circulation, RA grafts lose most of the muscular component of the media and of their spastic tendency, becoming very similar to internal thoracic artery grafts (16). On this basis, it is possible that the benefits of CCB are limited to the initial postoperative period.

The previous published data on the effect of CCB in patients with RA graft is controversial. In a small previous RCT, Gaudino et al. (17) assigned 120 patients who received the RA for CABG to continue or suspend the CCB using diltiazem after the first postoperative year and found no difference in graft patency, graft reactivity, scintigraphically-evident myocardial ischemia, or clinical outcomes at 5-year follow-up. Subsequently, the same authors in another small trial randomized 100 patients to receive or not the same CCB regimen from the early postoperative period and reported again lack of differences in clinical, scintigraphic, and angiographic outcomes (18). In an angiographic series of 50 patients, Moran et al. (19) found similar clinical outcomes and angiographic patency among RA patients who received CCB with or without diltiazem. Similarly, a post-hoc analysis of the Radial Artery Patency Study found that among 440 RA patients, the incidence of string sign (the highest degree of RA graft spasm) was not affected by the compliance with the prescribed postoperative CCB, although compliance with CCB use was high (419 of 440) (20). Due to the very high patency rate and excellent clinical outcomes of RA grafts, however, it is very likely that all the individual published studies were largely underpowered to detect even moderate differences in outcome.

FIGURE 3 Effect of the Duration of Chronic CCB on the Risk of MACE and RA Graft Occlusion



(Left) MACE; **(right)** RA graft occlusion. Reference point is 6-month duration, which corresponds to the median duration in the overall sample. CCB therapy duration <6 months was associated with increased risk of graft occlusion (hazard ratio, risk >1), whereas CCB therapy duration >6 months was associated with lower risk of graft occlusion (hazard ratio: risk <1). Abbreviations as in Figure 1.

Despite this lack of solid evidence, CCB is routinely prescribed in most centers after RA grafting. A 2003 survey of all Canadian cardiac surgery centers reported that some form of antispastic therapy was adopted in almost all institutions (25 of 27) after RA grafting (3), and to our knowledge, similar postoperative protocols are used in other parts of the world.

The chronic use of calcium-channel blockers or other antispastic agents is associated with nonnegligible side-effects and considerable costs. In a large community-based study, Kloner et al. (21) reported that in patients on chronic therapy with amlodipine, edema occurred in 24%, headache in 8.8%, and fatigue and dizziness in >4%. Also, the hypotensive effect of CCB may preclude the use of other preventive therapies such as beta-blockers and angiotensin-converting enzyme inhibitors. For these reasons, an objective evaluation of the effect of CCB in patients with RA grafts is of relevance for the patients and cardiovascular community.

Our data suggest that in patients with RA grafts, the use of CCB for at least the first 12 months is associated with better clinical and angiographic outcomes.

STUDY LIMITATIONS. Most importantly, although the original studies were randomized and had similar inclusion criteria, this post-hoc analysis shares the limitations of observational studies especially in terms of indication biases. Despite the extensive use of statistical adjustments, it is likely that hidden and unmeasured confounders and biases may persist. Matching and adjustment techniques can only adjust for measurable and measured variables, whereas they are ineffective for unknown or unmeasured confounders. Subtle but important differences in surgical expertise, preoperative and postoperative care, and complementary secondary prevention strategies may have influenced the observed results. Also, despite being the largest study on this topic published to date, the sample size of the analysis is limited and its estimates may be relatively imprecise. However, the reproducibility of the main finding in all the analyses using different statistical techniques is a strong argument in favor of the solidity of our main findings.

CONCLUSIONS

Our results show that the use of CCB is associated with higher patency rate and better clinical outcomes at 5 years in patients with RA grafts. Those data support the routine use of CCB, at least for the first 12 months after CABG using the RA.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients undergoing coronary revascularization using RA grafts, treatment with CCB drugs is associated with better midterm clinical and angiographic outcomes.

TRANSLATIONAL OUTLOOK: Our results support the routine use of CCB after coronary artery bypass using the RA.

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KEY WORDS CABG, calcium-channel blocker, radial artery

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.