De-escalation of antianginal medications after successful chronic total occlusion percutaneous coronary intervention: Frequency and relationship with health status

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Background Successful chronic total occlusion (CTO) percutaneous coronary intervention (PCI) can markedly reduce angina symptom burden, but many patients often remain on multiple antianginal medications (AAMs) after the procedure. It is unclear when, or if, AAMs can be de-escalated to prevent adverse effects or limit polypharmacy. We examined the association of de-escalation of AAMs after CTO PCI with long-term health status.

Methods In a 12-center registry of consecutive CTO PCI patients, health status was assessed at 6 months after successful CTO PCI with the Seattle Angina Questionnaire and the Rose Dyspnea Scale. Among patients with technical CTO PCI success, we examined the association of AAM de-escalation with 6-month health status using multivariable models adjusting for revascularization completeness and predicted risk of post-PCI angina (using a validated risk model). We also examined predictors and variability of AAMs de-escalation.

Results Of 669 patients with technical success of CTO PCI, AAMs were de-escalated in 276 (35.9%) patients at 1 month. Patients with AAM de-escalation reported similar angina and dyspnea rates at 6 months compared with those whose AAMs were reduced (any angina: 22.5% vs 20%, $P = .43$; any dyspnea: 51.8% vs 50.1%, $P = .40$). In a multivariable model adjusting for complete revascularization and predicted risk of post-PCI angina, de-escalation of AAMs at 1 month was not associated with an increased risk of angina, dyspnea, or worse health status at 6 months.

Conclusions Among patients with successful CTO PCI, de-escalation of AAMs occurred in about one-third of patients at 1 month and was not associated with worse long-term health status. (Am Heart J 2019;214:1-8.)

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Key points Question: *Can antianginal medications (AAMs) be de-escalated early after successful chronic total occlusion (CTO) percutaneous coronary intervention (PCI) without worsening health status outcomes?* **Findings:** *In a large US CTO PCI registry, patients whose AAMs were de-escalated reported similar angina and dyspnea rates at 6 months compared with those whose AAMs were not reduced. In a multivariable model, early de-escalation of AAMs was not associated with an increased risk of angina, dyspnea, or worse health status at 6 months.* **Meaning:** *Among patients with successful CTO PCI, early de-escalation of AAMs can be considered and appears to be safe.*

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Patients with coronary artery chronic total occlusions (CTOs) often present a significant challenge to cardiologists managing their angina symptoms. These patients frequently suffer from longstanding angina and rely on multiple antianginal medications (AAMs).[1] Current guidelines strongly endorse medical therapy,[2,3] including maximally tolerated AAMs, as first-line therapy for management of chronic stable angina in patients with obstructive coronary artery disease (CAD). However, many patients continue to experience lifestyle-limiting angina despite uptitration of these medications and are ultimately referred for coronary revascularization.[4] Despite this clear guidance on maximizing medications prior to revascularization, there are no clear guidelines on best practices regarding continuation or de-escalation of AAM therapy after successful revascularization. Because patients with complex coronary disease, such as CTOs, may have residual lesions or small vessel disease, it is possible that de-escalation of AAMs could lead to rebound angina.

Moreover, given that many AAMs (eg, nitrates, ranolazine, calcium channel blockers) are generally used for symptom relief and not mortality reduction, and given that these medications can be associated with adverse effects[5-8] and that patients often become frustrated with complex medication regimens, a thoughtful approach to de-escalation of medications that are no longer needed for symptom control should be an important component of the post-PCI treatment plan.

Given the additional technical challenges of CTO percutaneous coronary intervention (PCI) and the limited number of sites that offer this as an option for revascularization, attempts at medical management of angina are often even more intense in patients with CTOs prior to revascularization.[1,9-11] Furthermore, there are some data that empiric de-escalation of AAMs at the time of PCI may be associated with greater symptom burden, especially in patients with incomplete revascularization.[12] To help support providers in their understanding of when it is safe to attempt AAM de-escalation after CTO PCI, we used the **O**utcomes, **P**atient Health Status, and **E**fficiency I**N** **C**hronic **T**otal **O**cclusion Hybrid Procedures (OPEN-CTO) Registry, a contemporary 12-center registry of CTO PCI, to describe the frequency of AAM de-escalation after CTO PCI and its association with patients' symptoms.

Methods

Study design and population

The OPEN CTO Registry is a prospective, single-arm registry that enrolled patients with CTOs who underwent attempted CTO PCI at 12 US sites.[13] Eligible patients were ≥ 18 years of age, had symptoms suggestive of ischemic heart disease, and had CTOs of at least 1 epicardial coronary artery (defined as Thrombolysis in Myocardial Infarction grade 0 flow distal to the occlusion with a presumed duration of total occlusion of at least 3 months). CTO PCI operators were required to have performed at least 100 CTO PCI procedures over a minimum of 2 years before participating in OPEN CTO. *Technical success* of the procedure was defined as <50% residual stenosis and Thrombolysis in Myocardial Infarction 2 or 3 flow without any side branch occlusion. *Physiologically complete revascularization* was defined by the operators as successful treatment of all physiologically significant lesions at the time of the index procedure. Because the focus of this study was on the frequency and outcomes of reducing AAM treatment, we restricted the cohort to those whose index procedure was technically successful. Also, patients who were on no antianginal medications at baseline were excluded. Each participating site obtained Institutional Research Board approval, and all patients provided informed consent.

Assessment of health status

Angina and dyspnea were assessed at baseline and at 6 months after CTO PCI with the Seattle Angina Questionnaire (SAQ) and Rose dyspnea scale (RDS), respectively. The SAQ is a 19-item questionnaire with a 4-week recall period that measures 5 domains of health in patients with CAD: angina frequency (SAQ AF), angina stability, quality of life (QoL), physical limitation (PL), and treatment satisfaction.[14,15] The SAQ Summary Scale (SAQ SS) integrates the SAQ AF, SAQ QoL, and SAQ PL into a single summary score.[16] Domain and summary scores range from 0 to 100, with higher scores indicating fewer symptoms and better quality of life. A mean change of ~5 points is considered clinically meaningful.[14,15] The SAQ has undergone extensive reliability and validity testing[15,17] and is associated with long-term survival, hospitalization for acute coronary syndromes, and health care utilization among patients with chronic CAD.[18] The SAQ AF domain captures the frequency of angina and sublingual nitroglycerin use and has been shown to correlate closely with daily angina diaries.[19] The primary outcome for this study was the presence of any angina at 6 months after CTO PCI, which was defined as a SAQ AF score < 100.[20] We also examined the SAQ AF, SAQ QoL, SAQ PL, and SAQ SS scores as continuous variables.

The RDS is a 4-item questionnaire with a 1-month recall period that assesses patients' level of dyspnea with common activities (Supplemental Table I).[21] For each patient, the highest limitation associated with dyspnea was designated as the RDS score such that RDS scores range from 0 to 4, with 0 indicating no dyspnea and 4 indicating dyspnea with ordinary activities of washing and dressing. The RDS has been validated in patients with CAD and shown to be associated with quality of life, rehospitalization, and long-term survival in patients with CAD.[22]

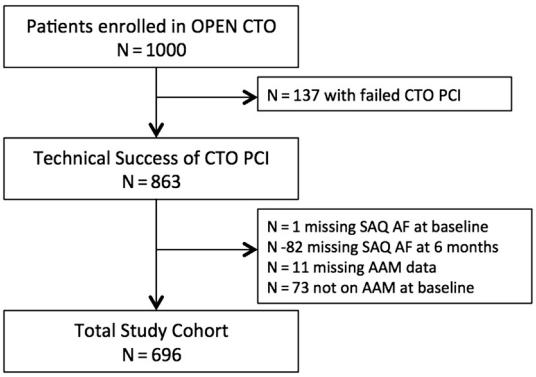
Definition of de-escalation of AAM

AAM de-escalation in early follow-up was defined as (1) being on fewer AAMs at 1 month compared with admission or (2) a decrease in AAM dose if there was no change in the number of AAMs taken. To define a change in AAM dose, we determined the maximum recommended dose of each AAM for treating angina and then calculated the patient's % of maximum dose. The proportion of maximum dose being taken for each agent was compared at admission and at 1 month for each patient, and each AAM class of medication was assumed to have a similar efficacy in treatment of angina, consistent with prior literature.[23,24] This allowed us to compare changes in medications within class (eg, change from diltiazem to amlodipine) and changes in medication classes (eg, change from carvedilol to isosorbide). For our primary analysis, any de-escalation of medications was considered significant. Patients who were on no antianginal medications at baseline were excluded.

Statistical methods

Demographic and clinical characteristics were compared among patients whose AAM were de-escalated compared to those whose AAM were not de-escalated at

Figure 1



Study patient population.

1 month using *t* tests for continuous variables and χ^2 tests for categorical variables. The proportion of patients who reported angina and the unadjusted health status scores at baseline and 6 months after CTO PCI were compared among groups using χ^2 tests and *t* tests, respectively. To examine the independent association of AAM de-escalation (vs continuation or escalation of AAM regimens) with angina, health status, and dyspnea at 6 months after successful CTO PCI, we constructed a hierarchical, multivariable logistic regression model to account for clustering by site and potential confounding. These models included the patient's predicted risk of post-CTO PCI angina (based on preprocedural factors) and completeness of revascularization. To determine the patient's predicted risk of post-CTO PCI angina, we used a previously published model that was developed to predict residual angina after conventional PCI and was subsequently validated in CTO PCI patients.[25] This model included the following preprocedural factors: age, self-reported avoidance of care due to cost, depression, number of AAM at admission, self-reported pain or discomfort (question from the EuroQol-5D), SAQ AF, and SAQ QoL.[7,25] Because β-blockers are a cornerstone treatment for patients with heart failure and acute myocardial infarction and might not be a target for de-escalation despite optimal angina symptom control, sensitivity analyses excluding all users of β-blockers and patients with history of heart failure using β-blockers were performed.

Next, we sought to describe predictors of AAMs de-escalation and variability in rate of AAMs de-escalation across participating sites. To accomplish this goal, we fit a hierarchical multivariable logistic regression model and included participating site as a random effect to account for the clustering of patients within each participating site. The outcome of this model was any de-escalation of AAMs, and the independent variables were selected a priori based on clinical judgment and literature review while balancing against risk of model overfitting. Variables included the following: age, sex, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, hypertension, diabetes mellitus, estimated glomerular filtration rate, history of heart failure, predicted risk of angina (based on the previously validated model as mentioned above), physiologically complete revascularization, left ventricular ejection fraction, number of antianginal medications at baseline, SAQ AF at baseline, SAQ AF at 1 month follow-up, RDS score at baseline, and RDS score at 1 month. Furthermore, variability in AAMs de-escalation rates among participating sites was studied using the median odds ratio, which estimates the average relative difference in 2 hypothetically identical patients receiving AAMs de-escalation if presenting to 2 different sites in the OPEN CTO registry. For example, median odds ratio of 1 suggests no site-level variation in AAMs de-escalation, whereas a median OR of 2 suggests a 2-fold difference in the odds of receiving AAMs de-escalation comparing 2 random sites providing care for patients with identical characteristics. Multiple imputation for the missing covariate data (all covariates had <5% missing information) was performed using IVEWARE software. All statistical analyses were performed with SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

Results

Patient characteristics

Among 1,000 patients enrolled in OPEN CTO who underwent CTO PCI, we excluded 137 patients who had technical CTO PCI failure, 83 patients with missing SAQ AF data at either baseline or follow up, 11 patients with missing AAM data, and 73 patient who were not on AAM at baseline. Accordingly, our analytic cohort included 696 patients (Figure 1). Participants' mean age was 65.6 years, 80% were men, and 90.4% were white

Table I. Demographic and clinical characteristics of patients whose AAMs were de-escalated versus not

	All patients N = 696	AAM de-escalation n = 276	No AAM de-escalation n = 420	*P* value
Age (y)	65.6 ± 10.0	65.6 ± 10.1	65.6 ± 9.9	.974
Male sex	79.9%	79.3%	80.2%	.774
White race	90.4%	92.0%	89.3%	.230
Current smoker	12.5%	12.0%	12.8%	.777
Prior myocardial infarction	47.1%	45.3%	48.3%	.431
Prior PCI	64.2%	65.2%	63.5%	.641
Prior CABG	36.8%	38.4%	35.7%	.471
PAD	17.1%	14.5%	18.8%	.139
Prior CVA	7.6%	7.6%	7.6%	.995
Heart failure	21.0%	18.1%	22.9%	.133
Hypertension	87.3%	88.3%	86.6%	.499
Diabetes	38.2%	38.0%	38.3%	.938
eGFR	77.2 ± 25.0	78.1 ± 25.4	76.6 ± 24.7	.456
Chronic lung disease	14.8%	14.1%	15.2%	.687
Predicted risk of residual angina (%)	0.2 ± 0.2	0.3 ± 0.2	0.2 ± 0.2	.002
Physiologic complete revascularization	85.0%	86.5%	84.0%	.370
Left ventricular ejection fraction	51.6 ± 13.3	52.3 ± 13.0	51.1 ± 13.5	.347
Post-PCI MI	2.0%	2.2%	1.9%	.804
CTO lesion length	60.9 ± 28.4	58.5 ± 27.7	62.5 ± 28.7	.072
Stent thrombosis	0%	0%	0%	NA
AAM and health status data				
AAM on admission				
Any AAM	100.0%	100.0%	100.0%	NA
Number of AAM	1.8 ± 0.8	2.0 ± 0.8	1.6 ± 0.7	<.001
β-Blocker	92.4%	90.9%	93.3%	.244
Calcium channel blocker	25.9%	28.3%	24.3%	.241
Long-acting nitrate	44.4%	59.4%	34.5%	<.001
Ranolazine	15.2%	25.0%	8.8%	<.001
AAM at 1 m				
Any AAM	92.4%	80.8%	100.0%	<.001
Number of AAM	1.6 ± 0.7	1.5 ± 0.7	1.6 ± 0.7	.003
β-Blocker	88.3%	79.0%	94.3%	<.001
Calcium channel blocker	22.6%	18.8%	25.0%	.057
Long-acting nitrate	32.1%	25.1%	36.7%	.001
Ranolazine	1.3%	1.1%	1.4%	.716
Health status at baseline				
SAQ AF	69.0 ± 27.3	64.9 ± 29.0	71.7 ± 25.8	.001
SAQ PL	66.1 ± 26.0	61.2 ± 24.3	66.8 ± 26.2	.058
SAQ QoL	48.3 ± 27.0	44.8 ± 26.8	50.5 ± 26.9	.005
SAQ SS	60.8 ± 22.2	58.3 ± 22.6	62.4 ± 21.8	.016
RDS score	2.0 ± 1.4	2.1 ± 1.4	2.0 ± 1.4	.532
Health status at 6 m				
SAQ AF	92.8 ± 16.5	91.5 ± 18.4	93.7 ± 15.1	.088
SAQ PL	94.7 ± 12.8	96.1 ± 9.2	94.5 ± 13.2	.305
SAQ QoL	80.8 ± 20.8	79.8 ± 21.4	81.5 ± 20.4	.280
SAQ SS	88.7 ± 14.7	87.8 ± 15.3	89.3 ± 14.3	.204
RDS score	1.0 ± 1.3	1.1 ± 1.3	1.0 ± 1.2	.242

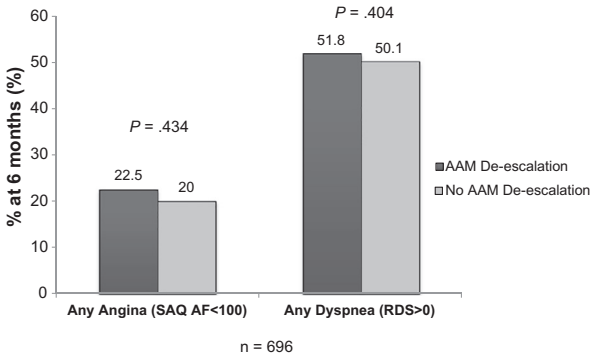
CABG, Coronary artery bypass graft; *PAD*, peripheral arterial disease; *CVA*, cerebral vascular accident; *eGFR*, glomerular filtration rate; *MI*, myocardial infarction.

(Table I). Cardiac comorbidities were common, with prior PCI in 64.2%, prior bypass graft surgery in 36.8%, prior myocardial infarction 47.1%, prior peripheral arterial disease in 17.1%, prior heart failure in 21.0%, hypertension in 87.3%, and diabetes in 38.2%. Complete physiologic revascularization was achieved in 85.0% of patients. Post-CTO PCI myocardial infarction occurred in 2.0% of patients.

Baseline angina and AAM

At admission prior to CTO PCI, the mean SAQ AF score was 69.0 ± 27.3 and the mean RDS score was 2.0 ± 1.4,

Figure 2



Angina and dyspnea rates at 6 months post-PCI. The rates of observed angina and dyspnea post-PCI in all patients with technical success of CTO PCI.

and all of patients were on at least 1 AAM with a mean (± SD) of 1.8 ± 0.8 AAMs per patient. Specific AAMs used were β-blockers in 92.4%, long-acting nitrates in 44.4%, calcium channel blockers in 25.9%, and ranolazine in 15.2% of patients (Table I). At 1 month, 92.4% of patients were on at least 1 AAM with a mean (± SD) of 1.6 ± 0.7 AAMs per patient. From admission to 1 month, AAMs were de-escalated in 276 patients (39.6%). The demographic and clinical characteristics of patients whose AAMs were de-escalated were generally similar to those whose AAMs were not de-escalated (Table I). However, patients whose AAMs were de-escalated reported, on average, a greater burden of baseline angina and worse quality of life at baseline and had a higher predicted risk of residual angina after PCI.

Six-month angina and health status

In unadjusted analysis, the proportion of patients who reported angina and dyspnea at 6 months after CTO PCI was similar to those whose AAM were de-escalated versus not de-escalated (any angina: 22.5% vs 20.0%, $P = .434$; any dyspnea: 51.8% vs 50.1%, $P = .40$) (Figure 2). The SAQ AF domain scores at 6 months were numerically lower in patients with AAM de-escalation (vs no de-escalation), but the difference was not clinically meaningful. The SAQ PL, SAQ QoL, SAQ SS, and RDS were all similar between the 2 groups (Tables I and II). In the multivariable model that adjusted for the patient's preprocedural risk for post-PCI angina, de-escalation of AAM at 1 month was not associated with long-term angina, angina-related health status, or dyspnea (Figure 3). Sensitivity analyses excluding all users of β-blockers and patients with history of heart failure using β-blockers showed similar results to the primary analysis and are available upon request.

Variability in AAMs de-escalation among OPEN CTO sites

The overall rate of AAMs de-escalation across the 12 OPEN CTO sites ranged from 1% to 15%. After adjusting for clinical characteristics, the median odds ratio for variability across sites was 1.02, indicating no meaningful site-level variability of AAMs de-escalation.

Table II. Association of de-escalation in AAM at 1 month after CTO PCI with health status at 6 months*

	Estimate (95% CI)*	*P* value
SAQ AF	−0.86 (−3.19 to 1.46)	.466
SAQ PL	1.41 (−0.70 to 3.53)	.189
SAQ QoL	−0.006 (−3.03 to 3.02)	.996
SAQ SS	−0.12 (−2.1 to 1.9)	.902
RDS score	0.003 (−0.20 to 0.20)	.999

* Adjusted estimate for difference in health status score in patients whose AAMs were de-escalated versus not. Estimates were adjusted for the patient's predicted risk of residual angina after PCI and complete revascularization.

Predictors of AAMs de-escalation

Significant predictors of AAMs de-escalation among patients with technically successful CTO PCI included worse SAQ AF at baseline ($P = .03$) and higher number of AAMs at baseline ($P < .001$) (Supplemental Table II).

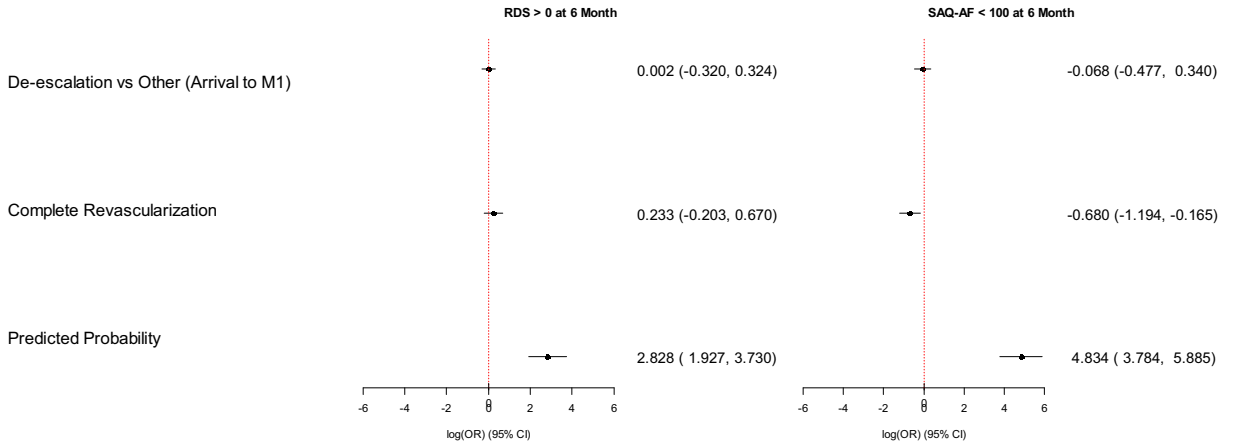
Sensitivity analyses

A sensitivity analysis was conducted regarding the use of β-blockers. Results were unchanged and suggest that de-escalation of non–β-blocker antianginals (in case of the presence of an indication for β-blocker continuation) could be considered.

Discussion

In a large, multicenter registry of patients undergoing CTO PCI, we found that 39% of patients had their AAM regimen de-escalated within 1 month after successful CTO PCI. Importantly, AAM de-escalation at 1 month was not associated with worse follow-up angina, dyspnea, and health status. No site-level variability in AAMs de-

Figure 3



Independent associations between AAM de-escalation and angina/dyspnea at 6 months after successful CTO PCI. Adjusted for the preprocedural risk of predicted residual angina and completeness of revascularization.

escalation was detected, and only baseline angina frequency and the number of AAMs were significant predictors of AAMs de-escalation. Our findings suggest that AAM de-escalation after successful CTO PCI can be safely considered and is not associated with increased risk of angina, dyspnea, or worse health status. Moreover, the lack of variability in de-escalation practice could suggest clinical inertia may exist to continue these medications after the procedure. Further study is needed to determine the ideal timing, barriers to de-escalation, and strategy of AAM de-escalation following successful CTO PCI.

Prior studies have generally focused on exploring the factors associated with angina after PCI.[26-29] However, scarce data exist on the management of AAMs after PCI and the impact of changes in AAM regimens on long-term ischemic symptoms. We recently published data on AAM de-escalation after conventional PCI and showed that 11% of patients had empiric AAM de-escalation at discharge after PCI.[12] We found that this empiric de-escalation was associated with increased risk of residual angina after PCI and worse long-term health status; however, this was primarily driven by patients with incomplete revascularization. AAM de-escalation was not associated with residual symptoms among those who underwent complete revascularization, consistent with the results of the present analysis. Prior literature showed that AAM escalation with ranolazine has not been shown to reduce risk of angina in patients with incomplete revascularization (sometimes due to untreated CTO lesion).[30] Our data demonstrate that AAM de-escalation can be safely attempted in a population of patients undergoing CTO PCI, particularly among patients with successful PCI who received complete revascularization. These findings are also consistent with the recently published EURO CTO trial, a randomized controlled trial of CTO PCI with optimal medical therapy versus optimal medical therapy alone. The EURO CTO trial showed that in patients with stable angina and CTO, CTO PCI is superior to medical therapy in angina relief and quality life.[31]

There are no published guidelines, algorithms, or recommendations to help guide AAM management post-PCI, especially after successful CTO PCI. Often, patients are on multiple AAMs at presentation, and it is unclear how to manage them after successful revascularization. It is not uncommon that patients are symptom free after successful PCI but continue to take potentially unnecessary AAM medications that were prescribed prior to the procedure. In our multicenter registry, the overall rate of AAM de-escalation rates was modest, and there was no site-level variability. This could represent strong clinical inertia where providers are less likely to de-escalate therapy despite adequate symptom control post-PCI. Although clinical inertia is one possible explanation for the lack of de-escalation, other clinical indications for medications continuation exist, such as treatment of heart failure and resistant hypertension. As AAMs generally do not have a survival benefit in patients with stable CAD (in the absence of other comorbidities, such as systolic heart failure or hypertension), a thoughtful de-escalation of these medications after successful revascularization likely makes sense if no other indication is present to justify continuation of these agents.

In light of the data presented in this study, it appears that it is not unreasonable to attempt to de-escalate AAM after successful CTO PCI, which may help avoid polypharmacy and limit unnecessary adverse effects and costs.[32] One strategy might be to try to de-escalate AAM therapy in follow-up among patients with successful CTO PCI, especially if they undergo physiologically complete

revascularization and they have low predicted risk of post-PCI angina. We have shown that de-escalation of AAM in this population is not associated with increased residual angina, dyspnea, or worse health status. However, it is important to realize that PCI does not eliminate angina in all patients (residual angina was still reported up to 20% of patients post successful CTO PCI[33]), and symptom-guided AAM management with appropriate follow-up is necessary, especially in patients with high predicted risk of post-PCI angina and incomplete revascularization.

The findings of our study should be interpreted in consideration of the following potential limitations. First, our data are observational, and residual confounding cannot be excluded in interpretation of these results. Randomized trials testing specific strategies of AAM de-escalation would be helpful to clarify best practices regarding AAM de-escalation. Second, we defined change in AAM regimens assuming equal antianginal properties for all AAM classes. Although this approach was based upon prior studies that have shown no difference in efficacy of angina relief across AAM classes,[23,24] we cannot exclude differences in responses to medications in individual patients. Third, the reasons for AAM de-escalation were not collected in this registry, and these could be physician or patient driven. Although we do not believe this would necessarily influence our findings, further studies of the reasons behind de-escalation could provide insights to help better understand patterns of AAM de-escalation and determine best practices. Likewise, no data were collected on the adverse effects of antianginal medications that would provide further insights into the need for AAM de-escalation in select cases. Fourth, complete physiologic revascularization was defined based on operator report and their assessment and was not adjudicated independently. Finally, β-blockers are believed to have mortality benefit in patients with depressed left ventricular ejection fraction[34] and patients with acute coronary syndrome,[35] and physicians might be hesitant to de-escalate these medications. However, our sensitivity analysis excluding de-escalation of BB showed similar results to the primary analysis, suggesting that de-escalating other non–β-blocker medications similarly does not affect health status long-term post successful CTO PCI.

In conclusion, we report that over 1 in 3 of patients undergoes AAM de-escalation in early follow-up after successful CTO PCI. Importantly, this was not associated with increased risk of residual angina, dyspnea, or worse health status at 6 months after successful CTO PCI. Although current guidelines do not provide guidance on when or if to de-escalate these medications that were started for symptom relief, our findings support considering attempts to de-escalate AAMs after successful CTO PCI. This strategy can simplify patients' medication regimens and avoid adverse effects from medications that are no longer providing benefit to the patient. Future research is needed to understand the ideal timing and strategy of AAM de-escalation post-PCI and its association with health status.

Disclosures

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Appendix. Supplementary data

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