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# Inter–Core Lab Variability in Analyzing Quantitative Coronary Angiography for Bifurcation Lesions

## A Post-Hoc Analysis of a Randomized Trial

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## ABSTRACT

**OBJECTIVES** This study sought to evaluate inter–core lab variability in quantitative coronary angiography (QCA) analysis of bifurcation lesions.

**BACKGROUND** QCA of bifurcation lesions is challenging. To date there are no data available on the inter–core lab variability of bifurcation QCA analysis.

**METHODS** The randomized Tryton IDE (Tryton Pivotal IDE Coronary Bifurcation Trial) compared the Tryton Side Branch Stent (Tryton Medical, Durham, North Carolina) with balloon angioplasty as side branch treatment. QCA was performed in an angiographic subcohort (n = 326) at 9-month follow-up. Inter-core lab variability of QCA analysis between the Cardiovascular Research Foundation and the Cardialysis core labs was evaluated before and after alignment of the used QCA methodology using angiographic data derived from this angiographic follow-up cohort.

**RESULTS** In the original analysis, before alignment of QCA methodology, the mean difference between the core labs (bias) was large for all QCA parameters with wide 95% limits of agreement (1.96 × SD of the bias), indicating marked variability. The bias of the key angiographic endpoint of the Tryton trial, in-segment percentage diameter stenosis (%DS) of the side branch, was 5.5% (95% limits of agreement: -26.7% to 37.8%). After reanalysis, the bias of the in-segment %DS of the side branch reduced to 1.8% (95% limits of agreement: -16.7% to 20.4%). Importantly, after alignment of the 2 core labs, there was no longer a difference between both treatment groups (%DS of the side branch: treatment group A vs. group B: 34.4 ± 19.4% vs. 32.4 ± 16.1%, p = 0.340).

**CONCLUSIONS** Originally, a marked inter-core lab variability of bifurcation QCA analysis was found. After alignment of methodology, inter-core lab variability decreased considerably and impacted angiographic trial results. This latter finding emphasizes the importance of using the same methodology among different core labs worldwide. (Tryton Pivotal Prospective, Single Blind, Randomized Controlled Study to Evaluate the Safety & Effectiveness of the Tryton Side Branch Stent Used With DES in Treatment of de Novo Bifurcation Lesions in the Main Branch & Side Branch in Native Coronaries [TRYTON]; NCT01258972) (J Am Coll Cardiol Intv 2015;8:305–14) © 2015 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**%DS** = percentage diameter stenosis

**CI** = confidence interval

**CRF** = Cardiovascular Research Foundation

**IDE** = investigational device exemption

**MLD** = minimal lumen diameter

**QCA** = quantitative coronary angiography

**RVD** = reference vessel diameter

Ever since the late 1970s, visual estimation of the severity of a stenosis on coronary angiography has been regarded as unreliable due to a marked intra- and interobserver variability (1,2). Therefore, quantitative coronary angiography (QCA) was introduced in the mid-1980s to provide an objective and reproducible quantification of coronary lesions (3,4). QCA parameters have been widely used as primary and secondary endpoints in numerous randomized clinical trials evaluating the efficacy of new technologies in percutaneous coronary interventions and the effect of new pharmaceutical agents on coronary artery disease progression/regression (5–7).

Due to the fractal geometry of the coronary tree, there is a natural tapering of the bifurcation, with differences in reference vessel diameter (RVD) among the proximal main branch, distal main branch, and side branch (8,9). Due to this natural tapering, the interobserver variability of visual estimation of lesion severity increases even more in bifurcation lesions (10). Furthermore, conventional QCA algorithms have the limitation of being inaccurate in bifurcation lesions because they have been developed and validated in a single straight coronary segment (11). To improve the accuracy of QCA in bifurcation lesions, dedicated bifurcation algorithms were developed, which subsequently have been used in recent clinical trials on bifurcation treatment (12–16).

To eliminate the potential bias stemming from the investigators, QCA analysis in clinical trials is usually performed at independent core laboratories (core labs). These core labs aim to provide unbiased and reproducible results by using validated QCA software and by using standard operating procedures during QCA analysis. Although intraobserver and interobserver variability of bifurcation QCA algorithms have been investigated before (14,16,17), to date no data are available on the differences in bifurcation QCA measurements between core labs. This study aimed to examine inter-core lab variability by comparing the QCA results of 2 core labs using data from the 9-month angiographic follow-up cohort of the randomized trial on the Tryton Side Branch Stent (Tryton Medical, Durham, North Carolina).

## METHODS

**SETTING.** Tryton IDE (Tryton Pivotal IDE Coronary Bifurcation Trial), an investigational device exemption (IDE) randomized trial, compared the Tryton Side Branch Stent with side branch balloon angioplasty, both in combination with a regular drug-eluting stent in the main branch, for the treatment of de novo true coronary bifurcation lesions. The primary endpoint (powered for noninferiority), at 9-month follow-up, was the difference in the occurrence of target vessel failure, defined as the composite of cardiac death, Q-wave or non-Q-wave target vessel myocardial infarction (>3× the upper limit of normal of creatine kinase isoenzyme), and target vessel revascularization. The key secondary endpoint (powered for superiority) was in-segment percentage diameter stenosis (%DS) of the side branch in a pre-specified subgroup of 374 subjects (with an expected loss to follow-up of 15%) undergoing planned repeat angiography at 9 months (the angiographic follow-up cohort).

Two core labs were assigned to perform different types of analyses in the angiographic follow-up cohort of the Tryton IDE trial. The Cardiovascular Research Foundation (CRF, New York, New York) was assigned to perform 2-dimensional QCA analysis of the complete angiographic follow-up cohort. Cardialysis B.V. (Rotterdam, the Netherlands) was assigned to perform 3-dimensional QCA and intravascular ultrasound analyses and for this purpose 9-month follow-up angiograms of 130 subjects included in the angiographic follow-up cohort were available at Cardialysis. Besides 3-dimensional QCA and intravascular ultrasound analyses, Cardialysis also performed 2-dimensional QCA analysis in this subgroup. The inter-core lab variability of the 9-month 2-dimensional QCA analysis between the 2 core labs was investigated in these 130 subjects. This initial analysis indicated diverging angiographic results between the 2 core labs (**Figure 1A**). Thereafter, both core labs disclosed and shared their QCA analysis plans to unravel potential explanations for these differences. Both core labs decided to perform a reanalysis of the total angiographic follow-up cohort using an identical QCA analysis plan, which they had agreed on (**Table 1**).

**INITIAL QCA ANALYSIS PLAN OF CRF.** At the start of the Tryton IDE trial, the dedicated bifurcation QCA algorithms were not yet validated against precision phantoms. Therefore, the initial QCA analysis plan of the trial, approved by the U.S. Food and Drug Administration and used for the main publication, included the use of a conventional single-vessel QCA algorithm (QAngio XA, version 7.2.34, Medis Medical Imaging Systems, Leiden, the Netherlands). For each bifurcation, 2 analyses were performed: one from the proximal main branch to the distal main branch, and the