Iwnetu, Rahel, Impact of Age on Technical and In-hospital Outcomes of Percutaneous Coronary Intervention for Chronic Total Occlusions. Master of Science (Clinical Research Management), March, 2016, 99 pp., 3 tables, 1 figure, 95 bibliographies, 32 titles.

Background: We sought to examine the effect of patient age on the outcomes of percutaneous coronary intervention (PCI) of chronic total occlusions (CTO). **Methods**: We examined clinical and angiographic data as well as outcomes of 1,216 CTO PCIs performed in 1,195 patients divided into three age groups (<65, 65-75, and ≥75 years old). **Results**: Increasing age was associated with higher prevalence of prior stroke (7.6% vs 12.6% vs 17.2% for <65, 65-75, and ≥75 years old respectively, p<0.001) and prior coronary artery bypass graft surgery (25.2% vs 39.8% vs 45.5%, p<0.001), but lower prevalence of current smoking (36.4% vs 25.7% vs 14.6%, p<0.001). Older patients were also more likely to have hypertension (88.1% vs 88.7% vs 94.0%, p=0.042) and have moderately or severely calcified lesions (48.4% vs 59.8% vs 75.0%, p<0.001). Technical success rate was similar in all age groups (91.1% vs 90.7% vs 85.7%, p=0.054), but a higher incidence of major adverse cardiac events (MACE) was noted in the ≥75 years old group (0.9% vs 3.0% vs 5.1%, p=0.002), largely due to higher rate of cardiac tamponade requiring pericardiocentesis (0% vs 0.7% vs 2.2%, p=0.004). Procedure time, contrast volume and air kerma radiation dose did not differ significantly between the three groups. **Conclusion**: CTO PCI can be performed with high success rates among older patients, but may carry higher risk for complications in this patient group.

IMPACT OF AGE ON TECHNICAL AND IN-HOSPITAL OUTCOMES OF PERCUTANEOUS CORONARY INTERVENTION FOR CHRONIC TOTAL OCCLUSIONS

Rahel Iwnetu, MD

APPROVED:

Patricia A. Gwirtz, PhD, FACC; Major Professor

Michael L. Smith, PhD; Committee Member

Emmanouil S. Brilakis, MD, PhD; Committee Member

Bavana V. Rangan, BDS, MPH; Committee Member

Meharvan Singh, PhD, Chair, Department of Biomedical Sciences

---

Meharvan Singh, PhD, Dean, Graduate School of Biomedical Sciences

IMPACT OF AGE ON TECHNICAL AND IN-HOSPITAL OUTCOMES OF PERCUTANEOUS CORONARY INTERVENTION FOR CHRONIC TOTAL OCCLUSIONS

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the

Graduate School of Biomedical Sciences

University of North Texas

Health Science Center at Fort Worth

in Partial Fulfillment of the Requirements

For the Degree of

MASTER OF SCIENCE

IN CLINICAL RESEARCH MANAGEMENT

By

Rahel Iwnetu, MD

Fort Worth, Texas

March 2016

ACKNOWLEDGEMENTS

I want to thank Dr. Emmanouil Brilakis for allowing me to be part of his research team at the Dallas VA Medical Center. I want to express my sincere appreciation of his guidance and support from the development of this research proposal until the culmination of my thesis. I want to thank him for taking time out of his extremely busy schedule to critically revise my writings. I also want to thank Dr. Bavana Rangan who has made my stay at the internship site a very rich experience of learning, hard work and fun. I am grateful for all the support, patience and guidance she provided me. She has been a great mentor and an advocate for me. I am also very fortunate to have great team members: Michele Roesle, Amy Atwell, Erica Resendes, Jose Roberto Martinez Parachini, Furqan Siddiqui, Pratik Kalsaria and Aya Alame. I greatly appreciate their help and support. My thanks also extends to the research fellows: Georgios Christakopoulos, Barbara Danek, Judit Karacsonyi , and especially Aris Karatasakis who have given me a great help in analyzing my data and writing the abstract for my project.

I want to thank Dr. Patricia Gwirtz for her invaluable guidance throughout my internship as my major professor and advisor. I would also like to thank Dr. Michael Smith for his generous suggestions as a committee member.

Last but not least, I would like to thank my family and friends for their support and encouragement throughout this entire process.

Study data were collected and managed using REDCap electronic data capture tools hosted at University of Texas Southwestern Medical Center.[1] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

[1]Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr; 42(2):377-81.

TABLE OF CONTENTS

LIST OF TABLES vi

LIST OF FIGURES vii

CHAPTERS

I. INTRODUCTION 1

II. BACKGROUND AND LITERATURE REVIEW 3

SPECIFIC OBJECTIVES 13

SIGNIFICANCE OF THE STUDY 13

MATERIALS AND METHODS 14

RESULTS 20

DISCUSSION 27

LIMITATIONS OF THE STUDY 30

CONCLUSION 30

III. INTERNSHIP EXPERIENCE 31

REFERENCES 34

.

LIST OF TABLES

Table 1 Baseline clinical characteristics of the study patients 21

Table 2 Angiographic characteristics of the study lesions according to age group 23

Table 3 Procedural characteristics and outcomes according to age group 25

LIST OF FIGURES

Figure 1 Comparison of technical, procedural and MACE rate between three age groups.......... 26

CHAPTER I

I. INTRODUCTION

Chronic total occlusions (CTO) of a coronary artery are present in approximately one third of patients who undergo diagnostic angiography with estimates ranging between18% to 52% (1-3). Even though CTOs are present in a considerable number of patients in everyday clinical practice, there is no clear consensus on optimal treatment strategies. Medical and surgical revascularizations were generally considered the accepted treatment options (4), until a few years ago when percutaneous coronary intervention (PCI) was introduced as an alternative approach for managing this problem. Many critics of this procedure argue that symptoms in CTO patients can easily be controlled with medications and are skeptical about the impact of CTO PCI on quality of life and patient survival (5). On the contrary, several observational studies have shown that successful CTO PCI is associated with symptom relief, decreased need for coronary artery bypass graft surgery (CABG), improvement in long-term survival and left ventricular function as compared with unsuccessful CTO PCI (6-11). Furthermore, recent technological advances alongside with increased clinical expertise and skills have significantly improved the procedural outcomes of CTO PCI (12-15).

CTO PCI is currently infrequently performed in the United States (16). Even fewer CTO PCIs are performed on older individuals, even though elderly patients constitute a substantial proportion of patients who are referred for PCI (17). The elderly is a rapidly growing segment of the population and they account for the highest proportions of hospitalizations and mortality for myocardial infarction (MI) and coronary heart disease (CHD) (18). Therefore, there is an expanding clinical need for optimizing treatments of the elderly, which requires solid scientific evidence for making good treatment decisions (19). Understanding how age impacts the benefits and risks of CTO PCI in older patients would be of great clinical value.

CHAPTER II

II. BACKGROUND AND LITERATURE REVIEW

Heart disease is the leading cause of death in both sexes and most ethnic groups in the United States (20). Coronary artery disease is the most common form of heart disease, accounting for 370,000 deaths each year (20). Coronary artery disease results in accumulation of atherosclerotic plaques in the tunica intima of affected blood vessels (21). Atherosclerotic changes can progressively narrow the coronary artery lumen and impair anterograde myocardial blood flow. In the most severe cases, complete blockage of the coronary arteries occurs, resulting in total coronary occlusion.

Definition

The term CTO has been used loosely in various reports making comparison of different studies difficult (22). As a result, a consensus document was published in 2005 in which a unified definition for CTOs was proposed (23). This definition is based on three criteria: the degree of lumen narrowing, antegrade blood flow grade, and age of the occlusion (23). CTOs are characterized by significant atherosclerotic vessel narrowing with lumen compromise that results in either i) complete interruption of antegrade blood flow as assessed by coronary arteriography (Thrombolysis in Myocardial Infarction [TIMI] grade 0 flow), also known as “true” total occlusions, or ii) with minimal contrast penetration through the lesion without distal vessel opacification (TIMI grade 1 flow), frequently referred to as “functional” total occlusions (23).

While the distinction between TIMI grade 0 and 1 is clearly described in the definition, the distinction in the literature has been rather blurry (22).

Ascertaining the last criteria, i.e., duration of coronary occlusion, is difficult in the absence of serial angiograms (23). In cases where serial angiograms are not available, the duration can be estimated from the available clinical information that is related to the history of acute coronary event or a sudden change in symptoms (22, 23). In general, total coronary occlusion greater than 3 months duration is considered to be chronic occlusion (23).

Prevalence

The prevalence of CTO is frequently estimated from the number of patients who undergo coronary angiography. Patients with CTO who are asymptomatic or mildly symptomatic may be less likely to undergo angiography and, therefore, are not included in this estimation making it difficult to capture the true prevalence of CTO in the general population (23). Nevertheless, CTO prevalence among patients who undergo coronary angiography varies widely. In 1993, Kahn et al identified a CTO in 35% of patients out of the 287 patients presenting with suspected or known heart disease (1). In a 2012 multicenter study conducted by Fefer et al., at least one CTO was present in 2,360 patients out of 14,439 examined, making the overall prevalence of CTO 18.2% among patients with coronary artery disease and 14.7% among all patients who underwent diagnostic coronary angiography (3). Christofferson et al. examined 8,004 consecutive patients who underwent cardiac catheterization between 1990 and 2000 at the Veterans Administration Hospital in Seattle, Washington. Of the 3,087 patients who had significant coronary artery disease and no previous coronary artery bypass graft surgery (CABG), a totally occluded artery was present in 1,612 (52%) patients (2). A similar study examined 1,699 consecutive patients who had undergone diagnostic angiography from 2011 to

2012 at the Veterans Affairs tertiary referral hospital in Dallas (24). The study revealed a 31% prevalence of coronary CTO among patients without CABG, vs 89% among patients with prior CABG.

Pathology

The hallmark of CTO is the presence of atherosclerotic plaque that forms a platform for the formation of thrombus, which in turn triggers the occlusive process (25). In the initial phase, thrombotic lesions are predominantly populated by erythrocytes and platelets that are embedded in a fibrin mesh (26). Subsequent invasion of the lesion by inflammatory cells is accompanied by formation of a proteoglycan-enriched extracellular matrix and myofibroblast infiltration into the thrombotic occlusion (27). The composition of the CTOs changes with further aging of the lesion, progressing from soft to hard plaque (28). Hard plaques are characterized by accumulation of calcium and collagen (24). Even though prominent accumulation of fibrocalcific material is noted at both proximal and distal ends of CTOs, significantly more accumulation is found at the proximal end (27).

Inflammation precedes neovascularization (27) and it is an important contributor of pathologic angiogenesis in CTOs (29). Srivatsa et al. reported that the extent of neovascularization correlated with the degree of inflammation (28). They also observed greater capillary formation in the adventitia of CTOs of less than one year duration. On the other hand, bridging collaterals with rich neovascularization were reported more frequently in CTOs older than one year (30). Other investigators have also found that the process of neovascularization can lead to the formation of micro-channels with an average diameter of 200 μm (28). These micro-channels can extend from the proximal to the distal lumen but mostly lead into the adventitia, small side branches, or vaso vasorum, which negatively affects the advancement of a guide wire through the obstruction and predispose to the development of complications (28,31,32). Contrary to prior reports, current studies affirm the occurrence of these micro-channels as very rare (33).

As the CTO lesion ages, it typically undergoes negative remodeling (32). The negative remodeling process is characterized by the replacement of soft plaque with fibrous tissue, mainly in the middle section of the occlusion (34). This process leads to artery vessel shrinkage, which is mostly observed in CTOs with duration of greater than 3 months. Negative remodeling is a frequent pathology (35) and it is one of the major determinants of luminal narrowing in the atherosclerotic human coronary artery (36).

Clinical manifestations

Ten to fifteen percent of CTO patients who are referred for PCI are asymptomatic (37). The majority of patients are referred for angiography because of anginal symptoms or significant ischemia on noninvasive ischemia testing (37). After examining 2,002 patients presenting with stable angina pectoris, Werner et al. reported that anginal symptoms were similar in CTO and non-CTO patients but congestive heart failure was more prevalent in the first group (38). In addition, ischemia was more common and severe in the CTO group (38). It is less likely for CTO patient to present with an acute coronary syndrome caused by the CTO itself (37).

Patients who have CTO on diagnostic angiography are older when compared with non CTO patients (mean age of 66 ± 11 years versus 64 ± 12 years respectively) (3). The majority of patients affected with CTO are men, who represent as many as 80% of patients with CAD and a CTO (3). Female patients who undergo CTO PCI tend to be older and have more comorbid conditions, such as hypertension and diabetes, when compared to their male counterparts (39). Multi-vessel coronary disease is seen less often in women in whom the left anterior descending coronary artery is more commonly involved (39). As compared with men, CTOs in women are less likely to have bridging collaterals or blunt stump and have shorter CTO length (39).

Among patients who have a single CTO, the occlusion is mostly located in the right coronary artery (47%) followed by left anterior descending artery (20%) and left circumflex artery (16%) (3). Occlusions in more than one coronary artery were observed in 17% (3). As compared with patients who did not have CTOs, CTO patients have higher prevalence of diabetes mellitus, hypertension, hyperlipidemia, heart failure and peripheral artery disease (3). They were also more likely to have multi-vessel disease, lower ejection fraction and prior myocardial infarction (2, 3).

Treatment

The treatment of CTO patients is determined on an individual basis. Clinical factors, such as the severity of ischemia, the presence of other symptoms and concomitant coronary artery disease, are factored in when considering treatment for CTO patients (37). The risk benefit analysis also encompasses angiographic and technical considerations (40). Revascularization strategies are generally designed for those patients who remain symptomatic and have a large burden of ischemia despite optimal medical therapy (37). On a consensus document published in 2005, Stone et al. outlined three general conditions that warrant PCI interventions when the CTO represents the only significant lesion in the coronary tree. These conditions are: (1) The occluded vessel is responsible for the patient's symptoms (PCI may also be considered in selected cases of silent ischemia if a large myocardial territory at risk is demonstrable); (2) the myocardial territory supplanted by the occluded artery is viable; and (3) the likelihood of success is moderate to high (>60%), with an anticipated major complication rate of death <1% and myocardial infarction <5% (40).

Three major categories of CTO crossing techniques are currently in use: antegrade wire escalation, antegrade dissection-reentry, and the retrograde approach. The most commonly used CTO crossing technique is antegrade wire escalation (41) that involves advancement of a micro catheter to the proximal CTO cap, followed by crossing attempts using various guidewires. The antegrade dissection/re-entry uses the sub-intimal space to pass the guidewire into the distal true lumen. This technique (especially extensive antegrade dissection/re-entry) is currently used less frequently due to concerns about higher rates of restenosis and re-occlusion (42). The retrograde approach involves advancement of a guidewire in a coronary segment distal to the occlusion via bypass grafts or collateral vessels (43). Crossing using the retrograde approach can sometimes be easier because the distal cap is softer and more frequently tapered, but the retrograde approach may be associated with increased procedural risk (35). The hybrid approach utilizes all the above techniques and is found to be safe and effective (44).

Benefits of CTO PCI

There are several benefits associated with CTO PCI. These include:

Improve anginal symptoms

Joyal et al. identified 13 observational studies that compared outcomes of successful versus failed CTO PCI in a total of 7,288 patients followed up for an average time of 6 years. These studies demonstrated significant reduction in residual/recurrent anginal symptoms in patients with successful recanalization of CTOs (8). In the Total Occlusion Angioplasty Study – Societá Italiana di Cardiologia Invasiva (TOAST-GISE) study, CTO PCI success was associated with 88% angina-free survival in comparison to 75% angina-free survival in CTO PCI failure cases at 12 months follow-up ($p = 0.008$) (9).

Improve left ventricular function

Improvement in global and regional left ventricular function has been demonstrated in successful CTO PCI as long as long term patency of the target vessels is maintained and the perfused myocardium is viable (45).

Improve survival

Suero et al. compared long-term survival between patients with and without a CTO among 2007 consecutive patients undergoing PCI of a non-acute coronary occlusion. The CTO and matched non-CTO patients had a similar in-hospital risk for major adverse cardiac event (MACE) and 10-year survival. Successful CTO recanalization was associated with an improved 10-year survival (10). In another study, Aziz et al. reported that successful revascularization of CTOs by PCI and coronary stenting was associated with improved survival and reduced need for CABG as compared with patients in whom CTO PCI failed (46).

Predictors of success/failure for CTO PCI

The duration of coronary occlusion is considered a strong predictor of PCI failure (4). In an earlier study, Bell et al. recorded a high success rate of 93.3% for occlusions between 8 and 30 days in contrast to the 64.4% success rate for occlusions with greater than 90 days (47). Other earlier studies have also confirmed this inverse relationship between duration of occlusion and success at revascularization with PCI (48-50).

Tapered morphology is another characteristic of CTO that was shown to have a favorable outcome with PCI. It was identified as an independent predictor of procedural success in 905 consecutive patients who had angioplasty from 1980 and 1989 in one institute (51). Tapered morphology was associated with 88% success rate in comparison to the 59% success rate in its absence (p = 0.01). Similarly, Maiello et al. identified tapered morphology as one of the variables that affected procedural success rate (52).

Earlier reports have identified the presence of bridging collateral as predictor of failure in CTO revascularization (50-52). Recent investigations have revealed that success rate may not be inversely correlated with bridging collaterals (9, 53). It is suggested that advances in guidewire technology have increased the success rates in occlusions with bridging collaterals to the point where CTOs should no longer be disqualified for PCI revascularization for this reason only (40). According to expert operators in Japan, severe tortuosity and calcification are the most important predictors of failed CTO recanalization in contemporary practice (54).

The presence of side branch (50-52) at the point of occlusion is another factor that has been reported as predictors of procedural failures. Higher success rate was reported in the absence of a side branch.

Outcome of CTO PCI

Patel et al. conducted a meta-analysis of 65 studies published between 2000 and 2011 reporting procedural complications of CTO PCI (55). These studies reported outcomes on 18,061 patients who underwent CTO PCI of 18,941 target vessels. The overall angiographic success rate ranged between 41.2% and 100% with pooled estimate of 77% (95% CI: 74.3% to 79.6%). Major adverse cardiovascular event (MACE) was reported in 15,718 patients ranging from 0% to 19.4% with pooled estimate of 3.1% (95% CI: 2.4% to 3.7%). The most commonly observed complications were perforation (2.9%, 95% CI: 2.2% to 3.6%) and contrast nephropathy (3.8%, 95% CI: 2.4% to 5.3%) on the other hand emergent CABG, stroke and radiation injury were the least common complications with rates of 0.1%, <0.01%, and <0.01%, respectively. Compared with successful procedures, unsuccessful procedures had significantly higher rates of death

(1.5% vs. 0.4%), stroke (0.4% vs. 0.07%), perforation (10.7% vs. 3.7%), and tamponade (1.7% vs. 0%).

Christakopoulos et al. analyzed 25 observational studies published from 1990 to 2014 that reported on the clinical outcomes of patients who underwent CTO PCI (56). Out of the 29,315 CTO PCI procedures performed on 28,486 patients, 20,778 were successful and 8,537 were unsuccessful. Procedural success was 71% (range 51% to 87%). After a mean follow up period of 3.11 years, compared with unsuccessful CTO PCI, successful CTO PCI was associated with lower mortality (OR 0.52, 95% CI: 0.43 to 0.63), less residual angina (OR 0.38, 95% CI: 0.24 to 0.60), lower risk of stroke (OR 0.72, 95 CI: 0.60 to 0.88), less need for CABG (OR 0.18 95% CI: 0.14 to 0.22), lower risk for MACE (OR 0.55, 95% CI: 0.43 to 0.71). Successful CTO PCI is associated with improved clinical outcomes regardless of the revascularization technique used (balloon angioplasty, bare metal stent, or drug eluting stent).

Outcome of CTO PCI in the elderly

Few studies have attempted to compare the procedural and long-term outcomes of CTO PCI in older and younger patients (19). Tanaka et al. conducted a single centered observational study to analyze and compare the safety and efficacy of CTO PCI between patients aged ≥ 75 years and those aged <75 years (57). In a retrospective analysis that included 300 patients (217 in the younger group, 67 patients over 75 years), he found no statistically significant difference in procedural success rate between the elderly and the younger patients. Successful PCI was also associated with significant improvements in cardiovascular death rates and was a significant predictor of cardiac survival in older patients (57). Another multinational study evaluated the procedural success rates and long-term clinical outcome of successful versus failed CTO revascularization in patients ≥ 75 years (58). Of the 1,791 patients who underwent CTO PCI, a total of 213 patients were ≥ 75 years-old. Procedural success among older patients was similar with that achieved in younger patients. Older patients with successful PCI had significantly lower risk for major adverse cardiac events (MACE [all-cause mortality, MI and need for CABG]) and the reduction in MACE was significantly greater as compared with younger patients.

SPECIFIC OBJECTIVES

The primary objectives of this project are to:

1. Determine the technical and in-hospital outcomes of patients in three age categories (< 65 years, ≥ 65 years and < 75 years, ≥ 75 years)
2. Compare the technical and in-hospital outcomes of patients ≥ 75 years with the younger age groups (< 65 years, ≥ 65 years and < 75 years)

SIGNIFICANCE OF THE STUDY

As the aging population expands, more and more elderly patients with CTO are likely to be referred and considered for PCI in daily practice. However, the risks and benefits of CTO PCI among elderly patients have received limited study. Advanced age may be associated with higher lesion complexity and higher risk patient characteristics that may affect both the short and long-term outcomes of CTO PCI. Doing more research in this area will help narrow the knowledge gap and assist practitioners in making better treatment decisions in this complex and high-risk, yet continually growing group of patients.

MATERIALS AND METHODS

This practicum project consisted of a retrospective review of medical records of all consecutive patients who underwent CTO PCI and were entered into the Prospective Global Registry for the Study of Chronic Total Occlusion Intervention (PROGRESS CTO) registry. The goal of this multicenter, investigator-initiated registry is to collect information on treatment strategies and outcomes of consecutive patients undergoing CTO PCI among various participating centers (59). The registry receives and catalogs datasets with pre-specified definitions from participating hospitals in the United States. Datasets pertaining to patient characteristics, clinical features, angiographic and procedural details and in-hospital outcomes are being collected and entered into the registry since January 2012. For collecting and managing its dataset, the registry uses REDCap, which is a self-managed, secure, web-based tool that is designed to support data collection strategies for research purposes (60). This study utilized data from the following 11 CTO PCI centers: VA North Texas Health Care System, Dallas, Texas; Piedmont Heart Institute, Atlanta Georgia; VA San Diego Healthcare System, San Diego, California; Massachusetts General Hospital, Boston, Massachusetts; Columbia University, New York, New York; Henry Ford Hospital, Detroit, Michigan; Peace Health St. Joseph Medical Center, Bellingham, Washington; Torrance Memorial Center, Torrance, California; St. Luke's Health System's Mid-America Heart Institute, Kansas City, Missouri; Medical Center of the Rockies, Loveland, Colorado, and Appleton Cardiology, Appleton, Wisconsin.

All patients who met the inclusion and exclusion criteria and were entered in the registry from January 2012 to September 2015 were included in the study. Patient information pertaining to demographic features, medical history, clinical presentation, coronary angiographic data, procedural characteristics and in-hospital outcomes were exported from REDCap into JMP software version 11 (SAS Institute, Cary, North Carolina) for analysis (See below for list and definition of variables). Prior to data analysis, the following inclusion and exclusion criteria were used for identifying patients that satisfy the criteria for enrollment in this study.

Inclusion criteria

- All patients who underwent CTO PCI from January 2012 to September 2015 at participating centers

Exclusion criteria

- Patients with missing date of birth
- Patients with missing record of technical success

Variable list and definition

Clinical variables

The following clinical variables were examined: age, sex, ethnicity, current smoking, hypertension, diabetes mellitus, dyslipidemia, prior heart failure, prior MI, prior CABG, prior PCI, prior stroke, peripheral artery disease, left ventricular ejection fraction, baseline creatinine, body mass index, angina (stable, unstable, silent ischemia).

Angiographic variables

The following angiographic variables were examined: CTO vessel, CTO length, moderate/severe calcification, moderate/severe tortuosity, prior failed CTO PCI, bridging collaterals, interventional collaterals, proximal cap ambiguity, blunt stump, CTO age, vessel diameter, J-CTO (Multicenter CTO Registry of Japan) score.

Procedural variables

The following procedural variables were examined: Technical success, procedural success, successful approach (antegrade wiring, antegrade dissection and re-entry, retrograde), stenting, fluoroscopic time, contrast volume, air kerma radiation dose, total procedural time, death, myocardial infarction, emergency PCI on target vessel, emergency CABG, cardiac tamponade, stroke, in-hospital MACE.

Definitions

- CTO is defined as a total coronary artery occlusion of at least 3 month duration with thrombolysis in myocardial infarction (TIMI) grade 0 flow (23).
- Estimation of occlusion duration is based on first onset of anginal symptoms, prior history of myocardial infarction in the target vessel territory, or comparison with a prior angiogram (15).
- Assessment of calcification is done by angiography and graded as mild (spots), moderate (involving ≤50% of the reference lesion diameter) and severe (involving >50% of the reference lesion diameter) (61).

- Moderate proximal vessel tortuosity is defined as the presence of at least 2 bends >70 degrees or 1 bend >90 degrees and severe tortuosity as 2 bends >90 degrees or 1 bend >120 degrees in the CTO vessel (61).
- Interventional collaterals refers to the presence of collateral channels that can be accessed and crossed using a wire and micro-catheter safely, that enter the distal vessel remote from the distal cap and facilitate retrograde wire escalation or retrograde dissection re-entry strategies (62).
- An ambiguous proximal cap refers to one where there are multiple branches, often collaterals, a flush occlusion and uncertainty as to the initial vessel course (62).
- J-CTO score utilizes 5 independent predictors: 1) calcification 2) bend >45° in the CTO segment 3) blunt proximal cap 4) length of occluded segment >20 mm 5) previously failed attempt (63). The CTO case complexity is stratified as easy (J-CTO score = 0), intermediate (score = 1), difficult (score = 2) and very difficult (scores = 3–5).
- CTO PCI technical success is defined as successful CTO revascularization with achievement of <30% residual diameter stenosis within the treated segment and restoration of TIMI grade 3 antegrade flow (23).
- CTO PCI procedural success is defined as technical success without in-hospital MACE (23).
- In-hospital MACE includes any of the following adverse events prior to hospital discharge: death from any cause, Q-wave myocardial infarction, recurrent angina requiring urgent repeat target vessel revascularization with PCI or CABG, tamponade requiring pericardiocentesis or surgery, or stroke (23).

- Q-wave MI is defined as cardiac enzymes (creatinine kinase) elevation of more than 3 times the normal value with development of Q-wave following the PCI (54).
- Urgent revascularization is defined as target vessel repeat PCI within 24 h or urgent CABG (54).
- Stroke is defined as ischemic or hemorrhagic stroke occurring during the patient hospitalization (64).

Sampling method and sample size

A convenient sampling method was used to enroll all consecutive patients with CTO PCI within the time period of January 2012 to September 2015. A total of 1,195 patients who satisfied the inclusion and exclusion criteria were included. Forty-five variables (see above for list of variables) were used to do statistical analyses that were useful in answering the primary objective of the study.

Statistical analysis

Data was first examined for inconsistencies and errors and later analyzed using JMP 11 software (SAS Institute, Cary, North Carolina). The variable age was recoded into three different age categories as follows: < 65 years, ≥ 65 years and < 75 years, ≥ 75 years. Initially the data was summarized using descriptive statistics. Continuous variables were presented as mean ± standard deviation and compared using student t statistics when the data is normally distributed or Wilcoxon rank-sum test was used for variables with skewed distribution. Categorical variables were presented as percentages and compared using chi square test or Fisher's exact test when the expected value in each cell is less than 5. Clinical characteristics, angiographic features, procedural findings and in-hospital outcomes were compared between the three age groups. All results with $p < 0.05$ were considered to be statistically significant.

Ethical clearance

IRB approval was obtained from the IRB at the UNT Health Science Center; additionally approvals were obtained from the coordinating center's IRB at University of Texas Southwestern, as well as the respective IRBs at the participating centers.

RESULTS

During the study period, a total of 1,195 consecutive patients who underwent CTO PCI and satisfied the inclusion and exclusion criteria were included in the study. The baseline clinical characteristics of the study population are listed in Table 1. The mean age of the total population was 66±10 years and most of the study participants were men (86.1%, 86.9%, 77.2% for < 65 years, ≥ 65 years and < 75 years, ≥ 75 years respectively). Increasing age was associated with high prevalence of prior stroke (7.6% vs 12.6% vs 17.2%, p<0.001) and hypertension (88.1% vs 88.7% vs 94.0%, p=0.042) although history of previous MI and heart failure was not significantly different between age groups. As compared with the younger age groups, the elderly (≥75 years) were more likely to have previous CABG (25.2% vs 39.8% vs 45.5%, p<0.001) but were less likely to have had a previous PCI, diabetes mellitus and peripheral arterial disease. Elderly patients are also less likely to be current smokers. Even though a higher proportion of the elderly had hyperlipidemia, this was not found to be statistically significantly different when compared with the other age groups.

Table 1 Baseline clinical characteristics of the study patients

Variable (%) Clinical Characteristics	Age <65 (Years) n=541	Age ≥65 and <75 (Years) n=421	Age ≥75 (Years) n=233	*p*
Age (years)*	56.7±6.7	69±2.9	79.6±3.7	0.001
Men	86.1	86.9	77.2	0.002
Hypertension	88.1	88.7	94	0.042
Hyperlipidemia	93.1	93.8	97.4	0.056
Diabetes Mellitus	46.2	46.2	41.8	0.489
Smoking	36.4	25.7	14.6	0.001
Heart failure	27.1	28.8	30.4	0.623
History of MI	41.9	42.3	43.7	0.898
History of CABG	25.2	39.8	45.5	0.001
History of stroke	7.6	12.6	17.2	0.001
Prior PCI	63.9	60.6	62.2	0.571
Peripheral arterial disease	13.3	18.7	17.2	0.066

CABG, coronary artery bypass graft surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention. * Values are mean ± standard deviation

The angiographic characteristics of the three age groups are listed in Table 2. Most CTOs were located in the right coronary artery with no significant difference in the distribution of the treated target vessels between the age groups. However, elderly patients were more likely to have moderate/severe calcification (48.4% vs 59.8% vs 75%, $p<0.001$) and have interventional collaterals (58.6% vs 60% vs 71.3%, $p=0.014$) when compared with their younger counterparts. There was no significant difference between the three age groups regarding CTO length, moderate/severe tortuosity, proximal cap ambiguity, prior CTO PCI failure, in-stent restenosis, and J-CTO score.

Table 2 Angiographic characteristics of the study lesions according to age group

Variable **Clinical Characteristics (%)**	**Age <65** **(Years)** **n=550**	**Age ≥65 and <75** **(Years)** **n=429**	**Age ≥75** **(Years)** **n=237**	***p***
CTO Target vessel				
RCA	60.4	54.2	53.6	
LCX	17.8	23.9	19.1	0.067
LAD	21.9	21.9	97.4	
CTO length (mm)*	30 (20-50)	30 (20-50)	30 (20-40)	0.691
Interventional collaterals	58.6	60	71.3	0.014
Moderate/Severe calcification	48.4	59.8	75	0.001
Moderate/Severe tortuosity	36.6	36.7	32.2	0.487
Proximal gap ambiguity	29.8	31.4	28.7	0.812
Prior CTO PCI failure	18.5	17.1	17.4	0.844
In-stent restenosis	14.8	16	12.9	0.578
J-CTO score*	2.4±1.3	2.6±1.16	2.6±1.15	0.060

CTO, chronic total occlusion; LAD, left anterior descending artery; LCX, left circumflex artery; PCI percutaneous coronary intervention; RCA, right coronary artery. *Values are mean ± standard deviation or median (interquartile range).

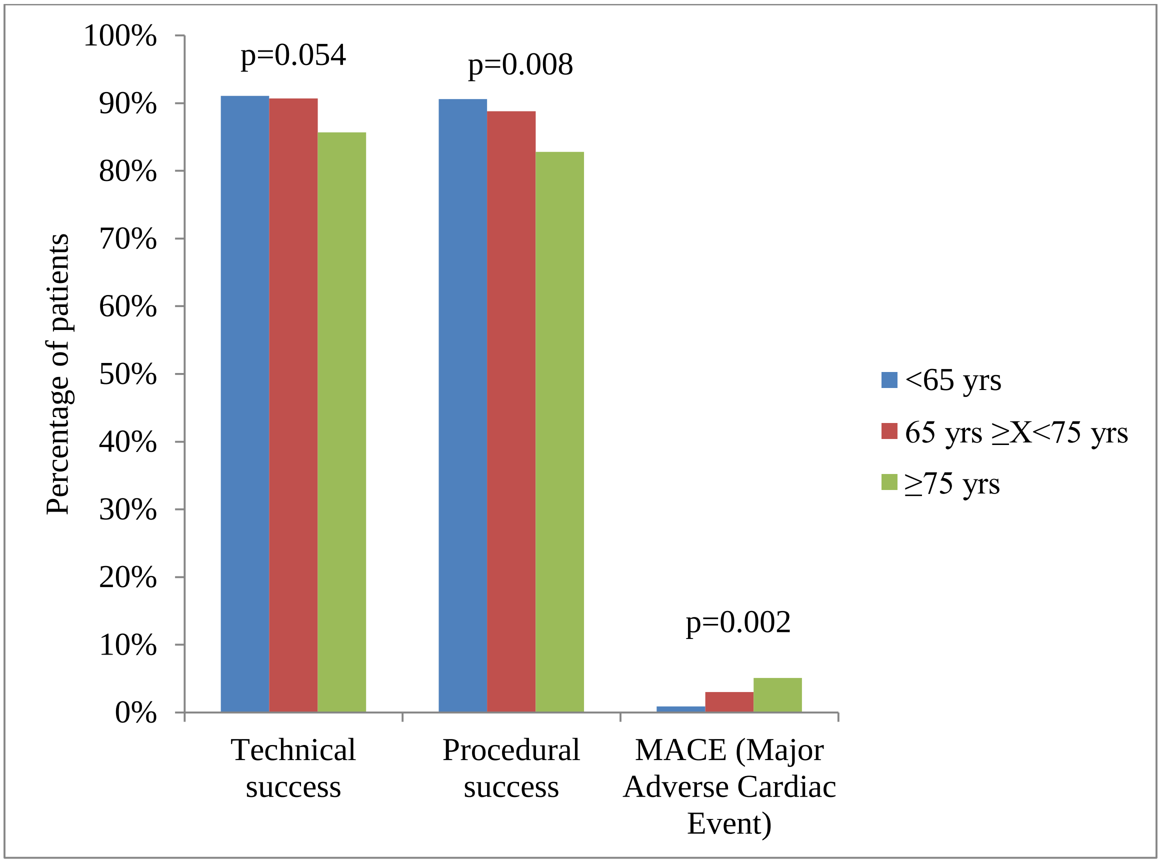
The overall technical and procedural success rate was 89.9% and 88.5%, respectively (Table 3). Technical success rate was similar in all age groups (91.1% vs 90.7% vs 85.7%, p=0.054), however procedural success rate was lower in the elderly when compared to the younger age groups (90.6% vs 88.8% vs 82.3%, p=0.008; Table 3, Figure 1). The overall in-hospital MACE rate was 2.5% with significantly higher rates observed in the elderly as compared with the other age groups (0.9% vs 3.0% vs 5.1%, p=0.002). The occurrence of death, MI, stroke and the performance of emergency CABG or PCI were comparable in all age groups but a significantly higher proportion of the elderly had emergency pericardiocentesis when compared with the younger age groups (0% vs 0.7% vs 2.2%, p=0.004). No significant difference was observed in procedure time, contrast volume and air kerma fluoroscopy dose between the three age groups.

Table 3 Procedural characteristics and outcomes according to age group

Variable (%)	**Age <65 (Years)**	**Age ≥65 and <75 (Years)**	**Age ≥75 (Years)**	***p***
Contrast Volume (ml)*	260 (197.5-363)	270 (200-364)	250 (190-350)	0.306
Air Kerma Fluoroscopy Dose (Gray)*	3.4 (2-5.3)	3.5 (2.2-5.6)	3.2 (1.8-5.4)	0.443
Procedure Time (min)*	126 (81-184)	127 (91-193)	130 (85.8-196.8)	0.298
Technical Success	91.1	90.7	85.7	0.054
Procedural Success	90.6	88.8	82.8	0.008
In-hospital MACE	0.9	3.0	5.1	0.002
Death	0.2	0.2	1.3	0.072
Myocardial Infarction	0.4	1.4	2.2	0.065
Stroke	0.2	0.5	0.4	0.714
Emergency Re-PCI	0.4	0.5	0	0.591
Emergency CABG	-	-	-	-
Emergency Pericardiocentesis	0	0.7	2.2	0.004

CABG, coronary artery bypass graft surgery; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention. * Values are median (interquartile range).

Figure 1 Comparison of technical, procedural and MACE rate between three age groups



DISCUSSION

The result of our study demonstrated that CTO PCI can be performed successfully in most elderly patients, however procedural success is lower as compared with younger patients and the incidence of MACE is higher.

Elderly patients are more likely to have extensive CAD and complex coronary lesions (65, 66). This condition is further complicated by the presence of multiple comorbidities such as hypertension, diabetes, stroke and peripheral artery diseases, all of which identified as independent determinants of death in elderly patients undergoing PCI (67-69). Indeed, low success rate and high rate of complication were associated in elderly patients undergoing PCI prior to the stenting era (70-72). The advent of drug eluting stents, advances in PCI technology and antithrombotic medications have drastically improved the outcome of PCI in the elderly (73-77). Success rate ranging from 69% to 77% were reported from centers that opened CTOs in elderly patients with high level of comorbidities (78-80). Our technical success rate of 85.7% in patients aged ≥75 years is higher than the above reports and is comparable to the success rate in younger age groups (91.1% vs 90.7% vs 85.7% for < 65 years, ≥ 65 years and < 75 years, ≥ 75 years respectively, p=0.054). Reports from two single institutions in Japan and France showed similar success rate in the elderly and younger age groups (Japan, 78.2% vs 74.3% for <75 and ≥75 respectively, p=0.41; France, 79% vs 77% for <75 and ≥75, respectively, p=0.66) however, lower success rate were recorded for the ≥75 age group when compared to our result (79, 80).

The higher success rates reported from our registry may be related to participation of more experienced high volume operators in the centers included in our study.

In-hospital mortality has significantly improved in the elderly who undergo PCI. Up to 19% of octogenarians experienced in-hospital death in the 1980's (81), however, mortality rapidly declined to 2-10% during subsequent years (68, 82, 83). A temporal trend analysis done by Singh et al. documented a significant downtrend in PCI related in-hospital mortality between 2001 and 2006 with the greatest reduction seen in the elderly (84). In-hospital mortality rates varying from 1.1 to 4.6 (69, 85-88) were recorded despite higher prevalence of comorbid and angiographic risks (84). Our in-hospital mortality rate of 1.3% is in line with the above finding and comparable to the younger age groups (0.5% vs 0.5% vs 1.3%, $p < 0.072$) even though our elderly patients were more likely to be hypertensive, to have prior stroke and CABG as well as have moderately and/or severely calcified lesions.

Previous reports show comparatively higher rate of in-hospital MACE in elderly patients when compared to younger age groups (68, 89-94). This finding was found to be true despite differences in defining MACE and age categories in different publications. In our study, MACE (comprising of death, MI, stroke, emergency PCI, emergency CABG and emergency pericardiocentesis) progressively increased as age increased and the difference in MACE rate between the age groups is found to be statistically significant (0.9% vs 3.0% vs 5.1%, $p=0.002$). Recent report from the German Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK) registry indicated an overall significantly higher MACE rate in patients ≥75 years undergoing elective PCI (0.6% vs 0.9% for <75 and ≥75 respectively) (95). The higher risk for MACE among older patients in our registry (5.1%) was in part driven by higher risk for emergency pericardiocentesis, suggesting that CTO PCI in the elderly may be associated with higher risk for coronary perforation.

LIMITATIONS OF THE STUDY

This is a retrospective study and selection bias might affect the final outcome of elderly patients included in this study. Furthermore, the registry collected data only on in-hospital outcome of patients included in the registry and we are not able to evaluate long-term outcomes. Inter-observer differences in interpreting clinical and angiographic variables might lead to variability in outcome interpretation and might have affected our analysis. There was no independent adjudication of angiographic findings and clinical outcomes.

CONCLUSION

Our data shows that CTO PCI can be performed with high success rates among elderly patients, but procedural success is lower than what can be achieved in younger patients, whereas the risk for MACE is higher. This information will be useful when discussing the risk/benefit ratio among elderly patients who are potential candidates for CTO PCI.

CHAPTER III

III. INTERNSHIP EXPERIENCE

My internship site was at the Dallas Veterans Affairs (VA) Medical Center, VA North Texas Health Care System. Dr. Emmanouil Brilakis is the Director of Cardiac Catheterization Laboratories at VA North Texas Health Care System, and Professor of Medicine at University of Texas Southwestern Medical School. Dr. Brilakis is Principal Investigator of an active clinical trial group and his areas of interest include chronic total occlusions, prevention and treatment of saphenous vein graft disease, antiplatelet treatment optimization post coronary stenting and radiation safety in the catheterization laboratory. The team consists of six research coordinators, one research assistant, three research fellows, and one team leader (Dr. Bavana Rangan). They are currently participating in >25 clinical trials, which include Industry Sponsored, VA funded and Investigator-Initiated single and multicenter trials.

During my internship, I had hands on practical experience in the following key areas of clinical research:

- Screening, recruiting and enrolling study participants
- Obtaining informed consent
- Collecting and documenting clinical research data
- Interviewing study participants, taking vital signs and performing ECG
- Handling and dispensing of study medication
- Scheduling follow up visits and procedures

- Collecting, labeling, processing, storage or shipment of clinical specimens
- Entering data in EDC and ensuring accuracy of data
- Generating and resolving queries
- Maintaining databases
- Compiling pre-study files
- Creating and maintaining study files
- Creating and maintaining regulatory and IRB binders
- Preparing documents for initial and continuing IRB submission
- Preparing modification to protocol change form
- AE and SAE reporting
- Completing and submission of safety report to IRB
- Communicating with IRB and sponsors
- Study initiation, completion and monitoring visits
- Maintaining study master list
- Maintaining study personnel list
- Maintaining ECG and angiography core lab database
- Insuring the accurate completion of informed consent before submission to RCO
- Reviewing and comprehending protocol including proceedings, timelines and inclusion and exclusion criteria
- Budgeting clinical trial

In addition to the above skills, I have also developed working knowledge in the following areas:

- Proposal development

- Data analysis
- Abstract, thesis and manuscript writing

Additionally, working with diverse group of people from different background and experience has helped me to develop my interpersonal skills and gave me ample opportunity to learn from an environment rich in knowledge and expertise.

Finally, as part of my internship experience, I submitted and was accepted to present in poster format, the abstract of my study results at the American College of Cardiology 65th Annual Scientific Session, Chicago, IL on April 2, 2016. The accepted abstract will also be published in the Journal of the American College of Cardiology April 2016 edition.

REFERENCES

(1) Kahn JK. Angiographic suitability for catheter revascularization of total coronary occlusions in patients from a community hospital setting. Am Heart J 1993 Sep;126(3 Pt 1):561-564.

(2) Christofferson RD, Lehmann KG, Martin GV, Every N, Caldwell JH, Kapadia SR. Effect of chronic total coronary occlusion on treatment strategy. Am J Cardiol 2005 May 1;95(9):1088-1091.

(3) Fefer P, Knudtson ML, Cheema AN, Galbraith PD, Osherov AB, Yalonetsky S, et al. Current perspectives on coronary chronic total occlusions: the Canadian Multicenter Chronic Total Occlusions Registry. J Am Coll Cardiol 2012 Mar 13;59(11):991-997.

(4) Puma JA, Sketch MH,Jr, Tcheng JE, Harrington RA, Phillips HR, Stack RS, et al. Percutaneous revascularization of chronic coronary occlusions: an overview. J Am Coll Cardiol 1995 Jul;26(1):1-11.

(5) Strauss BH, Shuvy M, Wijeysundera HC. Revascularization of chronic total occlusions: time to reconsider? J Am Coll Cardiol 2014 Sep 23;64(12):1281-1289.

(6) Grantham JA, Jones PG, Cannon L, Spertus JA. Quantifying the early health status benefits of successful chronic total occlusion recanalization: Results from the FlowCardia's Approach to Chronic Total Occlusion Recanalization (FACTOR) Trial. Circ Cardiovasc Qual Outcomes 2010 May;3(3):284-290.

(7) Hoye A, van Domburg RT, Sonnenschein K, Serruys PW. Percutaneous coronary intervention for chronic total occlusions: the Thoraxcenter experience 1992-2002. Eur Heart J 2005 Dec;26(24):2630-2636.

(8) Joyal D, Afilalo J, Rinfret S. Effectiveness of recanalization of chronic total occlusions: a systematic review and meta-analysis. Am Heart J 2010 Jul;160(1):179-187.

(9) Olivari Z, Rubartelli P, Piscione F, Ettori F, Fontanelli A, Salemme L, et al. Immediate results and one-year clinical outcome after percutaneous coronary interventions in chronic total occlusions: data from a multicenter, prospective, observational study (TOAST-GISE). J Am Coll Cardiol 2003 May 21;41(10):1672-1678.

(10) Suero JA, Marso SP, Jones PG, Laster SB, Huber KC, Giorgi LV, et al. Procedural outcomes and long-term survival among patients undergoing percutaneous coronary intervention of a chronic total occlusion in native coronary arteries: a 20-year experience. J Am Coll Cardiol 2001 Aug;38(2):409-414.

(11) Kirschbaum SW, Baks T, van den Ent M, Sianos G, Krestin GP, Serruys PW, et al. Evaluation of left ventricular function three years after percutaneous recanalization of chronic total coronary occlusions. Am J Cardiol 2008 Jan 15;101(2):179-185.

(12) Saito S, Tanaka S, Hiroe Y, Miyashita Y, Takahashi S, Satake S, et al. Angioplasty for chronic total occlusion by using tapered-tip guidewires. Catheter Cardiovasc Interv 2003 Jul;59(3):305-311.

(13) Kimura M, Katoh O, Tsuchikane E, Nasu K, Kinoshita Y, Ehara M, et al. The efficacy of a bilateral approach for treating lesions with chronic total occlusions the CART (controlled antegrade and retrograde subintimal tracking) registry. JACC Cardiovasc Interv 2009 Nov;2(11):1135-1141.

(14) Rathore S, Matsuo H, Terashima M, Kinoshita Y, Kimura M, Tsuchikane E, et al. Procedural and in-hospital outcomes after percutaneous coronary intervention for chronic total occlusions of coronary arteries 2002 to 2008: impact of novel guidewire techniques. JACC Cardiovasc Interv 2009 Jun;2(6):489-497.

(15) Michael TT, Karmpaliotis D, Brilakis ES, Fuh E, Patel VG, Mogabgab O, et al. Procedural outcomes of revascularization of chronic total occlusion of native coronary arteries (from a multicenter United States registry). Am J Cardiol 2013 Aug 15;112(4):488-492.

(16) Brilakis ES, Banerjee S, Karmpaliotis D, Lombardi WL, Tsai TT, Shunk KA, et al. Procedural outcomes of chronic total occlusion percutaneous coronary intervention: a report from the NCDR (National Cardiovascular Data Registry). JACC Cardiovasc Interv 2015 Feb;8(2):245-253.

(17) Brenes-Salazar JA, Forman DE. Advances in percutaneous coronary interventions for elderly patients. Prog Cardiovasc Dis 2014 Sep-Oct;57(2):176-186.

(18) Forman D, Wenger NK. What do the recent American Heart Association/American College of Cardiology Foundation Clinical Practice Guidelines tell us about the evolving management of coronary heart disease in older adults? J Geriatr Cardiol 2013 Jun;10(2):123-128.

(19) Yeh RW, Drachman DE. Coronary chronic total occlusion in the elderly: demographic inevitability, treatment uncertainty. Catheter Cardiovasc Interv 2013 Jul 1;82(1):93-94.

(20) CDC N. Underlying Cause of Death 1999-2013. 2015; Available at: http://wonder.cdc.gov/ucd-icd10.html. Accessed 06/19, 2015.

(21) Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005 Jun 28;111(25):3481-3488.

(22) Hoebers LP, Claessen BE, Dangas GD, Ramunddal T, Mehran R, Henriques JP. Contemporary overview and clinical perspectives of chronic total occlusions. Nat Rev Cardiol 2014 Aug;11(8):458-469.

(23) Stone GW, Kandzari DE, Mehran R, Colombo A, Schwartz RS, Bailey S, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part I. Circulation 2005 Oct 11;112(15):2364-2372.

(24) Jeroudi OM, Alomar ME, Michael TT, El Sabbagh A, Patel VG, Mogabgab O, et al. Prevalence and management of coronary chronic total occlusions in a tertiary Veterans Affairs hospital. Catheter Cardiovasc Interv 2014 Oct 1;84(4):637-643.

(25) Meier B. Total coronary occlusion: a different animal? J Am Coll Cardiol 1991 May;17(6 Suppl B):50B-57B.

(26) Kramer MC, van der Wal AC, Koch KT, Rittersma SZ, Li X, Ploegmakers HP, et al. Histopathological features of aspirated thrombi after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. PLoS One 2009 Jun 5;4(6):e5817.

(27) Jaffe R, Leung G, Munce NR, Thind AS, Leong-Poi H, Anderson KJ, et al. Natural history of experimental arterial chronic total occlusions. J Am Coll Cardiol 2009 Mar 31;53(13):1148-1158.

(28) Srivatsa SS, Edwards WD, Boos CM, Grill DE, Sangiorgi GM, Garratt KN, et al. Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. J Am Coll Cardiol 1997 Apr;29(5):955-963.

(29) Finn AV, Kolodgie FD, Nakano M, Virmani R. The differences between neovascularization of chronic total occlusion and intraplaque angiogenesis. JACC Cardiovasc Imaging 2010 Aug;3(8):806-810.

(30) Kinoshita I, Katoh O, Nariyama J, Otsuji S, Tateyama H, Kobayashi T, et al. Coronary angioplasty of chronic total occlusions with bridging collateral vessels: immediate and follow-up outcome from a large single-center experience. J Am Coll Cardiol 1995 Aug;26(2):409-415.

(31) Katsuragawa M, Fujiwara H, Miyamae M, Sasayama S. Histologic studies in percutaneous transluminal coronary angioplasty for chronic total occlusion: comparison of tapering and abrupt types of occlusion and short and long occluded segments. J Am Coll Cardiol 1993 Mar 1;21(3):604-611.

(32) Sionis DG, Tolis VA, Michalis LA. Chronic Total Coronary Occlusions: A Review of their Special Features and the Existing Techniques of Percutaneous Treatment. Hellenic J Cardiol 2003 Jan (44):136-142.

(33) Brilakis ES, Karmpaliotis D, Werner GS, Spratt JC, Uretsky BF, Luna M, et al. Developments in coronary chronic total occlusion percutaneous coronary interventions: 2014 state-of-the-art update. J Invasive Cardiol 2014 Jun;26(6):261-266.

(34) Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodeling in coronary atherosclerosis. Circulation 2002 Jan 22;105(3):297-303.

(35) Sakakura K, Nakano M, Otsuka F, Yahagi K, Kutys R, Ladich E, et al. Comparison of pathology of chronic total occlusion with and without coronary artery bypass graft. Eur Heart J 2014 Jul 1;35(25):1683-1693.

(36) Eefting FD, Pasterkamp G, Clarijs RJ, van Leeuwen TG, Borst C. Remodeling of the atherosclerotic arterial wall: a determinant of luminal narrowing in human coronary arteries. Coron Artery Dis 1997 Jul;8(7):415-421.

(37) Shah PB. Management of coronary chronic total occlusion. Circulation 2011 Apr 26;123(16):1780-1784.

(38) Werner GS, Gitt AK, Zeymer U, Juenger C, Towae F, Wienbergen H, et al. Chronic total coronary occlusions in patients with stable angina pectoris: impact on therapy and outcome in present day clinical practice. Clin Res Cardiol 2009 Jul;98(7):435-441.

(39) Claessen BE, Chieffo A, Dangas GD, Godino C, Lee SW, Obunai K, et al. Gender differences in long-term clinical outcomes after percutaneous coronary intervention of chronic total occlusions. J Invasive Cardiol 2012 Oct;24(10):484-488.

(40) Stone GW, Reifart NJ, Moussa I, Hoye A, Cox DA, Colombo A, et al. Percutaneous recanalization of chronically occluded coronary arteries: a consensus document: part II. Circulation 2005 Oct 18;112(16):2530-2537.

(41) Brilakis ES. Manual of Coronary Total Occlusion Interventions. A Step by Step Approach. 1st ed. MA, USA: Elsevier Inc.; 2014.

(42) Valenti R, Vergara R, Migliorini A, Parodi G, Carrabba N, Cerisano G, et al. Predictors of reocclusion after successful drug-eluting stent-supported percutaneous coronary intervention of chronic total occlusion. J Am Coll Cardiol 2013 Feb 5;61(5):545-550.

(43) Brilakis ES, Grantham JA, Thompson CA, DeMartini TJ, Prasad A, Sandhu GS, et al. The retrograde approach to coronary artery chronic total occlusions: a practical approach. Catheter Cardiovasc Interv 2012 Jan 1;79(1):3-19.

(44) Pershad A, Eddin M, Girotra S, Cotugno R, Daniels D, Lombardi W. Validation and incremental value of the hybrid algorithm for CTO PCI. Catheter Cardiovasc Interv 2014 Oct 1;84(4):654-659.

(45) Sirnes PA, Myreng Y, Molstad P, Bonarjee V, Golf S. Improvement in left ventricular ejection fraction and wall motion after successful recanalization of chronic coronary occlusions. Eur Heart J 1998 Feb;19(2):273-281.

(46) Aziz S, Stables RH, Grayson AD, Perry RA, Ramsdale DR. Percutaneous coronary intervention for chronic total occlusions: improved survival for patients with successful

revascularization compared to a failed procedure. Catheter Cardiovasc Interv 2007 Jul 1;70(1):15-20.

(47) Bell MR, Berger PB, Bresnahan JF, Reeder GS, Bailey KR, Holmes DR,Jr. Initial and long-term outcome of 354 patients after coronary balloon angioplasty of total coronary artery occlusions. Circulation 1992 Mar;85(3):1003-1011.

(48) Melchior JP, Meier B, Urban P, Finci L, Steffenino G, Noble J, et al. Percutaneous transluminal coronary angioplasty for chronic total coronary arterial occlusion. Am J Cardiol 1987 Mar 1;59(6):535-538.

(49) DiSciascio G, Vetrovec GW, Cowley MJ, Wolfgang TC. Early and late outcome of percutaneous transluminal coronary angioplasty for subacute and chronic total coronary occlusion. Am Heart J 1986 May;111(5):833-839.

(50) Tan KH, Sulke N, Taub NA, Watts E, Karani S, Sowton E. Determinants of success of coronary angioplasty in patients with a chronic total occlusion: a multiple logistic regression model to improve selection of patients. Br Heart J 1993 Aug;70(2):126-131.

(51) Stone GW, Rutherford BD, McConahay DR, Johnson W.L.Jr., Giorgi LV, Ligon RW, et al. Procedural outcome of angioplasty for total coronary artery occlussion: An analysis of 971 lesions in 905 patients. 1990;15(4):849-856.

(52) Maiello L, Colombo A, Gianrossi R, Mutinelli MR, Bouzon R, Thomas J, et al. Coronary angioplasty of chronic occlusions: factors predictive of procedural success. Am Heart J 1992 Sep;124(3):581-584.

(53) Stewart JT, Denne L, Bowker TJ, Mulcahy DA, Williams MG, Buller NP, et al. Percutaneous transluminal coronary angioplasty in chronic coronary artery occlusion. J Am Coll Cardiol 1993 May;21(6):1371-1376.

(54) Rathore S, Matsuo H, Terashima M, Kinoshita Y, Kimura M, Tsuchikane E, et al. Procedural and in-hospital outcomes after percutaneous coronary intervention for chronic total occlusions of coronary arteries 2002 to 2008: impact of novel guidewire techniques. JACC Cardiovasc Interv 2009 Jun;2(6):489-497.

(55) Patel VG, Brayton KM, Tamayo A, Mogabgab O, Michael TT, Lo N, et al. Angiographic success and procedural complications in patients undergoing percutaneous coronary chronic total occlusion interventions: a weighted meta-analysis of 18,061 patients from 65 studies. JACC Cardiovasc Interv 2013 Feb;6(2):128-136.

(56) Christakopoulos GE, Christopoulos G, Carlino M, Jeroudi OM, Roesle M, Rangan BV, et al. Meta-analysis of clinical outcomes of patients who underwent percutaneous coronary interventions for chronic total occlusions. Am J Cardiol 2015 May 15;115(10):1367-1375.

(57) Tanaka Y, Takeshita S, Takahashi S, Matsumi J, Mizuno S, Yamanaka F, et al. Comparison of short- and long-term outcomes of percutaneous coronary intervention for chronic total occlusions between patients aged >/=75 years and those aged <75 years. Am J Cardiol 2013 Sep 15;112(6):761-766.

(58) Hoebers LP, Claessen BE, Dangas GD, Park SJ, Colombo A, Moses JW, et al. Long-term clinical outcomes after percutaneous coronary intervention for chronic total occlusions in elderly

patients (>/=75 years): five-year outcomes from a 1,791 patient multi-national registry. Catheter Cardiovasc Interv 2013 Jul 1;82(1):85-92.

(59) ClinicalTrial.gov. Prospective Global Registry for the STudy of Chronic Total Occlusion Intervention (PROGRESS CTO). 2016; Available at: https://clinicaltrials.gov/ct2/show/NCT02061436?term=PROGRESS+CTO&rank=1. Accessed 01/09, 2016.

(60) Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009 Apr;42(2):377-381.

(61) Christopoulos G, Karmpaliotis D, Alaswad K, Yeh RW, Jaffer FA, Wyman RM, et al. Application and outcomes of a hybrid approach to chronic total occlusion percutaneous coronary intervention in a contemporary multicenter US registry. Int J Cardiol 2015;198(1):222-228.

(62) Hanratty C, Walsh S. Procedure planning: anatomical determinants of strategy. Curr Cardiol Rev 2014 May;10(2):108-119.

(63) Morino Y, Abe M, Morimoto T, Kimura T, Hayashi Y, Muramatsu T, et al. Predicting successful guidewire crossing through chronic total occlusion of native coronary lesions within 30 minutes: the J-CTO (Multicenter CTO Registry in Japan) score as a difficulty grading and time assessment tool. JACC Cardiovasc Interv 2011 Feb;4(2):213-221.

(64) Yamamoto E, Natsuaki M, Morimoto T, Furukawa Y, Nakagawa Y, Ono K, et al. Long-term outcomes after percutaneous coronary intervention for chronic total occlusion (from the CREDO-Kyoto registry cohort-2). Am J Cardiol 2013 Sep 15;112(6):767-774.

(65) Shanmugam VB, Harper R, Meredith I, Malaiapan Y, Psaltis PJ. An overview of PCI in the very elderly. J Geriatr Cardiol 2015 Mar;12(2):174-184.

(66) Kozlov KL, Bogachev AA. Coronary revascularization in the elderly with stable angina. J Geriatr Cardiol 2015 Sep;12(5):555-568.
(67) Bauer T, Mollmann H, Weidinger F, Zeymer U, Seabra-Gomes R, Eberli F, et al. Predictors of hospital mortality in the elderly undergoing percutaneous coronary intervention for acute coronary syndromes and stable angina. Int J Cardiol 2011 Sep 1;151(2):164-169.
(68) Batchelor WB, Anstrom KJ, Muhlbaier LH, Grosswald R, Weintraub WS, O'Neill WW, et al. Contemporary outcome trends in the elderly undergoing percutaneous coronary interventions: results in 7,472 octogenarians. National Cardiovascular Network Collaboration. J Am Coll Cardiol 2000 Sep;36(3):723-730.
(69) Feldman DN, Gade CL, Slotwiner AJ, Parikh M, Bergman G, Wong SC, et al. Comparison of outcomes of percutaneous coronary interventions in patients of three age groups (80 years) (from the New York State Angioplasty Registry). Am J Cardiol 2006 Nov 15;98(10):1334-1339.
(70) Kern MJ, Deligonul U, Galan K, Zelman R, Gabliani G, Bell ST, et al. Percutaneous Transluminal coronary angioplasty in octogenarians. Am J Cardiol 1988;61(6):457-458.
(71) Thompson RC, Holmes DRJ, Gersh BJ, Mock MB, Bailey KR. Percutaneous transluminal coronary angioplasty in the elderly: early and longterm results . J Am Coll Cardiol 1991;17(6):1245-1250.
(72) Kaehler J, Meinertz T, Hamm CW. Coronary interventions in the elderly. Heart 2006 Aug;92(8):1167-1171.
(73) Vasaiwala S, Forman DE, Mauri L. Drug-eluting stents in the elderly. Curr Treat Options Cardiovasc Med 2010 Jan;12(1):76-83.
(74) Groeneveld PW, Matta MA, Greenhut AP, Yang F. Drug eluting compared with bare metal coronary stents among elderly patients. J Am Coll Cardiol 2008;51(21):2017-2024.

(75) Mehran R, Claessen BE, Godino C, Dangas GD, Obunai K, Kanwal S, et al. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. JACC Cardiovasc Interv 2011 Sep;4(9):952-961.

(76) Brilakis ES, Grantham JA, Rinfret S, Wyman RM, Burke MN, Karmpaliotis D, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC Cardiovasc Interv 2012 Apr;5(4):367-379.

(77) Oqueli E, Dick R. Percutaneous coronary intervention in very elderly patients. In-hospital mortality and clinical outcome. Heart Lung Circ 2011 Oct;20(10):622-628.

(78) Hoebers LP, Claessen BE, Dangas GD, Park SJ, Colombo A, Moses JW, et al. Long-term clinical outcomes after percutaneous coronary intervention for chronic total occlusions in elderly patients (>/=75 years): five-year outcomes from a 1,791 patient multi-national registry. Catheter Cardiovasc Interv 2013 Jul 1;82(1):85-92.

(79) Tanaka Y, Takeshita S, Takahashi S, Matsumi J, Mizuno S, Yamanaka F, et al. Comparison of short- and long-term outcomes of percutaneous coronary intervention for chronic total occlusions between patients aged >/=75 years and those aged <75 years. Am J Cardiol 2013 Sep 15;112(6):761-766.

(80) Andre R, Dumonteil N, Lhermusier T, Lairez O, Van Rothem J, Fournier P, et al. In-hospital and long-term outcomes after percutaneous coronary intervention for chronic total occlusion in elderly patients: A consecutive, prospective, single-centre study. Arch Cardiovasc Dis 2015 Oct 21.

(81) Jeroudi MO, Kleiman NS, Minor ST, Hess KR, Lewis JM, Winters WL, et al. Percutaneous transluminal coronary angioplasty in octogenarians. Ann Intern Med 1990;113(6):423-428.

(82) Little T, Milner MR, Lee K, Constantine J, Pichard AD, Lindsay J,Jr. Late outcome and quality of life following percutaneous transluminal coronary angioplasty in octogenarians. Cathet Cardiovasc Diagn 1993 Aug;29(4):261-266.
(83) Kaul TK, Fields BL, Wyatt DA, Jones CR, Kahn DR. Angioplasty versus coronary artery bypass in octogenarians. Ann Thorac Surg 1994 Nov;58(5):1419-1426.
(84) Singh M, Peterson ED, Roe MT, Ou FS, Spertus JA, Rumsfeld JS, et al. Trends in the association between age and in-hospital mortality after percutaneous coronary intervention: National Cardiovascular Data Registry experience. Circ Cardiovasc Interv 2009 Feb;2(1):20-26.
(85) Peterson ED, Alexander KP, Malenka DJ, Hannan EL, O'Conner GT, McCallister BD, et al. Multicenter experience in revascularization of very elderly patients. Am Heart J 2004 Sep;148(3):486-492.
(86) Klein LW, Block P, Brindis RG, McKay CR, McCallister BD, Wolk M, et al. Percutaneous coronary interventions in octogenarians in the American College of Cardiology-National Cardiovascular Data Registry: development of a nomogram predictive of in-hospital mortality. J Am Coll Cardiol 2002 Aug 7;40(3):394-402.
(87) Dynina O, Vakili BA, Slater JN, Sherman W, Ravi KL, Green SJ, et al. In-hospital outcomes of contemporary percutaneous coronary interventions in the very elderly. Catheter Cardiovasc Interv 2003 Mar;58(3):351-357.
(88) Cohen HA, Williams DO, Holmes DR,Jr, Selzer F, Kip KE, Johnston JM, et al. Impact of age on procedural and 1-year outcome in percutaneous transluminal coronary angioplasty: a report from the NHLBI Dynamic Registry. Am Heart J 2003 Sep;146(3):513-519.

(89) Kaneko H, Yajima J, Oikawa Y, Tanaka S, Fukamachi D, Suzuki S, et al. Impact of aging on the clinical outcomes of Japanese patients with coronary artery disease after percutaneous coronary intervention. Heart Vessels 2014 Mar;29(2):156-164.

(90) Yan BP, Gurvitch R, Duffy SJ, Clark DJ, Sebastian M, New G, et al. An evaluation of octogenarians undergoing percutaneous coronary intervention from the Melbourne Interventional Group registry. Catheter Cardiovasc Interv 2007 Dec 1;70(7):928-936.

(91) From AM, Rihal CS, Lennon RJ, Holmes DR,Jr, Prasad A. Temporal trends and improved outcomes of percutaneous coronary revascularization in nonagenarians. JACC Cardiovasc Interv 2008 Dec;1(6):692-698.

(92) De Gregorio J, Kobayashi Y, Albiero R, Reimers B, Di Mario C, Finci L, et al. Coronary artery stenting in the elderly: short-term outcome and long-term angiographic and clinical follow-up. J Am Coll Cardiol 1998 Sep;32(3):577-583.

(93) Appleby CE, Ivanov J, Mackie K, Dzavik V, Overgaard CB. In-hospital outcomes of very elderly patients (85 years and older) undergoing percutaneous coronary intervention. Catheter Cardiovasc Interv 2011 Apr 1;77(5):634-641.

(94) Miura T, Miyashita Y, Motoki H, Shimada K, Kobayashi M, Nakajima H, et al. In-hospital clinical outcomes of elderly patients (>/=80 years) undergoing percutaneous coronary intervention. Circ J 2014;78(5):1097-1103

(95) Rittger H, Hochadel M, Behrens S, Hauptmann KE, Zahn R, Mudra H, et al. Interventional treatment and outcome in elderly patients with stable coronary artery disease. Results from the German ALKK registry. Herz 2014 Mar;39(2):212-218.