

Name:	Ajit A. Londhe
Affiliation:	Janssen Research & Development
Email:	alondhe2@its.jnj.com
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## Comparing the Effectiveness of Percutaneous Transluminal Angioplasty Against Clopidogrel in Peripheral Arterial Disease Patients

Ajit A. Londhe<sup>1,3</sup>, Jon D. Duke, MD MS<sup>2,3</sup>, Patrick B. Ryan, PhD<sup>1,3</sup>

<sup>1</sup>Janssen Research & Development, Titusville, NJ; <sup>2</sup>Regenstrief Institute, Indianapolis, IN; <sup>3</sup>Observational Health Data Sciences and Informatics (OHDSI), New York, NY

### Abstract

Peripheral arterial disease (PAD) is a circulatory problem affecting over 10 million adults in the United States annually. PAD patients' arteries become narrowed, harmfully reducing blood flow to the limbs. Clopidogrel is the primary drug treatment, but recent trends suggest increased usage of second-line percutaneous transluminal angioplasty (PTA) procedures (1). Our objective was to compare the risk of lower limb amputation in PAD patients between those on clopidogrel-only treatment and those who received PTAs post-clopidogrel.

### Introduction

Atherosclerosis occurs when "fat, cholesterol, calcium, fibrous tissue, and other substances" build up in the arteries, forming a thick plaque along the arterial wall (2). Diseases resulting from atherosclerosis are dependent upon the location of the plaque buildup: near the heart, coronary heart disease; near the neck, carotid artery disease; and if the arteries near the kidneys are restricted, chronic kidney disease (3). PAD is the condition that results when this plaque hardens in arteries near the limbs. As the blood flow becomes restricted, the loss of circulation can present symptoms ranging from limb pain, fatigue, and sores to loss of feeling in the extremities. Left untreated, the tissue in the affected limbs dies, causing gangrene; lower limb amputation may become necessary (4). Traditionally, PAD patients are treated using antiplatelet therapy drugs like clopidogrel in order to limit "platelet activation and subsequent risk of an atherothrombotic event" (5). However, recent Medicare payment data indicates that the use of PTA as a second-line treatment for chronic PAD patients grew by 70% from 2005 to 2013 (1). A PTA procedure entails the insertion of a catheter and balloon into the artery, with a mesh stent added to ensure that the artery remains open, circulation restored. With no clinical consensus on the effectiveness of PTA treatment over clopidogrel therapy, this study aims to compare the risk of lower limb amputation (LLA) between both cohorts post-treatment.

### Materials and Methods

All evidence was generated utilizing Observational Health Data Sciences and Informatics (OHDSI) tools against the Observational Medical Outcomes Partnership (OMOP) Common Data Model version 5; vocabulary concept sets and patient cohorts were designed in Atlas, with the phenotype definition of PAD sourced from the Mayo Clinic Electronic Medical Records and Genomics (eMERGE) Network study. The eMERGE definition, which identifies the presence or absence of PAD in a patient, has demonstrated a positive predictive value of 0.907 among true cases (6). As PAD "often goes undiagnosed by healthcare professionals" (4), this approach can be used to infer "definite" PAD status when using electronic medical records by requiring ankle-brachial index (ABI) measurements < 0.9. Alternatively, "definite" cases can be identified if the patient has 2 of the following 4 "related" criteria: claims-based diagnosis codes; history of cardiovascular procedures; Natural Language Processing (NLP) of physician notes; and medications for claudication (6). Due to the limitations of claims data, this study could not utilize ABI measurements directly. Furthermore, as NLP-derived physician notes were not available, the study cohorts were developed by requiring 2 of the remaining 3 "related" criteria. As generic clopidogrel was approved by the FDA in May 2012, a study window of June 1, 2012 to June 1, 2015 was chosen. One-to-one propensity score matching was utilized to balance the effect of known confounders between each cohort. Survival analysis of LLA within a 3-year risk window was conducted using Cox regression outcome models based on the matched populations and stratified on the propensity score. The final model retained the covariates used in the propensity score matching process. All analysis was executed using the CohortMethod and Cyclops R packages (7, 8) against data sourced from Truven Health MarketScan (Truven Health Analytics Inc, Ann Arbor, Michigan): Supplemental Medicare (MDCR; N = 9,254,795) and Commercial Claims and Encounters (CCAE; N = 121,849,814).

## Results

The PTA cohort (n = 7250, MDCR; n = 5702, CCAE) was considered to be the primary treatment and the clopidogrel-only cohort (n = 5209, MDCR; n = 3962, CCAE) was the comparator. Attrition from the usage of eMERGE's strict PAD definition, the study population parameters, and propensity score matching resulted in small cohort sizes (n = 541 pairs, MDCR; n = 396 pairs, CCAE). The area under the receiver-operator curve (AUC) for the propensity model was 0.73 (95% CI: [0.70, 0.75]) for MDCR and 0.74 (95% CI: [0.72, 0.77]) for CCAE; the propensity models appeared to be not significantly predictive of treatment, and were therefore effective in balancing the cohorts. The matched population was then trimmed to equipoise to remove "extreme" patients with no potential for propensity score matching. The resulting Cox regression models (Figure 1) had hazard ratio point estimates for PTA treatment of 0.51 (CI 95%: [0.21, 1.06]; p = 0.09) for MDCR and 0.69 (95% CI: [0.25, 1.65], p = 0.43) for CCAE. Based on these results, PTA patients had an estimated lower risk of LLA than clopidogrel-only patients for the majority of the 3-year risk window. This trend is more pronounced in MDCR than in CCAE, as the Kaplan-Meier curves converge sooner in CCAE (Figure 2).

MDCR: All Covariates	CCAE: All Covariates
<ul style="list-style-type: none"> <li>• Ulcer of foot</li> <li>• Eligible professional attests to documenting in the medical record they obtained, updated, or reviewed the patient's current medications</li> <li>• Corticosteroids, weak (group I)</li> <li>• Pain in limb</li> <li>• Cellulitis and abscess of foot excluding toe</li> </ul>	<ul style="list-style-type: none"> <li>• Ulcer of foot</li> <li>• Leukocytosis</li> <li>• Pain in limb</li> <li>• Hypo-osmolality and or hyponatremia</li> <li>• Benign essential hypertension</li> <li>• Edema</li> </ul>

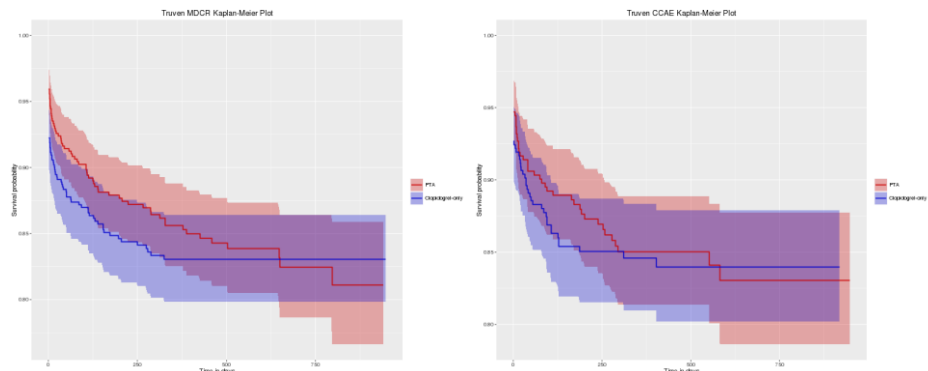
Figure 2: Cox Regression models

Figure 1: Kaplan-Meier Plots

## Conclusion

The hazard ratio estimates indicate that PTA may have a protective effect against lower limb amputation for PAD patients. However, as the confidence intervals around the two hazard ratio estimates are wide, overlapping, and inclusive of the null; and tests of significance are > 0.05, we

fail to reject the null hypothesis that the risk of LLA is the same among PTA patients and clopidogrel-only patients. Further study, benchmarked with negative controls, is needed to examine older PAD populations and LLA, with a stronger focus on demographics, visit type, provider, and location of PTA and subsequent LLA.



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