Risk Stratification For Critical Limb Ischemia And Amputation In Patients With Atherosclerosis: Insights From The TRA2P-TIMI 50 Trial

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Background

- Chronic critical limb ischemia (CLI) and amputation (AMP) are major morbidities of lower extremity peripheral artery disease (PAD) and diabetes (DM).
- In contrast to acute limb ischemia (ALI) which is abrupt ischemia in the setting of a usually thrombotic occlusion, CLI and related amputation (CLI/AMP) events are often subacute and multifactorial including elements of abnormal perfusion, infection, and vulnerability to wounds in the setting of microvascular disease and neuropathy.
- Due to its multifactorial nature, optimal prevention of CLI/AMP in patients with PAD and DM may require multidisciplinary systems of care including treatment of risk factors, optimization of diabetes care, podiatric care and attention to limb perfusion by cardiovascular specialists.
- Simple tools for risks stratification may be useful in identifying patients at highest risk who may benefit from such intensive care programs

Hypothesis

- We hypothesized that clinical factors including markers of PAD severity and the presence of diabetes could be utilized to define a simple risk stratification approach for CLI/AMP in patients with atherosclerosis.
- We hypothesized that both severity of PAD and the presence of DM would be predictors of CLI/AMP in a broad population with symptomatic atherosclerosis.

Methods

- TRA2P-TIMI 50 recruited 26,449 patients with atherosclerosis including patients with lower extremity peripheral artery disease (defined as an ABI ≤ 0.90 or a history of claudication and lower extremity revascularization for ischemia) and diabetes.
- The primary endpoint events of critical limb ischemia and amputation (CLI/AMP) were reviewed and categorized by blinded vascular specialists.
- Fontaine classification was used for symptomatic status including I – asymptomatic, IIa – intermittent claudication after ≥ 200 meters, IIb – intermittent claudication < 200 meters, III – rest pain, IV – ischemic ulcer or gangrene
- A classification and regression tree (CART) analysis was developed based on clinical characteristics. Tree-structured analysis were performed to identify statistically significant predictors with each node classified by tree, determined based on the strongest predictor for the endpoint using multivariable Cox proportional hazard regression modeling with stepwise selection method in conjunction with univariate Cox regression models. Stepwise selection using an alpha of 0.1 for entry and an alpha of 0.05 to remain in the model.

Results

Baseline characteristics associated with CLI/AMP are shown in Table 1

Table 1

Characteristic *n (%) unless otherwise specified*	CLI/AMP N=315	No CLI/AMP N=26,134	P-value
Age, median (IQR)	64 (58-71)	61 (53-69)	<0.001
Weight, kg, median (IQR)	79 (67-91)	81 (71-92)	0.0140
Male sex	229 (73)	19894 (76)	0.16
Caucasian race	263 (84)	22823 (87)	0.0397
Systolic BP, median (IQR)	140 (125-155)	131 (120-145)	<0.001
Current smoking	92 (29)	5406 (21)	<0.001
Hypertension	272 (86)	17902 (69)	<0.001
Hyperlipidemia	259 (82)	21735 (83)	0.65
Diabetes mellitus	167 (53)	6557 (25)	<0.001
Peripheral artery disease	279 (89)	5566 (21)	<0.001
Coronary artery disease	205 (65)	20486 (78)	<0.001
Myocardial infarction	141 (45)	19015 (73)	<0.001
Unstable angina	83 (27)	5615 (22)	0.0316
History of CABG/PCI	156 (50)	17105 (66)	<0.001
History of Atrial fib/flutter	20 (6)	988 (4)	0.0180
Heart failure	49 (16)	2021 (8)	<0.001
Stroke/TIA	73 (23)	6195 (24)	0.82
Carotid artery disease	65 (21)	2070 (8)	<0.001
eGFR	73 (61-88)	80 (67-94)	<0.001

All candidate predictors used for univariable Cox regressions include: Age, Weight, Sex, Caucasian, Systolic BP, Current smoker, history of hypertension, history of hyperlipidemia, history of diabetes, Prior MI, heart failure, history of unstable angina, Prior known Coronary Stenosis >=50% or Coronary revascularization (CABG/PCI), history of Atrial fibrillation/flutter, Hx of stroke/TIA, Prior known Carotid Stenosis >= 50%, Microvascular disease, eGFR, hs-CRP >=3, and PAD.
Candidate predictors used for multivariable Cox regression were selected from univariate Cox regression using alpha=0.05.

Overall there were 315 patients who experienced a CLI/AMP event during 3 years of follow up for an event rate of 1.45%. The strongest predictor of CLI/AMP was PAD followed by diabetes mellitus. Within the group of patients with PAD, history of CLI (Fontaine III/IV) was the strongest predictor followed by history of peripheral revascularization (Figure 1). In patients without PAD, however, diabetes mellitus was the strongest predictor of future CLI/AMP (Figure 2).

Table 2 – Predictors of CLI/AMP in All Patients

Predictors	Chi-square	HR (95% CI)	P-value
PAD	*168.5*	*17.0 (11.1-26.1)*	*<0.001*
Diabetes mellitus	40.3	2.1 (1.7-2.6)	<0.001
Hs-CRP ≥ 3	18.1	1.6 (1.3-2.1)	<0.001
MI	17.0	0.61 (0.48 – 0.77)	<0.001
Heart failure	9.1	1.6 (1.2-2.2)	0.0025
Systolic blood pressure	4.8	1.006 (1.001-1.012)	0.029

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Figure 1

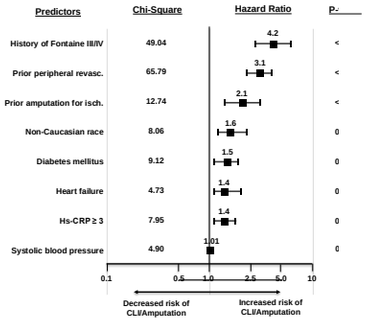


Figure 2

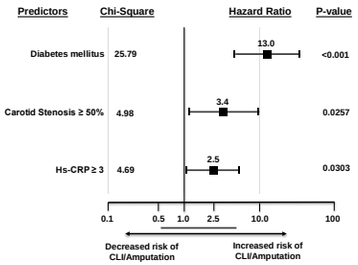
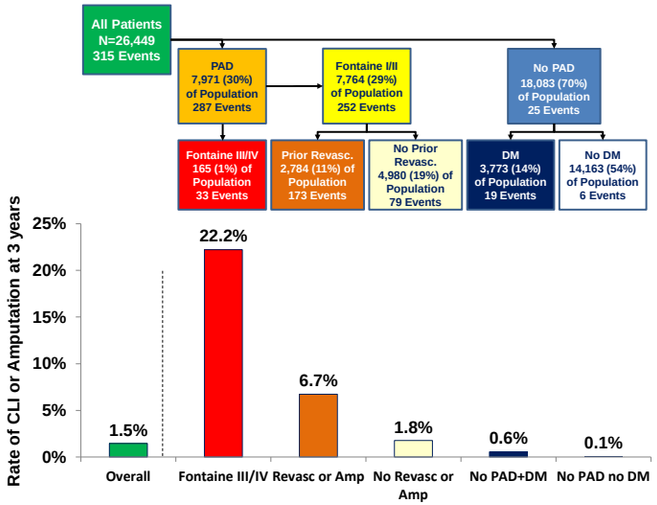


Figure 3 – Summary of Risk Stratification for CLI/AMP



- This CART approach enabled risk stratification of the population into 5 group with a broad range of event rates ranging from 0.1% to 22.2% at 3 years (Figure 3)

Conclusions

- In patients ***with PAD***, severity of disease is the strongest predictor of CLI/AMP, however, diabetes mellitus is still associated with ~2-fold hazard even after adjusting for severity.
- In patients ***without PAD***, DM is associated with a ~13-fold hazard of CLI/AMP.
- A CART approach allows stratification of risk with rates ranging from 22% to 0.1% at 3 years. Better understanding of the pathobiology and predictors of these events overall and within the risk strata may enable better develop and application of preventive interventions.

TRA2P-TIMI 50 was funded by a grant from Merck to Brigham and Women's Hospital

Author disclosure block: Dr. Bonaca. Dr. Creager and Dr. Sabatine were supported by the American Heart Association Strategically Focused Research Network in Vascular Disease under award numbers 18SFRN3390085 (BWH-DH SFRN Center) and 18SFRN33960262 (BWH-DH Clinical Project). The content is solely the responsibility of the authors and does not necessarily represent the official views of the American Heart Association.

The TIMI Study Group has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Aralez, AstraZeneca, Bayer HealthCare Pharmaceuticals, Inc., Daiichi-Sankyo, Eisai, GlaxoSmithKline, Intarcia, Janssen, The Medicines Company, MedImmune, Merck, Novartis, Pfizer, Poxel, Quark Pharmaceuticals, Roche, Takeda, and Zora Biosciences.

Marc P. Bonaca discloses consulting and advisory board activities for Amgen, Aralez, AstraZeneca, Bayer, Janssen, Merck, Novo Nordisk, Pfizer, and Sanofi