



RAPID Phase III – Perspectives from the Medical Device Industry

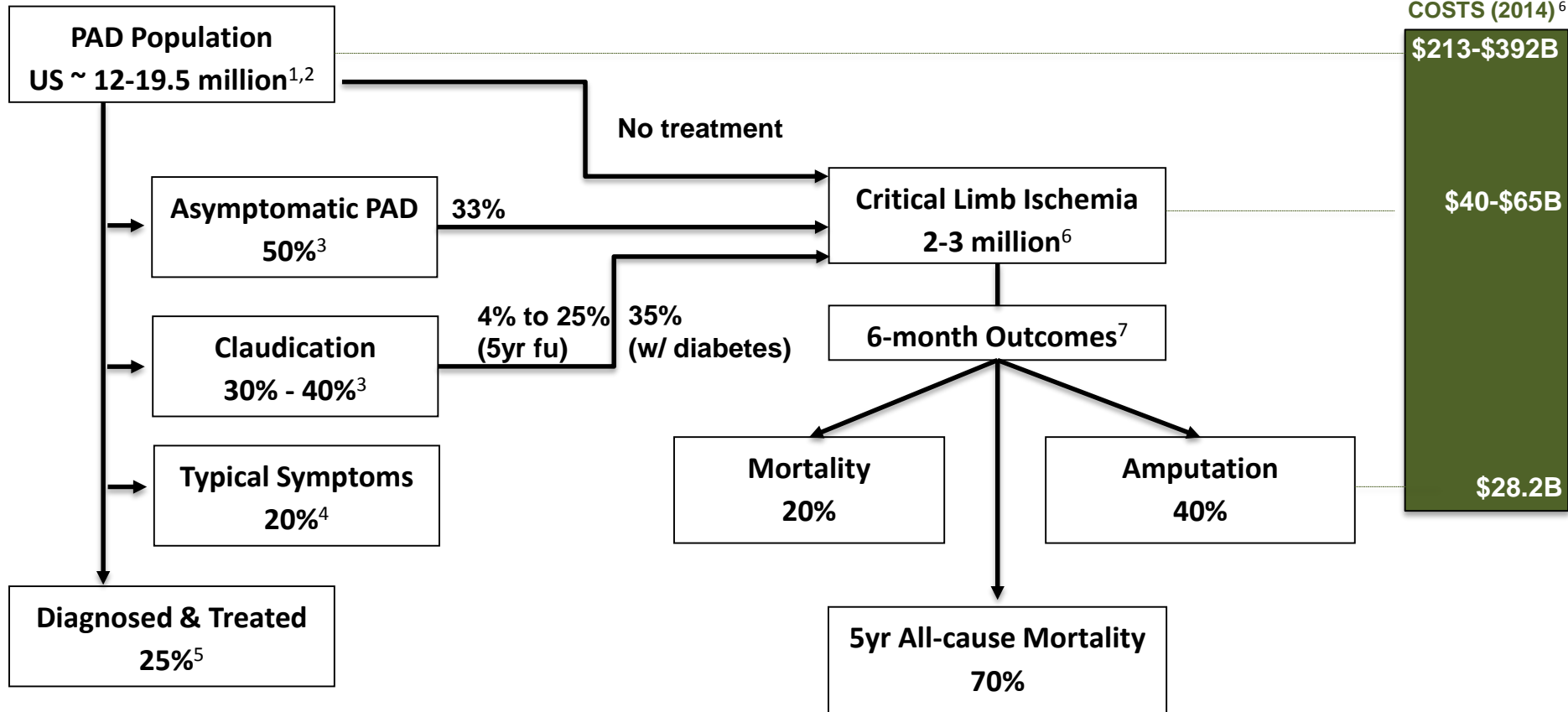
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PAD and Critical Limb Ischemia: Disease Status in the US



1. The Sage Group LLC. CLI Vol. 1. 2010.

2. The Sage Group LLC. The Diabetes Method. 2011.

3. Dhaliwal G and Mukherjee D. *Int J Angiol.* 2007;16:36-44.

4. White CJ and Gray WA. *Circulation.* 2007;116:2203-2215.

5. Becker GJ, et al. *J Vasc Interv Radiol.* 2002;13:7-11.

6. Yost M. Presented at VIVA 2015.

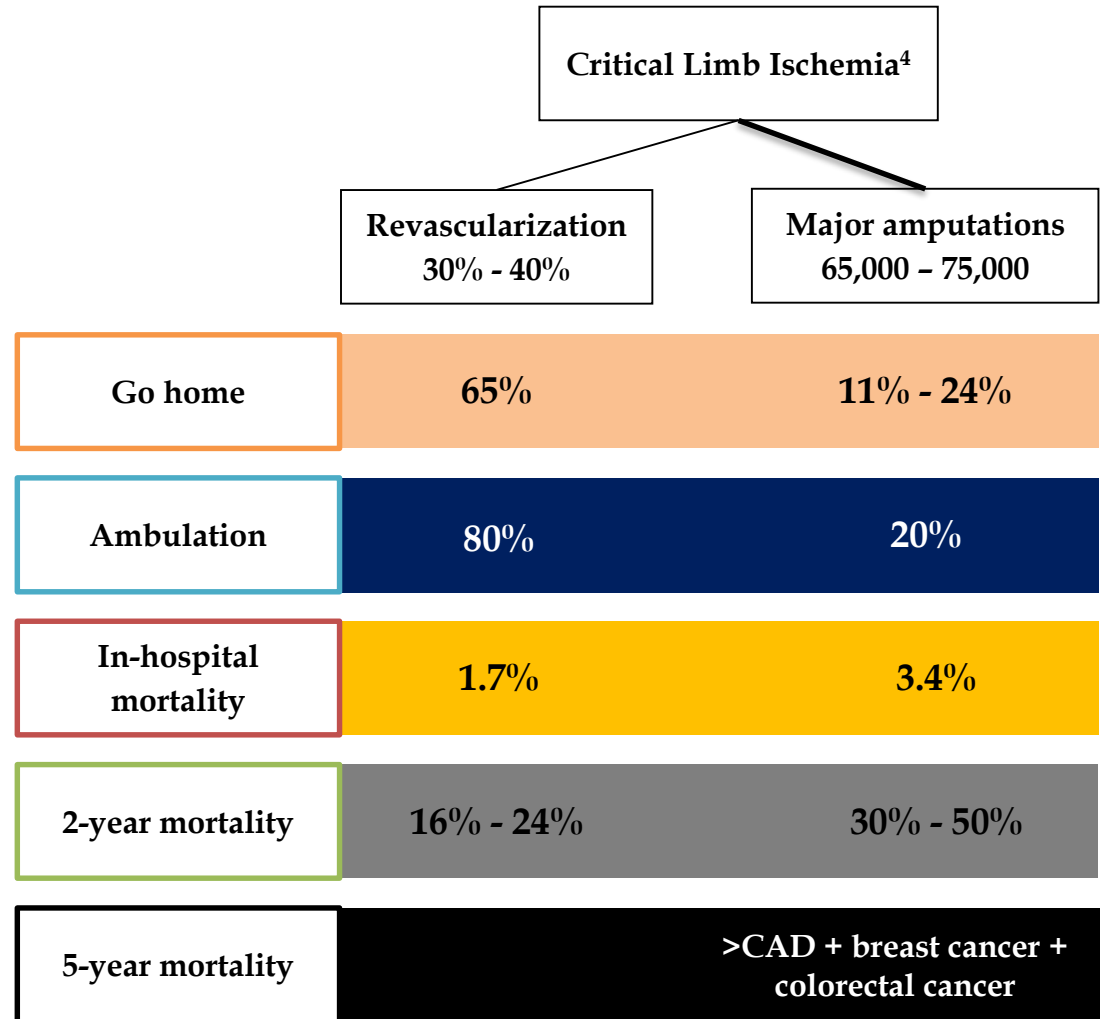
7. Dormandy

8. Hirsch AT, et al. *Circulation.* 2006;113:e463-654.

Treatment of CLI

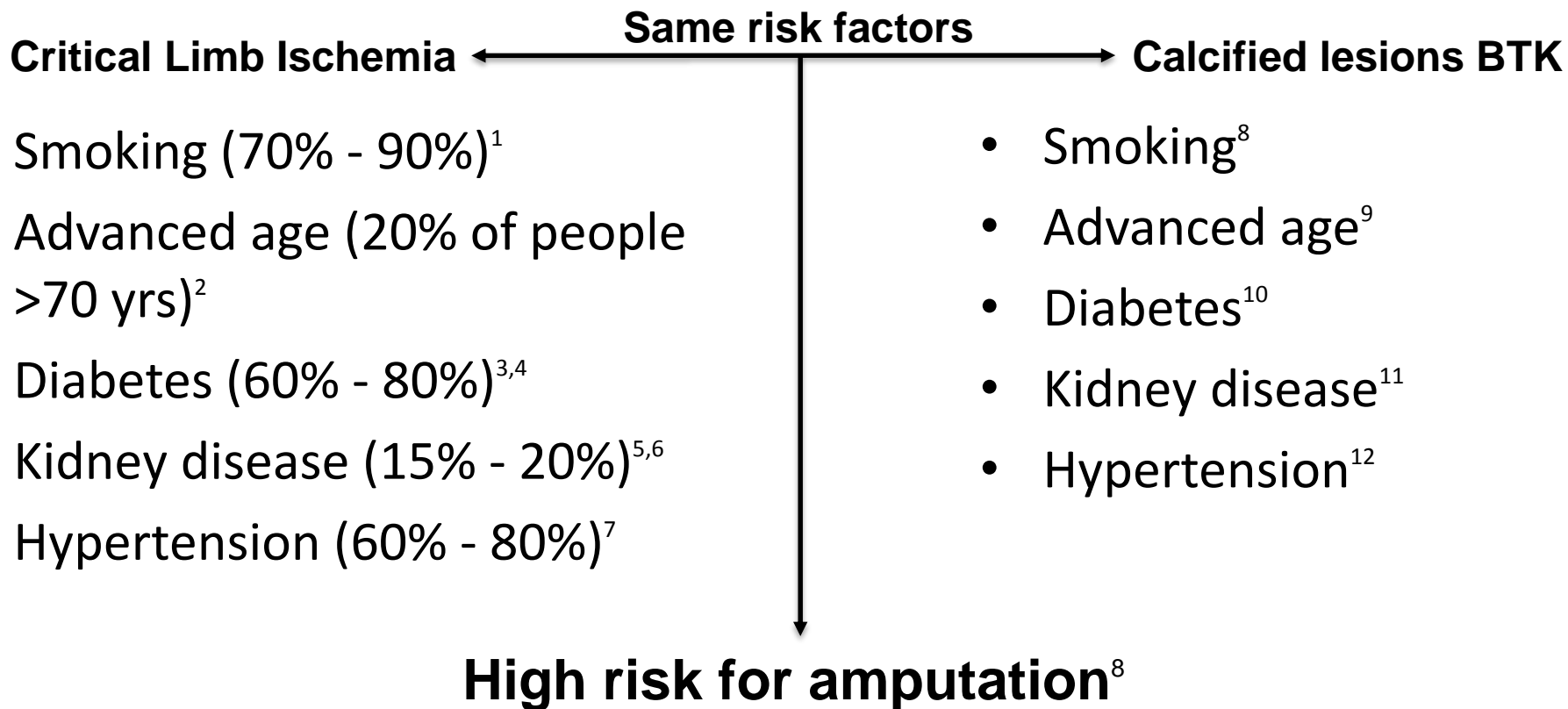
Inconsistent Guidelines

- TASC II 2007 Guidelines¹
 - Primary amputation only if aggressive vascular reconstruction is likely to fail (physician discretion)
 - Limb Preservation achieved through a multi-armed treatment involving antibiotics, revascularization and staged wound closure
- ACC/AHA 2006 Guidelines²
 - CLI Patients should undergo expedited evaluation and treatment of factors increasing amputation risk
 - Persistent CLI symptoms can be treated with additional revascularization procedures
 - Primary amputation evaluation only for those with very limited life expectancy and significant limb damage
- ESC 2011 Guidelines³
 - Treatment options: Surgical Revascularization > Endovascular therapy > prostanoids



1. Norgren L, et al. *J Vasc Surg.* 2007;45:S5-67.
 2. Hirsch AT, et al. *J Am Coll Cardiol.* 2006;47:1239-1312.
 3. ESO. *Eur Heart J.* 2011; 32(22):2851-906.
 4. Yost M. The socioeconomic cost of CLI and amputation. Presented at VIVA 2015.

Risk Factors



1. Davies MG. *Methodist DeBakey Cardiovasc J.* 2012;8:10-14.

2. Zeller T. *Vasc Med.* 2007;12:223-234.

3. Dormandy J and Rutherford RB. *J Vasc Surg.* 2000;31:S1-296.

4. 2014 Statistics Report. CDC Diabetes 2014.

5. Rajagopalan S, et al. *Circulation.* 2006;114:1914-1922.

6. LaMendola B, et al. *Dial Transplant.* 2010;39:490-494.

7. Gottsater A. *Eur J Vasc Endovasc Surg.* 2006;32:478-783.

8. Guzman RJ, et al. *J Am Coll Cardiol.* 2008;51:1967-1974.

9. Allison MA, et al. *Arterioscler Thromb Vasc Biol.* 2004;24:331-336.

10. Young MJ, et al. *Diabetologia.* 1993;36:615-621.

11. Mizobuchi M, et al. *J Am Soc Nephrol.* 2009;20:1453-1464.

12. Im SI, et al. *Clin Hypertens.* 2015;22:9.

Severely Calcified Lesions Are Challenging To Treat

- ❑ Severely calcified lesions respond poorly to angioplasty^{1,4}
 - Vessel recoil after balloon dilatation
 - Flow-limiting dissection related to high pressure used
- ❑ Severely calcified lesions make stent placement difficult^{2,3}
 - Higher stent implantation rate
 - Higher stent compression and/or fractures rate
- ❑ Calcified lesions lead to higher rate of procedural complications⁶ and higher incidence of MAE^{7,5}
 - Dissection, plaque rupture, embolization
 - TLR, binary restenosis, stent thrombosis, death
- ❑ Insufficient drug penetration and subsequent restenosis⁸

How do we measure effectiveness of various treatment options in real-world patients unless we can quantify poor outcome risk predictors, like calcification?

The majority of randomized controlled studies considered severe calcification of the lesion as an exclusion criterion.^{4,5}

1. Fitzgerald PJ, et al. *Circulation*. 1992;86:64-70
2. Henry M, et al. *Tex Heart Inst J*. 2000;27:119-126.
3. Rogers JH and Laird JR. *Circulation*. 2007;116:2072-2085.
4. Cioppa A, et al. *Cardiovasc Revasc Med*. 2012;13:219-223.

5. Rocha-Singh KJ, et al. *Catheter Cardiovasc Interv*. 2014;83:E212-220.
6. Mustapha J, et al. *Vascular Disease Management*. 2013;10:E198-207.
7. Kawaguchi R, et al. *Cardiovasc Revasc Med*. 2008;9:2-8.
8. Ichihashi S and Kichikawa K. *Ther Clin Risk Manag*. 2014;10:467-474.

Current Definition of Calcified Lesions

	Proposed Peripheral Arterial Calcium Scoring System (PACSS) ¹		Consensus Definitions from Peripheral Academic Research Consortium (PARC) ²		Calcium Burden Assessment ³	
Length of calcium	<5 cm ≥5 cm		≤1 cm ≥15 cm		< 3cm ≥ 3cm	
Type of lesion calcification degree	Intimal/Medial/Mixed		NR		Superficial	
Degree of lesion calcification	Unilateral/Bilateral		<180° ≥ 180°		0° - 360°	
Description	Grade 0	No visible calcium at the target lesion site				
	Grade 1	Unilateral calcification <5 cm; a) intimal calcification; b) medial calcification; c) mixed type	Focal	<180° (one side of vessel) and less than half the total lesion length	Grade 1	Circ 0-90°
	Grade 2	Unilateral calcification ≥5 cm; a) intimal calcification; b) medial calcification; c) mixed type	Mild	<180° and greater than half the total lesion length	Grade 2	Circ 0-180°
	Grade 3	Bilateral calcification <5 cm; a) intimal calcification; b) medial calcification; c) mixed type	Moderate	≥ 180° (both sides of vessel at same location) and less than half the total lesion length	Grade 3	Circ 0-270°
	Grade 4	Bilateral calcification ≥5 cm; a) intimal calcification; b) medial calcification; c) mixed type	Severe	>180° (both sides of the vessel at the same location) and greater than half the total lesion length	Grade 4	Circ 0-360°

Consistent calcium scoring system has not been established

1. Rocha-Singh KJ, et al. *Catheter Cardiovasc Interv.* 2014;83:E212-220.
2. Patel MR, et al. *J Am Coll Cardiol.* 2015;65:931-941.
3. Fanelli F, et al. *Cardiovasc Intervent Radiol.* 2014;37:898-907.

The Need For A Consistent Calcium Score

Calcified Lesions

- Angiography underestimates severity of calcification^{1,2}
- Technically challenging^{3,4,5}
- Higher procedural complication rates^{3,6}
- More costly to treat^{7,8}

The RAPID core data set currently does not include severity of calcification as a “condition” data element

1. Kashyap VS, et al. *J Endovasc Ther.* 2008;15:117-125.

2. Lankeren W, et al. *Cardiovasc Intervent Radiol.* 1998;21:367-374.

3. Fitzgerald PJ, et al. *Circulation.* 1992;86:64-70.

4. Henry M, et al. *Tex Heart Inst J.* 2000;27:119-126.

5. Rogers JH and Laird JR. *Circulation.* 2007;116:2072-2085.

6. Mustapha J, et al. *Vasc Dis Manag.* 2013;10:E198-207.

7. Meerkin D, et al. *J Invasive Cardiol.* 2002;14:547-551.

8. Parikh K, et al. *Catheter Cardiovasc Interv.* 2013;81:1134-1139.

PAD and CLI

- PAD & CLI are underdiagnosed and undertreated
- Inconsistent guidelines for CLI
 - Amputation is still the primary therapy – costly, high mortality rate
- The risk factors for CLI are the same as those for calcification, yet calcification excluded
 - Treatment of long and calcified lesions – more adjunctive devices, higher frequency of provisional stenting, more balloons – worse clinical and health economic outcomes
- **Lack of data about treatment and outcomes in CLI¹**
- **Evidence gap, insufficient information - RCTs and large, prospective, observational, real-world registries needed²**

1. Reinecke H, et al. *Eur Heart J.* 2015;36:932-938.

2. Jones WS, et al. *AHRQ Publication No.* 13-EHC090-EF.

RAPID Use Case – CLI Study

- Objectives
 - Determine consistent guidelines/treatment algorithm(s) for the treatment of CLI
 - Reduce the number of amputations
- Potential Study Design
 - Large, prospective, multicenter study
 - All endovascular devices eligible
 - Surgical revascularization?
 - QoL, 6MWT, MAEs, TLR/TVR, patency
 - Acute & long-term follow-up
 - Economic data capture
 - Link to CMS/private payor databases?

Does this Use Case Pass the Litmus Test?

Practice Guidelines Updated to Reflect
Real World Data

Addresses FDA's Focus Areas

Safe, effective and patient-centric outcomes

Cost of Healthcare Driven Down

CMS, private payors

Potential for Indications for Use
Expansion

Beyond Phase III – Expansion of Core Data Set

- Incorporation of other data elements
 - Example: calcification scale
- Establish revision cycles
 - How often?
- Who “owns” once initial CDS is finalized?
- Communication
 - Additional elements for consideration
 - Notification of changes/updates

Considerations

- Physician & industry agreement
- Assurance regulators will accept data for RAPID registry to support indication expansion or new technology
- Navigating informed consent
- Core data set maintenance & expansion
- Reliance on EHR data for registry data
- UDI adoption/use at hospitals