Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia

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Background: **Percutaneous transluminal angioplasty has been used with increasing frequency in the treatment of infrainguinal arterial occlusive disease. This meta-analysis aimed to assess the middle-term outcomes after crural angioplasty in patients with chronic critical limb ischemia and compare results with a meta-analysis of popliteal-to-distal vein bypass graft.**

Methods: **Data were retrieved from 30 articles published from 1990 through 2006 (63% of articles published between 2000 and 2006). All studies used survival analysis, reported a 12-month cumulative rate of patency or limb salvage, and included at least 15 infrapopliteal angioplasties. The outcome measures were immediate technical success, primary and secondary patency, limb salvage, and patient survival. Data from life-tables, survival curves, and texts were used.**

Results: **The pooled estimate of success was 89.0% ± 2.2% for immediate technical result. Results at 1 and 36 months were 77.4% ± 4.1% and 48.6% ± 8.0% for primary patency, 83.3% ± 1.4% and 62.9% ± 11.0% for secondary patency, 93.4% ± 2.3% and 82.4% ± 3.4% for limb salvage, and 98.3% ± 0.7% and 68.4% ± 5.5% for patient survival, respectively. Studies with >75% of the limbs with tissue loss fared worse than their respective comparative subgroup for technical success and patency but not for limb salvage or survival. No publication bias was detected.**

Conclusion: **The technical success and subsequent durability of crural angioplasty are limited compared with bypass surgery, but the clinical benefit is acceptable because limb salvage rates are equivalent to bypass surgery. Further studies are necessary to determine the proper role of infrapopliteal angioplasty. (J Vasc Surg 2008;47:975-81.)**

Percutaneous transluminal angioplasty (PTA) has become an acceptable form of treatment for patients with infrainguinal arterial occlusive disease. Even in the setting of chronic critical limb ischemia (CLI), broadly similar outcomes have been obtained when PTA and bypass surgery are compared.[1] With PTA, local anesthesia can be used, hospital stay is shorter, and morbidity and mortality rates may be lower.[2]

In contrast with femoropopliteal PTA, infrapopliteal or crural angioplasty PTA has been less frequently used, has been offered predominantly to patients with CLI, has produced more heterogeneous results, and still remains controversial.[3-5] Formerly restricted to patients with short stenotic lesions or to poor candidates for bypass surgery,[6] crural PTA has been used in recent years preferentially over bypass surgery by some groups.[2] This wide scope of use, the advent of new devices and techniques, the growing experience with endovascular therapy, and the competing interest in traditional bypass surgery justify an assessment of crural PTA. This meta-analysis of studies of crural PTA performed in patients with CLI aimed to estimate the middle-term patency and limb salvage, to investigate the relationship between these outcomes, and compare results with a meta-analysis of popliteal-to-distal vein by-pass graft.

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METHODS

Study identification. Articles published from January 1981 through October 2006 in the MEDLINE and Excerpta Medica Database (EMBASE) databases were searched. The descriptors used to find titles of possible interest were "infrapopliteal angioplasty," "below knee angioplasty," "crural angioplasty," and "tibial angioplasty." After reading the abstracts online, 70 articles were printed for complete reading. Articles referenced were read selectively, and the systematic review finally included 30 articles.[2-31] These selected articles covered a period from 1990 to 2006, 19 (63%) were published from 2000 to 2006, 5 (16%) from 1995 to 2000, and 6 (20%) between 1990 and 1995 (Appendix, online only.)

Criteria for inclusion. The articles included satisfied the following criteria: (1) a minimum of 15 crural PTAs, (2) a greater number of these procedures than femoropopliteal PTAs, when both were described together, (3) most patients with ischemic rest pain or tissue loss, (4) use of survival analysis to describe outcomes, and (5) a minimum follow-up of 12 months, at least for some patients. Although authors from two centers reported more than one study on the subject,[9,20-22] care was taken not to include any PTA more than once. Studies with incomplete data of demographic or clinical variables were not excluded (Table I).

Outcomes. The outcomes selected for meta-analysis included immediate technical success, primary and second-

Table I. Demographic and clinical variables for 30 studies conducted between 1990 and 2006

Variables[a]	*Original series*	*Studies with no data*
Patients	2557	
Limbs	2653	
Procedures	2693	
Mean age	70 (64-81)	5
Male sex	60 (40-84)	7
Hypertension	54 (16-88)	11
Diabetes mellitus	61 (13-100)	5
Renal failure	23 (10-100)	16
Smoking	50 (15-97)	17
Heart disease	58 (22-83)	11
Cerebrovascular disease	14 (7-26)	18
Occlusive lesion	41 (0-100)	7
Tissue loss	76 (11-100)	7

[a]Values are medians (range), except for patients, limbs, procedures, and results for studies with no data.

ary patency, limb salvage, and patient survival as recommended in The Society for Vascular Surgery/International Society for Cardiovascular Surgery A Hoc Subcommittee on Reporting Standards for Endovascular Procedures.[32] Primary patency reflects the fate of a single PTA procedure, and secondary patency reflects the fate of initial and subsequent PTA procedures altogether. Continued clinical or hemodynamic success was occasionally used as a surrogate for patency. Limb salvage and patient survival as outcomes of major importance were also studied.

Data extraction. We retrieved the data from life-tables and from survival curves that showed the number of crural PTAs, limbs, or patients at risk for all intervals. We also retrieved the data from texts and less complete survival curves, combined data from the text with a life-table or survival curve to generate data for a different outcome, and reviewed the data extracted from each study.

Comparison with bypass grafting surgery. A recent meta-analysis of popliteal-to-distal vein bypass grafts was used as a comparator meta-analysis.[33] This study used methods similar to those of the current meta-analysis and targeted the same population of patients. The median of the average age was 70 years, and the median prevalence rate was 72% for male sex, 86% for diabetes mellitus, 88% for tissue loss, and 19% for renal failure. Patency and limb salvage, but not patient survival, were estimated (Table II). The difference between secondary and primary patency was 1.6% and 4.4% at 1 and 36 months, respectively, whereas the difference between limb salvage and secondary patency was 0.2% and 5.6%.

Study quality. An ideal study should report the period of study, the rate of patients requiring crural PTA, the number of patients, limbs and procedures, the number of more proximal procedures, the clinical symptoms, the periprocedural complications (either procedural or nonprocedural), the rate and causes of early death, life-tables rather than graphs, the 1-month follow-up interval, an account for loss to follow-up, and the rates of technical success, primary and secondary patency, limb salvage, and patient survival. Of particular relevance is a link between predictive variables and each life-table. Other relevant items are the rate of tissue loss, the regimen of postoperative antithrombotic therapy, data on further bypass, and the absence of a flat tail in the survival curves for patency and limb salvage. Hence, a perfect study would score 21, with a decrease of 1 point for each unmet requirement. No blinding process was used when the studies were scored for quality.

Subgroup meta-analysis. The studies were subgrouped according to the proportion of limbs with tissue loss, the extension of the crural PTA, and the use of subintimal dissection. The assumption was made that tissue loss and limb salvage were associated and that studies that described crural PTA alone or subintimal angioplasty alone included more homogenous patients (Table III). Therefore, meta-analysis of such subgroups could be compared with both the meta-analysis of other subgroups and the comparator meta-analysis.

Sensitivity analysis. Complementary analyses aimed to quantify the effects of immediate technical success, to determine the contribution of repeat crural PTA in maintaining patency, and to explain why so many failed angioplasties did not lead to major amputation. Because several studies failed to report all of the outcomes of interest, specific subsets of studies that measured any two outcomes under comparison were used to further investigate the relationship between technical success and primary patency (n = 15), between secondary and primary patency (n = 11), and between limb salvage and secondary patency (n = 9).

To explore the relationship between limb salvage and secondary patency, not considered as salvaged were the limbs with persisting CLI, the limbs that received a successful bypass ≤ 1 month, and 25% of the limbs in diabetic patients in whom pain at rest could be a manifestation of painful diabetic neuropathy rather than truly ischemic rest pain.[34] Sensitivity analysis also excluded studies that included patients with claudication, scored the lowest for quality, used surrogates for primary patency, came from nonvascular services, or contained only patients with renal failure (Table IV). Finally, a funnel plots graph investigated publication bias (Fig 1).

Statistical methods. The meta-analysis combined monthly hazard rates from single series to yield a pooled estimate of success for each month of follow-up. The product of successive monthly pooled estimates of success then yielded a pooled measure of success for each outcome and a standard error was calculated for this measure at several intervals. Between-study variances calculated as previously reported were used to reduce the influence of study size on the pooled estimates.[35] The differences between groups (Table II) and subgroups (Table III) were assessed statistically with a method that judges the significance of differences by examining the overlap between confidence intervals and does not calculate *P* values.[36] A random-effects model of meta-analysis was preferred because patients, vascular specialists, and quality of care likely differ worldwide.

Table II. Meta-analysis results of crural percutaneous transluminal angioplasty and popliteal-to-distal bypass[a]

Result	*1 month*	*6 months*	*1 year*	*2 years*	*3 years*
Primary patency					
PTA	77.4 ± 4.1	65.0 ± 7.0	58.1 ± 4.6	51.3 ± 6.6	48.6 ± 8.0
Bypass	93.3 ± 1.1	85.8 ± 2.1	81.5 ± 2.0	76.8 ± 2.3	72.3 ± 2.7
P	<.05	<.05	<.05	<.05	<.05
Secondary patency					
PTA	83.3 ± 1.4	73.8 ± 7.1	68.2 ± 5.9	63.5 ± 8.1	62.9 ± 11.0
Bypass	94.9 ± 1.0	89.3 ± 1.6	85.9 ± 1.9	81.6 ± 2.3	76.7 ± 2.9
P	<.05	<.05	<.05		
Limb salvage					
PTA	93.4 ± 2.3	88.2 ± 4.4	86.0 ± 2.7	83.8 ± 3.3	82.4 ± 3.4
Bypass	95.1 ± 1.2	90.9 ± 1.9	88.5 ± 2.2	85.2 ± 2.5	82.3 ± 3.0
Patient survival					
PTA	98.3 ± 0.7	92.3 ± 5.5	87.0 ± 2.1	74.3 ± 3.7	68.4 ± 5.5
Bypass	NA	NA	NA	NA	NA

NA, Estimates not available; *PTA,* percutaneous transluminal angioplasty.
[a]Values are pooled estimate and standard error.

Table III. Subgroup meta-analysis of early death, technical success, and 12-month outcomes[a]

Variable	*Early death, median*	*Technical success, %*	*Primary patency, %*	*Secondary patency, %*	*Limb salvage, %*	*Patient survival, %*
All	1.8	89.0 ± 2.2	58.1 ± 4.6	68.2 ± 5.9	86.0 ± 2.7	87.0 ± 2.1
Tissue loss						
>75%	2.0	83.6 ± 3.0	52.5 ± 5.0	55.8 ± 5.2	86.1 ± 3.8	85.3 ± 3.8
<75%	1.3	93.3 ± 1.5	66.0 ± 5.3	74.0 ± 8.0	92.6 ± 2.3	87.3 ± 2.6
P		<.05		<.05		
Crural PTA						
Alone	0.6	88.7 ± 4.8	52.0 ± 11.8	74.0 ± 8.5	85.2 ± 5.5	85.7 ± 4.5
Combined	2.0	88.4 ± 2.6	58.1 ± 5.0	60.9 ± 5.8	86.8 ± 3.2	86.0 ± 2.7
Subintimal dissection						
Routinely	0.6	83.9 ± 2.7	55.9 ± 12.1	70.9 ± 11.4	88.7 ± 4.8	81.4 ± 4.2
Other	2.0	90.3 ± 2.7	58.0 ± 4.9	66.0 ± 7.1	84.8 ± 3.3	87.7 ± 1.9

PTA, Percutaneous transluminal angioplasty.
[a]Outcomes were estimated from different studies. Values are pooled estimates ± standard error.

Table IV. Sensitivity analysis for primary patency and limb salvage[a]

Reason for study exclusion	*Primary patency, %*	*Limb salvage, %*
Contained patients with claudication	−0.3	−1.8
One outlier in the funnel graph	+2.0	+2.9
Surrogates for patency	−1.3	. . .
Nonvascular services	+0.1	−0.2
All patients with renal failure	. . .	+0.1
All above simultaneously	+1.7	+1.7

[a]Values are changes in the 36-month pooled estimates.

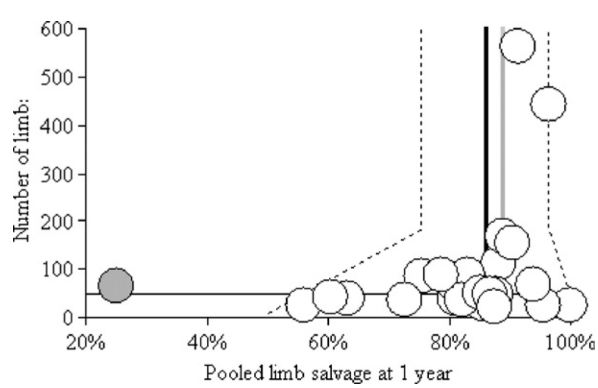

Fig 1. Inverted funnel graph shows one outlier *(gray circle)* whose exclusion increases the 12-month pooled estimate of limb salvage from 86% *(black vertical line)* to 89% *(gray vertical line)*. Symmetry for study size <50 does not indicate the presence of publication bias.

RESULTS

Characteristics of the original studies. Most of the 30 studies included targeted the population of patients with CLI generally (n = 24), but a few studies targeted diabetic patients (n = 2), patients with end-stage renal disease (n = 2), and poor candidates for bypass (n = 2). The mean age and the rates of male gender, hypertension, and diabetes mellitus were often reported, but most studies omitted the rates of smokers and patients with renal failure (Table I). Tissue loss and diabetes correlated moderately (n = 23, r = 0.63, P < .002), but no other important association was found in a correlation matrix of study variables. At least 141 of 2653 limbs (5.3%) did not have chronic CLI, but rather had intermittent claudication (n = 113), acute arterial occlusion (n = 18), or a failing graft (n = 10). In 21 studies, the most frequently treated artery was the tibioperoneal trunk (n = 8), the anterior tibial (n = 9), the peroneal (n = 4), or was not specified (n = 9). Of the 19 studies published since January 2000, only five reported the TransAtlantic Inter-Society Consensus classification of arterial lesions.[37]

The study design was retrospective in 26 of the 30 studies reviewed, of which eight came from United States and 22 from 11 European countries. Outcomes for primary a secondary patency, or both, were reported in 23 studies, and seven omitted patency. With respect to limb salvage, the number of articles that contributed at least one series to the meta-analysis was 25 initially and at 12 months, 17 at 24 months, and 10 at 36 months. Twenty-four studies (80%) reported the number of subsequent bypass grafts, but only 10 (33%) measured runoff. Nine studies used balloon angioplasty only, whereas the other 21 reported some technical peculiarities, which included subintimal angioplasty routinely (n =7) or occasionally (n = 4), stents (n = 3), atherectomy (n = 3), endografts (n = 1), thrombolytic therapy (n = 1), or a combination of these (n = 2). Overall, three crural PTAs alone were done for each crural PTA combined with a proximal PTA. The median score of study quality was 15 (range, 5-18), whereas the more common study defect was not using life-tables (n = 24) and not reporting the secondary patency (n = 22), the total number of PTA procedures (n = 20), and the losses to follow-up (n = 16).

Complications. In a total of 21 studies with 1743 crural PTAs, 136 (7.8%) procedure-related complications were reported. These included groin hematoma (n = 55), thrombosis (n = 37), embolism (n = 17), perforation (n = 13), dissection (n = 2), graft rupture (n = 1), false aneurysm (n = 5), gastrointestinal hemorrhage (n = 4), and unspecified complications (n = 2). Surgery other than amputation was required to treat the foregoing complications in 22 instances. Fifteen nonprocedural complications reported in five studies with 903 patients included nonfatal myocardial infarction, heart failure, or cardiac arrhythmia in 10, and azotemia in 5.

Main outcomes. The pooled estimate of immediate technical success was 89.0% ± 2.2% overall. The corresponding estimate was 91.4% ± 1.8% for 16 of the 22 studies of primary patency, 90.2% ± 2.9% for 10 of the 12 studies of secondary patency, and 85.0% ± 2.8% for 20 of the 25 studies of limb salvage. The middle-term estimates of primary patency, secondary patency and limb salvage were assessed reliably until 36 months (Fig 2).

In 14 studies primary patency was defined in a standard fashion, but nine other reported clinical or hemodynamic success only, which was used in the current study as a surrogate for primary patency, and seven did not report patency at all. No association was found between 12-month primary or secondary patency and any demographic or clinical variable. The pooled estimate of primary failure was 22.6% at 1 month, 2.4% to 5.8% from 2 to 6 months, and

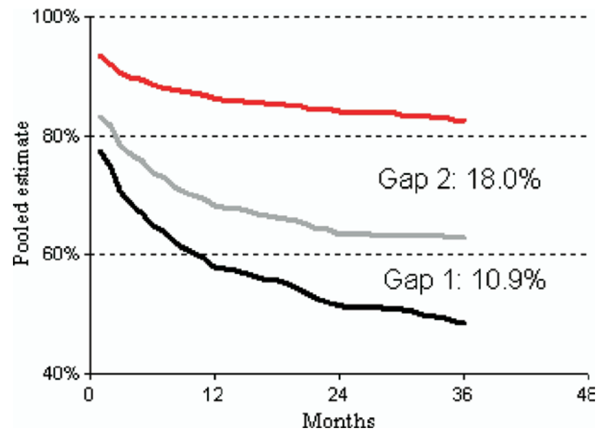

Fig 2. Meta-analysis estimates of primary patency *(black line)*, secondary patency *(gray line)*, limb salvage *(red line)*.

<2.7% from 7 to 36 months. Eight studies reported secondary patency in a standard fashion, three reported clinical success, and one reported tertiary patency, which measures the joint effect of repeated attempts at revascularization of any type. The pooled estimate of secondary failure was 16.7% ≤1 month, 1.1% to 4.3% from 2 to 6 months, and <2.3% from 7 to 36 months. The corresponding pooled estimates of patency were significantly worse than those estimated in the comparator meta-analysis (Table II).

The pooled estimate of amputation was 6.6% within the first month, 1.9% in the second month, 0.5% to 1.4% from 3 to 6 months, and was <0.8% from 7 to 36 months. The corresponding pooled estimates of limb salvage tended to be worse than those estimated in the comparator meta-analysis, but the difference was not significant (Table II). Limb salvage at 12 months correlated moderately with tissue loss (n = 21, $r = -0.60$, $P = .004$).

The median early mortality rate calculated for the data from 23 studies was 1.8%. In 10 studies with 1140 patients, 18 early deaths were attributed to complications of surgery (amputation in 2; bypass in 1), 8 to heart disease, and 7 to other causes, whereas 7 reported no early deaths for 228 patients, 6 did not discriminate the causes of 14 early deaths for 400 patients, and 7 omitted mortality information for 789 patients. Patient survival at 12 months correlated moderately with renal failure (n = 11, $r = -0.70$, $P = .02$), but was not associated with immediate technical success. The causes of late deaths in the studies reviewed were not reported with sufficient detail.

Subgroup meta-analysis. Subgroups did not differ significantly in patient survival and limb salvage at 1 and 12 months (Table III). The immediate technical success and the primary patency were significant better in the subgroup with >75% of the limbs with tissue loss. Patency and limb salvage results were slightly better for studies that used crural PTA combined with more proximal PTAs and for studies that used subintimal dissection routinely. In the latter studies, the inferior estimates of both technical suc-

Table V. Average difference (gap) between pooled estimates until 36 months

Studies	*Outcome*	*No.*	*Gap 1*	*Outcome*	*No.*	*Gap 2*
All	Primary patency	22	10.9%	Secondary patency	12	18.0%
	Secondary patency	12		Limb salvage	26	
Subgroups	Primary patency	11	7.6%	Secondary patency	9	21.9%
	Secondary patency	11		Limb salvage	9	

cess and 12-month survival contrasted with the superior estimates of 12-month limb salvage (Table III).

Sensitivity analysis. Of the 176 primary failures ≤1 month, 74 (42%) were immediate failures. When the results of the meta-analysis that included all available studies were contrasted with those obtained in the meta-analysis of specific subgroups, the difference between secondary and primary patency decreased from 5.9% to 2.0% at 1 month and from 14.3% to 9.4% at 36 months. The difference between secondary patency and patency increased from 10.1% to 11.7% at 1 month and decreased from 19.5% to 18.9% at 36 months. When the concept of early limb salvage excluded the limbs with persisting CLI or a successful bypass ≤1 month and the limbs with a hypothetical painful diabetic neuropathy, the difference between limb salvage and secondary patency in the specific subgroup of studies decreased from 11.7% to 6.4% at 1 month and from 18.9% to 13.3% at 36 months. Finally, the pooled estimate of primary patency and limb salvage changed by <3% at 36 months when selective exclusion of studies was done (Table IV), and the inverted funnel graph showed one outlier whose exclusion improved symmetry (Fig 1).

DISCUSSION

Low rates of early mortality have been alleged in favor of crural PTA in the management of CLI. The early death rate was slightly lower than that in the comparator meta-analysis (median, 1.8% vs 2.1%), but such rate may be higher when crural PTA is used as part of a PTA-first strategy. In this setting, Haider et al[2] recently reported an early mortality rate of 2.7% with the preferential use of infrainguinal PTA. In this current study, the procedure-related morbidity of 7.7% was tolerable when taking into account that surgical intervention other than amputation was done in 1.6% only.

The immediate technical failures of crural PTAs contributed 42% of the primary failures ≤1 month, whereas the primary patency estimates decreased at lower rates beyond that time. Of interest was that immediate technical failure limb salvage at 1 month correlated moderately, but such biologically plausible cause-and-effect association does not conform to the commonly held opinion that a failed attempt at crural PTA can be treated successfully with repeat crural PTA and does not harm subsequent attempts at bypass grafting.[3,9,7,20,22] Anyway, decreasing the rate of immediate technical failure is the key to improve patency and limb salvage. Clearly, this will depend on the development of more effective endovascular procedures and also on a better selection of cases, but these conditions may not be compatible each other. For example, subintimal dissection has extended the use of crural PTA for long occlusive lesions at the expenses of inferior rates of technical success.

Also as a consequence of high rates of technical failure, the pooled primary patency of 77.4% at 1 month for crural PTA did not match the pooled primary patency of 93.3% in the comparator meta-analysis.[33] Repeat attempts at PTA after immediate failure or loss of patency represent an advantage over repeat bypass grafting, which is troublesome and not always feasible, but such advantage has not been measured precisely. In the current overview, the relationship between primary and secondary patency was measured by using all available studies initially and by using a special subset of 15 studies in a second step (Table V). In the latter, the difference between secondary and primary patency of 11.7% at 36 months exceeded the difference of 4.4% in the comparator meta-analysis. By definition, this reflected the advantage of repeat crural PTA over revision bypass surgery in the maintenance of patency. Likewise, the difference between limb salvage and secondary patency of about 19% at 36 months exceeded by far the difference of 5.6% in the comparator meta-analysis.

Of interest was that the disparity between limb salvage and secondary patency was noted earlier in the first month and increased slowly thereafter; One should therefore pay attention to the preoperative conditions and perioperative events when trying to explain that disparity. With regards to preoperative conditions, there were fewer limbs with tissue loss and fewer diabetic patients than in the comparator meta-analysis. The studies reported that patients with fewer limbs with tissue loss not only fared better for limb salvage but also for the other outcomes, possibly because of less advanced arterial disease. In addition, limbs with rest pain require less complete revascularization to avert CLI and to avoid amputation. Although diabetic patients with tissue loss are in greater danger of amputation, diabetic patients with pain at rest in their lower extremities do not always have truly limb-threatening ischemia[38] but rather painful diabetic neuropathy, a condition that afflicts 25% of this population but does not jeopardize limb viability.[34]

Three main factors may have influenced the wide gap between limb salvage and secondary patency:

- CLI persisted after crural PTA failure, but a proximal PTA remained patent.[39]

- Subsequent bypass graft surgery avoided a certain number of amputations. Indeed, in the nine studies that described both limb salvage and secondary patency, there were 157 secondary losses of patency but only 56 amputations, thus leaving 82 losses to be explained. Because there were at least 114 crural PTAs combined to a more proximal PTA and at least 25 subsequent bypasses, the joint effect of these procedures can explain the magnitude of Gap 2 (Table V), at least in part.
- Possibly not all patients had truly limb-threatening ischemia.[38] Despite the loss of patency, these hypothetical patients could have remained with mild rest pain or small ulcers indefinitely or could have amputation delayed.

The growing experience, the many technical refinements of PTA—notably subintimal dissection—and the continuous improvement in limb salvage found in the cumulative meta-analysis justify the prospect of better outcomes for crural PTA in the near future. As a reflection of the state of the art, Haider et al[2] recently reported an early death rate of 2.7% for 166 angioplasty (67%) and 80 bypass patients (33%) in the femoropopliteal axis and 32 angioplasty (28%) and 82 (72%) bypass patients in the infrapopliteal area, whereas additional attempts at revascularization after PTA failure included more bypasses than PTA procedures. These data indicate that the crural PTA-first strategy is not necessarily safer, is of limited use, and complements rather than replaces bypass surgery. Amputation-free survival and the quality of life for strictly comparable patients have shown no difference between a PTA-first strategy and a bypass-first strategy, but the latter has been more costly.[1]

The current study has several limitations attributable to shortcomings in the existing literature combined with the nonrestrictive criteria of inclusion adopted. First, because in several studies of small size the follow-up time was naturally short, only a few studies were available for the meta-analysis of middle-term outcomes. Second, the subgrouping of studies did not separate patients with or without tissue loss completely and included fewer studies in the subgroup of both crural PTA alone and in the subgroup of subintimal angioplasty. Third, some topics could not be properly addressed, notably the relationship between technical failure, further intervention, and the fate of the index limb. Finally, some attractive features of crural PTA could not be addressed at all, namely the use of local anesthesia, the avoidance of surgical incision, a shorter length of hospital stay, patients' preferences, the impact on costs, and the use of a crural PTA with low chance of success faced with an imminent major amputation.

Internal and external validity of the inferences from this meta-analysis seem supported. The studies were reviewed in sufficient number, used data of acceptable quality, and reported high response rates, whereas the systematic review used an inclusive set of entry criteria compatible with real life. Subgroup meta-analysis showed that a low proportion of tissue loss and crural PTA combined to proximal PTA introduced a measurable bias in favor of crural PTA compared with the meta-analysis of surgical bypasses (Table III). Finally, sensitivity analysis mitigated other limitations by excluding several studies for different reasons and by creating a scenario to explain the disparity between limb salvage and secondary patency.

CONCLUSION

Despite comparison of crural PTA with bypass grafts that shows better primary and secondary patency than with open surgical procedures, limb salvage is comparable between the two series and shows the potential of PTA for treating CLI. The choice of this therapeutic method as an initial option or not during patient's treatment demands experience and judgment from the surgical team. The ideal situation is the one where surgical teams that are traditionally involved with limb salvage operations and distal bypass get experience with PTA practice. This universe of medical practice is wide. Although PTAs can be repeated, they are not innocuous. Some urgent situations can result as a failure of attempted PTA, and a surgical bypass grafting may be required. On the other hand, surgical bypass may benefit from endovascular technology, from the operation to the postoperative period, as these techniques are more and more involved in bypass-saving procedures. Elucidation of the proper role of crural PTA requires further studies.

AUTHOR CONTRIBUTIONS

Conception and design: MA, CP
Analysis and interpretation: MA, MR, NDL
Data collection: MA, FBN, MR
Writing the article: MA, NDL
Critical revision of the article: NDL, AD
Final approval of the article: MR, FBN, AD, CP, NDL
Statistical analysis: MA, CP, NDL
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MR and NDL participated equally.

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Appendix (online only). Characteristics of the 30 original studies reviewed

First author	*Patients*	*Limbs*	*Diabetes, (%)*	*Tissue loss, %*	*Crural PTAs*	*Combined PTA, %*
Haider[2]	32	32	NA	NA	32	NA
Kudo[3]	52	52	NA	NA	52	NA
Boyer[4]	49	49	73.5	59.2	49	NA
Parsons[5]	66	66	NA	NA	66	0
Spinosa[6]	40	44	60.0	90.9	50	58.0
Wölfle[7]	84	89	88.1	94.4	89	0
Marzelle[8]	23	23	76.0	87.0	25	36.0
Vraux[9]	36	40	72.2	77.5	40	20.0
Treiman[10]	25	25	48.0	24.0	25	0
Brosi[11]	29	38	60.0	NA	38	52.6
Aulivola[12]	79	90	78.0	100	90	31.1
Sigala[13]	52	52	100	76.9	52	0
Brillu[14]	37	37	48.6	64.9	37	51.4
Brown[15]	40	40	63.6	NA	55	0
Bull[16]	168	168	52.4	36.3	168	34.5
Danielsson[17]	140	155	57.1	62.6	155	76.1
Favre[18]	24	25	50.0	54.2	25	0
Löfberg[19]	82	86	74.4	89.4	92	59.8
Ingle[20]	77	77	46.0	51.9	79	0
Vraux[21]	46	50	60.9	92.0	50	0
Nydahl[22]	27	28	33.0	85.7	28	67.9
Tisi[23]	51	51	NA	NA	51	25.5
Söder[24]	60	72	76.7	90.3	72	NA
Barton[25]	43	NA	51.2	NA	48	47.9
Lazaris[26]	24	24	NA	NA	24	41.7
Sivananthan[27]	38	41	13.2	10.5	50	88.0
Faglia[28]	564	564	100	82.5	564	26.8
Bosiers[29]	443	443	44.0	19.9	443	NA
Schwarten[30]	96	112	62.5	76.0	112	6.3
Ascher[31]	30	32	73.0	50.0	32	87.5

NA, Data not available; *PTA,* percutaneous transluminal angioplasty.