BMJ Open Diabetes Research & Care

Lower extremity reamputation in people with diabetes: a systematic review and meta-analysis

Rongqi Liu,[1,2] Brian J Petersen ,[1] Gary M Rothenberg,[3] David G Armstrong[4]

To cite: Liu R, Petersen BJ, Rothenberg GM, *et al*. Lower extremity reamputation in people with diabetes: a systematic review and meta-analysis. *BMJ Open Diab Res Care* 2021;**9**:e002325. doi:10.1136/bmjdrc-2021-002325

► Supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2021-002325).

Received 11 April 2021
Accepted 9 May 2021

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[1]Podimetrics Inc, Somerville, Massachusetts, USA
[2]Harvard University T H Chan School of Public Health, Boston, Massachusetts, USA
[3]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan, USA
[4]Department of Surgery, USC Keck School of Medicine, Los Angeles, California, USA

Correspondence to
Brian J Petersen;
authors@podiography.org

ABSTRACT

In this study, we determined the reamputation-free survival to both limbs and to the contralateral limb only following an index amputation of any-level and assessed whether reamputation rates have changed over time. We completed a systematic search using PubMed and screened a total of 205 articles for data on reamputation rates. We reported qualitative characteristics of 56 studies that included data on reamputation rates and completed a meta-analysis on 22 of the studies which enrolled exclusively participants with diabetes. The random-effects meta-analysis fit a parametric survival distribution to the data for reamputations to both limbs and to the contralateral limb only. We assessed whether there was a temporal trend in the reamputation rate using the Mann-Kendall test. Incidence rates were high for reamputation to both limbs and to the contralateral limb only. At 1 year, the reamputation rate for all contralateral and ipsilateral reamputations was found to be 19% (IQR=5.1%–31.6%), and at 5 years, it was found to be 37.1% (IQR=27.0%–47.2%). The contralateral reamputation rate at 5 years was found to be 20.5% (IQR=13.3%–27.2%). We found no evidence of a trend in the reamputation rates over more than two decades of literature analyzed. The incidence of lower extremity reamputation is high among patients with diabetes who have undergone initial amputations secondary to diabetes, and rates of reamputation have not changed over at least two decades.

INTRODUCTION

Every year, more than one million people undergo a lower extremity amputation (LEA) secondary to diabetes, resulting in a limb loss every 20 s worldwide.[1] LEAs are life-altering events that are associated with substantial morbidity and mortality,[2] poor quality-of-life,[3] prolonged inpatient stays,[4] and high readmission rates.[5] After a period of prolonged steady decline of LEA rates, over the past decade rates of LEA have rebounded by 50%.[6]

Despite these well-known negative consequences of amputations and known increasing incidence, risk for subsequent amputation following an initial amputation has been reported to be high. A large-scale study in 71 300 Medicare beneficiaries undergoing dysvascular amputation found that 26% of patients with diabetes required subsequent reamputation within 12 months.[2] Similarly, Borkosky *et al*[7] estimated that one in every five patients who had undergone initial ray amputation required reamputation. Considering all-level index LEAs among patients with diabetes, Kanade *et al*[8] found that within 2 years, as many as 45.9% with a prior LEA required reamputation, with 22% incidence of contralateral LEA.

Synthesizing these data and data from other trials examining reamputation, two recent meta-analyses of postamputation outcomes among patients with diabetes estimated a 1-year reamputation rate of 19.8% after partial ray amputation[7] and 28.4% after transmetatarsal amputations (TMAs).[9] However, these studies only reported data on certain distal index amputations. They were also limited in reporting only at specific durations after an index amputation instead of reporting a reamputation-free survival distribution over time. Additionally, neither study considered whether the subsequent amputation occurred to the same or contralateral limb. Finally, neither study considered how reamputation rates are evolving over time.

Thus, closer scrutiny and analysis of all available evidence is needed to understand the progression of limb loss for patients with diabetes after any level of index amputation. The purpose of this study is to synthesize available data on reamputation rates and estimate the reamputation-free survival following index amputations of all levels for those with diabetes and to determine whether reamputation rates have improved over time.

METHODS

Nomenclature

For the purpose of this review, we adopted definitions from the International Standards Organization.[10] 'Amputation' was defined as surgical removal of the whole or part of a limb. 'Index amputation' is a first or primary amputation. 'Reamputation' was defined as a subsequent amputation. Any soft tissue surgeries such as reoperation, debridement, revascularization surgeries, or secondary wound closure are not considered an amputation or reamputation. 'Revision' was defined as a surgical procedure on a previously amputated limb without changing the level of amputation, and was also excluded from the definition of reamputation. 'Contralateral amputation' was defined as an amputation to the contralateral limb after an index amputation. Contralateral amputations were considered reamputations for the purpose of this review.

Search strategy

Our systematic review relied a study protocol preregistered with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol (PROSPERO 2020 CRD42020206148). On June 10, 2020, under a preregistered protocol, a systematic search was conducted using PubMed with the following search query: (reamputat* OR re-amputat* OR "secondary amputation" OR "repeat amputation" OR "subsequent amputation") AND ("diabetes" OR "neuropathy" OR "Diabetic Foot"[Mesh]). No date restrictions were placed on the searches. To augment the PubMed search, we screened and reviewed citations from included studies for eligibility.

Inclusion criteria

To be eligible for inclusion in the systematic review, studies must have been written in English and published in a journal indexed by PubMed. Only original research articles were included, including cohort studies, case–control studies, prospective clinical trials, and retrospective chart reviews. Case reports, review articles, and meta-analyses were excluded. Studies that only investigated amputation or that did not have specific data regarding reamputations were excluded. Studies must have reported on the time point at which reamputation was performed relative to the timing of the index amputation.

We included in the meta-analysis only those studies included in the systematic review that exclusively enrolled participants with diabetes mellitus.

Data compilation

Data were extracted by a primary reviewer and independently assessed by a secondary reviewer for accuracy. A third author adjudicated any disagreements between the primary and secondary reviewers. We completed full-text reviews for those studies which the primary reviewer believed could plausibly meet the inclusion criteria based on the title and abstract.

Articles selected for full-text review were summarized and data were extracted including country, year, number of participants, age, percentage of participants with diabetes, numbers and levels of index amputations, numbers and levels of reamputation, mortality, and mean follow-up duration in months. For studies including a reamputation-free survival curve, these data were digitized at an interval of 1 year.

Risk of bias assessment

We did not complete a risk of bias assessment for this systematic review and meta-analysis because we are not synthesizing the results of an intervention but instead are reporting on and synthesizing epidemiological data and thus for our purposes publication bias is unlikely.

Statistical analysis

Given the broad inclusion criteria of the studies included, we used a random-effects model because we anticipated heterogeneity in the reamputation incidence data reported resulting from differences in the studies' year undertaken, care environment, nature of the index amputation, and inclusion criteria of the studies comprising our analysis.

Because reamputation incidence data at multiple durations from the index amputation were available, we did not conduct a conventional random-effects meta-analysis at isolated time points, which may have resulted in inconsistent non-monotonic estimates of the reamputation rates. For example, using such a modeling approach, depending on the data and studies reporting data at the time points considered, the random effects point-estimate of the year 3 reamputation rate could have been found to be lower than the year 5 reamputation rate.

Instead, to address this potential issue and satisfy the random-effects assumption, we fit a parametric survival distribution to the data in a multilevel model with hyperparameters over the inputs to the survival distribution. We used a log-logistic parametric survival distribution. The distribution was formulated with a shape parameter and a median parameter as input. We assumed beta distributions over the shape and median parameters of the log-logistic distribution and solved for the four unknown inputs to the two beta distributions by maximizing the log-likelihood over the reported reamputation rates from the included studies. We then sampled the posterior distribution using a Markov chain Monte Carlo Ensemble sampler to estimate the uncertainty in the survival distribution estimate.

We completed this aforementioned analysis for studies with 100% of participants with diabetes mellitus that reported on contralateral or all reamputation rates. We included forest plots for all reamputations as well as the maximum-likelihood parametric survival distributions and IQRs for each category of reamputation.

To determine whether reamputation rates are improving over time, we extracted the residual between the maximum likelihood estimator from the parametric survival model analysis and the point estimates from the individual studies. We tested for a trend using the non-parametric Mann-Kendall test at a significance level of α=0.05.

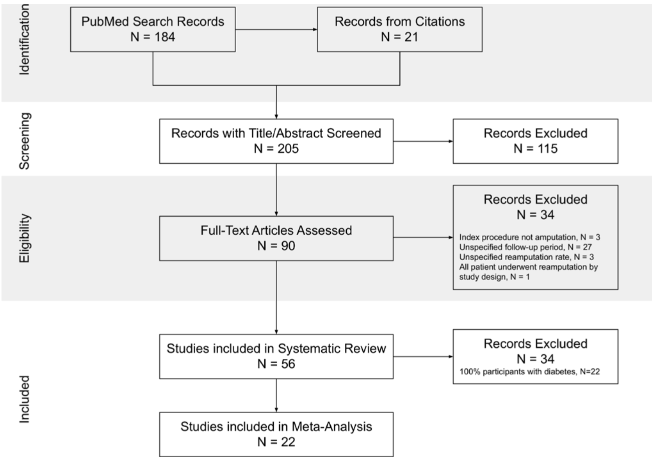

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

RESULTS

Included studies

Figure 1 shows the PRISMA flowchart for those studies included in the systematic review and meta-analysis. The keyword search yielded 184 unique citations screened for eligibility, and the citations for these studies were screened to obtain 21 further articles of relevance. Overall, 205 articles were identified and screened. Screening by title and abstract excluded 115 articles for relevance, leaving 90 for full-text review. Another 34 articles were excluded because they did not meet inclusion criteria or lacked sufficient reporting to inform our outcomes of interest. The final quantitative synthesis included 56 studies, and after screening on those with enrollment consisting of 100% patients with diabetes, the meta-analysis included 22 studies.

Systematic review study characteristics

Online supplemental table 1 summarizes the salient characteristics of the 56 studies included in the systematic review.[2 5 8 11–63] The publication year ranged from 1967 to 2020. Forty-two (75%) were retrospective and 14 (25%) were prospective studies. The majority of included studies (26, 46%) reported outcomes for populations in the USA, and a handful of studies (15, 27%) reported data in European countries. Only four studies reported outcomes outside of the USA or Europe.[12 17 47 59]

The combined studies included in the systematic review summarize the risk of reamputation in 58 272 participants with 58 684 index amputations. Study cohorts ranged from 11 to 17 786 participants with average ages ranging from 46 to 77 years. Most studies reported a majority of participants with diabetes (range: 23%–100%). Indications for index amputation were clarified in 30 studies, with the most commonly reported reasons including gangrene, infection, ischemia, diabetes related, and osteomyelitis. Weighted values were calculated to account for variations in sample size. The initial amputation levels included both distal (partial foot, TMA, and amputation at the ankle) and proximal LEAs (above the ankle).

Methods and follow-up durations varied across studies, but follow-up at 30 days (perioperative), 1, 3, and 5 years were most common. In total, 22 studies reported follow-up at 1 year (12 months), 7 studies at 3 years (36 months), and 12 studies at 5 years (60 months). There were isolated data for other time points such as 3, 6, and 48 months after index amputation. Four articles that followed patients up to 5 years also reported outcomes at 1 year, 3 years, or both.

Meta-analysis

Of the 56 studies included in the systematic review, 22 included participants with diabetes mellitus exclusively and were thus included in the meta-analysis.[11 14 16–19 22 28 37 38 42 47 50 51 53 55 57–59 61 62] There are 31 discrete incidence values from 22 studies reporting either ipsilateral or contralateral reamputations, and 8 incidence values from 5 studies[11 19 22 38 42] reporting on contralateral reamputations. A total of 21 145 primary amputation cases were followed for the all reamputation meta-analysis, and 1129 primary amputation cases were followed for contralateral reamputation meta-analysis.

Figure 2 shows the reamputation-free survival curves for contralateral and all reamputations through 6 years, and figure 3 shows a forest plot for the reamputation rates at three distinct time points from the index amputation for all reamputations. At 1 year, the reamputation rate for all contralateral and ipsilateral reamputations was found to be 19% (95% CI=0.4% to 45.2%; IQR=5.1%–31.6%), and at 5 years, it was found to be 37.1% (95% CI=9.4% to 58.9%; IQR=27.0%–47.2%). The contralateral reamputation rate at 5 years was found to be 20.5% (95% CI=6.2% to 36.1%; IQR=13.3%–27.2%).

We observed no trend in the reamputation rate as a function of study year at a significance level of α=0.05 (p=0.4; Kendall τ=−0.11).

DISCUSSION

This study was designed to determine the survival distribution of all-level reamputations to both the ipsilateral and contralateral limbs and to assess whether reamputation rates are improving over time. We found high incidence rates for both categories of reamputation. At 1 year, the reamputation rate for all contralateral and ipsilateral reamputations was found to be 19% (IQR=5.1%–31.6%), and at 5 years, it was found to be 37.1% (IQR=27.0%–47.2%). The contralateral reamputation rate at 5 years was found to be 20.5% (IQR=13.3%–27.2%). There was no evidence of a trend in the reamputation rates over the period spanned by the studies in the meta-analysis (p=0.4; Kendall τ=−0.11).

Our results reflect the high recidivism rates following index amputations documented throughout the literature: for many patients with diabetes after an initial partial-foot amputation, a subsequent proximal amputation is required, sometimes at the transfemoral level.[16 53] Murdoch *et al*[42] reported that 1 year after index

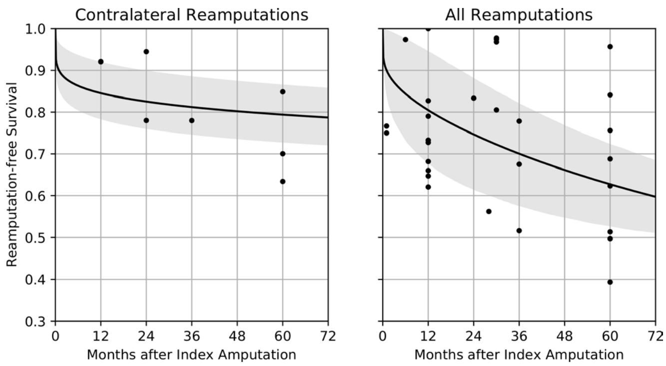

Figure 2 Reamputation-free survival curves for contralateral reamputations (left) and all reamputations (right) among patients with diabetes. The solid line is the maximum-likelihood estimate of the log-logistic survival model. The shaded area represents the IQR.

amputation, 60% of all patients had a second amputation, 21% had a third amputation, and 7% had a fourth amputation. Similarly, Kono and Muder[34] reported that approximately 50% of patients required ipsilateral reamputation by 3 years after the index amputation. In addition to the reamputation rates, the reoperation rate has also remained high. A chart review of 52 patients found a total of 85 additional operations required, with some patients undergoing as high as four additional operations,[64] although some patients included in this study had prior amputation history, so the subsequent amputations could be confounded by the progression of other underlying health conditions and thereby contribute to an overestimation of the reamputation rate. Nonetheless, evidence has suggested that patients with diabetes are at high risk of perioperative death,[13 14 21] and therefore, any additional operations would presumably impose additional risk of mortality.

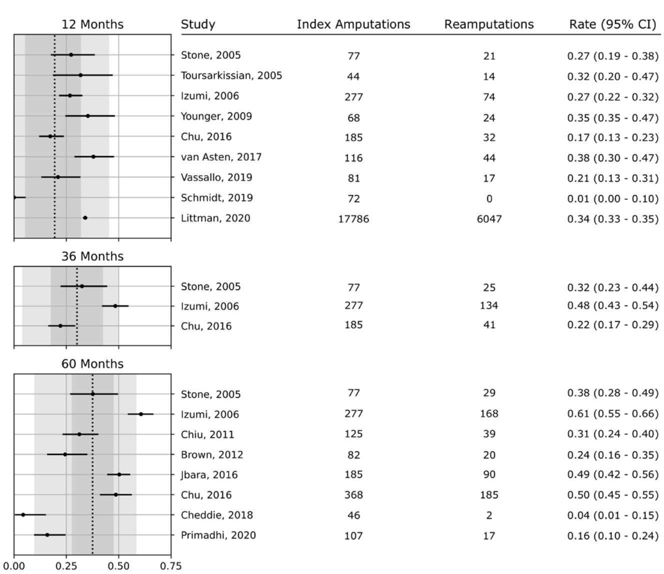

Figure 3 Estimates of all reamputation rates among patients with diabetes. The lighter shading represents the 95% CI, and the darker shading represents the IQR.

Our results suggest there has been no major change in the reamputation rate over a prolonged period. Follow-up work should investigate whether the incidence of reamputation is changing relative to the incidence of index amputation, but this more sophisticated analysis was outside the scope of the present investigation. Improvements in reamputation rate may be impeded by challenges of selecting the optimal level of index amputation, poor surgical wound healing and rehabilitation following amputation, and likelihood of recurrence of diabetic foot wounds particularly with the introduction of further foot deformity and gait deviation post amputation. Routinely, the most distal location is chosen for wounds in order to preserve the integrity of the remaining foot, resulting in an amputation of the digits. However, some studies have demonstrated that a lower level of index amputation is associated with higher risks of re-ulceration and a lower rate of healing.[65] In addition, persons with diabetes can also experience a significant progression of the underlying disease process.[21] This in turn leads to a higher risk of more proximal ipsilateral reamputation or amputation of the contralateral limbs.

Our review identified inconsistent anatomic definitions used among the studies, making comparisons across studies challenging. For example, a contralateral amputation was defined as amputation at or proximal to the transmetatarsal level on the opposite lower limb,[30] any amputation of the contralateral foot or leg,[8 42] or a new amputation at a lower level than the index amputation.[56] Other studies either did not provide a precise definition[21] or further divided subsequent amputations on the contralateral side by anatomical levels.[19 38] Standardized definitions are needed for future research to mitigate the methodological discrepancies and allow for a more accurate comparison of published results regarding index and reamputation status.

We executed a comprehensive search strategy without any date restrictions and extracted articles that were cited by each of the identified studies. This allowed us to retrieve a high volume of articles and facilitated our examination of changes in the reamputation rate over time. The main strength of this study is that by reviewing and synthesizing the extant literature, we were able to provide an estimate of survival from reamputation for both limbs and for the contralateral limb. In addition, our review primarily focused on patients with diabetes, and therefore the results are relevant to clinical decision making and selection of the appropriate measures used to prevent reamputation in people with diabetes at high risk of future foot complications. This work contributes to existing knowledge of the high re-ulceration rate of the ipsilateral and contralateral limb. It has been estimated that after ulcer healing, 40% of patients have a recurrence within 1 year, and as high as 65% within 5 years. Taken together, the current evidence suggests the tremendous financial as well as the medical burden of foot complications on the diabetic population and highlights the importance of diabetic ulcer prevention.

This study had several limitations. First, like most meta-analyses, ours was limited by publication bias of the studies underlying our analysis. We believe that this limitation is somewhat mitigated in our case by the fact that we are not analyzing the results from the intervention groups of randomized studies but instead relying on data observational studies. Second, many studies identified were retrospective studies and thereby lacked granularity on the progression of reamputation status per year, which limited the amount of data available for our meta-analysis. This limited literature evidence revealed a need for more prospective research with extended follow-up periods, in order to synthesize long-term results and investigate the key determinants of the performance of different diabetic care systems. Finally, we did not perform a formal assessment of risks of bias because all papers included in this review were observational in nature and have a low risk of bias for our purposes.

The incidence of lower extremity reamputation is high among patients with diabetes who have undergone initial amputations secondary to diabetes. Long-term reamputation-free survival decreased with longer follow-up, and patients with diabetes are at a distinctly higher risk of reamputation at any follow-up lengths. For all-level or contralateral reamputation rates, the lack of significant downward trends over the past 50 years calls for improved prevention efforts. This systematic review and meta-analysis revealed high heterogeneity in study design and confirmed the need to standardize outcome reporting methods in future studies. Additional focus on prevention for those with recent amputations is necessary to reduce overall incidence of LEA.

Contributors RL and BJP: study concept and design, acquisition of data, analysis of data, interpretation of results, and preparation of the manuscript. GMR: study concept and design, and preparation of the manuscript. DGA: preparation of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests RL is an employee of Podimetrics Inc. BJP is an employee and shareholder of Podimetrics Inc. GMR is a consulting medical director for Podimetrics Inc. DGA is on the scientific advisory board of Podimetrics Inc.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request to the corresponding author.

ORCID iD

Brian J Petersen http://orcid.org/0000-0002-9552-5859

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Supplemental Table 1. Study characteristics (N=56 published reports)

Author, Year	Country	Study Design	Number of Patients	% Diabetic	Mean Age/Age Range	Number of Primary Amputations	Time for Reporting (Months)	Number of Reamputations	Reamputation laterality	Included in meta-analysis
Aftabuddin, 1997[12]	Bangladesh	Retrospective chart review	450	5% diabetes-associated complications	46 (18-68)	450	72	36	All	
Ahn, 2019[13]	USA	Retrospective	203	82%	Median 62 (53.0-71.0)	203	1	88	All	
Baykal, 2014[14]	Turkey	Prospective cohort	30	100%	70.2 (46-91)	30	1	7	All	Yes
Beaulieu, 2015[5]	USA	Retrospective chart review	717	75%	56	717	2	95	All	
Blume, 2007[15]	USA	Retrospective comparative study	80	89%	62 (21-91)	91	12	25	All	
Brown, 2012[16]	USA	Retrospective chart review	82	100%	53.4 - 63.8	82	60	20	All	Yes
Cheddie, 2018[17]	South Africa	Prospective cohort	46	100%	61 (29-80)	46	60	2	All	Yes
Chiu, 2011[18]	Taiwan	Prospective cohort	125	100%		125	60	39	All	Yes
Choi, 2014[63]	South Korea	Retrospective chart review	154	100%	63.9	154	30	30	All	Yes
Chu, 2016[19]	China	Prospective	185	100%	69.27 ± 9.39 (38 – 86)	185	12	32	All	Yes
							36	41	All	
							60	90	All	
							60	28	Contralateral	
Czerniecki, 2019[20]	USA	Retrospective cohort	5260	74.20%	64.9 ± 9.5	5260	12	1283	All	
Dillingham, 2005[2]	USA	Retrospective cohort	3565	74%	73.7 (21-107)	3555	12	924	All	
Ebskov, 1980[21]	Denmark	Retrospective chart review	2029	53%		2029	12	241	Contralateral	
							24	361	Contralateral	
							36	552	Contralateral	

							48	899	Contralateral	
							48	830	All	
Elsharawy, 2011[22]	Saudi Arabia	Prospective cohort	32	100%	66.9 ±11.7	32	1	8	All	Yes
							28	14		
Eneroth, 1992[23]	Sweden	Prospective cohort	177	40%	77 (43-95)	177	6	19	All	
Fard, 2020[24]	Netherlands	Retrospective cohort	382	56%	71.9 ± 12.5	380	12	70	Contralateral	
Font-Jiménez, 2016[25]	Spain	Retrospective	353	75.3	68.7±10.8	265	12	80	All	
Glaser, 2013[26]	USA	Retrospective chart review	1715	77%	66.7± 13.5; 68.56± 13.4	1715	12	189	All	
							12	69	Contralateral	
							60	324	All	
							60	162	Contralateral	
Häller, 2020[27]	Switzerland	Retrospective cohort	185	74%	67 (24-91)	185	36	71	All	
Izumi, 2006[11]	USA	Retrospective cohort	277	100%	53.8 ± 10.4	277	12	74	All	Yes
							12	22	Contralateral	
							36	134	All	
							36	61	Contralateral	
							60	168	All	
							60	83	Contralateral	
Jbara, 2016[28]	USA	Retrospective	368	100%	61.87 ± 14.52	368	60	185	All	Yes
Jindeel, 2012[29]	USA	Retrospective chart review	847	88%	Male: 53.7 Female: 58.95	1169	12	312	All	
Johannesson, 2009[30]	Sweden	Prospective cohort	290	46%	DM: women: 77±9, men: 76±11; Non DM: women: 83±8, men: 79±8	133	120	52	All	

							120	52	Contralateral	
Johannesson, 2010[31]	Sweden	Prospective cohort	217	14%	77	217	12	30	All	
							12	12	Contralateral	
Jupiter, 2020[32]	USA	Retrospective chart review	5980	71%	63.4 ± 13.3	5980	1	81	All	
Kacy, 1982[33]	USA	Retrospective chart review	100	55%		113	60	17	All	
Kanade, 2007[8]	UK	Retrospective chart review	205	43%	68.59 ± 10.80	316	24	145	All	
							24	46	Contralateral	
Kono, 2012[34]	USA	Retrospective	116	80%	66.8 ± 11.0	116	6	45	All	
							36	57	All	
Landry, 2011[35]	USA	Retrospective case-control	57	79%	60.7 (13.4)	62	4	22	All	
Lin, 2020[36]	USA	Retrospective cohort	11597	82%	62 ± 13 among DM	11597	12	2270	All	
Littman, 2020[37]	USA	Retrospective chart review	17786	100%		17786	12	6047	All	Yes
Matsuzaki, 2012[38]	Japan	Prospective cohort	31	100%	67.5 (46-87)	36	24	6	All	Yes
							24	2	Contralateral	
Mazet, 1967[39]	USA	Retrospective chart review	541			541	24	119	Contralateral	
							60	198	Contralateral	
McCallum, 2012[40]	USA	Retrospective chart review	11	91%		12	1	1	All	
Møller, 1985[41]	Denmark	Retrospective	64	34%		64	12	28	All	
Murdoch, 1997[42]	USA	Retrospective	90	100%		90	120	54	All	Yes
								8	Contralateral	
Nagashima, 1993[43]	Japan	Retrospective cohort	114	23%	61.4 (46-75)	114	36	17	All	
Nayak, 2016[44]	Denmark	Retrospective cohort	81	39%	71 ± 11.8	81	3	13	All	
Netz, 1983[45]	Sweden	Retrospective	283	40%	DM: 72.8± 8.6 Atherosclerosis:	302	12	45	All	

					77.5± 8.6					
Pollard, 2006[46]	USA	Retrospective chart review	91		0.87	101	24	31	All	
Primadhi, 2020[47]	Indonesia	Retrospective chart review	107	100%	56.2 ± 7.9	107	60	17	All	Yes
Rosen, 2014[48]	Israel	Retrospective cohort	188	76%	72 (25-103)	208	2	40	All	
Rucker-Whitaker, 2003[49]	USA	Retrospective case-control	120	62%-72%	AA: 66.6 (11.2%), White: 64.2 (12.9%)	120	60	32	All	
Schmidt, 2019[50]	USA	Prospective	72	100%	56.9 ± 12.8	72	12	0	All	Yes
Sizer, 1972[51]	USA	Retrospective chart review	577	100%	56.8	692	144	357	All	Yes
Stirnemann, 1987[52]	Switzerland	Retrospective cohort	413	24%-53%	BK: 70 (47-86); TG: 72 (54-93); AK: 74 (55-93)	413	50	55	All	
Stone, 2005[53]	USA	Retrospective chart review	74	100%	64 (45-81)	77	12	21	All	Yes
							36	25	All	
							60	29	All	
Thomas, 2001[54]	UK	Retrospective chart review	41	71%	71 (40-91)	41	96	15	All	
Toursarkissian, 2005[55]	USA	Retrospective chart review	41	100%	59 ± 11	44	12	14	All	Yes
Vaccaro, 2002[56]	Italy	Retrospective chart review	701	47%		738	12	35	All	
								7	Contralateral	
van Asten, 2017[57]	USA	Prospective cohort	122	100%	18-89	116	12		All	Yes
Vassallo, 2019[58]	Malta	Prospective	81	100%	70 ± 12.3	81	12		All	Yes
Viswanathan, 2010[59]	Bangladesh	Prospective cohort	177	100%	55.0 (10.0)	177	30	4	All	Yes
	India		194	100%	60.0 (10.3)	194	30	5	All	
	Tanzania		155	100%	55.6 (11.6)	155	30	5	All	
Wied, 2017[60]	Denmark	Retrospective case-control	74	53%	72.3 ± 11.0	74	1	20	All	
Wong, 2013[61]	Singapore	Prospective cohort	151	100%	55.2	151	6	4	All	Yes
Younger, 2009[62]	Canada	Retrospective comparative	68	100%	Successful: 60.4 ± 11.8	68	12	24	All	Yes

	study	Failed: 56.3 ± 10.9

Data presented as mean (range), mean ± standard deviation, or %.