Surgical Bypass of Femoral-Popliteal Arterial Disease: A Meta-analysis of Randomized and Prospective Trials

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Abstract

Objectives. To better define historical graft patency rates and adverse events following surgical bypass for femoral-popliteal arterial disease in patients with and without critical limb ischemia (CLI) and compare with contemporary studies. **Background.** Bypass surgery has traditionally been recognized as the standard treatment for femoral-popliteal arterial disease although this area is understudied and rates in unselected, "real-world" patients remain poorly defined. **Methods.** A systematic literature search was conducted to identify studies reporting outcomes after femoral-popliteal bypass surgery since 1990. Studies were selected if they were randomized controlled trials or prospective multicenter registries that reported 30-day major adverse events and/or 12-month patency rates. **Results.** The search yielded 1192 studies, 52 studies of which met eligibility criteria. This included 45 randomized trials and >15,000 patients. Following femoral-popliteal bypass surgery with any graft type, 30-day event rates were 1.8% all-cause mortality, 2.4% myocardial infarction, 0.9% stroke, 2.0% target-lesion revascularization, 2.1% above-the-ankle amputation, 2.0% deep vein thrombosis, 2.0% major bleeding, and 5.4% procedure-related infections. At 12 months, reported patency rates with autologous vein graft bypass were 78.9% primary patency, 86.7% primary assisted patency, and 86.8% secondary patency. Patency rates were lower with synthetic grafts. Event rates were similar when compared with more contemporary randomized controlled trials of bypass patients. **Conclusion.** Despite limitations in historical trials studying femoral-popliteal bypass surgery in CLI and non-CLI patients, rates of graft patency and major adverse events are similar in more contemporary, high-quality trials.

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Key words: critical limb ischemia, femoral-popliteal bypass surgery, patency, peripheral arterial disease

Based on recent estimates, peripheral arterial disease (PAD) affects approximately 11% of the adult population in the United States, while critical limb ischemia (CLI), a more severe form of PAD defined by rest pain or tissue loss, afflicts greater than 1% of the adult population.[1] CLI is associated with significant mortality and amputation risk[2] and various surgical and endovascular treatments are available for its management.[3]

Although surgical management of PAD and CLI with autologous vein grafts has traditionally been considered the standard approach, it is still associated with significant morbidity and mortality.[4-6] As a result, endovascular treatments, including stenting, drug-coated balloons (DCBs), and atherectomy, are now far more frequently used in practice, with promising outcomes even in CLI patients.[7-12] Still, until recently, there were limited high-quality trials comparing various treatments,[9,13-17] and it had proven difficult to establish benchmarks for lower-extremity bypass surgery given inconsistencies between different trial populations, endpoints, and endpoint definitions.[18] As new technologies and techniques emerge for the treatment of PAD,[19-25] it is important to redefine reported event rates for surgical treatment.[26]

To this end, in 2009, the Society for Vascular Surgery (SVS) suggested using objective performance goals (OPGs) for major adverse cardiac events (MACEs) and major adverse limb events (MALEs) in patients with CLI requiring femoral-popliteal bypass surgery.[4] Subsequent studies questioned the generalizability of the performance goals that were developed, given that they were based on only 3 randomized controlled trials (RCTs) and

TABLE 1. Patient demographics by patient group.

Demographics	Safety Group (n = 15,649)	Autologous Vein Graft Patency Group (n = 3397)	*P*-Value
Mean age (years)	67.5% (13,606)	68.2% (3157)	.58
Female sex	37.3% (14,570)	32.8% (3057)	<.001
Diabetes	41.2% (15,152)	32.4% (3283)	<.001
Hypertension	58.5% (3669)	51.7% (2765)	<.001
Dyslipidemia	37.8% (2375)	31.6% (2216)	<.001
History of smoking	49.6% (15,152)	59.8% (3177)	<.001
Coronary artery disease or prior myocardial infarction	40.1% (4380)	26.6% (3177)	<.001
Cardiovascular disease or prior stroke	14.8% (11,910)	14.3% (2166)	.55
Renal disease	10.7% (1532)	—	—
End-stage renal disease	7.5% (10,255)	12.3% (697)	<.001
Critical limb ischemia	54.5% (14,789)	61.8% (3397)	<.001

Data presented as percent (# of patients with available data) unless otherwise noted.
Three groups include patients with data on major adverse events (safety) and patients.

excluded patients with end-stage renal disease (ESRD) and prosthetic grafts, which constitute a significant portion of current bypass procedures.[18,27,28] Additionally, the performance goals were only developed for patients with CLI, while new endovascular trials often enroll a combination of patients both with and without CLI,[19-25] and important safety endpoints, such as major bleeding and/or infection, were not benchmarked.

The goal of this study is to define the historical rates of graft patency and various adverse events for femoral-popliteal bypass surgery reported in the literature in a broader "real-world" population and compare these with rates from recent randomized trials.

Methods

Study selection. A meta-analysis was performed following the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[29] A search of MEDLINE, Embase, and Cochrane Database of Systematic Reviews was conducted to find studies reporting outcomes after femoral-popliteal bypass surgery with any graft type in patients with PAD. Search terms are detailed in **Supplemental Table S1**. Studies were screened by at least 2 independent authors (TS, MIG, and DT) and were included if they were RCTs or prospective multicenter registries that reported safety outcomes (mortality, target-lesion revascularization [TLR], target-limb amputation, deep vein thrombosis [DVT], pulmonary embolism, bleeding, and infection) at 30 days and/or patency outcomes at 12 months. Studies were excluded if they were published before 1990, included fewer than 20 patients in the arm of interest, did not report outcomes for the procedure of interest, or contained overlapping data with another study. References from selected studies were screened to identify additional relevant studies.

Endpoint selection. Procedural safety endpoints were calculated at 30 days to reflect procedure-related complications. Eight safety outcomes commonly reported as major adverse events (MAEs) in bypass surgery patients were identified. These include all-cause mortality, myocardial infarction (MI), stroke, TLR, major amputation, DVT, major bleeding, and infection. Data from all approved surgical graft types were combined to calculate safety events. *Major amputation* was defined as any amputation at or above the ankle of the treated limb, and *DVT* was defined as any clinically identified DVT regardless of the limb. *Major bleeding definitions* varied across studies, but only studies reporting bleeding requiring transfusion or reoperation were included. Reported infections varied by study, but only studies reporting surgically related infections judged to be clinically significant by the operators such as deep surgical wound infections, graft infections, sepsis, and pneumonia were included.

Primary patency, primary assisted patency, and secondary patency were selected as the efficacy endpoints and were reported at 12 months for various graft types (autologous vein and synthetic). *Primary patency* was defined as uninterrupted patency without any surgical or endovascular reintervention. *Primary assisted patency* was defined as uninterrupted patency that may have required a prophylactic intervention. *Secondary*

TABLE 2. Thirty-day safety outcomes.

Major Adverse Events Component	Number of Studies Reporting	Total Subjects	Total Events	Combined Estimated Rate % (95% CI)
All-cause mortality	28	14,564	310 (2.1%)	1.79 (0.90-2.67)
Myocardial infarction	11	12,291	164 (1.3%)	2.38 (1.27-3.50)
Stroke	5	11,085	76 (0.7%)	0.94 (0.34-1.53)
Target-lesion revascularization	4	562	10 (1.8%)	1.98 (0.99-2.96)
Major amputation	13	2971	65 (2.2%)	2.07 (0.57-3.57)
Deep vein thrombosis	8	10,965	106 (1.0%)	1.97 (0.80-3.140)
Major bleeding	5	10,018	126 (1.3%)	2.02 (0.57-3.47)
Infection	7	10,217	834 (8.2%)	5.44 (2.16-8.72)
Composite (no overlap)				18.59 (13.97-23.21)
Composite (10% overlap)				16.7%
Composite (15% overlap)				15.8%
Composite (20% overlap)				14.9%
Composite (25% overlap)				13.9%

The composite endpoint of all major adverse events under various assumptions are shown (such as assuming a certain percent of adverse events occurred in patients who already had another adverse event occur). CI = confidence interval.

patency was defined as current patency after reintervention for occlusion.[30]

Data extraction and analysis. For each study selected during the screening stage, at least 2 authors (TS, MIG, and DT) independently read the full text and extracted data of interest including 30-day safety outcomes and 12-month patency rates, when available. Type of study (RCT or prospective multicenter registry), location, dates of patient enrollment, number of patients, patient demographics and inclusion/exclusion criteria, types of grafts, and methods of patency assessment were also extracted.

Continuous variables such as age were reported as means and categorical variables regarding comorbidities were presented as percentages. *P*-values were calculated comparing different groups using *t* testing. Average age was calculated by averaging the mean age for all studies included, while for comorbidities the overall percent in the population from all studies was reported. Weighted estimates and 95% confidence intervals (CIs) of the safety and efficacy endpoints were calculated using inverse variance weighting and normal approximation methods. A composite of all MAEs was calculated by first summing individual event rates assuming no overlap between events and then adjusting for 10%-25% overlap, which is the range of overlap observed in other studies reporting these events in the PAD population.[4,27,31]

The event rates from the meta-analysis were compared with event rates from contemporary RCTs with at least 1 arm of surgically treated patients with femoral-popliteal artery disease published since the initial search.[14-17]

Results

Search results. The search yielded 1192 results. These were narrowed down to 117 papers after abstract screening (**Figure 1**). After full text screening for eligibility criteria, 65 more papers were excluded for not meeting inclusion/exclusion criteria or data duplication. Finally, a total of 52 studies (45 RCTs and 7 prospective multicenter studies) were included in the meta-analysis.[5,9,32-81] Forty-five studies including 8179 patients reported 12-month patency outcomes.[32-76] Thirty-four studies including 15,649 patients reported data on 30-day safety endpoints.[5,9,32,33,35-37,41,44,46,50,51,54,59-63,65-75,77-81]

Patient characteristics. Baseline characteristics were calculated for patients with available safety data on MAEs (n = 15,649) and patients in autologous vein graft studies reporting any type of patency (n = 3397) (**Table 1**). The 2 groups had no significant difference in mean age; however, they did have significant differences in other patient characteristics including sex, diabetes, hypertension, dyslipidemia, smoking history, coronary artery disease, cerebrovascular disease, ESRD, and CLI.

Major adverse events. Thirty-day event rates for selected MAEs are reported in **Table 2**, with all events besides TLR and major amputation having data from greater than 10,000 patients. Rates of mortality, MI, stroke, TLR, major amputation, and major bleeding were 1.8%, 2.4%, 0.9%, 2.0%, 2.1%, and 2.0%, respectively. The composite MAE endpoint ranged from 13.9% (assuming 25% of

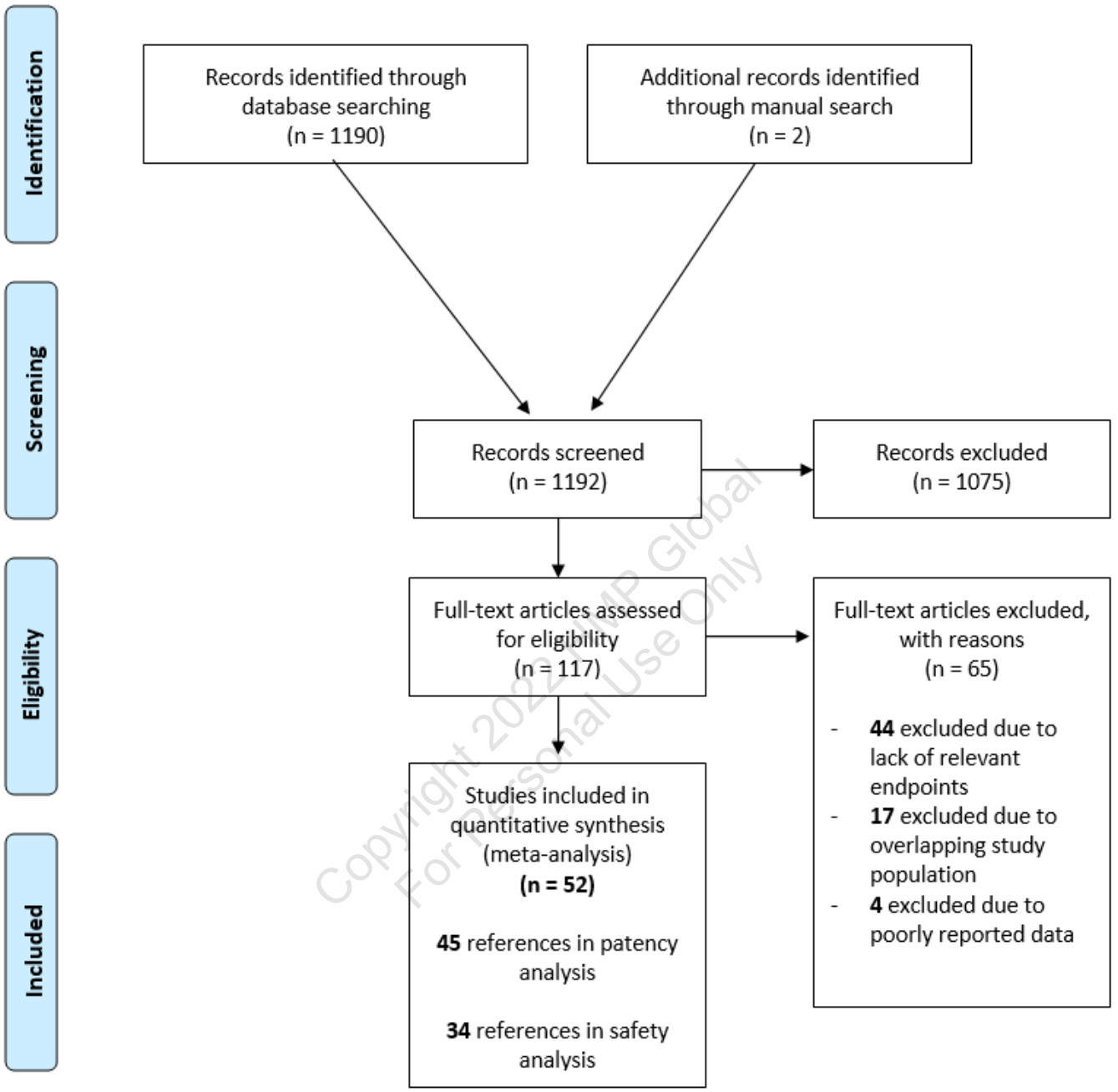

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for study selection.

events occur in patients who already experienced another event) to 18.6% (assuming no events overlapped).

Patency rates. Of the 45 studies that reported patency, 15 reported data on any type of patency in autologous vein grafts and 32 reported data on synthetic grafts. **Table 3** presents the 12-month patency rates by graft type. In total, data on primary patency, primary assisted patency, and secondary patency were available in 7796 patients, 3691 patients, and 5175 patients, respectively. Primary patency for autologous vein grafts was 78.9%, primary assisted patency was 86.7%, and secondary patency was 86.8%. With synthetic grafts (PTFE/Dacron), the rates were lower: primary patency 72.2%, primary assisted patency 74.6%, and secondary patency 76.7%. **Table 4** compares the patient populations and event rates from the surgical arms of contemporary randomized controlled trials with those derived from the meta-analysis for the safety group and the autologous vein graft patency group.

TABLE 3. Twelve-month patency rates by graft type.

Graft Type	Primary Patency[32-73]			Primary Assisted Patency[32,33,36-38,43, 52,56,58,65,68,70,71,74-76]			Secondary Patency[32,33,35-38,41,42,44, 45,47,48,53-56,58-60,65-71,73,76]		
	Number of Studies	Number of Patients	Patency Rate % (95% CI)	Number of Studies	Number of Patients	Patency Rate % (95% CI)	Number of Studies	Number of Patients	Patency Rate % (95% CI)
All*	42	7796	72.44 (68.69-76.18)	16	3691	79.34 (72.51-86.17)	28	5175	81.56 (76.55-86.58)
Autologous vein	12	3014	78.87 (73.23-84.50)	9	2305	86.71 (79.46-93.96)	9	2189	86.84 (81.30-92.39)
Synthetic (PTFE/Dacron)	32	4355	72.15 (67.64-76.66)	11	1324	74.64 (63.56-85.71)	24	2924	79.69 (73.43-85.94)
PTFE	28	3163	70.65 (65.66-75.63)	11	1210	74.50 (63.47-85.53)	22	2446	79.10 (72.24-85.97)

*"All" includes autologous vein grafts and synthetic grafts (Dacron/PTFE). CI = confidence interval; PTFE = polytetrafluoroethylene.

Discussion

This meta-analysis provides historical 30-day safety and 12-month patency event rates for surgical bypass of femoral-popliteal arterial disease in an unselected, real-world patient population. Prior benchmarks set in 2009 used a relatively limited patient population from 3 RCTs and only included patients with CLI who received venous grafts.[4] As later studies revealed, this was not a representative population of patients who undergo procedures for PAD.[18,27] The current meta-analysis includes a much broader patient population including 45 RCTs and 7 prospective multicenter registries and includes patients with venous and synthetic grafts. In addition, it includes patients with and without CLI, which is important given that most real world populations receiving these interventions have both types of patients, and CLI is a significant risk factor for many safety and patency endpoints.[4,78] In the current study, 55% of patients had CLI in the safety group and 62% had CLI in the patency groups.

Our results confirm that autologous vein grafts have significantly better patency rates compared with synthetic grafts in this population (**Table 3**). It is important to note that there were significant limitations in patency definitions and how patency was reported and ascertained in the surgical literature. For example, the methodology for determining patency varied across studies and even within sites of the same study; some studies excluded patients with early graft failure from analysis or kept them in the primary patency group even after reintervention. Many studies did not require objective imaging at 12 months unless symptoms were present, despite other studies demonstrating that "silent" occlusions are often found in patients without symptoms who received routine imaging follow-up.[57] Additionally, imaging results were not usually evaluated by independent core labs. These limitations likely result in overestimation of reported patency rates of surgical grafts and should be contextualized when comparing to endovascular devices and to more contemporary randomized trials including bypass patients. Similarly, in most of the trials included in the meta-analysis, major adverse events were site reported and not adjudicated by an independent clinical events committee.

Despite these significant limitations in historical trials, event rates for patency and major adverse events are similar to those reported in the recent, large, high-quality Best Endovascular vs. Best Surgical Therapy in Patients With Critical Limb Ischemia (BEST-CLI) trial (**Table 4**).[17] This may represent a balance of conflicting factors. On one hand, historical trials likely underreported major adverse events due to less rigorous follow-up and overreported patency given varying definitions and lack of mandated testing for graft stenosis. On the other hand, although newer trials including BEST-CLI had more rigorous follow up and used standardized definition that more accurately ascertained adverse events and graft stenoses, they included a population with lesions amenable to either surgery or endovascular intervention which likely was a selected population predisposed to lower event rates.

Study limitations. As with any meta-analysis, this study is a retrospective analysis of heterogenous studies with variable study populations, endpoint definitions, and endpoint ascertainment methods. Additionally, given limited reported data on outcomes in various subgroups in these trials, including above-the-knee or below-the-knee bypasses and degree of distal runoff, more granular analyses could not be undertaken. Still, this analysis

TABLE 4. Comparison of historical event rate in surgical bypass with contemporary studies.

	Safety Endpoint Group	Autologous Vein Graft Patency Group	Enzmann et al.[14]	Eleissawy et al.[15]	ZILVERPASS[16]	BEST-CLI[17] Cohort 1*
Demographics						
Number of patients (n)	15,649	3397	53	25	107	718
Mean age (years)	67.5	68.2	68.3	72.0	69.6	66.9
Female sex	37.3	32.8	22.6	24.0	24.3	28.0
Diabetes	41.2	32.4	35.8	44.0	31.8	72.1
Hypertension	58.5	51.7	79.2	80.0	81.3	87.1
Dyslipidemia	37.8	31.6	49.0	68.0	65.4	73.2
Smoking history	49.6	59.8	39.6	44.0	80.4	37.1
Renal disease	10.7	—	3.7 (end stage)	—	12.1	9.4 (end stage)
Coronary artery disease	40.1	26.6	26.4	48.0	29.9	42.3
Critical limb ischemia	54.5	61.8	51.0	56.0	44.9	100
Graft type						
Vein	NA	100	100	44.0	0	94.2
Synthetic	NA	0	0	56.0	100	5.8
Safety (30 days)						
Mortality	1.8 (0.9-2.7)	—	0	0	0	2
Myocardial infarction	2.4 (1.3-3.5)	—	—	8.0	—	3
Stroke	0.9 (0.3-1.5)	—	—	—	—	1
Target-lesion revascularization	2.0 (1.0-3.0)	—	2	0	—	5 (major or minor reintervention)
Major amputation	2.1 (0.6-3.6)	—	0	0	0	2
Deep vein thrombosis	2.0 (0.8-3.1)	—	—	0	—	—
Major bleeding	2.0 (0.6-3.5)	—	—	0	1	—
Infection	5.4 (2.2-8.7)	—	—	8.0	—	—
Patency (12 months)						
Restenosis definition	—	varies by study	<50% stenosis	<30% stenosis	<50% stenosis	NA
Primary patency	—	78.9 (73.2-84.5)	72	72.0	72.5	—
Primary assisted patency	—	86.7 (79.5-94.0)	81	78.2	—	—
Secondary patency	—	86.8 (81.3-92.4)	83	81.6	95.9	—

Values are percentages unless otherwise noted.
*Estimated from measuring Kaplan-Meier curves.
NA = not available.

includes only RCTs and prospective multicenter registries to limit bias and includes many studies in an effort to bench-mark real-world PAD populations treated with surgical femoral-popliteal bypass. Although the initial literature search was done in 2018, the goal of this study is to contextualize historical event rates in the setting of new randomized data.

Conclusion

Based on the results of this meta-analysis, surgical bypass for femoral-popliteal artery disease in a "real-world" population including 50%-60% CLI patients has a 30-day MAE rate of 13.9%-18.6% and a 12-month primary patency rate of 78.9% for

autologous vein grafts, and 72% for synthetic grafts. Despite limitations in the historical literature, these event rates were similar to contemporary randomized trials.

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Supplemental Materials

Supplemental Table S1. Literature search details.

Search ID	Search Terms	Results
1.1	surgery OR bypass surgery	5,563,957
1.2	ischemia OR ischaemia OR claudication OR rest pain OR gangrene OR ulcer OR ulceration OR ulcers OR occlusive OR Rutherford OR Fontaine	1,229,117
1.3	infrainguinal OR infra-inguinal OR femoro-distal OR femoro-popliteal OR femoropopliteal OR femorotibial OR femoro-tibial OR fem-pop OR fem-tib OR SFA OR superficial femoral	34,212
1.4	randomised OR randomized OR RCT OR prospective OR observational OR registry	3,530,360
1.5	1.1 AND 1.2 AND 1.3 AND 1.4	1774
1.6	1.5 remove duplicates	1326
1.7	1.6 AND English	1242
1.8	1.7 AND PDAT [1990-current]	1190

Search dates 1.1-1.8: 2018-09-10