Infrainguinal Angioplasty Outcomes For Critical Limb Ischemia. Does an Aggressive Approach Result in Better Outcomes?

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Abstract

PURPOSE: From January 2018 more aggressive infrainguinal angioplasties were performed in our institution with a focus on establishing straight-in-line flow to the foot. Our aim is to provide real-world data that demonstrate the impact such an approach could have on clinical outcomes, namely, amputation free survival. **MATERIALS AND METHODS:** Infrainguinal primary angioplasties for critical limb ischemia from 2016 to 2019 were pulled from electronic patient records and cross referenced with a list of all major amputations. Factors including age, gender, deprivation score, diabetes status, and renal function were obtained along with mortality data. Kaplan-Meier curves and Hazard plots were produced for amputation-free survival (AFS), overall survival and limb salvage rates (LS) and comparisons were made based on procedure year and patient factors. **RESULTS:** Significant improvement in AFS was shown with Hazard ratio of 0.55 (0.41-0.74, *P*<.001) for procedures performed post change in practice. Of the 485 limbs that underwent infrainguinal angioplasty, 215 suffered amputation. Amputation-free survival was 70.3% and 36.6%, and LS was 81.9% and 78.2%, at 1 and 4 years respectively. Increasing age, eGFR and absence of tissue loss were associated with improved AFS while diabetes status, male sex, and deprivation score were not. **CONCLUSION:** Our data emphasize the importance of achieving straight-in-line flow to the foot, and this has now become accepted as the definition of technical success in our institution. Amputation-free survival needs to be reported when looking at clinical outcomes as our data show that LS can be misleading in the long term.

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Key words: peripheral vascular disease, critical limb ischemia, angioplasty, infrainguinal angioplasty, amputation-free survival, endovascular

The approach to infrainguinal endovascular treatments for critical limb ischemia (CLI) has rapidly evolved over the years with technologies such as lithotripsy, atherectomy and drug-eluting balloons (DEB) or stenting (DES), and more aggressive techniques to achieve straight-in-line flow to the foot. However, despite these advances, the mortality and morbidity related to CLI remain high.

Most trials supporting the use of newer devices and technologies use proxy endpoints such as patency and target lesion revascularization (TLR) rates while ignoring hard clinical outcomes such as amputation-free survival (AFS).[1] Studies looking at the impact of establishing straight-in-line flow to the foot have been more encouraging, with reportedly improved limb salvage (LS) when using more aggressive techniques such as those recommended by Gandini et al,[2] and possibly improved wound healing (but not AFS) when performing multivessel treatments and pedal arch interventions.[3] In fact, the recently published CIRSE standards of practice on below-the-knee revascularization recommend the use of these techniques but did not recommend the use of DEB/DES or atherectomy in standard clinical practice due to low levels of evidence.[4]

In our center, as of 2018, we began to adopt a more aggressive strategy in our endovascular treatments with a focus on establishing straight-in-line flow to the foot, as advocated in the CIRSE standards of practice. However, the prolonged duration required to complete these complex procedures is invariably associated with a significant logistical burden when the demand for interventional radiology services is dramatically increasing.

Given the impact of this new approach on the local service, we sought to determine whether translation of these resource intensive recommendations into routine practice was associated with improved patient outcomes.

Caldicott guardian approval was obtained for ethical approval.

Methods

Study design and participants. This single-center retrospective cohort study used data from patients who underwent infrainguinal primary percutaneous transluminal angioplasty (PTA) in our institution between 2016 and 2019 (n=1043).

Only procedures which were performed for CLI, defined as tissue loss or rest pain (Rutherford classification 4 to 6), were included. Any limb previously treated with infrainguinal PTA was excluded as we could not accurately distinguish between a re-intervention for restenosis or reocclusion of a previously treated vessel as opposed to a planned intervention following failure to establish straight inline flow to the foot with a different approach (eg, targeting a different vessel or attempting a retrograde approach). Procedures on limbs with bypass grafts were also excluded, leaving a final data set of 485 primary procedures. Procedures which were abandoned due to technical factors were included in the final analysis.

Variable and statistical analysis. Age and patient sex were identified by patient Scottish community health index (CHI) number and included as continuous and categorical variables respectively. Estimated glomerular filtration rate (eGFR) prior to the procedure was obtained from electronic patient records as calculated by the MDRD equation (ref *Ann Intern Med* 1999 Mar 16;130(6):461-70) and reported as categorical variables (<15ml/min, 15-30mls/min, >30mls/min). HbA1c was identified from the SCI-Diabetes database (www.sci-diabetes.scot.nhs.uk) and included as a categorical variable. Scottish index of multiple deprivation was extracted from the SIMD database (www.SIMD.scot). SIMD uses multiple characteristics (housing, skills and training, income, employment, health, education, geographic access and crime) to produce an area-based ranking index and is used as an estimate of co-morbidity and deprivation, with 1 being the most deprived quintile and 5 the most affluent.[5]

AFS (time to amputation or death), overall survival (time to death) and LS rates (time to amputation only) were calculated using Kaplan-Meier curves and comparisons of different groups made using log-rank test. To analyze the effect of multiple covariates on survival, the Cox proportional hazards model was applied and hazard ratios reported. Dependencies analyzed included age, sex, eGFR, diabetes status, SIMD and procedure year (pre vs post departmental practice change).

DEBs were utilized in re-interventions but not in primary PTA. We also began using SUPERA (Abbott) stenting for long superficial femoral artery recanalizations that demonstrated significant post PTA dissections. These approaches however were all performed on a case-by-case basis at the discretion of the performing interventional radiologist. The accepted standard for technical success was achieving straight in-line flow to the foot with a minimum of one vessel.

CIRSE standards of practice on below-the-knee revascularization also recommend the use of transcollateral techniques and venous arterialization for "no-option" patients, however, these were not performed throughout the observed time period, and we did not utilize Shockwave, atherectomy, or below-the-knee stenting.

Medical management has not progressed over the observed time frame to account for the change in outcome. Medical treatment for peripheral vascular disease has remained single antiplatelet therapy, high-dose statin therapy, smoking cessation, blood pressure and diabetes control along with weight management and increased physical activity. Newer lipid lowering therapies (PCSK9 inhibitors) are available, however, only in the context of familial dyslipidemia syndromes and are not widely used locally in this context. Direct oral anticoagulant agents such as rivaroxaban are also not yet in routine use.[6] Follow-up post PTA is clinical without routine follow-up imaging. All CLI patients are discussed at a weekly MDT consisting of vascular surgeons and interventional radiologists, and all endovascular interventions for CLI patients are performed by interventional radiologists in our institution.

Results

Between September 2016 to September 2020, 485 limbs (from 435 patients) underwent primary infrainguinal PTA. **Table 1** shows patient characteristics pre- and post-change in practice implemented in 2018 with no statistically significant differences between the two groups.

Kaplan-Meier curves **(Figure 1)** demonstrate marked improvement in AFS following implementation of change in practice. Hazard ratio for AFS was 0.55 (0.41-0.74, P <.001) for procedures performed post change in practice in 2018/19 compared to procedures performed in 2016/17 **(Figure 2)**.

For CLI, 215 amputations were performed in the observed period and 116 (54%) of these underwent prior PTA. **Figure 3** shows Kaplan-Meier curves of both AFS and overall survival plotted on the same graph with **Figure 4** showing Kaplan-Meier curve of LS rate alone. AFS was 70.3% and 36.6% and LS was 81.9% and 78.2% at 1 and 4 years respectively. Most amputations (81.6%, n = 80) occurred within the first 6 months of PTA. Tables giving survival rates per year for AFS, overall survival and LS can be found in the electronic supplementary material.

Increasing age, eGFR and absence of tissue loss were significantly associated with improved AFS. Diabetes status, male sex, and SIMD score were not associated with negative outcomes. Hazard ratio for AFS was 0.55 (0.36-0.83, P=.004) for patients with eGFR of >60 compared to <30. Increasing age was found

Table 1. Demographics table showing patients characteristics for 2016/2017 cohort and 2018/2019 cohort

	2016/2017 (n=186)	2018/2019 (n=299)	
Age, median (IQR)	76 (17)	73 (16)	P=0.27*
Male sex, n (%)	110 (59)	184 (62)	P=0.6†
eGFR, n (%)			
<30	18 (10)	39 (13)	P=0.53†
30-59	52 (28)	82 (27)	
>60	116 (62)	178 (60)	
Diabetic, n (%)	62 (50)	95 (47)	P=0.72†
SIMD quintile, n (%)			
1	22 (12)	30 (10)	P=0.4†
2	61 (33)	80 (27)	
3	40 (22)	62 (21)	
4	28 (15)	49 (16)	
5	26 (14)	59 (20)	
NA	9 (5)	19 (6)	
Tissue loss, n (%)	140 (75)	233 (78)	P=0.4†

† =. * = eGFR = estimated glomerular filtration rate; IQR =

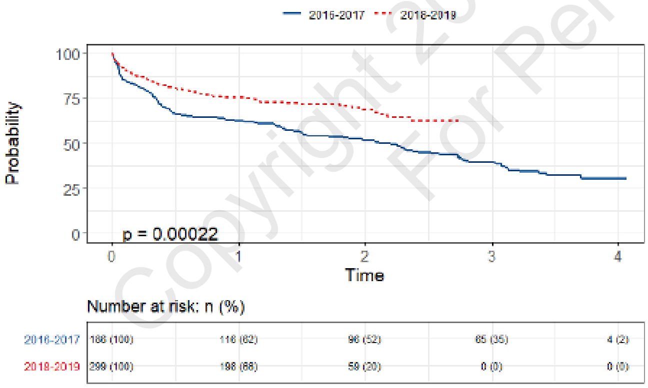

FIGURE 1. Kaplan-Meier curves showing amputation free survival for 2016/2017 cohort (pre change in practice) and 2018/2019 (post change in practice).

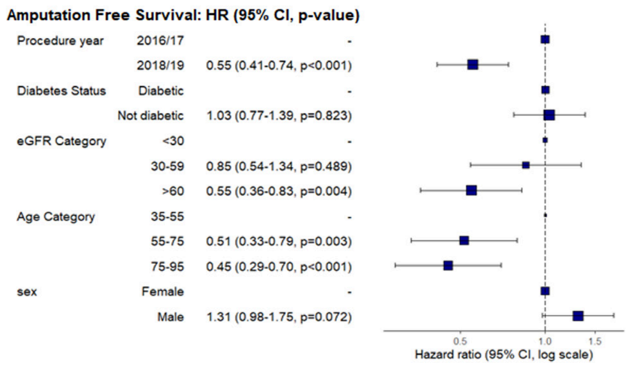

FIGURE 2. Hazard plot showing Hazard Ratios for when procedure was performed (pre- or post-change in practice), and patient factors.

to be a positive predictor for survival, with categories 55-75 and 75-95 having hazard ratios of 0.51 (0.33-0.79, *P*=.003) and 0.45 (0.29-0.7, *P*≤.001) compared to 35-55 category, respectively. Kaplan-Meier curves for dependencies can be found in the supplementary material.

Discussion

The results of the BASIL trial which compared PTA vs bypass surgery performed between 1999 and 2004 were highly impactful and are largely responsible for the angioplasty first approach most centers adopt today, with further analysis of results being

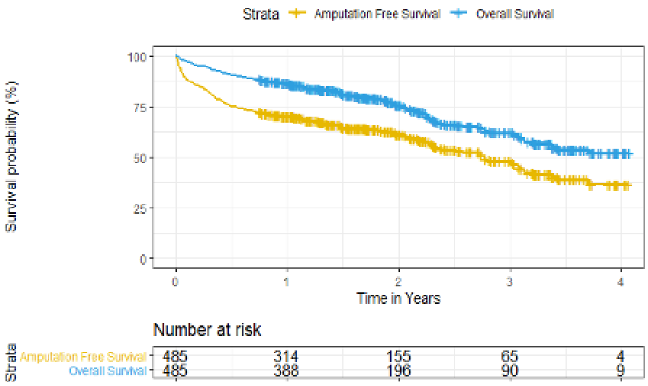

FIGURE 3. Kaplan-Meier curves for amputation free survival and overall survival for the entire cohort.

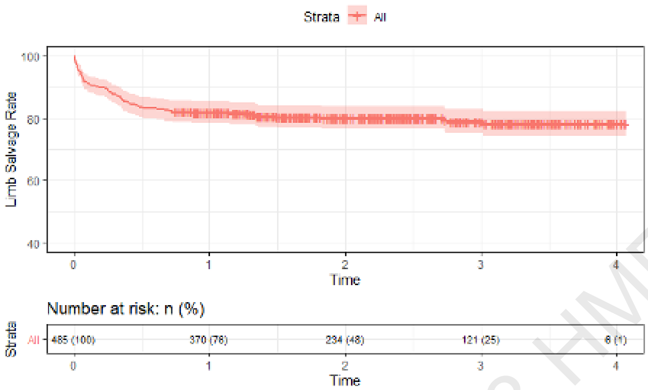

FIGURE 4. Kaplan-Meier curve for limb salvage for the entire cohort.

published as recently as 2010.[7] However, a PTA performed in 1999 is very different from that performed today and many would argue that these data are now outdated, but there are little meaningful published real-world data in long-term outcomes to show that patient outcomes have improved. In a recent editorial published in CVIR Endovascular,[1] Reekers points out that hard clinical endpoints like AFS are often ignored and quotes Duff et al in highlighting that the little recent data we do have makes for sobering assessment of CLI burden—a poor clinical prognosis translating into diminished quality of life and high costs for millions of patients who continue to face a 15%–30% amputation and a 30% mortality risk at 1 year depending on the level of disease severity. He goes on to say that there are strong indications that our new endovascular revascularization techniques reduce the number of reinterventions but unfortunately not always the amputation risk.[8]

Our data confirm that patient outcomes are indeed poor, as outlined by Duff et al and Reekers, with an AFS of only 36.6% at 4 years, when only approximately 26% of all amputations underwent prior PTA. LS rates were indeed better than expected, with most major amputations occurring within 6 months of first PTA attempt, however, sustained LS after this could be due to patient mortality which was very high in our cohort. This emphasizes the importance of AFS as the preferred outcome measure in CLI, as LS rates alone can be falsely reassuring particularly when looking at long term outcomes (78.2% at 4 years as opposed to 36.6% AFS). Improvements in overall survival of patients with better care could result in worse LS rates, and similarly more interventions performed on older patients with poor overall survival will result in much improved LS. Quoting LS rates in studies can be meaningless without overall survival and AFS.

However, we also demonstrate a very significant improvement in outcomes with the advent of more aggressive (and time-consuming) endovascular approaches to treating CLI. A patient presenting for PTA in 2018/19 was half as likely to lose their life or limb at any given time compared to one presenting in 2016/17. Our results were largely unexpected by both interventional radiologists and vascular surgeons and anecdotally we did not feel that patient outcomes were improving. We cannot say for certain that it was the change in our approach in endovascular treatments that has led to improved outcomes, and therefore the correlation between change in endovascular approach and patient outcomes remains fully speculative given we do not have technical success rates. However, there were no other changes during this period to explain improved outcomes. There was no change in wound care or in medical therapy (eg, newer lipid lowering agents or the use of low dose rivaroxaban).

It is difficult to find such marked improvements in outcomes in trials investigating new technologies, suggesting that spending time and effort and improving the skills of the interventionist to establish straight-in-line flow to the foot will have a greater impact on outcomes compared to changes in the use of balloons and stents which seem to have an impact on re-intervention and patency rates, but not necessarily AFS.[9,10] Changes in clinical practice concerning treatment of the underlying lesion, while easier to adopt, are unlikely to be as impactful as adopting strategies which focus on achieving straight-in-line flow to the foot. Improving endovascular techniques and making use of devices to achieve this, such as re-entry devices and newer wires and catheters could potentially carry a greater impact on outcomes, despite this being much harder to demonstrate scientifically given operator dependence.

Contrary to what one would expect when looking at a combined outcome of both amputation and mortality, older age groups fared significantly better than younger ones in our population. This potentially reflects an underlying practice of being more likely to attempt revascularisation on younger patients compared to older patients. In fact, a notable area for improvement in our service to CLI patients is in the proportion of patients suffering from CLI who are offered PTA before suffering from an amputation. 54% of all amputations that occurred within the observed period did not undergo PTA to save their limb, either due to presenting too late to the vascular team with an unsalvageable limb or deemed to have no endovascular option during the MDT. Efforts need to be made to improve referral of patients with CLI to the vascular department for successful revascularisation to be an option.

Studies have shown that socioeconomic deprivation is associated with worse outcomes following PTA[11] and increased risk for amputation in general,[12] with data from the National Vascular Registry (NVR) in England demonstrating socio-economic deprivation is linked to an approximate twofold increase in risk of adverse outcomes after PTA.[11] However, our data looking at patients receiving the same care in a single center in Scotland did not show any statistically significant difference in outcomes. The other unexpected finding was being unable to show a difference in outcomes between diabetic and non-diabetic patients. A study on 15,332 patients in Germany demonstrated an increased risk for amputation, but not mortality in diabetic patients however we could not corroborate these findings on our smaller population looking specifically at patients who underwent PTA[13]. One possible reason for this is that diabetic patients have better clinical monitoring for limb status with regular visits to podologists who can refer directly to our vascular service, potentially resulting in more prompt referral for tissue loss and better time to revascularisation, however we could not demonstrate this with the data we had available.

Limitations. There are several limitations to this retrospective study. We did not have pertinent information such as technical success, and what was done in the individual procedures (for example stenting vs PTA only). Identifying which procedures achieved technical success (defined as achieving straight-in-line flow to the foot) is the missing link which would have confirmed that this was the reason for improved outcomes in 2018/19.

We could not accurately determine reintervention rates as several of the procedures were performed in a staged fashion rather than being true reinterventions and these could not be distinguished from each other retrospectively.

We also could not accurately classify the complexity of the underlying disease both from an angiographic and clinical perspective. An attempt was made to retrospectively classify disease as per TASC classification however these schemes are limited by the necessity to focus on individual lesions and good interobserver agreement could not be established which has already been well documented. A study looking at inter-observer agreement on the TASC II classification of femoropopliteal lesions concluded that the scheme allows for wide individual interpretations and, therefore, the common use of this classification as a basis for decision making and reporting outcomes could be questioned.[14,15] Patient selection was based on the clinical presentation of rest pain or tissue loss, which we know can be subjective. We could easily distinguish between tissue loss and rest pain but could not accurately distinguish between Rutherford 5 and 6 retrospectively.

We could not include re-interventions in our data as it was impossible to distinguish between a true reintervention involving revascularization of a previously treated vessel as opposed to a second (or third) intervention performed to establish straight in line flow to the foot due to time constraints in the initial intervention.

A prospectively maintained registry would be the way to address these limitations. Using the WIFI classification would have given a more objective way of classifying our patients from a clinical perspective. This system gives a wholistic approach to the clinical assessment of patients with CLI through the combined assessment of wound, infection and ischemia based on ankle/brachial pressure index or toe pressure index in diabetic patients.[16] When it comes to the angiographic classification of our patient cohort, the GLASS classification is a more recent scheme which is not limited by focussing on individual lesions and shows some promise in reducing the high interobserver disagreement seen in TASC.[17] Appropriate classification of patients must be done if we are to accurately compare different patient cohorts.

Conclusion

There is a lack of good real world outcome data for infrainguinal endovascular procedures available in the literature. While measuring outcomes in CLI is a challenge, evaluating our service to these patients must happen particularly when techniques are constantly evolving, and more resources are required. This should ideally be done through prospectively maintained registries, which make use of recent validated classification systems such as WIFI and GLASS, record technical success and the techniques and devices used, and focus on AFS as the primary outcome. Our data builds upon the growing evidence supporting the importance of establishing straight-in-line flow to the foot and this is now the accepted definition of technical success in our practice. Adopting guidelines such as those set out in the CIRSE standards of practice can bring about a significant improvement in patient outcomes in CLI and resources need to be allocated to allow this to happen. Because of the poor outcomes of these patients, anecdotal experience can be very disheartening, but the process of evaluating our service to these patients can be surprisingly encouraging.

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Ethical approval obtained through Caldicott Guardian attached as supplementary material.

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Supplemental Materials

SUPPLEMENTAL TABLE 1. AMPUTATION FREE SURVIVAL RATES PER YEAR

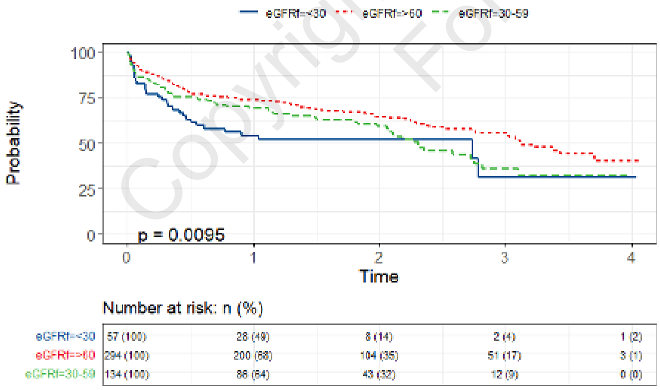
Time (years)	No at risk	No of events	Amputation Free Survival (%)	Lower 95% CI	Upper 95% CI
1	314	171	70.3	66.3	74.4
2	155	159	61.4	56.9	66.2
3	65	90	48.0	42.5	54.3
4	4	61	36.6	29.4	45.7

SUPPLEMENTAL TABLE 2. OVERALL SURVIVAL RATES PER YEAR

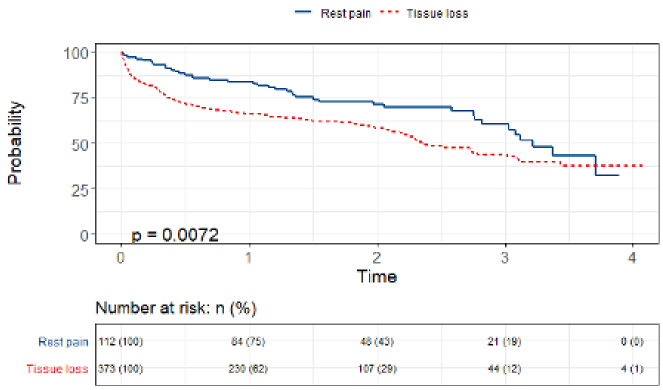
Time (years)	No at risk	No of events	Overall Survival (%)	Lower 95% CI	Upper 95% CI
1	388	97	86.8	83.8	89.8
2	196	192	75.7	71.5	80.1
3	90	106	62.2	56.7	68.2
4	9	81	52.1	45.1	60.3

SUPPLEMENTAL TABLE 3. LIMB SALVAGE RATES PER YEAR AND FOR THE FIRST 6 MONTHS

Time (years)	No at risk	No of events	Limb Salvage (%)	Lower 95% CI	Upper 95% CI
½	405	80	83.5	80.3	86.9
1	370	8	81.9	78.5	85.4
2	234	7	80	76.5	83.7
3	121	2	78.9	75.1	82.9
4	6	1	78.2	74.3	82.4



SUPPLEMENTAL FIGURE 1. Kaplan-Meier curves showing amputation free survival according to eGFR.



SUPPLEMENTAL FIGURE 2. Kaplan-Meier curves showing amputation free survival according to clinical indication.

Supplemental Materials

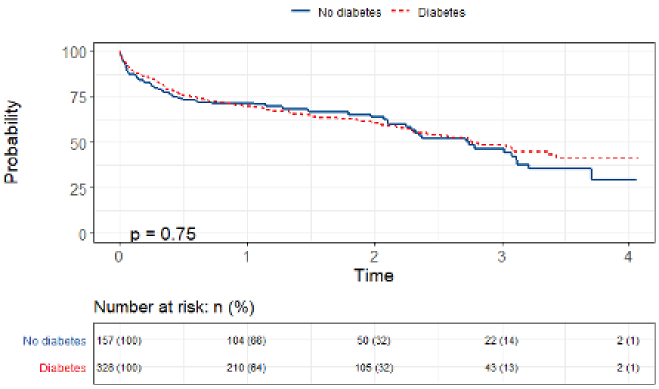


FIGURE 3. Kaplan-Meier curves showing amputation free survival according to diabetes status.

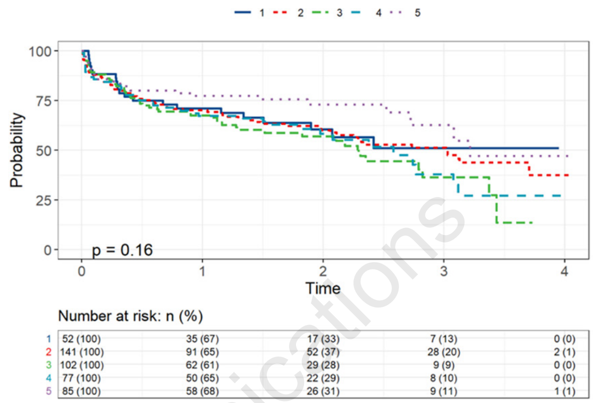


FIGURE 4. Kaplan-Meier curves showing amputation free survival according to Scottish deprivation index (1= most deprived, 5= most affluent).