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Efficacy and Safety of Drug-Eluting Balloon Angioplasty in the Treatment of Hemodialysis Arteriovenous Fistula Stenosis:

A Systematic Review and Meta-analysis

Sofia Alexandra da Gama Paz Dias

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Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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Autor: Sofia Alexandra da Gama Paz Dias

6º ano do Mestrado Integrado em Medicina
Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto
Centro Hospitalar Universitário de Santo António
Número mecanográfico: 201706886
Endereço de correio eletrónico: up201706886@up.pt

Orientador: Doutora Ivone Fernandes Santos Silva, MD, PhD

Assistente Hospitalar Graduada do Serviço de Angiologia e Cirurgia Vascular, Centro Hospitalar Universitário de Santo António
Professora Associada Convidada do Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto
Endereço de correio eletrónico: heitor.ivone@gmail.com

Coorientador: Dr. João Diogo Jorge de Castro, MD

Interno de Formação Específica do Serviço de Angiologia e Cirurgia Vascular, Centro Hospitalar Universitário de Santo António
Endereço de correio eletrónico: joaodiogocastro@outlook.com

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Autor

Assinado por: **Sofia Alexandra da Gama Paz Dias**
Num. de Identificação: 14610135
Data: 2024.06.01 19:41:26 +0100

CHAVE MÓVEL

(Sofia Alexandra da Gama Paz Dias)

Orientador

Assinado por: **Ivone Fernandes Santos da Silva**
Num. de Identificação: 11101263
Data: 2024.05.30 18:06:54+01'00'

CHAVE MÓVEL

(Doutora Ivone Fernandes Santos Silva, MD, PhD)

Coorientador

Assinado por: **JOÃO DIOGO JORGE DE CASTRO**
Num. de Identificação: BI14136618
Data: 2024.05.30 21.08.57 GMT Daylight time

CHAVE MÓVEL

(Dr. João Diogo Jorge de Castro, MD)

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Resumo

Introdução:

A disfunção do acesso vascular, devido especialmente a estenose venosa, representa uma das causas mais frequentes de morbilidade em doentes sob hemodiálise. A angioplastia transluminal pecutânea (PTA) é atualmente o *gold standard* para tratamento de fístulas estenosadas, com taxas de patência de 26-62% um ano pós-intervenção. Esta revisão sistemática e meta-análise têm por objetivo determinar a eficácia do uso de balões eluidores de fármaco (DEB) no tratamento de estenoses em fistulas arteriovenosas para hemodiálise, bem como a sua segurança, comparativamente à PTA.

Métodos:

Foi realizada uma pesquisa da literatura através das bases de dados bibliográficas PubMed® e Scopus® a todos os estudos randomizados (RCTs) e estudos coorte que comparam o uso de angioplastia com DEB e PTA no tratamento de estenoses em fistulas ou próteses arteriovenosas para hemodiálise. A pesquisa incluiu artigos publicados entre janeiro de 2012 e dezembro de 2023. O risco de viés nos RCTs foi avaliado segundo a ferramenta de avaliação de risco de viés da organização *Cochrane®* (RoB 2.0), e a qualidade dos estudos coorte foi determinada pela escala *Newcastle-Ottawa*. O risco relativo de perda de patência primária na lesão alvo e de perda de patência primária do circuito foi estimado agregando a *hazard ratio* dos RCTs e estudos coorte separadamente. A segurança do tratamento foi avaliada através da razão dos riscos de mortalidade por todas as causas aos 12 e 24 meses, entre grupos de intervenção.

Resultados:

Dezoito estudos, incluindo um total de 1894 doentes, cumpriram os critérios de elegibilidade, sendo 14 RCTs e 4 estudos coorte. A angioplastia com DEB demonstrou uma maior eficácia na manutenção da patência da lesão alvo, quando comparado com a PTA, tanto entre os RCTs como entre os estudos coorte (HR 0.76, 95% CI 0.60-0.98, I^2 = 69%, e HR 0.55, 95% CI 0.38-0.82, I^2 = 0%, respetivamente). As análises de subgrupos não identificaram qualquer correlação deste resultado com o tipo de acesso usado, a presença de estenoses primárias ou restenoses, a idade do acesso vascular, o uso de pré-dilatação, ou dose de paclitaxel usada.

Do mesmo modo, a análise de 9 RCTs demonstrou um menor risco de perda de patência do circuito de hemodiálise em doentes tratados com DEB, em comparação com PTA (HR 0.85, 95% CI 0.77-0.94, I^2 = 49%).

A mortalidade por todas as causas foi analisada em 16 estudos aos 12 meses (RCTs: RR 0.99, 95% CI 0.69-1.44, I^2 = 0%; Estudos coorte: RR 0.99, 95% CI 0.18-5.53, I^2 = 0%) e 5 estudos aos 24 meses (RCTs: RR 1.20, 95% CI 0.86-1.67, I^2 = 0%; Estudos coorte: RR 1.67, 95% CI 0.42-6.56, I^2 = 0%). Não foram encontradas diferenças significativas entre os grupos submetidos a tratamento com DEB ou PTA.

Conclusão:

Esta análise demonstra a superioridade no uso de DEB quando comparados com PTA, para o tratamento de estenoses de fistulas arteriovenosas para hemodiálise, sem diferença na taxa de mortalidade.

Palavras-chave: Angioplastia transluminal percutânea; Balão eluidor de fármaco; Hemodiálise; Fistula arteriovenosa; Estenose;

Abstract

Introduction:

Vascular access dysfunction, especially due to venous stenosis, represents one of the most prominent causes of morbidity in patients undergoing hemodialysis. Percutaneous transluminal angioplasty (PTA) is the gold standard treatment for stenotic fistulas, with patency rates of 26-62% 1-year after PTA. This systematic review and meta-analysis aims to determine the efficacy of drug-eluting balloons (DEB) for the treatment of hemodialysis arteriovenous fistula stenosis, as well as its safety, when compared to PTA.

Methods:

An electronic literature search was conducted using the PubMed® and Scopus® databases for all randomized controlled trials (RCTs) and cohort studies comparing the use of DEB angioplasty with PTA for the treatment of stenotic hemodialysis arteriovenous fistulas or grafts. The search was carried out from January of 2012 to December of 2023. Risk of bias for RCTs was accessed with the Cochrane® risk of bias tool (RoB 2.0), and quality of cohort studies with the Newcastle-Ottawa Scale. The relative risk of loss of target lesion primary patency and loss of circuit primary patency were estimated by pooling the hazard ratio of RCTs and cohort studies, separately. Safety was evaluated using risk ratio of all-cause mortality at 12 and 24 months, between intervention groups.

Results:

Eighteen studies were found to meet the eligibility criteria, 14 of which were RCTs and 4 were cohort studies, including a total of 1894 patients. DEB demonstrated a greater efficacy in maintaining target lesion patency when compared to PTA, both amongst RCTs and cohort studies (HR 0.76, 95% CI 0.60-0.98, I^2 = 69% and HR 0.55, 95% CI 0.38-0.82, I^2 = 0%, respectively). Subgroup analyses found no significant correlation with type of access used, primary versus restenosis, vascular access age, use of predilation and paclitaxel dose.

Similarly, 9 RCTs demonstrated a lower risk of overall access circuit patency loss for DEB, when compared to PTA (HR 0.85, 95% CI 0.77-0.94, I^2 = 49%).

All-cause mortality was analyzed for 16 studies at 12 month (RCTs: RR 0.99, 95% CI 0.69-1.44, I^2 = 0%; Cohort Studies: RR 0.99, 95% CI 0.18-5.53, I^2 = 0%) and 5 studies at 24 months (RCTs: RR 1.20, 95% CI 0.86-1.67, I^2 = 0%; Cohort Studies: RR 1.67, 95% CI 0.42-6.56, I^2 = 0%). We found no significant difference between DEB and PTA groups.

Conclusion:

Our analysis demonstrated a superiority of DEB for the treatment of upper limb hemodialysis arteriovenous fistula stenosis, when compared to PTA, with no difference in mortality rate.

Key-words: Percutaneous transluminal angioplasty; Drug-eluting balloon; Hemodialysis; Arteriovenous fistula; Stenosis;

MeSH Terms:
Angioplasty, Balloon*
Arteriovenous Fistula*
Renal Dialysis*
Humans
Vascular Access Devices
Vascular Patency
Paclitaxel

Abbreviations

AVF - arteriovenous fistula
AVG - arteriovenous grafts
CI - confidence interval
CPP - circuit primary patency
DEB - drug-eluting balloons
ESVS - European Society for Vascular Surgery
HPB – high pressure balloon
HR - hazard ratio
KDOQI - Kidney Disease Outcomes Quality Initiative
KRT - kidney replacement therapy
NH - neointimal hyperplasia
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTA - percutaneous transluminal angioplasty
RCTs - randomized controlled trials
RR - Risk Ratio
TLPP - target lesion primary patency
VA - vascular access

Index

List of Tables

List of Figures

Introduction

The worldwide prevalence of kidney failure is estimated at roughly 0,1%, with nearly 4 million people living on kidney replacement therapy (KRT)[1,2]. The most commonly chosen KRT is undoubtedly hemodialysis, representing 69% of all treatments[2]. According to the European Society of Vascular Surgery guidelines, the first option for hemodialysis vascular access is an autogenous arteriovenous fistula (AVF), and it has proven to develop fewer post-operative complications and need for surgical or endovascular revisions, when compared to alternative options such as arteriovenous grafts (AVG) or central venous catheters[3]. Nevertheless, vascular access (VA) dysfunction still represents one of the most prominent causes of morbidity in patients undergoing hemodialysis, accounting for almost one third of hospitalizations in this population, ultimately increasing the burden for patients, as well as caregivers and generating high healthcare costs[2].

Dysfunction in matured fistulas is mostly due to venous stenosis, which may contribute to inefficient hemodialysis clearance, VA thrombosis and eventually AVF abandonment[4-6]. Upstream events such as trauma at the time of VA creation, hemodynamic shear stress, repetitive canulation, non-laminar flow and endothelial dysfunction secondary to uremia cause injury to the vessel wall[7]. This results in the proliferation of vascular smooth muscle cells and myofibroblasts (α-smooth muscle actin positive cells), and their migration to the intima, leading to an excessive deposition of extracellular matrix, vascular fibrosis and venous neointimal hyperplasia (NH), the primary cause of VA stenosis[8,9]. VA flow dysfunction can manifest with clinical signs (arm edema, weak or discontinuous thrill, high pitch systolic bruit, increased bleeding time), and may be associated to increased venous pressures, increased urea recirculation and decreased flow rates[6].

The development of VA stenosis culminates in relatively low primary patency rates for AVFs (62-68% at 1-year and 38-56% at 2-years), as well as for AVGs (40-50% at 1-year and 20-30% at 2-years)[3]. Stenoses can develop at any point on the access circuit, with the most common location in AVFs being the juxta-anastomotic area (around 50%), whereas in AVGs the majority are located at the venous anastomosis (around 60%)[10, 11].

Clinically significant VA stenoses are primarily treated with percutaneous transluminal angioplasty (PTA), with patency rates of 26-62% for AVFs and 20% for AVGs, 1-year after PTA[3, 12-14]. Therefore, although PTA does prolong the lifespan of stenotic VAs, barotrauma caused by the angioplasty represents a risk factor for further development of repeated stenoses. These restenoses post-PTA have notably higher cellular proliferation rates in comparison to *de novo* stenoses, and lead to low patency rates and a greater need for reintervention[15, 16].

Having this in mind, research has been focusing on mechanisms to lower the rate of reinterventions needed to maintain and increase lifetime of hemodialysis VA. Angioplasty with drug-eluting balloons (DEB) has proven to be a promising potential solution. DEB coated with paclitaxel, a lipophilic, antiproliferative substance that infiltrates the vessel wall, inhibit local cell migration and proliferation, reducing NH at the target lesion[17, 18]. Paclitaxel's lipophilic properties allow it to be passively absorbed through the cell membrane, maintaining a prolonged effect upon the vessel wall. In addition, DEB include a hydrophobic excipient to facilitate this transport. At present, there are several types of drug-coated angioplasty balloons, with paclitaxel concentrations ranging from

2 to 3.5 μg/mm^2, and different excipient formulas[19]. Several randomized controlled trials (RCTs) and cohort studies have shown promising results for DEB, in comparison to current gold-standard conventional PTA in prolonging patency rates after angioplasty[20-31]. Furthermore, the use of DEB has already proven successful in enhancing the patency of other vessels, like coronary arteries, as well as femoropopliteal arteries[32-35]. However, consensus has yet to be reached on its overall benefit compared to PTA for the treatment of stenotic hemodialysis access[36-41].

Our systematic review and meta-analysis aims to analyze the most recent published evidence and determine if there is superiority in the use of DEB in terms of risk of patency loss, as well as its safety, when compared to the conventional approach with PTA in hemodialysis AVF stenosis.

Material and Methods

This Systematic Review and Meta-Analysis was carried out in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[42].

Search Strategy

An electronic literature search was conducted using the PubMed® and Scopus® for publications comparing the use of DEB and conventional PTA, from January of 2012 to December of 2023. The following search terms were used: ("AVF" OR "AV access" OR "arteriovenous access" OR "fistula" OR "fistulas" OR "fistulae" OR "hemodialysis" OR "haemodialysis" OR "dialysis" OR "AVF angioplasty" OR "arteriovenous fistula angioplasty" OR "AVF patency" OR "arteriovenous fistula patency" OR "AVF stenosis" OR "arteriovenous stenosis" OR "AVG" OR "arteriovenous graft" OR "arteriovenous grafts") AND ("paclitaxel-eluting balloons" OR "paclitaxel-coated balloons" OR "drug-coated balloons" OR "drug-eluting balloons" OR "DCB" OR "DEB"). Results were downloaded to EndNote 21.1 (Clarivate), where duplicates were removed.

Articles identified were initially screened according to title and abstract, in order extract the relevant literature. Selected studies were then examined in their entirety, to identify inclusion criteria and outcomes of interest.

Selection Criteria

The selection included RCTs and cohort studies analyzing adult (≥18 years) patients with primary or restenotic lesions in upper limb hemodialysis AVF and AVG, undergoing endovascular revascularization with DEB, using PTA as a control. We considered PTA as non-specialized balloon angioplasty procedures recommended by Kidney Disease Outcomes Quality Initiative (KDOQI) and European Society for Vascular Surgery (ESVS) guidelines as primary treatment for AVF stenosis, namely standard balloon or high-pressure balloon (HPB) angioplasty[3, 6].

The primary outcome was efficacy of DEB compared to PTA, determined by the loss of target lesion primary patency (TLPP) or target lesion revascularization after index procedure. The secondary outcomes included loss of circuit primary patency (CPP) and all-cause mortality at 12 months and 24 months. The absence of a primary outcome report determined the exclusion of the study from quantitative analysis. All studies had a minimum of 6 months follow-up. In studies reporting unadjusted and adjusted estimates, we used the unadjusted results, for a better comparability to other studies.

As exclusion criteria, the following was established: in vitro tests; animal studies; case reports; conference abstracts; repeated reporting; protocols; reviews; commentaries; letters; studies not written in English or Portuguese language; full text not available; single arm cohort studies; cross-over study designs; studies using endovascular treatment other than DEB and PTA, namely cutting-balloons, stents, scoring balloons or hydrostatic balloons; central venous access; central venous target lesion (proximal to or including the subclavian vein); in-stent stenosis; fistulas that were

explicitly immature or had not yet been used for hemodialysis; studies focused solely on thrombotic lesions. In studies with more than one publication, the most recent literature was used for analysis.

Assessment of Quality and Risk of Bias

Individual study risk of bias for RCTs was evaluated using the Cochrane risk of bias tool (RoB 2.0)[43], through the assessment of appropriate randomization process, deviation form intended interventions, missing outcome data, measurement of the outcomes and selection of reported results. As for the quality of cohort studies the Newcastle-Ottawa Scale for non-randomized studies was used, which assessed the selection cohorts, comparability between them and outcomes presented. A score of >5 was considered a determinant for a high-quality study[44].

Data Analysis and Statistical Methods

RCTs and observational studies were analyzed separately, taking into account the methodological differences inherent to each study design[45]. In the studies that reported the hazard ratio (HR) and 95% confidence interval (CI) for loss of TLPP and CPP, we used this information to estimate the variance of the lnHR (V). In the studies in which this was not provided, the observed and expected events in the intervention and control arms was used to estimate the HR and V, taking into account results reported at different timeframes, in order to calculate an average HR for the total follow-up in each study[46]. A random effects model was used to estimate the pooled HR of loss of TLPP and CPP, in cases where the heterogeneity was >50% to account for methodological or clinical heterogeneity, otherwise common effects model was preferred. The same logic was applied to the pooled all-cause mortality, expressed as risk ratio (RR) with 95% CI. Results were deemed statistically significant when the 95% CI for the pooled HRs did not include 1. A 95% CI lesser than 1 determined a protecting effect for DEB, whereas a 95% CI greater that 1 meant a risk effect for DEB, when compared to PTA.

I^2 was used to evaluate statistical heterogeneity, with values of <40% representing low heterogeneity, 40-75% moderate heterogeneity and >75% considerable heterogeneity[45]. Funnel plots were used to access the publication bias, determined by the asymmetry present in the diagrams.

We also performed subgroup analysis of the primary outcome to investigate the possibility of a variation in treatment efficacy in different patient groups. Subgroups were created according to the type of access used (AVF versus AVG), primary stenosis versus restenosis, age of the vascular access, use of predilation and the paclitaxel concentration.

The library meta from R 4.3.1 software was used for this meta-analysis.

Results

Literature search and study selection

In total, 340 articles were identified in both databases (PubMed® and Scopus®) using the above query. Following the elimination of duplicates (n=122), 218 articles were screened though abstract and title. After initial screening, 67 papers were retrieved, and evaluated in full-text to identify inclusion and exclusion criteria. The number and reasoning for excluded studies is specified in **Figure 1**. Twenty studies were found to meet the inclusion criteria, however two of these did not report the primary outcome (loss of TLPP) and were therefore excluded from the quantitative analysis. Finally, 18 studies were approved for inclusion in the meta-analysis (**Table I and II**).

Study characteristics

Out of the eighteen studies selected for the meta-analysis, 14 were RCTs[16, 20-25, 47-53] and 4 were cohort studies[28-31], including a total of 1894 patients (939 patients treated with DEB and 955 patients treated with PTA). Within the cohort studies, there was one prospective[31] and 3 retrospective study designs[28-30]. Eight of the selected publications referred to multicenter studies[16, 20, 21, 47, 49-51, 53]. Extracted study characteristics are presented in **Table I** and **Table II**.

Regarding the hemodialysis VA, the majority of studies included only patients with autogenous AVFs, with 7 studies including both AVFs and AVGs[22, 25, 47, 48, 51, 53], and 2 RCTs were dedicated solely to the study of grafts[20, 23]. Although several studies did not report vascular access age, most had an average of > 2 years.

The proportion of recurrent to primary stenosis was variable across studies, with two cohort studies focusing only on primary stenosis[29, 31], while one cohort and 2 RCTs included solely restenotic lesions[23, 28, 53]. Of note, even though central vein target stenosis was an exclusion criterion for this review, in Trerotola *et al*. one patient presented with subclavian vein stenosis as a protocol deviation, with no statistical significance[50].

Before the index angioplasty procedure, 11 studies opted for a predilation of the stenosis[16, 20-22, 29-31, 49-52], and 2 other studies performed predilation at the operator's discretion[25, 28]. Seven different brand of DEB were used across all studies, including IN.PACT™ (n = 11), APERTO® (n = 2), SeQuent® (n = 1), Advance® (n = 1), Lutonix™ (n = 3) and Passeo® (n = 1), with one study using two different brands of DEB in their intervention group[30]. Most studies did not report Paclitaxel dose, and in the ones that did, drug dose ranged from 2 to 3.5 μg/mm^2.

Target lesion and access circuit patency were monitored through physical examination, duplex ultrasonography, angiography, or a combination of methods. In most studies, patency endpoints were determined by physical and/or functional signs of VA dysfunction, caused by significant anatomical stenosis, while some took only anatomical aspect into consideration[16, 22, 53].

Quality and Risk of Bias

For the RCTs, due to the visual difference between conventional and coated balloons, there was an overall inability to blind the intervention from the operator, which generated a moderate risk of bias in the deviation from the intended intervention parameter for all RCTs. The lack of concealment of treatment groups also increased the risk of bias in the measurement of the outcome in all trials, except the ones that explicitly blinded the outcome assessors, as well as follow-up staff and physicians[16,22,23,52,53,57]. As for the bias in the randomization process, several studies had insufficient descriptions of the process used, increasing the risk[16, 21, 47, 50, 51]. Risk of bias for missing outcomes data was high in three RCTs for the failure to recruit the initially planned necessary number of patients[48, 52, 53], and in another two for the absence of missing data or censorship description[21, 51]. In addition, Lookstein *et al*. had a higher risk of bias in this parameter as there was an extension of the follow-up period, with several patients not reconsenting[16] (**Figure 2 and 3**).

For the non-randomized cohort studies selected, the Newcastle-Ottawa Scale demonstrated high quality for all studies included (**Table III**). As a prospective study with a retrospective control group, Lučev *et al*. had its score reduced for selection of a temporarily remote non-exposed cohort[31].

Loss of Target Lesion Primary Patency

All 18 selected studies reported the patency of the target lesion after index angioplasty. The hazard ratio was estimated for each of the 14 RCTs and 4 cohort studies, and pooled to create two separate analysis.

Amongst the RCTs, looking at the random effects model, it is clear that DEB demonstrated reduction in risk of loss of TLPP when compared to the use of conventional PTA (HR 0.76, 95% CI 0.60 to 0.98), although there was moderate heterogeneity (I^2 = 69%) (**Figure 4 A**). Only Björkman *et al.* presented very different results from the remaining studies, with significantly worst outcomes for DEB[52]. Additionally, publication bias is unlikely given the approximate symmetry of the funnel plot (**Figure 4 B**).

The analysis of cohorts studies also favoured the use of DEB over PTA for decreasing the risk of loss of patency at the target lesion, using the common effect model (HR 0.55, 95% CI 0.38 to 0.82), with no apparent heterogeneity (I^2 = 0%) (**Figure 5**). Although the funnel plot is apparently not symmetrical, an analysis of less than 10 studies limits the viable interpretation for publication bias.

Loss of Circuit Primary Patency

Only nine RCTs reported the loss of CPP. Upon analysis of the pooled hazard ratios, the rate of overall hemodialysis access circuit patency loss was higher in patients that underwent initial PTA, in comparison to those with DEB angioplasty (HR 0.85, 95% CI 0.77 to 0.94). Heterogeneity was

found to be moderate (I^2 = 49%) (**Figure 6**). Once again, even though the funnel plot might be visually asymmetrical, the number of studies included in the analysis is too scarce to determine a risk of publication bias.

Only one cohort study reported the loss of CPP, therefore no quantitative analysis was carried-out in this group[30].

Mortality

All-cause mortality was analyzed for 16 studies at 12 months. In the 13 RCTs analyzed, 1538 patients were included (n = 765 for DEB and n = 773 for PTA), with a total number of deaths of 51 (6.7%) in the DEB group and 52 (6.7%) in the PTA group. In the 3 cohort studies analyzed, 305 patients were included (n = 145 for DEB and n = 160 for PTA), with a total number of deaths of 2 (1.4%) in the DEB group and 2 (1.3%) in the PTA group. The pooled data using a common effects model determined no significant difference in 12-month all-cause mortality between groups both within RCTs (RR 0.99, 95% CI 0.69 to 1.44, I^2 = 0%) and within cohort studies (RR 0.99, 95% CI 0.18 to 5.53, I^2 = 0%) (**Figure 7** and **8**).

Three RCTs and 2 cohort presented their all-cause mortality at 24 months. In a total of 649 RCT patients, there were 115 deaths (n = 63 (19.3%) for DEB and n= 52 (16.3%) for PTA), with a non-significant difference between the two intervention groups (RR 1.20, 95% CI 0.86 to 1.67, I^2 = 0%) (**Figure 9**). As for the cohort studies, in a pool of 88 patients (n = 44 for DEB and n= 44 for PTA), 5 (11.4%) from the DEB group and 3 (6.8%) from the PTA group died within 24 months, representing a non-significant difference between groups (RR 1.67, 95% CI 0.42 to 6.56, I^2 = 0%) (**Figure 10**). There was no evidence of heterogeneity in any of the all-cause mortality analysis.

Cost effectiveness

Two studies included in our meta-analysis, both RCTs, analyzed the cost-effectiveness of DEB, when compared to the conventional PTA approach. Novak *et al*. reported a 32% cost increase with the use of DEB, with an additional USD 11.80/day for the initial procedure. However, the increased time-to-reintervention after DEB angioplasty meant that the overall cost for maintaining access patency was lower in this group[22]. Similarly, Kitrou *et al*. also performed a cost-effectiveness analysis with a favorable outcome for DEB, namely incremental cost-effectiveness ratio 2250 euros per primary patency year of access gained, with incremental net benefits of 1000 euros for willingness-to-pay threshold of 5000 euros[25].

Subgroup Analysis

When comparing studies recruiting exclusively autogenous AVF with those that included only AVG, no significant difference was found in terms of DEB efficacy on the target lesion (p=0.90). Similar

results were found between studies that included solely restenotic lesions, and those combining both primary and restenotic lesions (p=0.72). Subgroup analysis was also carried out in studies with and without the use of predilation, which did not demonstrate statistically significant difference (p=0.88). In addition, with only one study reporting the use of a low-dose (2.0μgmm^2) DEB, the effect of paclitaxel dose was examined by grouping studies that used DEB coated with >3.0μg/mm^2 and those using ≤3.0μg/mm^2 and found no significant difference in primary outcome (p=0.28). Finally, to determine the effect of VA age a meta-regression was carried-out that concluded no significant correlation with DEB efficacy, both within RCTs and cohort studies (p=0.57 and p=0.22, respectively). Due to the lack of data for subgroup classification, and the fact that subgoups with a single study should not be include, only the last variable was analyzed for cohort studies. (**Figures 11** to **16)**

Discussion

The superiority of DEB over conventional PTA still remains controversial. Although literature continues to emerge favoring the use of DEB in stenotic hemodialysis access[36-38], some recent analyses contrast this evidence with equivalent efficacy outcomes for DEB and PTA[39-41].

As a treatment for stenosis in other vessels, DEB have already proven successful in enhancing the patency outcomes for coronary arteries, as well as femoropopliteal arteries, where the consistent superiority in several RCTs has rendered the drug-eluting technology use as a routine practice[34, 35]. However, the anatomical differences inherent to arteriovenous fistulas, along with the non-physiological hemodynamics that create a continuous stress upon the vessel wall, may render different patency outcomes[54].

Our meta-analysis aimed to compare the efficacy of DEB and conventional endovascular treatment by combining the results of 18 studies, including the most recent large scale studies[20, 22, 29, 47] and long-term results of previously analyzed trials[16], and also taking into account the results of RCTs and cohort studies.

Efficacy

Through the pooled HRs from each study selected, we concluded that there is a significant reduction in the risk of loss of TLPP and CPP with the use of DEB angioplasty as opposed to PTA in stenotic hemodialysis upper limb arteriovenous access. The results favoring the use of DEB were evident not only for RCTs, but also for cohort studies, which contrasts with Abdul *et al.'s* previously published meta-analysis, that demonstrated statistically significant positive results only within retrospective cohorts[41]. This may be due to the increasing number large RCTs recently published presenting positive results for DEB. However, it is important to keep in mind that our patency outcomes were associated to substantial heterogeneity within RCTs, which may deem these results less reliable.

Looking at the forest plot for TLPP in RCTs, there is a clear outlier, with contrasting outcomes in comparison to the remaining studies. Björkman *et al.* presented a shorter target lesion revascularization-free survival for DEB during the 12-month follow-up[52]. These discrepant results may have increased the statistical heterogeneity of our analysis. To explain this occurrence, the authors suggested that this could have been due to the low average fistula age, which is indeed significantly shorter than the rest of our included studies (less than 6 months). However, our subgroup analysis according to vascular access age did not find a correlation corroborating this hypothesis (**Figure 16**). On the other hand, the early recruitment discontinuation in this study, which ended up having a much lower number of patients than the required protocol, may have compromised the results.

Seeing as the use of DEB in hemodialysis access stenosis is still a relatively new concept, with ongoing investigation and not yet included in American or European guidelines, the ideal population, vessel characteristics, paclitaxel dose, vessel preparation and application technique is

still uncertain. This was reflected in the methodological variations between the included studies and may have contributed to the statistical heterogeneity. In an attempt overcome this issue, subgroup analyses were carried out, aggregating studies with similar baseline and methodological characteristics.

Comparing studies that included only native AVF and those including only AVG, there was no significant difference between outcomes in terms of risk of TLPP loss (**Figure 11**). This is in line with Han *et al.*'s conclusions of similar improvement on risk of patency loss with the use of DEBs for both VA types within 6 and 12 months[36].

At present, there are several different DEB available in the market, with paclitaxel concentrations ranging from 2 to 3.5 μg/mm^2, and different excipient formulas[19]. The dose dependent effect of paclitaxel on restenosis rate reduction has previously been demonstrated for DEB use in femoropopliteal arteries by Katsanos *et al*., with superior results for standard paclitaxel dose (3.0 μg/mm^2 and 3.5μg/mm^2), as opposed to low-dose (2.0μg/mm^2)[55]. Similary, Fong *et al.* found a better TLPP outcome only for standard paclitaxel dose, with no advantage between 3.0μg/mm^2 and 3.5μg/mm^2. Due to a lack of low-dose balloon use in our study sample, subgroups were aggregated in ≤3.0μg/mm^2 and >3.0 μg/mm^2, with no significant difference in efficacy between them. It must, however, be noted that we did not take into account the DEB length, surface area or the excipient used, which may have resulted in different nominal doses delivered (**Figure 12**).

As forementioned, recurrent AVF stenoses have notably higher cellular proliferation rates in comparison to primary stenoses, leading to lower patency rates post-PTA[15, 16, 56]. With a more pronounced neointimal hyperplasia, it has been postulated that DEB could have greater benefits for recurrent stenoses than primary stenoses[57]. Three of the studies included in our meta-analysis examined the separate patient level outcomes for primary and recurrent stenotic lesions, and could not find statistically significant differences[20, 47, 50]. Likewise, in our subgroup analysis, studies that included only restenotic lesions showed similar outcomes to those that included both primary lesions and restenosis (**Figure 13**).

Finally, predilation was also a point of heterogeneity between studies protocols. Although some studies opted to not predilate vessels before DEB use, an increasing amount of literature has pointed in favor of this practice, as the apparent fractures and fissures created by the previous angioplasty on the vessel wall may allow for a more efficient and homogenous delivery of paclitaxel, as well as reducing its loss during the passing of the stenosis[58]. Comparing the HR for loss TLPP in studies where predilation was performed, and those where it was not, results appear to be similar (**Figure 14**).

Mortality

Recently, concerns have been raised over the long-term safety of paclitaxel-coated devices, namely in a meta-analysis by Katsanos *et al*. published in 2018[59]. This publication suggested an increase mortality risk within two to five years after treatment of femoropopliteal artery stenosis with

paclitaxel-coated balloons and stents. Although this hypothesis became extremely concerning upon its release, prompting the US Food and Drug Administration (FDA) to raise a red-flag on the overall use of these devices in 2019[60], investigation into DEB use in endovascular procedures for hemodialysis access has unanimously discarded the increased mortality risk[61]. In fact, as of February 2023, the FDA had officially declared the long-term safety of drug-eluting devices, upon the analysis of additional data from several RCTs, with follow-ups ranging from two to five years[62].

This statement is in agreement with the conclusions drawn from the studied included in our meta-analysis, where we found similar risk of mortality for patients who had undergone DEB angioplasty, in comparison to those treated with PTA. This was evident within 12 months of follow-up, but also after 24 months.

Cost effectiveness

Cost effectiveness is an important aspect that should always be weighed in determining the overall superiority of an improved device for a conventional technique in the real-world clinical practice. In order to evaluate a potential decrease in overall VA maintenance cost with the use of DEB instead of PTA, two single-centered RCTs included in our meta-analysis analyzed cost-effectiveness within a European context, suggesting a better overall performance for DEB[22, 25].

In line with these findings, the 12 month outcomes of Lookstein *et al*.'s[16] trial have been used to evaluate the long-term cost-effectiveness of DEB in the US context, in a separate publication, where cost saving were apparent not only within 12 months post-angioplasty, but also in 2.5 and 3-year projections[63].

As investigation into new endovascular treatments for AVF stenosis grows, it is essential to further compare the cost-effectiveness of DEB and PTA in larger cohorts, but also to compare it to other emerging novel techniques.

Limitations

Firstly, although inclusion of cohort studies increased our sample size and contributed to the demonstration of real-world evidence of the benefit of DEB use in clinical practice, the retrospective design and absence of randomization in these studies increases the risk of selection bias in the overall analysis.

Secondly, the studies included in this meta-analysis had substantial protocol heterogeneity. The methods for stenosis evaluation, patency endpoints, fistula and stenosis location, vessel preparation and technical procedure were not homologous, which may have contributed to the heterogeneity in results. Although we attempted to find sources of heterogeneity by performing subgroup analysis according to patient and study characteristics that had previously been noted to contribute to VA patency, we were not able to account for several other covariates with prognostic potential.

Finally, although our systematic review and meta-analysis did not undergo previous registration, it did follow the recommendations published in the PRISMA statement and checklist.

Conclusion

Our analysis demonstrated there is a significant reduction in the risk of loss of AVF and AVG patency with the use of DEB angioplasty as opposed to conventional PTA in the treatment of stenotic hemodialysis upper limb VA. Furthermore, this approach does not increase the risk of mortality of patients within 12 and 24 months and seems to be a cost-effective option.

Future research should encompass long-term follow-up of larger cohorts, focusing on the evaluation of specific subgroups, to mitigate the heterogeneity amongst the study populations and stenotic fistula characteristics, and determine which lesions or patients would benefit the most from the use of drug-eluting balloon angioplasty.

Appendix

Table I. Baseline Characteristics of included Cohort Studies.

Author (year)	Study Design	No. of patients		Patient age, DEB vs. PTA (mean/median years)	Male sex, DEB vs. PTA (%)	AVF or AVG	Primary or Restenosis	Fistula age, DEB vs. PTA (mean/median years)	DEB Brand (dose)	Control Balloon	Predilation	Max available follow up (months)
		DEB	PTA									
Kocaaslan 2020	Retrospective Cohort	44	43	55.7 ± 11.1 vs. 57.3 ± 10.2	47.9 vs. 42.1	AVF	Primary Stenosis	0.94 vs. 0.86	IN.PACT (NR)	standard balloon	Predilation	12
Patanè 2019	Retrospective Cohort	70	86	(71 ± 13 and 70 ± 8) vs. 68 ± 14	58.5 vs. 76.0	AVF	Primary or restenosis	(2.58 and 2.58) vs. 2.33	IN.PACT (NR) + Lutonix (NR)	standard balloon + HPB	Predilation	12
Haave 2019	Retrospective Cohort	13	13	76 (IQR 63-79) vs. 64 (IQR 55-79)	85 vs. 62	AVF	Restenosis	1.42 vs 1.42	IN.PACT (NR)	standard balloon	Predilation (at operator's discretion)	24
Lučev 2018	Prospective Cohort	31	31	62.81 ± 17.2 vs. 67.03 ± 8.44	51.6 vs. 48.4	AVF	Primary Stenosis	0.70 vs. 1.67	IN.PACT (NR)	standard balloon	Predilation	24

DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; AVF, arteriovenous fistula; AVG, arteriovenous graft; HPB, high pressure ballons; NR, not reported.

Table II. Baseline Characteristics of included RCTs.

Author (year)	No. of patients		Patient age, DEB vs. PTA (mean/median years)	Male sex, DEB vs. PTA (%)	AVF or AVG	Primary or Restenosis	Fistula age, DEB vs. PTA (mean/median years)	DEB Brand (dose)	Control balloon	Predilation	Max available follow up (months)
	DEB	PTA									
Maleux 2023	51	52	72.3±11.8 vs. 67.4±15.3	49 vs. 74.5	AVF + AVG	Primary and restenosis	3.0 vs. 3.5	APERTO (3.0 µg/mm2)	standard balloon	No	12
Lookstein 2023	170	160	65.8 ± 13.1 vs. 65.5 ± 13.4	65.9 vs. 63.1	AVF	Primary and restenosis	NR	IN.PACT (3.5 µg/mm2)	standard balloon + HPB	Predilation	36
Goo 2023	94	92	62.91 ± 13.15 vs. 65.32 ± 12.59	41.5 vs. 40.2	AVG	Primary and restenosis	2.9 vs. 3.8	IN.PACT (3.5 µg/mm2)	standard balloon + HPB	Predilation	12
Novak 2022	38	38	71 (IQR 65, 78) vs. 69 (IQR 64, 76)	55 vs. 47	AVF + AVG	Primary and restenosis	1.56 vs. 1.42	SeQuent (3 µg/mm2)	standard balloon + HPB	Predilation	12
Fransson 2022	22	20	68 (IQR 59 - 76) vs. 62 (IQR 57-77)	68 vs. 65	AVF + AVG	Primary and restenosis	NR	Advance (NR)	standard balloon + HPB	No	12
Yin 2021	78	83	56 ± 13 vs. 54±13	56 vs. 51	AVF	Primary and restenosis	NR	Aperto (3.0 µg/mm2)	HPB	Predilation	12
Trerotola 2020	141	144	64±15 vs. 61±13	62 vs. 59	AVF	Primary and restenosis	3.12 vs. 2.89	Lutonix (2 µg/mm2)	standard balloon + HPB	Predilation	24
Moreno-Sánchez 2020	61	65	69 ± 12.99 vs. 71 ± 11.31	78.6 vs 66.7	AVF + AVG	Primary and restenosis	NR	Passeo (NR)	HPB + standard balloon	Predilation	12
Liao 2020	22	22	70.4±10.6 vs. 65.9±15.9	13.6 vs. 40.9	AVG	Restenosis	2.3 vs. 2.8	IN.PACT (NR)	standard balloon	No	12
Karmota 2020	30	30	54.7 ± 13.2 vs 49.2 ± 11.5	43.3 vs. 53.3	AVF	NR	4.6 vs 4.1	Lutonix (NR)	standard balloon	Predilation	12
Björkman 2019	18	18	67.4 (IQR 46–87) vs. 67.0 (IQR 28–82)	55.5 vs. 71.2	AVF	Primary and restenosis	0.45 vs 0.80	IN.PACT (3.5 µg/mm2)	standard balloon	Predilation	12
Roosen 2017	16	18	80 (IQR 71 - 86) vs. 83 (IQR 78 - 86)	43.8 vs. 77.8	AVF + AVG	Restenosis	NR	IN.PACT (NR)	standard balloon	No	24
Kitrou[a], 2015	20	20	64.3 ± 14.5 vs. 57 ± 14.2	60 vs. 70	AVF	Primary and restenosis	2.13 vs. 2.74	IN.PACT (NR)	HPB	No	12
Kitrou, 2015	20	20	65.7 ± 13.2 vs. 62.5 ± 15.4	75 vs. 70	AVF + AVG	NR	2.5 vs. 2.5	IN.PACT (3 µg/mm2)	HPB	Predilation (at operator's discretion)	12

DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; AVF, arteriovenous fistula; AVG, arteriovenous graft; HPB, high pressure ballons; NR, not reported.

Table III. Newcastle-Ottawa Scale quality assessment of included cohort studies.

Cohort Studies	Study Design	Selection				Comparability of cohorts	Outcome			Total Quality Scores
		Representetiveness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of the exposure	Outcome of interest was not present at start of study	Control for important factors	Assessment of outcome	Follow-up period long enough for the outcome to	Adequacy of follow-up evaluation of cohorts	
Kocaaslan 2020	Retrospective Cohort	*	*	*	*	*	*	*	*	8
Patanè 2019	Retrospective Cohort	*	*	*	*	*	*	*	*	8
Haave 2019	Retrospective Cohort	*	*	*	*	*	*	*	*	8
Lučev 2018	Prospective Cohort	*		*	*	*	*	*	*	7

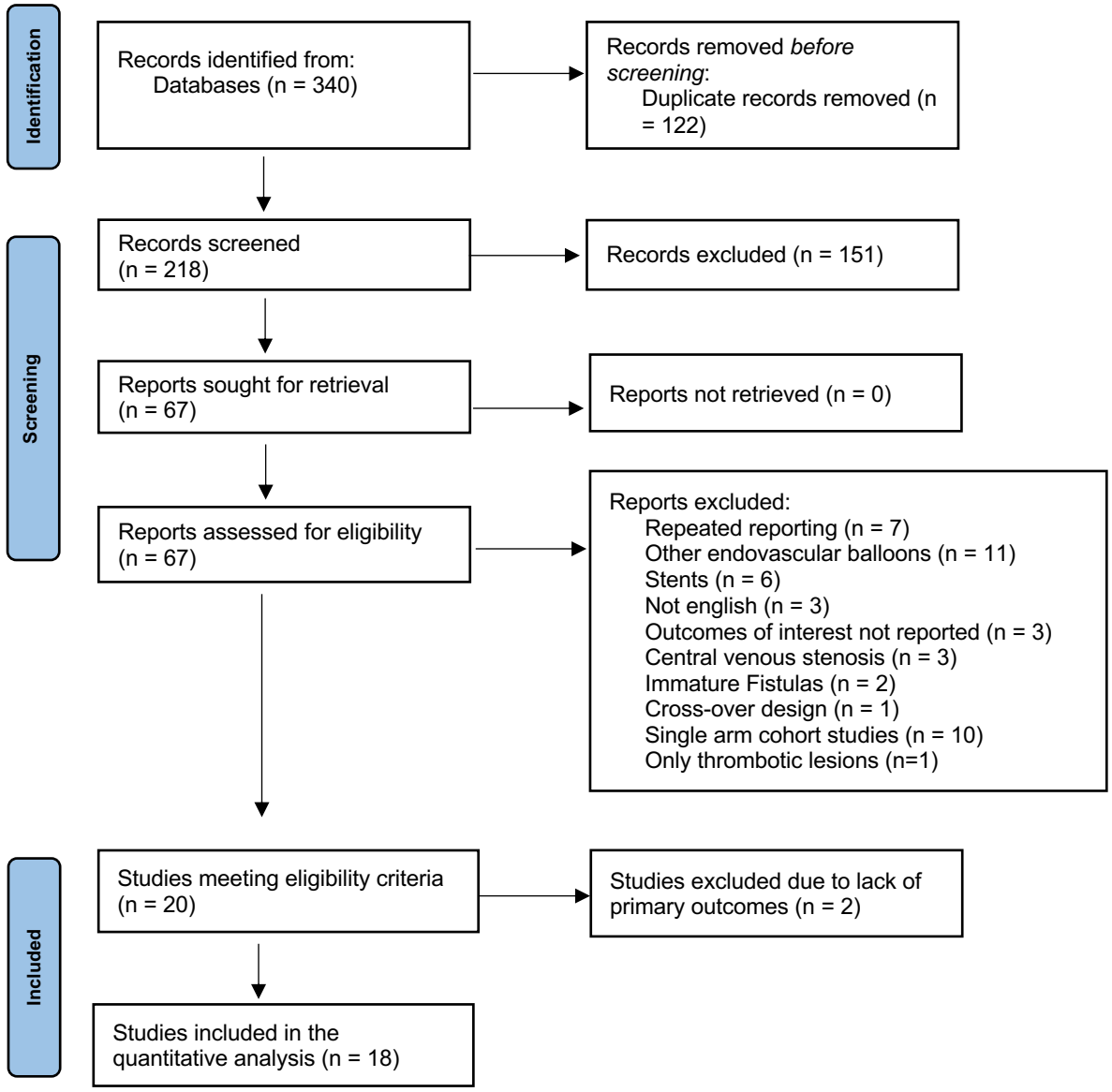


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the selection of studies included in our analysis.

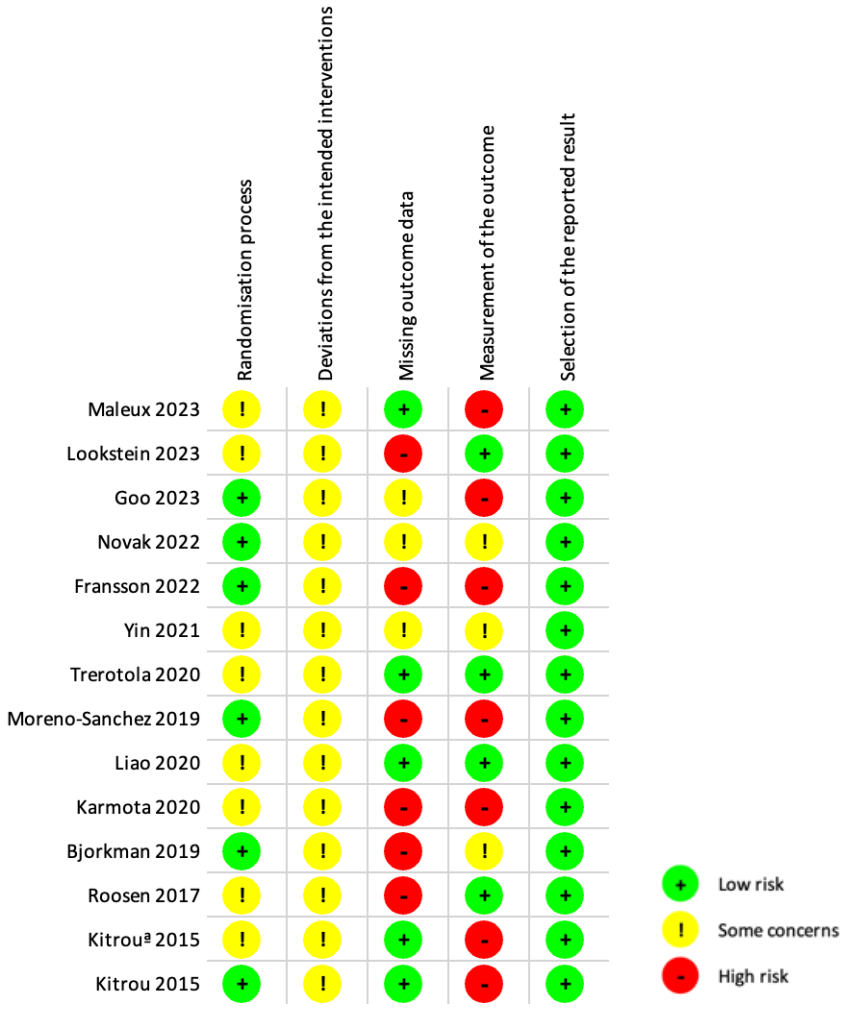


Figure 2. Risk of bias summary of included RCTs.

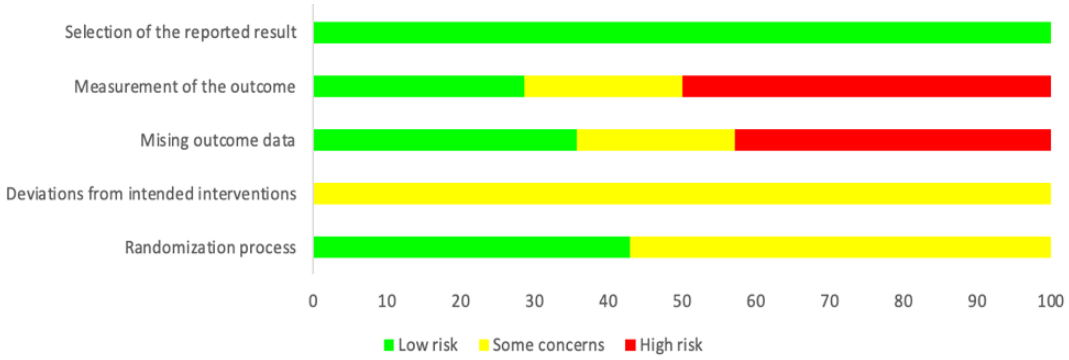
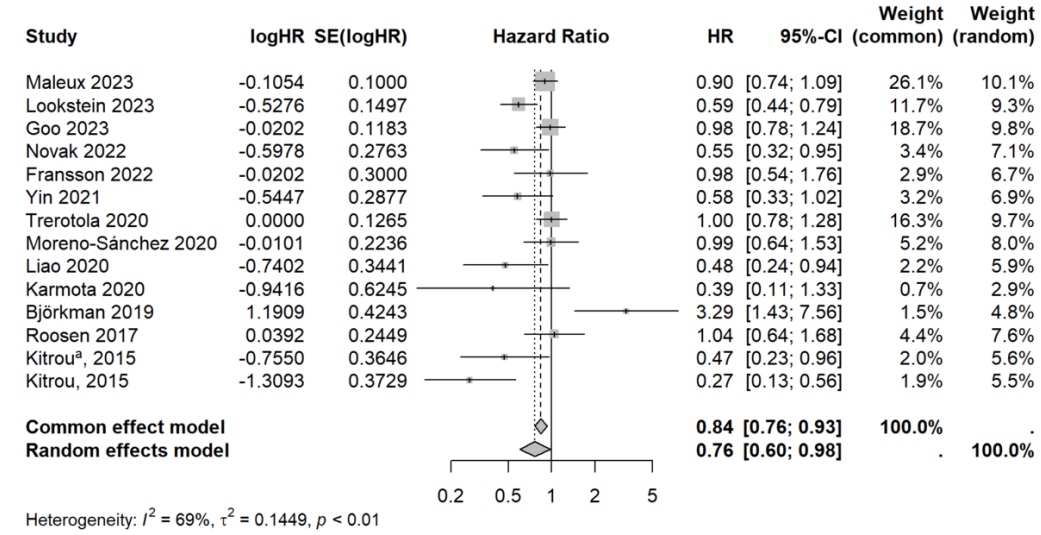


Figure 3. Risk of bias graph of included RCT.

A.



B.

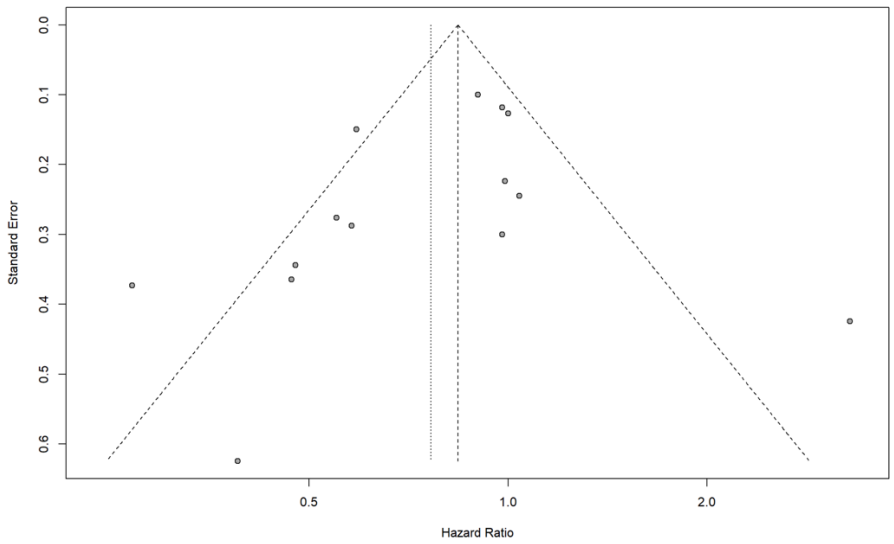
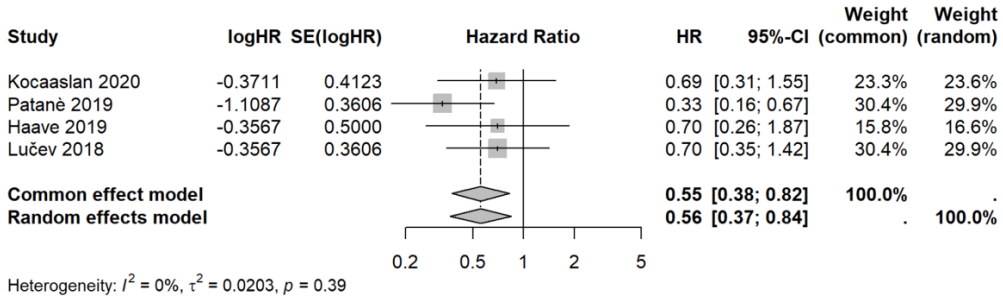


Figure 4. Forest plot of pooled HRs (A) and publication bias funnel plot (B) for loss of TLPP after angioplasty AVF using DEB, compared to PTA, in RCTs.

A.



B.

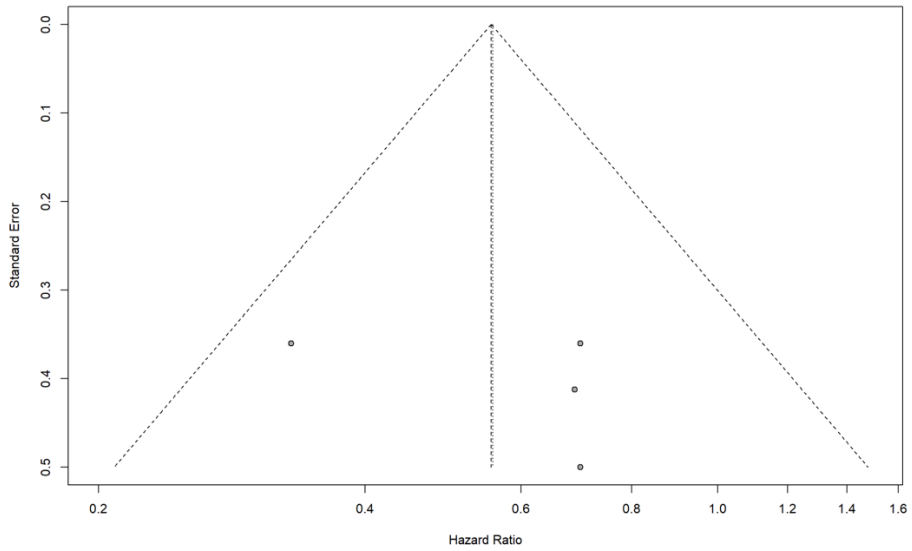
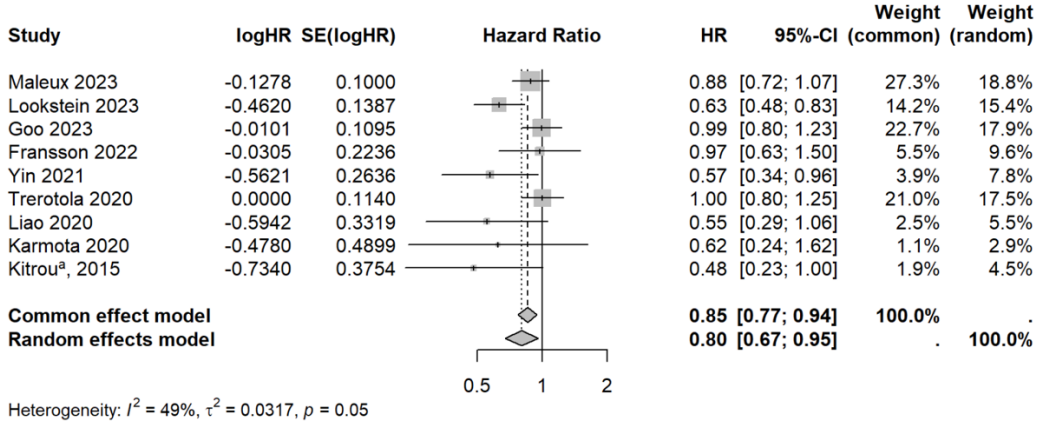


Figure 5. Forest plot of pooled HRs (A) and publication bias funnel plot (B) for loss of TLPP after angioplasty of AVF using DEB, compared to PTA, in cohort studies.

A.



B.

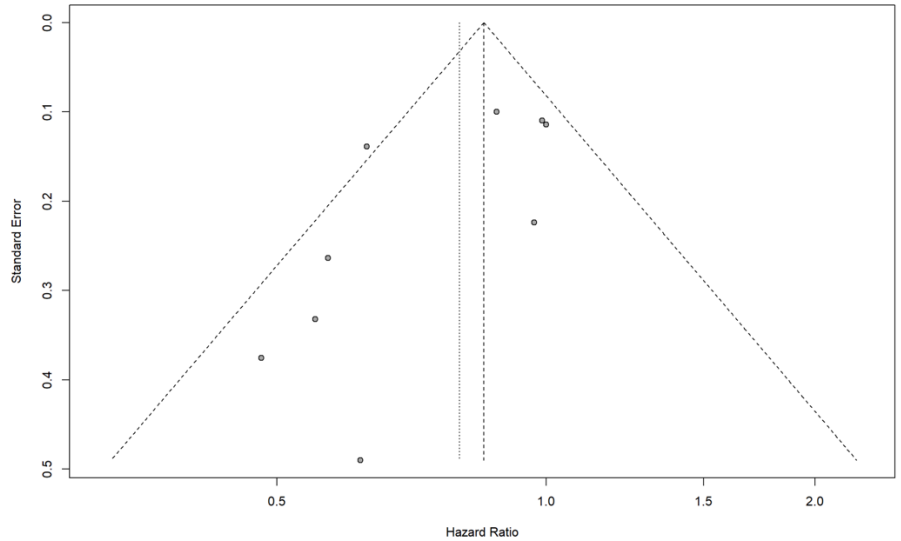


Figure 6. Forest plot of pooled HRs (A) and publication bias funnel plot (B) for loss of CPP after angioplasty of AVF using DEB, compared to PTA, in RCTs.

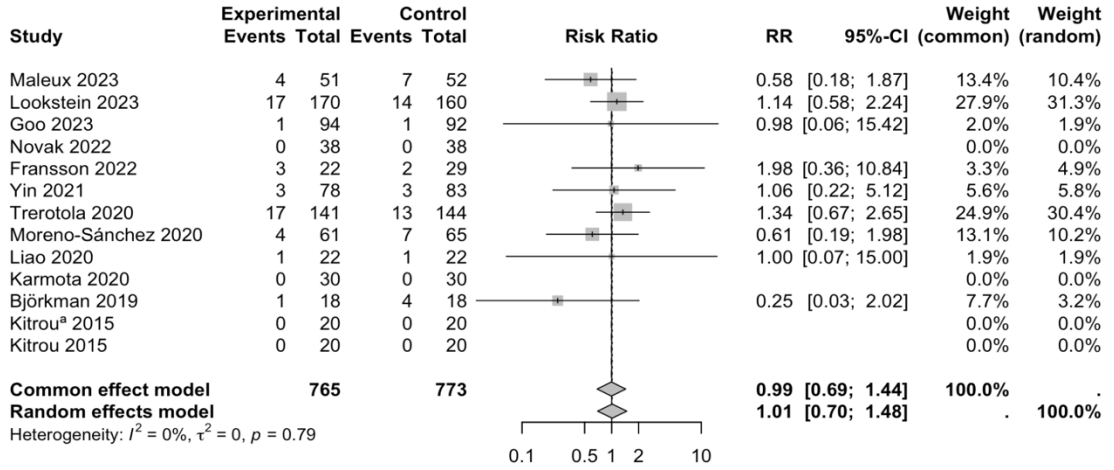


Figure 7. Forest plot of RR for all-cause mortality at 12 months after angioplasty of AVF using DEBs, compared to PTA, in RCTs.

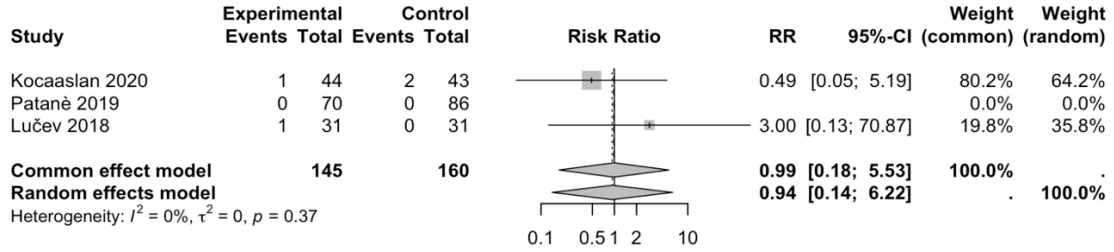


Figure 8. Forest plot of RR for all-cause mortality at 12 months after angioplasty of AVF using DEB, compared to PTA, in cohort studies.

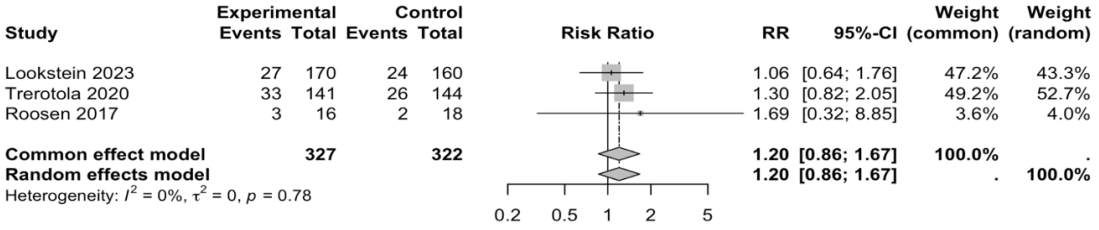


Figure 9. Forest plot of RR for all-cause mortality at 24 months after angioplasty of AVF using DEB, compared to PTA, in RCTs.

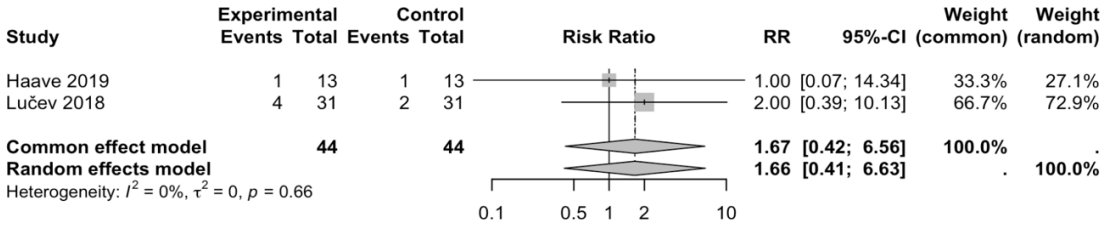


Figure 10. Forest plot of RR for all-cause mortality at 24 months after angioplasty of AVF using DEB, compared to PTA, in cohort studies.

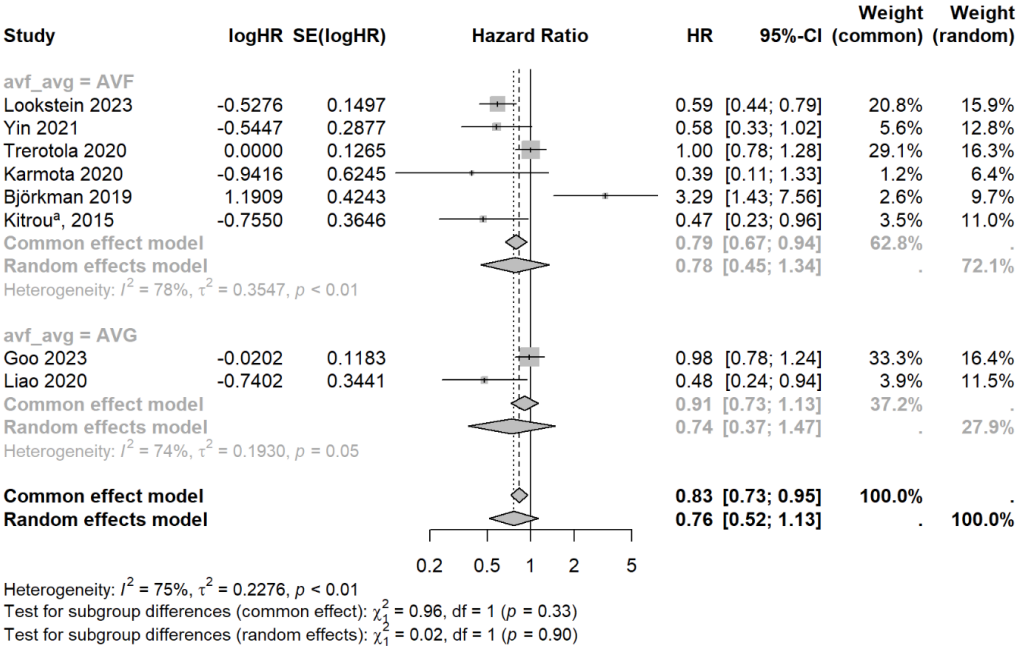


Figure 11. Subgroup analysis on loss of TLPP for studies including only AVF vs. studies including only AVG, for RCTs.

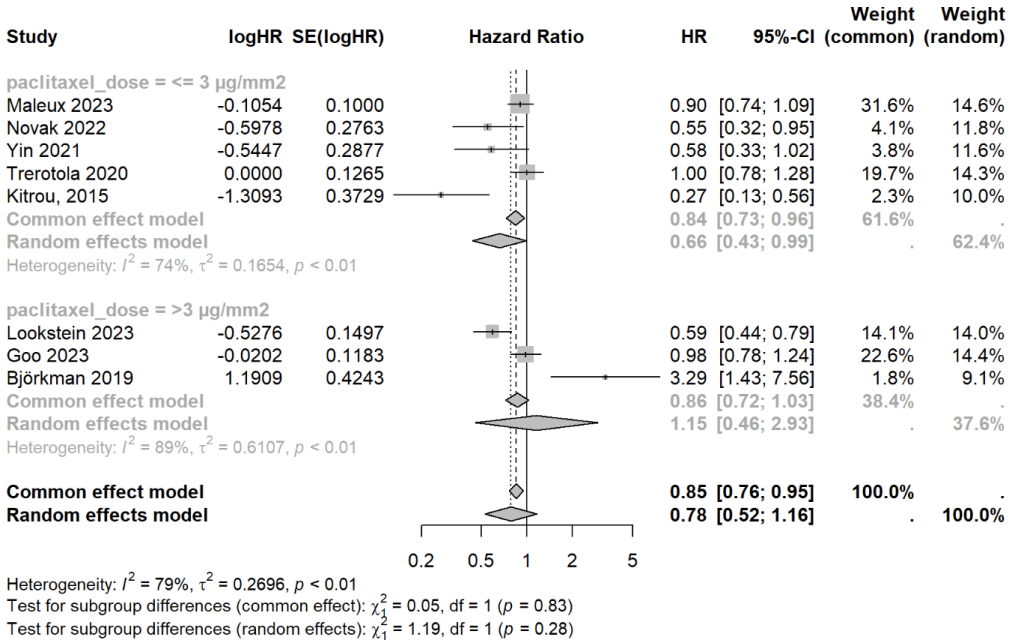


Figure 12. Subgroup analysis on loss of TLPP for studies using DEB with paclitaxel dose >3 μ g/mm² vs. ≤3.0 μ g/mm², for RCTs.

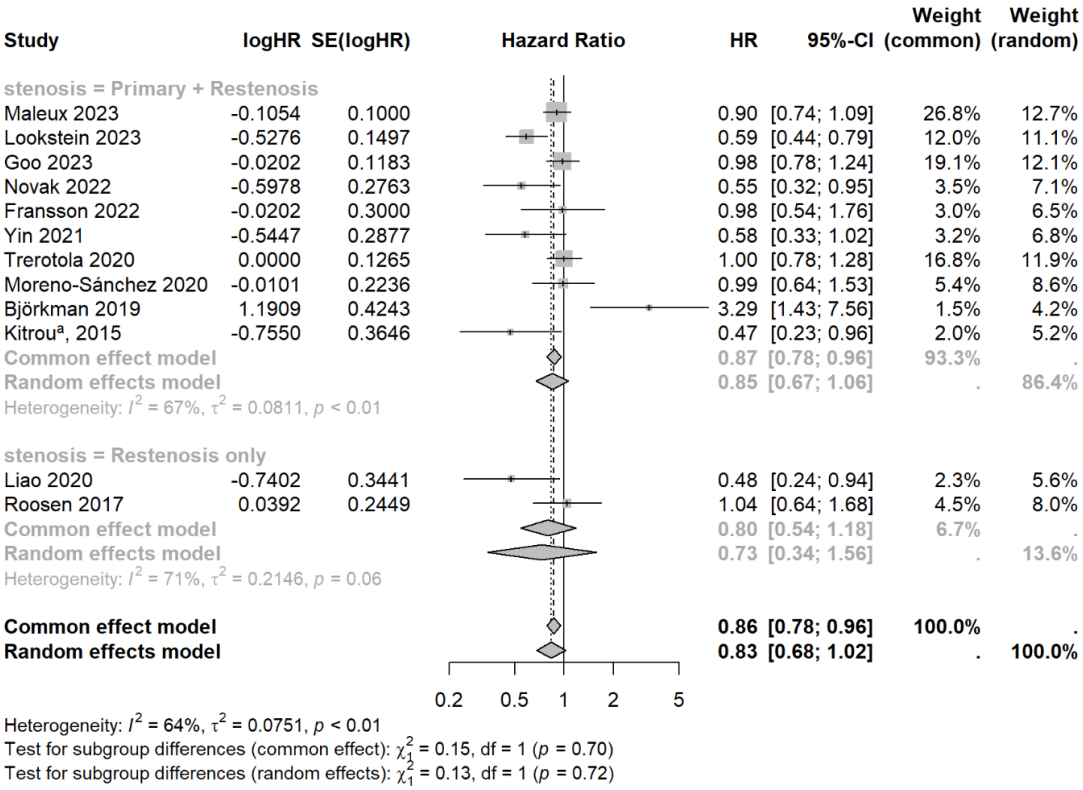


Figure 13. Subgroup analysis on loss of TLPP for studies including primary stenotic lesions vs. restenotic lesions, for RCTs.

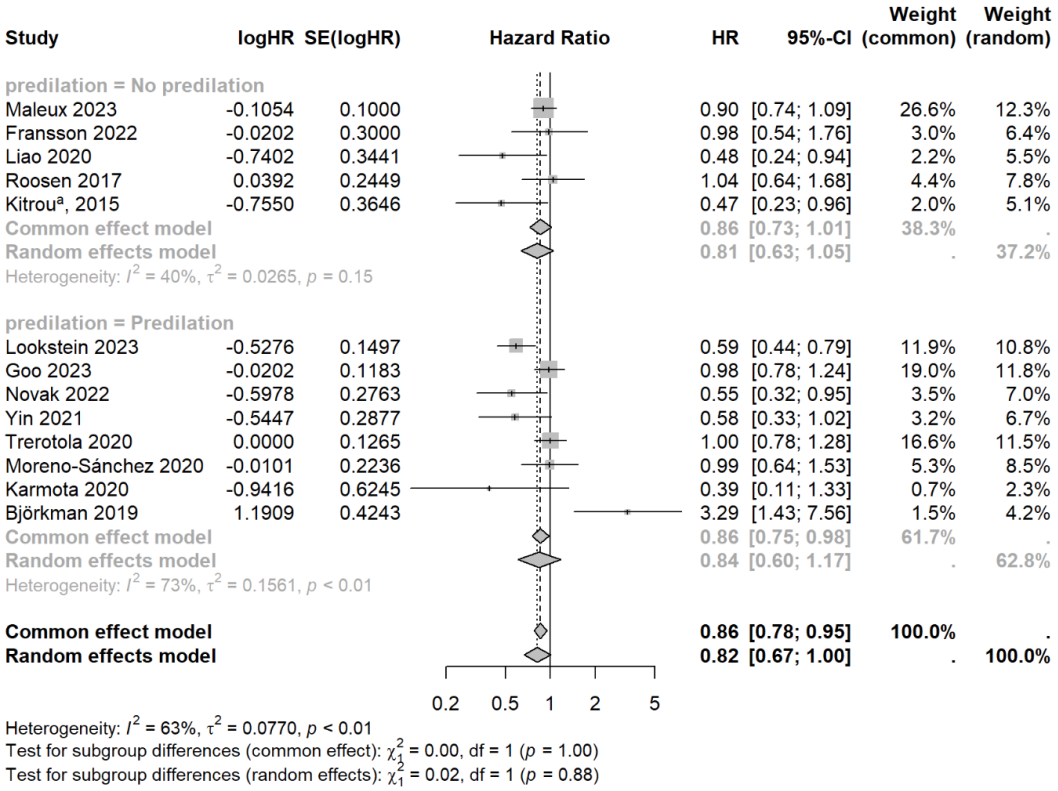


Figure 14. Subgroup analysis on loss of TLPP for studies using predilation vs. no predilation, for RCTs.

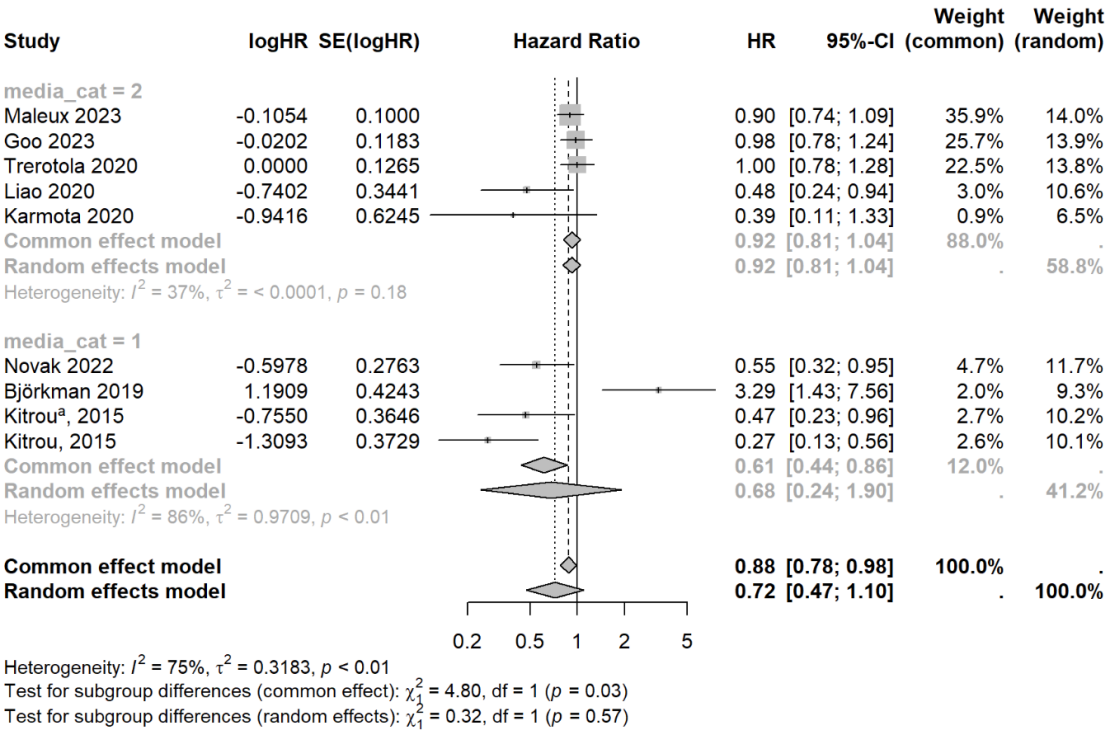


Figure 15. Subgroup analysis on loss of TLPP for vascular access age, in RCTs.

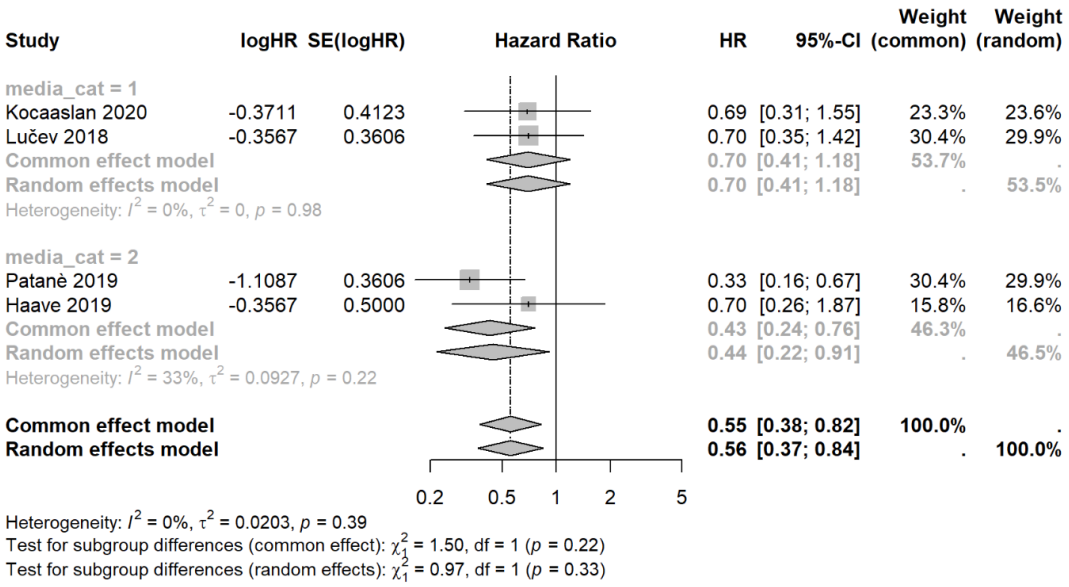


Figure 16. Subgroup analysis on loss of TLPP for vascular access age, in cohort studies.

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