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Antiplatelet and anticoagulant use in randomised trials of patients undergoing endovascular intervention for peripheral arterial disease: systematic review and narrative synthesis

SHORT TITLE:

Antithrombotic therapy in randomised trials of lower limb endovascular intervention

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What does this study/review add to the existing literature and how will it influence future clinical practice

This systematic review demonstrates the lack of standardisation and poor reporting of antithrombotic therapy in randomised controlled trials of endovascular intervention. It shows a high degree of heterogeneity in antiplatelet regimens for trials of peripheral endovascular intervention, and an increasing trend for use of dual antiplatelet therapy post intervention. The results highlight the need for clarity in the reporting of antithrombotic therapy as a co-intervention in trials of endovascular intervention and the need for a randomised trial of antiplatelet therapy after endovascular intervention.

ABSTRACT

Objectives

Randomised trials of new devices for peripheral arterial endovascular intervention are published regularly. The evidence for which antiplatelet and/or anticoagulant (antithrombotic) therapy to use after an intervention is lacking. The aim of this systematic review was to examine the antithrombotic regimens in randomised trials for peripheral arterial endovascular intervention to understand choices made and trends with time or type of device.

Data Sources

Medline, Embase, and Cochrane Library databases.

Review Methods

Randomised trials including participants with peripheral arterial disease undergoing any endovascular arterial intervention were included.

Trial methods were assessed to determine whether an antithrombotic protocol had been specified, its completeness, and the agent(s) prescribed. Antithrombotic therapy protocols were classed as periprocedural (preceding and during intervention), immediate postprocedural (up to 30 days following intervention) and maintenance postprocedural (therapy continuing beyond 30 days).

Results

Ninety-four trials were included in narrative synthesis. Study quality was low. None of the trials justified their antithrombotic therapy protocol.

Only 29% of trials had complete periprocedural antithrombotic protocols, and 34% had complete postprocedural protocols. In total, 64 different periprocedural protocols, and 51 separate postprocedural protocols were specified.

Antiplatelet monotherapy and unfractionated heparin were the most common choices of regimen in the periprocedural setting, and dual antiplatelet therapy (55%) was most commonly utilised post-procedure. Over time there has been an increasing tendency to use dual therapy (P<0.001). This corresponds with the introduction of newer technologies and trials focussed on below the knee intervention.

Conclusions

Randomised trials comparing different types of peripheral endovascular arterial intervention have a high level of heterogeneity in their antithrombotic regimens. Antiplatelet therapy need to be standardised in trials comparing endovascular technologies to reduce potential confounding. To do this, an independent randomised trial specifically examining antiplatelet therapy following peripheral arterial endovascular intervention is needed.

KEY WORDS

Platelet aggregation inhibitors; Review, systematic; Peripheral Arterial disease; endovascular intervention

Introduction

New devices to perform endovascular treatment for peripheral arterial disease are made available frequently. Within the last ten years, drug eluting technology, atherectomy devices and new stents have all become available. Randomised trials to support their use are also published with some regularity and are often sponsored by the manufacturer of the device as part of the regulatory process(1).

Antiplatelet or anticoagulant therapy is usually given as a co-intervention when a peripheral arterial endovascular intervention is performed. The literature to support the choice of antithrombotic therapy after peripheral endovascular intervention is lacking(2), especially when compared to the literature on percutaneous coronary intervention(3). Guidelines to direct antithrombotic regimens after peripheral arterial endovascular intervention are therefore limited and conflicted(4-7). What is clear however, is that more aggressive antiplatelet regimens have a significantly higher major bleeding risk(2). The true risks and benefits of an endovascular intervention cannot be understood without concomitant regard for antithrombotic therapy.

A recent survey of international practice has shown that prescribing after peripheral arterial endovascular intervention is heterogeneous, and that dual antiplatelet therapy is often used(8). There is no evidence to guide this practice, but anecdotally some of the recent randomised trials for new devices used dual antiplatelet regimens. With the recent concern about a higher mortality rate in the intervention arm of some of these trials(9), it is more important than ever to understand factors which could potentially lead to confounding of outcomes.

The aim of this systematic review was therefore to examine antiplatelet and anticoagulant (antithrombotic) use as co-interventions in randomised trials of

peripheral arterial endovascular intervention in order to compare regimens, try to understand choices made and examine the trends over time.

Methods

A systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(10). MEDLINE and EMBASE were searched via Ovid from inception to 15th January 2019 focussing on randomised trials including patients undergoing any endovascular intervention for peripheral arterial disease. The Cochrane library database and the Cochrane collaboration central register of controlled clinical trials were searched separately. There was no language restriction on any search. The grey literature was not specifically searched. The full search strategy is shown in Appendix A. The study was registered on PROSPERO on 14/05/2019 (URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=135100).

Screening and selection

Randomised controlled trials including participants with chronic atherosclerotic peripheral arterial disease of the lower limb undergoing any endovascular intervention as the main therapy or adjunctive therapy with another endovascular intervention were included. Non-randomised trials were excluded. Trials studying patients treated with open surgery or conservative treatments were excluded. Trials including any patients with non-atherosclerotic lower limb disease such as aneurysms were excluded as were trials examining acute disease presentations. Study selection was performed by screening titles and abstracts (KC and 50% of excluded studies checked by HC). Full texts of potentially eligible studies were

screened by two of the authors (KC and HC) independently. Disagreements were resolved by discussion or consulting a third author (RH).

Data extraction and definitions

Two authors (HL and KC) independently extracted data. If any disagreements arose a consensus was reached with reference to a third author (GKA). The following data were extracted from each study using a pre-specified proforma: year of publication; endovascular interventions; number of patients; population; primary outcome; Rutherford classification; target artery (divided into 'iliac' which included common and external iliac, 'femoropopliteal' and 'below the knee'); antithrombotic agents(s), dose and duration (i.e. antithrombotic protocol). The protocols were classified as periprocedural phase (during or before the procedure), immediate postprocedural phase (up to 30 days post-procedure) and maintenance postprocedural phase (more than 30 days post-procedure).

Antithrombotic protocols were analysed based on how well they were specified in each published trial, which was defined as follows:

1. Did not mention any protocol
2. Failed to completely specify a protocol (incomplete protocol)

   Subgroups:

   A. The protocol was only 'recommended', and the use was left at the discretion of the treating physician.

   B. Unspecified antithrombotic agent(s).

   C. The antithrombotic agent was clearly specified but the dosage was unspecified.

   D. More than one protocol was specified.

3. Had a completely specified protocol (complete protocol)

   To meet requirement (3) the following criteria had to be met:

   A. The antiplatelet/anticoagulant agent(s) was/were specified

   B. Antithrombotic dosage was specified

   C. The duration of antiplatelet/anticoagulant prescription/administration was specified

   D. The antiplatelet/anticoagulant protocol was applied to all the subjects in the trial.

Antiplatelet agents were grouped into: Aspirin alone; $P2Y_{12}$ receptor antagonist alone; Dual antiplatelet therapy ('Dual therapy'; combination of aspirin and $P2Y_{12}$ receptor antagonist); other antiplatelet combination; no antiplatelet agent. Anticoagulation was grouped into: Unfractionated heparin ('heparin';) low molecular weight heparin; other anticoagulant (including direct oral anticoagulant); no anticoagulant.

Quality assessment

There is no validated assessment tool to measure the quality of study protocols. Even though there is no formal analysis of the results from the included studies, a marker of quality was felt to be important for adding context to the outcomes examined in narrative review. The quality of included trials was therefore assessed using the Cochrane Risk of Bias Assessment tool.

Narrative synthesis

Trial protocols were grouped as percentages of total numbers of trials in any given pre-specified group. Subgroup analyses were performed by type of endovascular

intervention. Trials with more than one protocol were considered separately. Dual antiplatelet trends were additionally examined over time and with target artery.

Meta-analysis was not performed as the objective of this review was to assess medication protocols across randomised trials reporting outcomes for endovascular interventions. These trials do not break down results by medication. To tabulate results by type of endovascular intervention the number of intervention arms from separate trials were combined.

Statistical analysis

Statistical analysis was performed in the R statistical programming environment version 3.5.1. Changes in frequency of dual antiplatelet use with time were assessed using logistic regression analysis. Comparisons of antiplatelet use according to the different arterial segments treated were performed using Fisher's exact test. P-values less than 0.05 were considered significant.

Results

The PRISMA flow diagram is shown in Figure 1. A total of 5025 publications were identified by the search strategy, of which 456 were assessed as full text. Ninety-four randomised trials were included for narrative synthesis.

The majority of trials (54, 57%) treated more than 50% of patients for claudication (Rutherford 1-3). Twenty-one (22%) included more than fifty percent of patients with chronic limb threatening ischaemia (Rutherford 4-6). Nine (10%) gave a mean or median Rutherford score so were impossible to assess accurately and ten (11%) gave no information of degree of ischaemia or symptoms (Appendix B).

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The most frequent primary outcome measure from the included trials was primary patency (28 trials, 30%). Included studies most commonly compared plain balloon angioplasty with arterial stenting (bare metal, covered, drug eluting or absorbable; 23 trials, 24%), followed by plain balloon angioplasty vs. drug coated balloon angioplasty (21 trials, 22%). Appendix B shows details of all included trials, and a summary of all trial comparisons is provided in Appendix C. Thirty-eight trials (40%) were company sponsored. None of the trials justified their antithrombotic therapy protocol.

Quality of included studies

The overall quality of studies was judged as being low. Eighty-nine studies (95%) had a high risk of bias in at least one domain, however much of the high risk was due to a lack of personnel blinding which is impractical in many trials of this type.

There were more concerning sources of bias from allocation concealment being unclear in 70% of trials and blinding of outcome assessment being unclear in 72% of trials. There was also evidence of selective reporting (32%) and incomplete reporting (29%).

Periprocedural protocols

Completeness of protocol

Of the 94 included trials, 4 (4%) specified separate antithrombotic protocols for each intervention arm (see 'Trials with different antithrombotic regimens in each periprocedural arm'). Heparin and antiplatelet agents could not be cleanly separated periprocedurally as many trials used them interchangeably or even used heparin in one arm and antiplatelet agents in another.

Of the 90 remaining randomised trials there were 64 different periprocedural protocols. Thirteen studies (14%) did not mention any periprocedural protocol, 51 (57%) had incomplete protocols and 26 (29%) had complete protocols (Tables 1 and 2).

The most common reason for an incomplete periprocedural protocol was an unspecified antithrombotic dose (24 of 51 trials). Many of these trials had ambiguous terms or sentences used for describing periprocedural protocols including:

- "Clopidogrel saturation was obtained."(15)

- "Appropriate anticoagulation was administered per physician discretion."(16)

- "Systemic intraprocedural anticoagulation was mandatory."(17)

Periprocedural antithrombotic agents

- *Antiplatelet monotherapy in combination with anticoagulant therapy*: The most common periprocedural protocol was to use both an antiplatelet and an anticoagulant (44, 49%, Tables 1 and 2 and Appendix E). The antiplatelet used most commonly was aspirin (18 trials, 19%) but the dose varied from 80mg to 325mg. Clopidogrel was the second most common used by 10 trials (11%) with no dose specified in four trials and five using 300mg.

  Heparin was the most commonly used anticoagulant in combination with an antiplatelet agent. However, the dose varied from 2500iu to 7500iu and was different in all but 21 of the 44 trials, which used 5000iu.

- *Antiplatelet monotherapy alone*: Antiplatelet monotherapy alone was used in 10 trials (11%), the most common agents were aspirin and clopidogrel in 9 of these 10 trials.

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- *Anticoagulant therapy alone*: Heparin alone was used in 17 trials (19%). Again, the dose varied, but 5000iu was most commonly used (6 of the 17 trials). Heparin was either not used or not specified in 19 trials (20%).

- *Dual antiplatelet therapy in combination with anticoagulant therapy*: Dual antiplatelet therapy in combination with heparin was used by 25 trials (28%) in the periprocedural phase (Tables 1 and 2). Dual therapy was not used without heparin.

   The dose and duration of dual antiplatelet therapy varied widely (Appendix E) and ranged from 75mg to 300mg for both agents. Aspirin and clopidogrel together were used most frequently (20 of the 25 studies) but ticlopidine, prasugrel, unspecified theinopyridines and abciximab were each used in one trial.

   There was a tendency for more recent trials incorporating antiproliferative drug technology to incorporate the use of dual antiplatelet therapy periprocedurally, with 19% of plain balloon angioplasty vs bare metal stent trials using dual antiplatelet therapy compared to 33% use in the plain balloon angioplasty vs drug eluting stent trials (Table 1).

Trials with different antithrombotic regimens in each periprocedural arm
Four trials (4%) specified separate antithrombotic protocols for each intervention arm. Rand et al(11, 12) compared plain balloon angioplasty with plain balloon angioplasty and covered stenting and used enoxaparin 2x40mg/d for 3 days in the plain balloon angioplasty group, and clopidogrel 300mg as loading dose in the covered stenting group. Krankenberg et al(13) compared plain balloon angioplasty with plain balloon angioplasty and bare metal stenting and used heparin 3,000-

5,000IU for all participants, then aspirin 500mg or 100mg/d for at least 10 days in the plain balloon angioplasty group and dual antiplatelet therapy (aspirin as per the control group and clopidogrel 300mg) in the plain balloon angioplasty and bare metal stenting group. Gallino et al(14) compared plain balloon angioplasty with brachytherapy and used aspirin 100mg in the plain balloon angioplasty group; and dual antiplatelet therapy (aspirin 100mg and clopidogrel 300mg) in the brachytherapy group.

Postprocedural protocols

Completeness of protocol

Of the 94 included randomised trials, 7 (7%) trials specified separate postprocedural protocols for each intervention arm (see 'Trials with different antithrombotic regimens in each postprocedural arm'). Of the 87 remaining randomised trials there were 52 different postprocedural protocols (Tables 3 and 4). These are detailed in Appendix F. Only 31 (36%) trials specified one single protocol for all participants. A total of 56 (64%) trials either did not mention or had an incompletely specified protocol. The most common reason was that the protocol was only 'recommended' and its use was left to the discretion of the treating physician (13 trials, 15%). Examples of ambiguous terms or sentences used for describing periprocedural protocols include:

- "Alternative dual antiplatelet therapy regimens could be followed if justified by individual patient requirements."(21)

- "Continuation of clopidogrel was left to the discretion of the physician."(22)

- "At discharge, acetylsalicylic acid at a dose of 150mg daily was recommended for a prolonged period of time."(23)

Postprocedural antithrombotic agents

Of the remaining 87 trials, 48 (55%) used antiplatelet agents in the immediate

postprocedural phase and 12 (14%) in the maintenance post procedural phase

(Tables 3 and 4 and Appendix F). One trial used oral anticoagulation and one used

warfarin for the first 12 weeks then aspirin.

Immediate postprocedural phase

Sixty-seven trials (71%) specified an immediate phase postprocedural regimen

which was antiplatelet therapy in all but the two trials above (Tables 3 and 4 and

Appendix F).

- *Antiplatelet monotherapy*: Fifteen trials used antiplatelet monotherapy alone

  as an immediate post procedural phase treatment. Aspirin alone was used by

  13 trials (15%), although the dose ranged from 100mg to 300mg. Two trials

  used clopidogrel 75mg alone.

- *Dual antiplatelet therapy*: Dual antiplatelet therapy was used in 48 trials

  (55%). Only 19 (22%) of these trials completely specified the protocol. This

  was most commonly aspirin and clopidogrel (38 of 48 trials) with a wide

  variation in doses of each.

Maintenance postprocedural phase

Fifty-five trials (63%) specified postprocedural maintenance phase therapy (Tables 3

and 4 and Appendix F).

- *Antiplatelet monotherapy*: Antiplatelet monotherapy was the most commonly

  used maintenance therapy in 43 of the 55 trials specifying a maintenance

  phase drug. Forty-one of these used aspirin which had the same range of

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doses as the immediate phase protocols. Ten of the trials specifying aspirin did not specify the dose or duration.

- *Dual antiplatelet therapy*: Dual antiplatelet therapy was used in 12 trials (14%), 3 of which did not specify the agent, dose and/or duration of therapy. Where specified, clopidogrel and aspirin was the commonest combination (8 trials, 9%). Maintenance phase therapy was not specified in 32 trials (37%).

 Over time there has been an increasing tendency to use dual therapy (Figure 3a, P<0.0001). This corresponds with the introduction of newer technologies such as drug coated balloons and drug eluting stents (Table 3) and also more trials focussed on below the knee intervention (Figure 3b). A greater proportion of these trials used dual therapy in the maintenance phase of the protocol than the trials comparing plain balloons or stents in the femoropopliteal segment (37/71 trials in the fem-pop segment used dual therapy, compared with 12/17 trials of below the knee intervention, P=0.030).

Trials with different antithrombotic regimens in each postprocedural arm
Seven (7%) trials specified separate postprocedural protocols for each intervention arm. The DEBATE-SFA trial compared femoropopliteal plain balloon angioplasty plus bare metal stenting with drug coated balloon angioplasty plus bare metal stenting, the former receiving postprocedural aspirin monotherapy, and the latter dual antiplatelet therapy(18). InPeria II compared infrapopliteal plain balloon angioplasty with bare metal stenting. The plain balloon angioplasty group received twice daily enoxaparin 40mg in addition to aspirin, whereas the stenting group received four weeks of clopidogrel, with subsequent reversion to aspirin monotherapy(12). The ACHILLES trial compared infrapopliteal plain balloon

angioplasty with drug eluting stenting; the plain balloon angioplasty group received aspirin monotherapy and the drug eluting stent group was additionally administered clopidogrel for 6 months(19). The FAST trial compared plain balloon angioplasty with bare metal stenting and administered postprocedural aspirin monotherapy to the plain balloon angioplasty group, and dual antiplatelet therapy (aspirin and clopidogrel) to bare metal stenting patients for at least 4 weeks(13). An Austrian study compared infrapopliteal plain balloon angioplasty with carbon-coated stenting. Postprocedurally all patients received lifelong aspirin and twice-daily enoxaparin for 3 days, whereas the stented patients additionally received clopidogrel for 4 weeks(11). DEBATE in SFA was a 3-armed study (bare metal stenting vs bare metal stenting plus cilostazol vs drug eluting stent for femoropopliteal lesions). Bare metal stent patients received clopidogrel for 1 month and aspirin for 12 months. Bare metal stent plus cilostazol patients received additional aspirin for 12 months but no clopidogrel, and those in the drug eluting stent group received dual antiplatelet therapy for 12 months(20). The PAB trial evaluated the effect of probucol and/or brachytherapy on restenosis following femoropopliteal plain balloon angioplasty. All patients received aspirin, but those undergoing stenting and brachytherapy additionally received clopidogrel for "an unlimited time" after the procedure(14).

Discussion

There is marked heterogeneity in antithrombotic therapy used in randomised trials of endovascular intervention for peripheral arterial disease. There has been an increasing use of dual antiplatelet therapy with time, which corresponds with the introduction of newer technologies and the new focus towards more distal

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intervention. None of the trials justified their antithrombotic therapy protocol. The overall quality of included studies was low.

The marked heterogeneity and lack of justification of antithrombotic regimens is a reflection of the low-quality design of many trials included in this study. Even though a formal meta-analysis was not performed, a risk of bias assessment was included as a marker of study quality. This showed a concerning amount of 'unclear' bias such as detection bias and attrition bias which can be compensated for by good trial design and follow up. Taken together with a dependence on patency outcomes, a lack of clinically meaningful outcomes, and a lack of independence from company sponsorship in 40% of trials, the overall quality of included trials can only be judged as low. The reliance on participants with claudication in these trials also reduces the generalisability of their findings to the chronic limb threatening ischaemia patient, even though they remain the most at risk after endovascular intervention.

Perioprocedurally, aspirin remains the most widely adopted antiplatelet monotherapy, despite randomised evidence favouring clopidogrel(2, 5). The reasons for this were unclear, but clopidogrel has only relatively recently come off patent so cost may be a factor. There is the potential to reduce cardiovascular events periprocedurally by using clopidogrel in future trials.

Postprocedurally there was an increasing tendency to utilise dual antiplatelet therapy with time. This coincides with the introduction of newer technologies such as drug coated balloons and drug eluting stents, and more trials of below the knee interventions. It is impossible to know which of these factors has contributed to the change in regimens towards dual therapy and there was no justification in trial protocols for the choice. However, the problem with choosing an antithrombic protocol for a trial of endovascular intervention is that there is no good evidence

base on which to base the decision(2), and this is probably why almost every trial that reports a protocol does something different. While there is neither randomised evidence to guide heparin or antiplatelet therapy, the greatest long-term impact seems to be from the antiplatelet agent rarer than the heparin. There is separate randomised evidence showing dual antiplatelet therapy reduces graft loss events after open prosthetic lower limb bypass(2) as well as reducing stent thrombosis events after percutaneous coronary intervention (24). This may have influenced the choices made during trial design. 'Real world' antiplatelet and anticoagulant practice following peripheral arterial endovascular intervention is known to vary by practitioner with some using dual therapy and some monotherapy(8). Again, it is impossible to know whether this has influenced trial design or vice versa. It is arguably most likely that clinical practice and trial design evolved together, influenced by cardiology practice.

There is the potential for confounding in these trials as a result of differences in antithrombotic regimens. Dual antiplatelet therapy increases the major bleeding risk(2), which may contribute to late mortality if regimens were continued long term. This is especially relevant in the current climate, as the trials included in this systematic review contributed to the late mortality results attributed to paclitaxel(9).

The strengths of this review are the clear, all-encompassing search protocol and robust reporting of results. This review has some limitations. It was impossible to tell whether some trials used antiplatelet agents alone in the periprocedural phase or whether they simply made no statement on heparin/anticoagulant use. The practitioners involved in these studies may have given a drug such as heparin which would be common practice. Because of this lack of clarity it was impossible to confidently separate antiplatelet and anticoagulant use in these trials, which means

some of the periprocedural regimens may not reflect 'real life' practice during procedures. They are, however, accurate from a published protocol perspective which is how the results are presented. Authors were not contacted for this information as the lack of reporting was used as a marker of quality; this information is vital when reporting trials in this area. The results summarised pertain to the number of trials included and are not proportionally representative of the number of participants included, as the trials recruited varying numbers of participants. Lastly, no time limits were set, and drug availability has not been uniform over the period evaluated.

Randomised trials comparing different types of peripheral endovascular arterial intervention have a high level of heterogeneity in their antithrombotic regimens and were of low quality. Antiplatelet therapy need to be standardised in trials comparing endovascular technologies to reduce potential confounding. To do this, an independent randomised trial specifically examining antiplatelet therapy following peripheral arterial endovascular intervention is needed.

Conflicts of interest:

None to declare.

Figure 1. PRISMA flow diagram showing the searching, screening and selection process for included studies.

Figure 2. Risk of bias graph for included studies. This is the review authors' judgements about each risk of bias item presented as percentages across all included studies. The darker the bar the higher risk of bias in that domain.

Figure 3. The use of dual antiplatelet therapy in the postprocedural phase of randomised controlled trials of lower limb endovascular intervention over (A) time and (B) by arterial territory. Chart A. P<0.001 for increasing use of dual therapy with time. Chart B. P=0.030 for a greater proportion of dual antiplatelet therapy use in trials of below the knee intervention compared to femoropopliteal intervention. BTK = Below The Knee

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