International Journal of Cardiology 223 (2016) 186–194

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Meta-analysis of uninterrupted as compared to interrupted oral anticoagulation with or without bridging in patients undergoing coronary angiography with or without percutaneous coronary intervention

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ARTICLE INFO

Article history:
Received 30 June 2016
Accepted 4 August 2016
Available online 4 August 2016

Keywords:
Oral anticoagulation
Atrial fibrillation
Percutaneous coronary intervention
Bridging anticoagulation
Heparin
Meta-analysis

ABSTRACT

Objectives: To assess safety and effectiveness of different periprocedural antithrombotic strategies in patients receiving long-term oral anticoagulation and undergoing coronary angiography with or without percutaneous coronary intervention (PCI).

Methods: Studies comparing uninterrupted oral anticoagulation (UAC) with vit. K antagonists vs interrupted oral anticoagulation (IAC) with or without bridging anticoagulation before coronary procedures were eligible for inclusion in the current meta-analysis. Endpoints selected were 30-day composite of major adverse cardiovascular or cerebrovascular and thromboembolic events (MACCE) and major bleeding.

Results: Eight studies (7 observational and 1 randomized controlled trial [N = 2325pts.]) were included in the analysis. There was no difference in MACCE between UAC and IAC; RR (95%CIs): 0.74 (0.34–1.64); p = 0.46 but there was a statistically significant MACCE risk reduction with UAC as compared to IAC with bridging: 0.52 (0.29–0.95); p = 0.03. Likewise, there were no statistically significant differences between UAC vs IAC in regard to major bleeding: 0.62 (0.16–2.43); p = 0.49; but as compared to IAC with bridging, UAC was associated with statistically significant 65% lower risk of major bleeding: 0.35 (0.13–0.92); p = 0.03. Additionally, meta-regression analysis revealed significant linear correlation between log RR of MACCE ($\beta = -4.617$; $p < 0.001$) and major bleeding ($\beta = 6.665$; $p = 0.022$) and mean value of target INR suggestive of higher thrombotic and secondary haemorrhagic risk below estimated INR cut-off of 2.17–2.27 within 30 days.

Conclusions: Uninterrupted OAC is at least as safe as interrupted OAC, and seems to be much safer than interrupted OAC with bridging anticoagulation in patients undergoing coronary angiography with or without PCI.

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http://dx.doi.org/10.1016/j.ijcard.2016.08.089
0167-5273/

1. Introduction

Up to 20–30% of patients with atrial fibrillation (AF) or mechanical heart valves who are candidates for chronic oral anticoagulation (OAC) present with concomitant ischemic heart disease and often require coronary angiography with or without percutaneous coronary intervention (PCI) with stenting [1]. The decision whether to continue the OAC throughout periprocedural period, interrupt OAC days before planned procedure or, if need be, bridge OAC with e.g. low molecular weight heparin (LMWH) represents a substantial challenge to the physician who must balance the risks of periprocedural haemorrhage, thrombotic complications, and thromboembolism. Currently, a standard guideline recommendation for patients undergoing elective surgery or invasive diagnostic procedures is to discontinue vit. K antagonists (VKAs) since uninterrupted anticoagulation (UAC) is associated with an increase in bleeding and access-site complications [2,3]. Interrupted anticoagulation (IAC) with or without bridging, on the other hand, is associated with prolonged hospitalization, extra inconvenience of heparin administration, and potential thromboembolism associated with sub-therapeutic anticoagulation. An expert consensus paper from the working group on thrombosis of the European Society of Cardiology (ESC) on the other hand recommended UAC as the preferred strategy for AF patients at moderate to high risk of thromboembolism and undergoing PCI, with radial access as preferred option even during therapeutic coagulation (international normalized ratio [INR 2–3]) [4]. These recommendations are however based on circumstantial evidence given there are no adequately powered randomized controlled trials (RCTs) addressing this issue.

Recently available Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) randomized trial [5] demonstrated that at 30 days in patients with AF who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation markedly decreased the risk of major bleeding and was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism defined as composite of stroke, systemic embolism or transient ischemic attack.

Given the possible worse outcomes with bridging OAC we performed a comprehensive systematic review and meta-analysis to assess the safety of uninterrupted OAC with VKAs in the setting of coronary angiography with or without PCI, as compared to IAC with or without bridging anticoagulation.

2. Methods

2.1. Data sources and search strategy

Established methods were used in compliance with the PRISMA statement for reporting systematic reviews and meta-analyses in health care interventions [6]. The PRISMA checklist is available as S1 Table. PubMed, CINAHL, the Cochrane Register of Controlled Clinical Trials (CENTRAL) and Google Scholar databases were screened for published randomized and observational studies. Exemplary PubMed search query is reported as S2 Table. Search terms were: "*periprocedural anticoagulation*"; "*uninterrupted anticoagulation*"; "*interrupted anticoagulation*"; "*long-term OAC*"; "*chronic OAC*"; "*bridging anticoagulation*"; "*discontinued warfarin*"; "*vit. K antagonist*"; "*coronary angiography*"; "*percutaneous coronary intervention*"; "*percutaneous transluminal coronary angioplasty*"; "*trial*". No language restrictions were imposed. Databases were searched until March 2016. The most updated or inclusive data for each study were used for abstraction. References of original articles and previous meta-analyses were reviewed manually and cross-checked.

2.2. Selection criteria, quality assessment and outcomes

Studies were included if having met all of the following criteria: 1) patients undergoing coronary angiography with or without PCI; 2) patients on long term VKA anticoagulation; 3) results reported separately for UAC vs IAC strategies; 4) both thromboembolic and bleeding outcomes addressed in a single study. Information regarding bridging OAC in the IAC group was not necessary for the inclusion. Studies were excluded if solely assessing postprocedural strategies. Narrative reviews, case reports, letters to the editor etc., were not considered.

Two independent reviewers (MK and PS) selected the studies for the inclusion, extracted studies and patients characteristics of interest and relevant outcomes. Three authors (MK, PS and LA) independently assessed the trials' eligibility and risk of bias. Any divergences were resolved by consensus. The bias risk for RCTs was assessed using the components recommended by the Cochrane Collaboration, i.e.: random sequence generation and random allocation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting, and other sources of bias [7]. Quality of observational studies was appraised with Newcastle–Ottawa Scale, a tool used for assessing the bias (the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest) in case–control and cohort studies included in a systematic review and/or meta-analyses [8].

Endpoints assessed were in-hospital/30 days: 1) composite of major adverse cardiovascular or cerebrovascular and thromboembolic events (MACCE) and 2) major bleeding. Outcome definitions as per protocol were applied.

2.3. Statistical analysis

Data were analysed according to intention-to-treat principle wherever applicable. Risk Ratios (RRs) and 95% Confidence Intervals (CIs) served as primary index statistics. Data was pooled in the meta-analysis using DerSimonian and Laird random effects model as more conservative approach for observational data accounting for between and within study variability [9]. Results for the comparison of UAC vs IAC with bridging were reported separately. A weighted random-effects meta-regression analyses [10] for two investigated outcomes were performed by regressing log RR against several variables in the experimental group: 1) target international normalized ratio (INR); percentage of patients presenting with 2) acute coronary syndrome (ACS) or; 3) receiving glycoprotein inhibitors (GPIs) and; 4) extent of radial access; using the inverse of the variance of the log RR as weight. A separate analysis of outcomes in patients with AF as primary indication for OAC was performed as well. In case there were "0 events" reported in both arms, calculations were repeated, as a sensitivity analysis, using Risk Difference (RD) and respective 95% CIs. We evaluated potential publication bias by constructing a "funnel plot" in which the standard error of the log RR was plotted against the RR. The asymmetry of the plot was estimated both visually [11] and by a linear regression approach [12]. Heterogeneity was assessed by Cochran Q test [13]. Review Manager V.5.1 (The Nordic Cochrane Centre, Kobenhavn, Denmark) and Comprehensive Meta-Analysis version 2 (Biostat; Englewood, NJ) were used for statistical computations. Results of the weighted random effects meta-regression analyses are reported as β coefficients and 2-sided p values.

3. Results

3.1. Study selection

Study selection process along with reasons for exclusion is described in Fig. 1. Systematic search of the online databases returned 31 potentially eligible records that were retrieved for scrutiny. Of those, 23 were further excluded as not pertinent to the design of the meta-analysis or not meeting the explicit inclusion criteria. One RCT and 7 published observational studies [14–22] enrolling N = 2325 patients were eventually included in the analysis. S3 Table lists detailed findings on the bias assessment.

Patients were evenly divided into UAC (N = 1165) and IAC (N = 1160) subsets. Summary of included studies — as well as baseline patient characteristics are listed in Table 1. Patient populations were broadly similar across single studies being mostly elderly (mean age between 66.0 and 73.2 years) with AF as most common indication for OAC accounting for 77% of cases (1790/2325). Percutaneous coronary intervention was performed in 100% of patients in 3 studies [14,17,21] whereas the remaining reported a mixture of diagnostic and invasive coronary procedures. In total, PCI was performed in 81% of patients (1873/2325). Radial access was used in one third of the cases (34.7% [771/2221]). Mean target INR substantially differed between UAC and IAC (2.34 vs 1.65 respectively; $p < 0.0001$ in random effects model).

3.2. Major adverse cardiovascular or cerebrovascular and thromboembolic events

Funnel plot constructed for the endpoint of MACCE revealed signs of moderate asymmetry (S1 Figure) but this was not confirmed with Egger's test $p = 0.61$. There was no difference in the occurrence of MACCE between the two groups; RR (95%CIs): 0.74 (0.34–1.64); $p =$