Meta-analysis of safety and efficacy of uninterrupted warfarin compared to heparin-based bridging therapy during implantation of cardiac rhythm devices


CRD summary
The authors concluded that the strategy of uninterrupted warfarin therapy throughout pacemaker or implantable cardioverter-defibrillator implantation was associated with decreased risk of bleeding without increasing risk of thromboembolic events. Clinical variations between the included studies and some of the methodological limitations identified mean the authors conclusion may not be reliable.

Authors' objectives
To assess the efficacy and safety of perioperative heparin-based bridging therapy versus uninterrupted warfarin therapy in patients undergoing pacemaker or implantable cardioverter-defibrillator implantation.

Searching
MEDLINE (1950 to 2012), EMBASE (1988 to 2012), Cochrane Central Register of Controlled Trials (CENTRAL) (fourth quarter 2011) were searched for studies published in English. Search terms were reported. Reports presented at scientific meetings and relevant conference proceedings papers in cardiology from 1994 to 2011 and bibliographies of the 10 most recent narrative reviews were searched. Additional searches were performed by using the names of 11 authors who were frequently cited in relevant narrative reviews.

Study selection
Eligible studies were randomised controlled trials (RCT), case-control or cohort studies that compared the safety and efficacy of uninterrupted warfarin therapy to heparin-based bridging in patients who underwent pacemaker or implantable cardioverter-defibrillator implantation. Outcomes of interest were bleeding and thromboembolic events. Only studies published in peer-reviewed journals were eligible.

Type of heparin used were unfractionated or low molecular weight. Timing of heparin administration ranged from six hours to 24 hours. Pre-operative INR (international normalised ratio) ranged from 2.0 to 2.6 for uninterrupted warfarin and 1.1 to 1.5 for heparin-based bridging. Most patients were also taking aspirin before operation. In the included studies, the clinical indications for warfarinisation were atrial fibrillation, cerebral vascular accident, deep vein thrombosis, pulmonary embolism and transient ischaemic attack.

Type of procedures performed were generator changes, permanent pacemaker, implantable cardioverter defibrillator and cardiac resynchronisation devices, where reported. Operator experience varied across the studies.

Two reviewers independently performed the study selection. Any disagreements were resolved by a third reviewer.

Assessment of study quality
The study quality was assessed using the MINORS (methodological index for non-randomised studies) quality assessment tool (12 indexes). The total score ranged from zero to 24 points (≥16 points indicated high quality).

Two reviewers independently assessed study quality.

Data extraction
Data were extracted to calculate odds ratios (OR) and standardised mean differences (SMD) and their 95% confidence intervals (CI). Study authors were contacted for additional data.

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Pooled odds ratios and standardised mean differences and 95% confidence intervals were calculated using fixed-effect
model (inverse variance method) where there was no evidence of heterogeneity; otherwise a random-effects model (DerSimonian-Laird method) was used. Heterogeneity was assessed using Q test and I² statistic (I² < 25% was considered low, 25% to 50% as moderate and >50% to 75% as high heterogeneity). Publication bias was assessed using funnel plot and Begg and Mazumdar’s tests. Sensitivity analyses were performed by excluding individual trials and recalculating pooled odds ratio. Subgroup analyses were performed according to the study design, heparin type and timing of heparin administration.

Results of the review
Eight studies (2,321 patients) were included in the review: five cohort studies and three randomised trials. MINORS scores ranged from 16 to 23 points which indicated higher quality studies. Follow-up ranged from one week to eight weeks. There was no evidence of publication bias.

The meta-analysis of the overall result showed that uninterrupted warfarin therapy was associated with significantly lower risk of postoperative bleeding complications compared to heparin-based bridging therapy (OR 0.30, 95% CI 0.18 to 0.50; I²=42.58; eight studies) and reduced length of hospital stay (SMD 2.39 days, 95% CI 2.1 to 2.69; four studies). Similar results were found when uninterrupted warfarin was compared with different heparin types (unfractionated or low molecular weight) and the timing of heparin administration (≥24 hours or ≤12 hours after device implantation).

When subgroup analysis was performed according to study designs (observational and RCT), the effect of uninterrupted warfarin therapy was no longer significant in RCTs. There was no significant difference in risk of thromboembolic events between the two groups (four studies). Heterogeneity was not available to report these findings. Sensitivity analyses did not significantly alter the findings.

Authors’ conclusions
The strategy of uninterrupted warfarin therapy throughout pacemaker or implantable cardioverter-defibrillator implantation was associated with decreased risk of bleeding without increasing risk of thromboembolic events. This strategy was a viable alternative to heparin-based bridging therapy.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. The search covered various relevant sources. Studies in languages other than English were not searched for so relevant studies may have been missed. Appropriate methods to reduce reviewer error and bias were used for some stages of the study selection and quality assessment; it was unclear whether similar methods were used for data extraction. Quality of the included trials was assessed but inappropriate use of non-randomised quality assessment tool for randomised controlled trials limited the reliability of the review findings. Study details were presented. Appropriate methods were used to pool data but in most analyses the statistical heterogeneity was not reported so the reliability of the results was uncertain. The authors did not consider reporting non-significant result of bleeding observed by RCTs in their conclusion.

Clinical variations between the included studies and some of the methodological limitations identified mean the authors conclusion may not be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that larger studies were needed to evaluate the effect of procedure type on bleeding outcomes in patients undergoing uninterrupted warfarin therapy and heparin-based bridging therapy. Further studies were needed to evaluate the safety and efficacy of continuing oral anticoagulation in these patients.

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Not stated.

Bibliographic details
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.