Κλινικά παραδείγματα διαχείρισης της αντιπηκτικής αγωγής σε ασθενείς με κολπική μαρμαρυγή

Ασθενής με κολπική μαρμαρυγή προς καρδιοανάταξη

ΚΩΝΣΤΑΝΤΙΝΟΣ Π. ΛΕΤΣΑΣ
Β’ ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΓΝΑ ‘ΕΥΑΓΓΕΛΙΣΜΟΣ’
The TRENDS study also suggests that AF durations of <48 h may still expose the patient to higher thromboembolic risks, albeit in a paroxysmal AF population.

Cardioverting such patients without achieving therapeutic anti-coagulation may pose a higher risk of stroke.

Ασθενής 55 ετών με CHADS2VA2Sc score 1 προσέρχεται στα επείγοντα με παροξυσμική κολπική μαρμαρυγή από 12ώρου. Αποφασίζεται φαρμακευτική ανάταξη στα επείγοντα με φάρμακο της κατηγορίας IC. Δεν υπάρχει δυνατότητα TEE. Ποιά είναι η ενδεδειγμένη αντιπηκτική αγωγή στα επείγοντα πριν την χορήγηση του αντι-αρρυθμικού φαρμάκου?

1. Edoxaban 60mg
2. Rivaroxaban 20mg
3. Apixaban 10mg
4. Κλασσική ηπαρίνη
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter (class IIa)

For cardioversion of AF/atrial flutter, effective anticoagulation is recommended for a minimum of 3 weeks before cardioversion (class I)

Transoesophageal echocardiography (TOE) is recommended to exclude cardiac thrombus as an alternative to preprocedural anticoagulation when early cardioversion is planned (class I)

Early cardioversion can be performed without TOE in patients with a definite duration of AF <48 hours (class I)

In patients where thrombus is identified on TOE, effective anticoagulation is recommended for at least 3 weeks (class I)
Ερώτηση

Ασθενής 55 ετών χωρίς δομική καρδιοπάθεια με CHADS2VA2Sc score 0 προσέρχεται στα επείγοντα με παροξυσμική κολπική μαρμαρυγή από 6 ώρου. Ποιο από τα παρακάτω είναι σωστά?

1. Χορήγηση ηπαρίνης και άμεση φαρμακευτική ανάταξη
2. Χορήγηση DOAC για 21 ημέρες και προγραμματισμένη ηλεκτρική ανάταξη
3. Χορήγηση DOAC, διενέργεια TEE και στην συνέχεια φαρμακευτική ή ηλεκτρική ανάταξη
4. 1 + 3
Anticoagulation with heparin or a NOAC should be initiated as soon as possible before every cardioversion of AF or atrial flutter (class IIa)
Μπορούμε να χορηγήσουμε DOAC στα επείγοντα?

- Στοιχεία από τις μελέτες X-VeRT (ribaroxaban), ENSURE AF (edoxaban) και EMANATE (apixaban).

- Στις μελέτες αυτές, οι περισσότεροι ασθενείς που έλαβαν DOAC 2-4h πριν την ανάταξη είχαν υποβληθεί σε TEE.

- Παρά το γεγονός ότι η χρήση τους προτείνεται στα πλαίσια άμεσης ανάταξης, η χορήγηση κλασσικής ηπαρίνης/ενοξαπαρίνης είναι η θεραπευτική αντιμετώπιση πρώτης επιλογής.
Προγραμματισμός για ανάταξη.
Συστάσεις EHRA 2016.
Ερώτηση

Ασθενής 66 ετών με CHADS2VA2Sc score 5 (ηλικία, ΑΕΕ, καρδιακή ανεπάρκεια και ΣΔ) προσέρχεται στα επείγοντα με ταχεία παροξυσμική κολπική μαρμαρυγή από 36ώρου. Ποιο από τα παρακάτω είναι σωστά?

1. Χορήγηση ηπαρίνης και φαρμακευτική/ηλεκτρική ανάταξη
2. Χορήγηση DOAC και φαρμακευτική/ηλεκτρική ανάταξη
3. Χορήγηση DOAC για 21 ημέρες και προγραμματισμένη ηλεκτρική ανάταξη
4. Διενέργεια TEE, χορήγηση αντιπηκτικού και φαρμακευτική/ηλεκτρική ανάταξη
Based on retrospective data, previous recommendations on the safe time-window in which a cardioversion can be performed in new-onset AF used ≤48 h as the ‘gold standard’ for non-protected cardioversion.

However, new evidence has emerged that initiating pre-cardioversion anticoagulation in patients with AF episodes of <24 h or even <12 h would provide even better safety.
In the FinCV study, a retrospective analysis on a large population cohort, high-lighted relevant issues regarding embolic complications after cardioversion of AF <48 h duration without peri-procedural anticoagulation.

Although the overall rate of thromboembolic complications (0.7%) is documented as comparable to previous studies, it is found that in patients with heart failure and/or diabetes, the rate of embolic complications increased to 9.8%.

J Am Coll Cardiol 2013;62:1187-92
The FinCV Study

- The risk of definite TEC increased significantly from 0.4% in patients with a CHA2DS2-VASc score of 0 to 1 to 2.3% in those with score of ≥5 (p < 0.001).

- The incidence of definite TEC was significantly lower in 2,298 cardioversions performed during anticoagulation (0.1% vs 0.7%, p [0.001]), and the preventive effect of anticoagulation was significant in patients with a score of ≥2 (0.2% vs 1.1%, p [0.001]).

- Importantly, periprocedural anticoagulation reduced the risk of TEC by 82%. The overall risk of these complications was low after failed cardioversion.

Am J Cardiol 2016;117:1294-1298
Time to cardioversion longer than 12 hours was an independent predictor for thromboembolic complications.

<table>
<thead>
<tr>
<th></th>
<th>Total No. of Patients</th>
<th>No. (%) of Patients by Time to Cardioversion$^b$</th>
<th>P Value$^c$</th>
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<td></td>
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<td>&lt;12 h (n = 2440)</td>
<td>12-&lt;24 h (n = 1840)</td>
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<td>13 (2.4) [1.1-3.6]</td>
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<td>4 (1.0) [0-2.0]</td>
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Ερώτηση

Ασθενής 50 ετών με CHADS2VA2Sc score 0 υποβάλλεται σε επιτυχή φαρμακευτική ανάταξη παροξυσμικής κολπικής μαρμαρυγής.

1. Πρέπει να λάβει αντιπηκτικά για 4 εβδομάδες
2. Πρέπει να λάβει αντιπηκτικά για 7 ημέρες μετά την ανάταξη
3. Δεν πρέπει να λάβει αντιπηκτικά μετά την ανάταξη γιατί είναι χαμηλού κινδύνου.
In patients at risk for stroke, anticoagulant therapy should be continued long-term after cardioversion according to the long-term anticoagulation recommendations, irrespective of the method of cardioversion or the apparent maintenance of sinus rhythm. In patients without stroke risk factors, anticoagulation is recommended for 4 weeks after cardioversion (class I).
Incidence of Thromboembolic Complications Within 30 Days of Electrical Cardioversion Performed Within 48 h of AF onset

- Among 567 cardioversions in 484 patients without therapeutic anticoagulation (mean CHA2DS2-VASc score, 2.3), 6 had neurological events (1.06%), all in patients on aspirin alone.

- Among 898 cardioversions in 709 patients on therapeutic anticoagulation (mean CHA2DS2-VASc score, 2.6), 2 neurological events occurred (0.22%), both off anticoagulation at the time of stroke.

- No thromboembolic events occurred in patients with CHA2DS2-VASc score <2.
157 patients of low thromboembolic risk (CHA2DS2VASc score 0-1).

Subcutaneous low-molecular-weight heparin (LMWH) was administered (enoxaparin 1 mg/kg every 12 h) until the dysrhythmia was no longer present.

None of them received post-cardioversion anticoagulation.

At the thirty days outcome, none of the 150 enrolled patients who completed a follow-up visit has reported TIA or stroke, nor died.

These findings suggest that routine post-procedural short-term anticoagulation may be considered as an overtreatment in this very low-risk subset of patients.
Ασθενής 66 ετών με CHADS2VA2Sc score 2 προσέρχεται με κολπική μαρμαρυγή αγνώστου ενάρξεως (Crea 0.7mg/dl, ΣΒ 90Kg). Λόγω ορθοπαιδικού προβλήματος λαμβάνει ναπροξένη. Αποφασίζεται προγραμματισμένη ηλεκτρική ανάταξη σε 21 μέρες. Ποια δόση απιξαμπάνης θα χορηγήσετε?

1. 2.5 mg x 2
2. 5 mg x 2
3. 5 mg x 1
Ασθενής 55 ετών με CHADS2VA2Sc score 1 προσέρχεται στα επείγοντα με κολπική μαρμαρυγή αγνώστου ενάρξεως. Τίθεται σε αγωγή με διλτιαζέμη για έλεγχο συχνότητας και αποφασίζεται προγραμματισμένη ηλεκτρική ανάταξη σε 21 μέρες. Ποια δόση απιξαμπάνης θα χορηγήσετε?

1. 2.5 mg x 2
2. 5 mg x 2
3. 5 mg x 1
Προσοχή στην συγχορήγηση φαρμάκων...

### Τακτικά Αντιαγωθητικά

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### άλλα καρδιακά φάρμακα

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### Αντιβιοτικά

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### Φαρμακοκινητική

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European Heart Journal 2016
Ερώτηση

Είναι ασφαλή τα νεότερα αντιπηκτικά σε σχέση με τα κουμαρινικά αντιπηκτικά στην ανάταξη της κολπικής μαρμαρυγής;

1. ΝΑΙ
2. ΟΧΙ
The X-VeRT trial: rivaroxaban

- An early cardioversion strategy was carried out after TEE in most cases!!!!

- In the early cardioversion strategy group in X-VeRT, rivaroxaban or a VKA was given with a goal of between 1 and 5 days before planned cardioversion and continued for 6 weeks post-cardioversion.

- In patients randomized to rivaroxaban, medication was started at least 4 h before cardioversion. Patients with a LA thrombus detected during the study did not undergo cardioversion. In these patients, study treatment was stopped and patients were treated according to local standard of care and followed for 30 days.

- In the delayed cardioversion strategy group, patients were treated with either a VKA or rivaroxaban for at least 3 weeks and up to a maximum of 8 weeks before cardioversion. Oral anticoagulation with a VKA was considered adequate if the INR was maintained in the range 2.0–3.0 for at least three consecutive weeks prior to cardioversion. Oral anticoagulation with rivaroxaban was considered adequate if the pill count was ≥80% for three consecutive weeks prior to cardioversion. Rivaroxaban or the VKA was continued for 6 weeks after cardioversion.

- The primary efficacy outcome occurred in 5 (two strokes) of 978 patients (0.51%) in the rivaroxaban group and in 5 (two strokes) of 492 patients (1.02%) in the VKA group [risk ratio 0.50; 95% confidence interval (CI) 0.15 – 1.73]. In the rivaroxaban group, four patients experienced primary efficacy events following early cardioversion (0.71%) and one following delayed cardioversion (0.24%). In the VKA group, three patients had primary efficacy events following early cardioversion (1.08%) and two following delayed cardioversion (0.93%). Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs (P < 0.001). Major bleeding occurred in six patients (0.6%) in the rivaroxaban group and four patients (0.8%) in the VKA group (risk ratio 0.76; 95% CI 0.21 – 2.67).

European Heart Journal 2014; 35: 3346–3355
Patients randomly assigned to the vitamin K antagonist group in X-Vert received warfarin or another vitamin K antagonist at the investigator’s discretion, based on local clinical practice; hence, vitamin K antagonist use was heterogeneous, being locally controlled and supplied, and not centrally controlled as in ENSURE-AF.

These protocol aspects could have resulted in less optimally controlled and stable anticoagulation in the warfarin group of X-Vert; only 77% of patients in X-Vert underwent cardioversion within the target time range of 1–5 days (in the early [ie, TEE-guided] stratum) or 21–25 days (in the delayed cardioversion stratum) after randomisation.

Additionally, in the delayed cardioversion group, only 36% of patients receiving vitamin K antagonist were cardioverted within the target time range, because of failure to achieve adequate anticoagulation.
The ENSURE-AF trial: edoxaban

- 2199 patients were enrolled and randomly assigned to receive edoxaban (n=1095) or enoxaparin–warfarin (n=1104).
- In the non-TEE-guided stratum, patients received edoxaban for a minimum of 21 days before cardioversion followed by the procedure and an additional 28 days of treatment.
- In the TEE-guided group, patients randomly assigned to the edoxaban group had to start treatment at least 2h before electrical cardioversion.
- Mean time in therapeutic range on warfarin was 70.8% (SD 27.4).
- The primary efficacy endpoint occurred in five (<1%) patients in the edoxaban group versus 11 (1%) in the enoxaparin–warfarin group (odds ratio [OR] 0.46, 95% CI 0.12–1.43).
- The primary safety endpoint occurred in 16 (1%) of 1067 patients given edoxaban versus 11 (1%) of 1082 patients given enoxaparin–warfarin (OR 1.48, 95% CI 0.64–3.55).

The EMANATE trial: study design

- This is a randomized, active-controlled, open-label study of approximately 1,500 patients randomized 1:1 to apixaban or usual care (parenteral heparin and/or oral anticoagulation with VKAs (goal international normalized ratio [INR] 2.0-3.0).

- The protocol encourages an image-guided approach (transesophageal echocardiography [TEE] or computed tomography [CT]) or anticoagulation for a minimum of 3 weeks before cardioversion.

- Anticoagulation is administered from randomization until 30 days after cardioversion. If cardioversion is not performed, anticoagulation will be administered for a maximum of 90 days.

- The apixaban dose is 5 mg BID, with a dose reduction to 2.5 mg BID if at least 2 of the following exist: age >80 years, weight <60 kg, or serum creatinine >1.5 mg/dL.

- Five doses of apixaban will be administered before cardioversion to achieve steady-state blood levels.

- If an immediate cardioversion is planned, a single 10 mg dose (or 5 mg if the dose is down-titrated) is administered at least 2 hours before cardioversion to more rapidly bring exposure up to steady state.

Am Heart J 2016;179:59-68
The EMANATE trial: patient disposition

Randomized (N=1500)

Apixaban (n=753)
- Died (n=2)
- Lost to follow-up (n=0)
- Completed follow-up (n=736, 97.7%)
- Withdrew consent: refused follow-up* (n=15, 2.0%)

Heparin/VKA (n=747)
- Died (n=1)
- Lost to follow-up (n=1)
- Completed follow-up (n=730, 97.7%)
- Withdrew consent, refused follow-up* (n=15, 2.0%)

Mean Follow-up from randomization to withdrawal was 29 days, range 1-83 days

Mean Follow-up from randomization to withdrawal was 23 days, range 1-81 days

ESC 2017
Διενέργεια TEE πριν την ανάταξη

Image-Guided Strategy (n=840)

- Thrombus-present (First Image) (n=61)
  - Complete follow up, no outcome events

  - Apixaban (n=30)
  - Heparin/VKA (n=31)

- Actual treatment
  - Apixaban (n=29)
  - Heparin/VKA (n=1)
  - Heparin/VKA (n=31)

- Repeat Imaging was 37 ± 9 days (mean +/- ISD) after first image
  - Thrombus (+) (n=11/23)
  - Thrombus (-) (n=12/23)
  - No further imaging (n=6)
  - No further imaging (n=1)
  - Thrombus (+) (n=8/18)
  - Thrombus (-) (n=10/18)
  - No further imaging (n=13)
Stroke / Systemic embolic outcomes

**Graph Description:**
- **Apixaban (events: 0/753):** 5 ischemic, 1 hemorrhagic stroke with 0 systemic embolic events
- **Heparin/VKA (events: 6/747):**

**Number at risk:**
- **Apixaban:** 752
- **Heparin/VKA:** 747

**P-value:** 0.0164

**Legend:**
- Red line represents Apixaban with no events.
- Blue line represents Heparin/VKA with 6 events.

**X-axis:** Time to stroke/SE (days)
- 0, 30, 60, 90 days

**Y-axis:** Proportion of patients with stroke/SE
- 0.000, 0.005, 0.010, 0.015, 0.020

Source: ESC 2017
The ARISTOTLE Trial: apixaban

- 265 first cardioversions in patients assigned to apixaban and 275 in those assigned to warfarin.
- Transesophageal echo-cardiographic data were available in 171 patients (203 cardioversions): 86 patients (97 cardioversions) assigned to apixaban and 85 patients (106 cardioversions) assigned to warfarin.
- The minimum duration of therapy before cardioversion was 4 days for warfarin and 1 day for apixaban.

No stroke or systemic emboli occurred in the 30-day follow-up period.

Major cardiovascular events after cardioversion of atrial fibrillation are rare and comparable between warfarin and apixaban.

J Am Coll Cardiol 2014;63:1082–7
Safety profile of apixaban

- 3/735 major bleedings in apixaban group vs. 6/721 in heparin/VKA group
Συμπεράσματα

- TΕΕ πριν την ανάταξη κολπικής μαρμαρυγής >24h ???

- Η ανάταξη κολπικής μαρμαρυγής <12h σε ασθενείς μικρού θρομβοεμβολικού κινδύνου (0-1) είναι ασφαλής και δεν απαιτεί TΕΕ.

- Τα νεότερα αντιπηκτικά είναι ασφαλή στην ανάταξη της κολπικής μαρμαρυγής.

- Η επιλογή του DOAC πρέπει να εξατομικεύεται.
The ARISTOTLE Trial: apixaban

- 265 first cardioversions in patients assigned to apixaban and 275 in those assigned to warfarin.

- Transesophageal echo-cardiographic data were available in 171 patients (203 cardioversions): 86 patients (97 cardioversions) assigned to apixaban and 85 patients (106 cardioversions) assigned to warfarin.

- The minimum duration of therapy before cardioversion was 4 days for warfarin and 1 day for apixaban.

> No stroke or systemic emboli occurred in the 30-day follow-up period.

- Major cardiovascular events after cardioversion of atrial fibrillation are rare and comparable between warfarin and apixaban.
The RELY trial: dabigatran

- In the RE-LY trial, 1983 cardioversions were done in 1270 patients (647 in the dabigatran 110 mg twice daily group, 672 in the dabigatran 150 mg twice daily group, and 664 in the warfarin group).

- The occurrence of stroke and major bleeding within 30 days in patients receiving either dose of dabigatran was low and similar to event rates on warfarin with or without TEE guidance.

The ENSURE trial: edoxaban

- 2199 patients were enrolled and randomly assigned to receive edoxaban (n=1095) or enoxaparin–warfarin (n=1104).

- The TEE-guided group: Patients randomly assigned to the edoxaban group had to start treatment at least 2h before electrical cardioversion. The next dose of edoxaban was taken the day after cardioversion and then continued on a 24-h cycle until day 28 post cardioversion.

- The non-TEE-guided group: In the edoxaban group, patients received edoxaban for a minimum of 21 days before cardioversion followed by the procedure and an additional 28 days of treatment.

- Mean time in therapeutic range on warfarin was 70·8%.
Findings of TEE in appropriately anticoagulated patients with persistent AF prior to planned cardioversion

- TEE revealed LA thrombi in seven (5.8%) of the patients. In warfarin and NOACs groups thrombi were revealed in five (7.0%) and two (4.1%) patients, respectively.
- TEE did not reveal any thrombi in patients with normal left ventricular (LV) function.
- Thrombi were found in two (6.1%) patients with slightly decreased LV function, and in five (17.9%) patients with markedly decreased LV function.
- CHA2DS2-VASc score of all 7 patients was ≥5.