Clinical Study Outline
Study No. K9
Version No. 1
Date December 30, 2009

STUDY PROTOCOL

AntiThrombotic Agents in Atrial Fibrillation (ATA-AF)

Routine Management of Atrial Fibrillation: a Survey in Italian routine practice

Study Coordination:

ANMCO Research Center
Via La Marmora 34,
50121 Florence – Italy
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Signature page for Study Chairman and Co-Chairman

Protocol ATA-AF

Approved by:

Dr. Giuseppe Di Pasquale (Study Chairman) signature date 30/12/2009

Dr. Giovanni Mathieu (Study Co-Chairman) signature date 30/12/2009
Signature page for Principal Investigator

Protocol ATA-AF

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

(Principal Investigator) ____________________________ signature ____________________________ date ____________________________
LIST OF ABBREVIATIONS

ANMCO = Italian Association of Hospital Cardiologists
AF = atrial fibrillation
ATA = antithrombotic agents
VKA = Vitamin K Antagonists
CHADS$_2$ = Cardiac Failure, Hypertension, Age, Diabetes, Stroke (Doubled)
INR = International Normalized Ratio
LV = Left Ventricular
IRB = Institutional Review Board
IEC = Independent Ethics Committee
(e)CRF = electronic Case Report/Record Form
ECG = Electrocardiogram
SUMMARY

Background. Atrial Fibrillation (AF) prevalence is rising and it has a substantial impact on morbidity and mortality. Patients with AF have a higher risk of stroke than unaffected patients. Despite the well documented efficacy in the prevention of stroke and the recommendations of international guidelines, vitamin K antagonists (VKA), are difficult to use and they are often not prescribed to many patients with AF. There are few studies characterizing different antithrombotic strategies in patients with AF in a real practice situation.

Aim of the study. To collect information on the clinical features of patients with AF and to identify independent predictors of the prescription/no prescription of the different antithrombotic treatments.

Study design. ATA-AF is a national, multicenter, observational study carried out in non selected patients with AF referred to a representative sample of Cardiology and Internal Medicine Departments.

Study Population and Methods. All consecutive patients discharged from about 400 Cardiology and Internal Medicine Departments with a documented diagnosis of AF and patients admitted to a day care unit for the management of AF will be included in the study. AF can be diagnosed during the hospitalization or in the 12 months before the enrolment. Documented AF means electrocardiographic diagnosis or AF reported in a discharge summary. Participating centers will also include each patient with a diagnosis of AF (current or within the previous 12 months) visited during his/her usual out patients clinic activity. The recruitment period will be of 4 week or until the enrollment of at least 20 patients hospitalized and 20 ambulatory patients. Before the study start, regional meetings to share the protocol and the recommendations on the use of antithrombotic therapy in AF will be organized. Patients will be split in one of the following groups: B) Not treated with antithrombotic; C)Treated with VKA; D) Treated with antiplatelets or other antithrombotic agents.

Substudy. In a sample of nearly 80 centers follow up data will be collected over a 12 month period with the aim 1) to assess the safety profile of antithrombotic treatment; 2) to collect information about the incidence of all-cause mortality, all cause hospitalizations; stroke and other thrombotic events and minor and major hemorrhages, 3) to measure patients’ satisfaction and the perception of the quality of received cares.

Statistical considerations. Being the study fully observational, a definite sample size has not been defined. The participating centers should recruit nearly 6000 patients. All patients enrolled will be included in the analysis. Statistical tests may be carried out for exploratory purposes, as appropriate. Multivariable analysis will be performed to explore relationship between baseline covariates and prescription patterns and to identify the independent predictors of non prescription of VKA.
1. BACKGROUND

Atrial fibrillation (AF), the most frequently observed sustained arrhythmia in clinical practice, affects 0.4% of the general population and occurs in up to 4% of people older than 60 years of age, and in up to 9% of the population over 80 years of age\(^1\). The impact of AF on mortality and morbidity is substantial as well as substantial are its socio-economic consequences in relationship to hospital admissions, chronic disease management and disabilities. AF is an independent risk factor for stroke; patients with AF have a four to five fold higher risk for stroke than unaffected subjects\(^2,3\). Patients with paroxysmal AF have an annualised stroke rate (3.2%) similar to that seen in patients with chronic AF (3.3%)\(^4\). In patients with AF the coexistence of other factors may increase the risk of stroke\(^5\). The annual stroke risk in untreated patients with AF is age dependent, being 1% in the 50-59 age group, 3% in the 60-69 age group, 10% in the 70-79 age group and 24% in patients aged 80 to 89\(^6,7\). Thus, older patients are not only more prone to have AF but, when affected by AF, their risk of stroke is considerably increased compared with younger patients. In a meta-analysis on vitamin K antagonists and aspirin for stroke prevention in patients with AF the occurrence of stroke was decreased by 60% and 20%, respectively, compared to placebo or no treatment\(^8\). The magnitude of benefit with warfarin is increased with inherent risk of stroke. This finding has important clinical implications: because bleeding complications are more common in elderly patients, and these patients may be less likely to receive vitamin K antagonists\(^9,10\). Despite the well-documented efficacy, it is widely recognised that vitamin K antagonists are difficult to use for several reasons, including a narrow therapeutic window, the need for frequent monitoring and the difficulty in maintaining a stable therapeutic INR and the multiple food and drug interactions\(^11\). For all these reasons vitamin K antagonists are too often not given when indicated, despite international guidelines recommend their use, as a class I indication, in the large majority of patients with AF\(^1\).

Despite the increased interest, due to the rising prevalence of AF and the greater awareness of its deleterious consequences, only few studies have attempted to characterize different antithrombotic strategies in a real clinical practice situation\(^12,13\). Because of the several therapeutic options, it is of interest to identify independent predictors of the prescription/no-prescription of the different antithrombotic treatments, through an analysis of the decision making process focused on the single operator.
2. STUDY DESIGN AND SETTING

This study is aimed at gathering information on the clinical features of patients with AF referred to a representative sample of Cardiology or Internal Medicine Departments, and at characterizing the use of antithrombotic agents (ATA) in patients with AF.

2.1 Study objectives

2.1.1 Primary objectives

- To define the demographic, clinical characteristic, use of resources, prescription patterns of patients affected by AF according to the following categories:
  A) Total population of patients with AF
  B) Patients not treated with ATA
  C) Patients treated with vitamin K antagonist
  D) Patients treated with antiplatelet agents and other antithrombotic drugs

2.1.2 Secondary Objectives

- To correlate the level of risk of thrombotic events (CHADS<sub>2</sub> score) and vitamin K antagonist use.
- To identify the independent predictors of non prescription of vitamin K antagonist, in those patients with an established indication, according to current guidelines.
- To verify the adherence to guidelines for management of antithrombotic treatment in AF in the Italian clinical practice, as estimated in nearly 400 Italian Cardiology and Internal Medicine centres.

2.2 Study design

Patients discharged from Cardiology and Internal Medicine Departments with a documented diagnosis (primary or secondary) of AF (first detected episode, paroxysmal, persistent or permanent, see table below) or patients admitted to a day care unit for the management of AF will be included in the study. About 400 care centres in Italy will participate. Diagnosis of AF can be occurred during the hospitalization or within twelve months before the enrolment.

Further, the responsible physician of each participating centre will include in the study each patient, with a diagnosis of AF (current or within the previous twelve months), visited during his/her usual out-patient clinic activity. Documented diagnosis of AF means electrocardiographic diagnosis or AF reported in a discharge summary. In each centre the recruitment period will be of 4 week duration or until the enrolment of at least 20 hospitalized and 20 ambulatory patients. Regional meetings with the participating centers will be organized before the study start to share the protocol of
the study and the recommendations on the use of antithrombotic therapy in AF. At the enrollment the responsible clinician will consider to treat, continue to treat or not to treat the individual patient with ATA. Patients will be disposed, according to clinical judgement, in one of the following groups: B) not treated C) treated with vitamin K antagonists; D) treated with antiplatelet agents or other antithrombotic drugs.

Atrial Fibrillation classification

<table>
<thead>
<tr>
<th>AF Category</th>
<th>Defining Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>First detected</td>
<td>Only one diagnosed episode</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>Recurrent episodes that self-terminate in less than 7 days</td>
</tr>
<tr>
<td>Persistent</td>
<td>Recurrent, sustained atrial fibrillation episodes that last more than 7 days or that was previously terminated by therapeutic intervention.</td>
</tr>
<tr>
<td>Permanent</td>
<td>Continuous atrial fibrillation which cannot be converted to normal sinus rhythm by pharmacologic or electrical techniques.</td>
</tr>
</tbody>
</table>

2.3 Study population

2.3.1 Inclusion Criteria

1. All consecutive patients with a diagnosis of AF (first detected episode, paroxysmal, persistent or permanent) (valvular or non valvular), confirmed by ECG or in a discharge summary in the previous 12 months, discharged from Cardiology and Internal Medicine departments after having been admitted for any reason or admitted to a day care unit for the management of AF (i.e. electrical or pharmacological cardioversion).

2. All consecutive ambulatory patients with a diagnosis of AF (first detected episode, paroxysmal, persistent or permanent), confirmed by ECG or by a discharge summary in the previous 12 months, seen during the usual out-patient clinic activity by the physician who is responsible of the study in the participating Cardiology and Internal Medicine departments.

3. Age ≥ 18 years.
4. Informed consent.
In patients without chronic AF or admitted for reasons other than AF, the qualifying episode of AF should have occurred during the hospital stay or within twelve months before the enrolment. The patients need not to be in AF at the time of the enrolment.

2.3.2 Exclusion Criteria
1. Patients with AF as a complication of an acute coronary syndrome (within 1 week from symptoms onset).
2. Patients with AF associated with cardiothoracic surgery (within 1 week from surgery).
3. Patients enrolled in other clinical studies.
4. Patients already enrolled in ATA-AF from an other center.

3. DATA COLLECTION
Database management and quality control for this study are under the responsibility of the ANMCO Research Centre. Investigators will enter the information required by the protocol into a web-based CRFs. The data entry program will check for data consistency and completeness.
Data analysis will be performed at the ANMCO Research Centre.
The database is property of the promoter of the study (HCF-ANMCO) and will be located in the ANMCO Research Centre.
It is expected that nearly 6000 patients will be included in the study. No follow-up visits have been foreseen for the registry (see Appendix II for Substudy).

3.1 Representativeness of centers
The participating centers will be selected considering their geographical distribution and levels of technology.
Specifically, an appropriate number of centers from Northern, Central and Southern part of Italy will be selected and invited to participate. Among the 3 different areas of Italy, cardiology centers will be selected considering the presence in the hospital of:
1. cardiology beds,
2. cardiology beds and interventional cardiology,
3. cardiology beds, interventional cardiology and cardiac surgery.
Internal Medicine centers will be selected considering the presence in the hospital of:
1. absence of cardiology beds,
2. cardiology beds,
3. cardiology beds and interventional cardiology with or without cardiac surgery.
3.2 Monitoring procedures
The study will be monitored to ensure overall quality of data. The Steering Committee of the study delegates the monitoring aspects to the monitoring group of the Coordinating Centre (ANMCO Research Centre). All centres participating in the study will be monitored according to monitoring procedures set out by HCF for observational studies. The investigator must maintain source documents for each patient in the study, including documentation of AF, notes containing demographic and medical information, copies of laboratory and clinical tests. All information on (e)CRF must be traceable in the patient’s file. The investigator must also keep the original informed consent form signed by the patient. The investigator must give the monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries.

3.3 Ethical aspects
The last revision of the Helsinki Declaration provide the general framework for the ethical conduction of the study. The protocol, the proposed informed consent form and other information to subjects must be submitted to the Institutional Review Board/Independent Ethics Committee for approval. A signed and dated statement that the protocol and informed have been approved by the IRB/IEC must be given to the Coordinating Center before study initiation

3.3.1 Informed consent
The Coordinating Centre will supply a proposed informed consent form, which is part of the protocol and complies with regulatory requirements which must be approved by the IRB/IEC together with the protocol.
Modified versions of the informed consent form proposed by individual Investigators and approved by their IRB/IEC must be forwarded (together with the documentation of protocol approval) to the Coordinating Center for approval.

3.3.2 Privacy rules
According to the Italian legislation (which complies with and implements European Union regulations), participating patients must be duly informed, and give their explicit signed agreement, on the way their rights to the confidentiality of personal data are duly respected.
4. STATISTICAL CONSIDERATIONS
Since the trial is fully observational, no definite sample size has been calculated. However, considering previous surveys and registry, the participating centers should recruit nearly 6000 patient in one month of enrolment.
All patients enrolled will be included in the analysis. The sample of the whole population of patients with AF, that of the specific cohorts of patients (not treated with ATA, treated with vitamin K antagonist, treated with antiplatelet agents and other antithrombotic drugs) should allow a reliable description of the demographic-epidemiological features, use of resources and outcomes of real world patients with AF according to the different prescription patterns. Since this is an observational study, descriptive summaries will be presented for all the patients, and for subgroups of patients. Statistical tests may be carried out for exploratory purposes, as appropriate.
A multivariable analysis will be performed to identify the independent predictors of non prescription of vitamin K antagonist.

5. PUBLICATION POLICY
The study will be published anyhow, independently from the final results. Manuscript and abstracts will be prepared through cooperation between the Steering Committee and the ANMCO Research Centre. The Steering Committee agrees to provide manuscript and abstracts to the financial supporter for review and comments. A period of 5 working days for presentational material and abstract(s) and 15 working days for a scientific journal submission will be required for the review.
REFERENCES


Appendix I – Informative and Informed consent

Informativa per il paziente

Study Title: AntiThrombotic Agents in Atrial Fibrillation (ATA-AF)

Routine Management of Atrial Fibrillation: a Survey in Italian routine practice

Titolo dello Studio: Uso degli antitrombotici nella fibrillazione Atriale (ATA-AF)

Gentile Signore/Signora,
intendiamo informarla che in questo Ospedale è in corso una iniziativa finalizzata a raccogliere informazioni sulla gestione dei pazienti con Fibrillazione Atriale, patologia da cui lei è risultato affetto.

L’iniziativa, promossa dall’Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), dalla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari-ONLUS (HCF) e dalla Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI), ha lo scopo di descrivere quella che è la pratica clinica routinaria in Italia nella gestione dei pazienti con fibrillazione atriale in un campione rappresentativo di cardiologie e medicine interne. Lo scopo è quello di raccogliere dati sulle caratteristiche cliniche, l’uso di risorse e le terapie prescritte a questi pazienti.

La fibrillazione atriale è una condizione clinica non rara, specialmente nei pazienti dai 60-65 anni in poi, in soggetti molto anziani può anche interessare un paziente su 10. In presenza di fibrillazione atriale, il cuore perde la sua capacità di battere in maniera ritmica e batte in modo caotico cioè aritmico. Questa aritmia può presentarsi sia in un cuore sano che in un cuore malato, non sempre i pazienti avvertono sintomi e, nel caso in cui questi siano presenti, possono essere di diversa gravità, da semplici palpitationi a difficoltà di respiro. La presenza di fibrillazione atriale comporta dei rischi: molti studi hanno dimostrato che la fibrillazione atriale comporta un rischio maggiore di embolia cerebrale (si parla di embolia cerebrale quando un piccolo grumo di sangue coagulato blocca un’arteria del cervello, causando un danno alle cellule cerebrali). Il rischio non è però uguale per tutti i pazienti, ma dipende dalle malattie già presenti e da altri fattori. Il suo medico è in grado di calcolare il suo rischio personale e di stabilire il trattamento più adatto a lei sia per quanto riguarda l’aritmia sia per quanto riguarda il rischio di embolia.

In questo studio saranno solo esaminate le modalità con cui i pazienti vengono gestiti e curati, senza che questo comporti alcun cambiamento rispetto alla normale pratica clinica; in particolare, saranno raccolte informazioni sul trattamento anticoagulante volto ad evitare gli episodi ischemici, specialmente gli episodi ischemici cerebrali. L’analisi di questi dati renderà possibile individuare le eventuali aree di potenziale miglioramento nella cura dei pazienti affetti da fibrillazione atriale. Al termine dello studio Lei sarà informato sui risultati dello stesso.
L’iniziativa si propone di rilevare dati senza interferire in alcun modo con la condotta clinica di ciascun Centro; in particolare non prevede la somministrazione di farmaci sperimentali né l’esecuzione di esami diversi da quelli abitualmente effettuati su pazienti come Lei. Le chiediamo pertanto unicamente il suo consenso al trattamento dei dati personali.

I dati verranno raccolti in forma rigorosamente anonima su una scheda specifica e trasmessi al database in conformità con le leggi in vigore e tutto lo studio verrà condotto in accordo alla dichiarazione di Helsinki ed alle norme di buona pratica clinica. Lo studio è stato approvato dal Comitato Etico di riferimento di questo Ospedale.

La Sua partecipazione a questo studio è volontaria. Lei può ritirare in qualsiasi momento la Sua adesione alla partecipazione allo studio ATA-AF, senza che questo condizioni in alcun modo la possibilità di essere adeguatamente seguito e curato presso questa struttura.
Per qualsiasi altro dubbio o per ogni chiarimento si rivolga al Dott._________________presso questo centro.
Consenso alla partecipazione allo studio

Study Title: AntiThrombotic Agents in Atrial Fibrillation (ATA-AF)
Routine Management of Atrial Fibrillation: a Survey in Italian routine practice

Titolo dello Studio: Uso degli antitrombotici nella fibrillazione Atriale (ATA-AF)
Gestione della Fibrillazione Atriale: survey sulla pratica clinica in Italia

Io sottoscritto _______________________ ho ricevuto le informazioni relative al progetto ed ho letto quanto scritto nell’informativa. Accetto di prendere parte allo studio ATA-AF. Autorizzo lo staff di questa struttura a visionare le mie cartelle cliniche ed a compararne i dati con quelli raccolti sulla scheda raccolta dati del progetto.
Sono consapevole che i dati raccolti potranno essere utilizzati solo per scopi scientifici.
Dichiaro inoltre che mi è stata data l’opportunità di rivolgere domande e richieste di chiarimenti e di aver ricevuto risposte chiare e esaustive.
Confermo che mi è stata consegnata copia sia del documento informativo che di consenso.

Acconsento/non acconsento inoltre ad informare il mio medico curante della mia partecipazione al presente progetto.

____________________________________  ______________________
Nome e Cognome del paziente       Firma Paziente

Nome e Cognome del legale rappresentante del paziente (se previsto)       Firma legale rappresentante

____________________________________  ______________________
Nome e Cognome del medico che raccoglie il consenso       Firma Medico

Data __/__/____
Informativa e Consenso Informato - Privacy

Study Title: AntiThrombotic Agents in Atrial Fibrillation (ATA-AF)

Routine Management of Atrial Fibrillation: a Survey in Italian routine practice

Titolo dello Studio: Uso degli antitrombotici nella fibrillazione Atriale (ATA-AF)


TITOLARI DEL TRATTAMENTO E RELATIVE FINALITÀ

Il nostro Centro e la Fondazione Italiana per la Lotta alle Malattie Cardiovascolari-ONLUS, che ha commissionato lo studio che Le è stato descritto, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme della buona pratica clinica (decreto-legge n. 211/2003), tratteranno i Suoi dati personali, in particolare quelli sulla salute e, soltanto nella misura in cui sono indispensabili in relazione all’obiettivo dello studio, altri dati relativi alla Sua origine e ai Suoi stili di vita, esclusivamente in funzione della realizzazione dello studio e a fini di farmacovigilanza.

A tal fine i dati indicati saranno raccolti dal Centro partecipante e trasmessi alla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari.

Il trattamento dei dati personali relativi alla sua condizione clinica è indispensabile allo svolgimento dello studio: il rifiuto di conferirli non Le consentirà di parteciparvi.

NATURA DEI DATI

Il medico che La seguirà nello studio La identificherà con un codice: i dati che La riguardano saranno trasmessi alla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari, registrati, elaborati e conservati unitamente a tale codice, alla Sua data di nascita, al sesso, e ai dati relativi alla sua condizione clinica. Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo.

MODALITÀ DEL TRATTAMENTO

I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Sua partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale della Fondazione Italiana per la Lotta alle Malattie Cardiovascolari o i collaboratori della stessa che eseguono per conto della prima il monitoraggio e la verifica dello studio, il Comitato etico e le autorità sanitarie italiane potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.
Esercizio dei diritti
Potrà esercitare i diritti di cui all’art. 7 del D.Lgs. 196/2003 (es. accedere ai Suoi dati personali, integrarli, aggiornarli, rettificarli, opporsi al loro trattamento per motivi legittimi, ecc.) rivolgendosi direttamente al Dott. __________________ prensso il nostro centro, per il suo tramite, alla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari.
Potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio. Non saranno in tal caso raccolti ulteriori dati che La riguardano, ferma restando l’utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

Consenso
Sottoscrivendo questo modulo acconsento al trattamento dei miei dati personali per gli scopi della ricerca nei limiti e con le modalità indicate nell’informativa fornitami con il presente documento.

Dichiaro che mi sono state preventivamente fornite, al momento iniziale della raccolta dati, le prescritte informazioni circa le caratteristiche, le finalità e le modalità del trattamento dei dati personali, esplicitate per iscritto nel documento allegato (informativa per il paziente).

Nome e Cognome dell’interessato (in stampatello) ____________________________
Firma dell’interessato ______________________________________________________
Data ______________________

Nome e Cognome del legale rappresentante del paziente (se previsto) __________
Firma legale rappresentante ________________________________________________

Nome e cognome del referente dello studio che raccoglie il consenso____________
Firma di chi raccoglie il consenso _____________________________________________
Data ______________________
APPENDIX II – Substudy

In a sample of nearly 80 centres participating in the survey, follow-up data will be collected over a 12 months period. Patients will be followed at 6 and 12 months after the inclusion in the registry with the aim:

- To assess in all patients (B, C and D groups, see page 8) the safety profile, including bleeding, of antithrombotic treatments in patients with AF managed outside the context of a clinical trial. Since the study is fully observational, and the drugs prescribed by investigators are those of clinical practice, information on adverse reactions will be collected using the standard procedures adopted in clinical practice according to the Italian rules.
- To collect information in patients with AF treated with different antithrombotic strategies about the incidence of:
  - mortality,
  - all-cause hospitalisations,
  - stroke and other thromboembolic events,
  - minor and major haemorrhages (for definition see below),
  - rate and causes of antithrombotic drugs discontinuation.
- To measure patient satisfaction and the perception of the quality of the received cares related to the different antithrombotic treatment strategies. Validated questionnaires will be used (Toronto University Atrial Fibrillation Severity Scale and SF-36).

Hemorrhages definition:

Major hemorrhage: Fatal bleeding

or

Life threatening bleeding: bleeding with a decrease in the hemoglobin level of at least 5 g/dL or bleeding requiring transfusion of at least 4 units of blood or inotropic agents or necessitating surgery

or

Reduction in the hemoglobin level of at least 2 g/dL, transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ

Minor hemorrhage: All bleeding not included in the above categories
Informativa per il paziente – Studio e Sottoprogetto

Study Title: AntiThrombotic Agents in Atrial Fibrillation (ATA-AF)
Routine Management of Atrial Fibrillation: a Survey in Italian routine practice

Titolo dello Studio: Uso degli antitrombotici nella fibrillazione Atriale (ATA-AF)

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L’iniziativa, promossa dall’Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO), dalla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari-ONLUS (HCF) e dalla Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti (FADOI), ha lo scopo di descrivere quella che è la pratica clinica routinaria in Italia nella gestione dei pazienti con fibrillazione atriale in un campione rappresentativo di cardiologie e medicine interne. Lo scopo è quello di raccogliere dati sulle caratteristiche cliniche, l’uso di risorse e le terapie prescritte a questi pazienti.

La fibrillazione atriale è una condizione clinica non rara, specialmente nei pazienti dai 60-65 anni in poi, in soggetti molto anziani può anche interessare un paziente su 10. In presenza di fibrillazione atriale, il cuore perde la sua capacità di battere in maniera ritmica e batte in modo caotico cioè aritmico. Questa aritmia può presentarsi sia in un cuore sano che in un cuore malato, non sempre i pazienti avvertono sintomi e, nel caso in cui questi siano presenti, possono essere di diversa gravità, da semplici palpitazioni a difficoltà di respiro. La presenza di fibrillazione atriale comporta dei rischi: molti studi hanno dimostrato che la fibrillazione atriale comporta un rischio maggiore di embolia cerebrale (si parla di embolia cerebrale quando un piccolo grumo di sangue coagulato blocca un’arteria del cervello, causando un danno alle cellule cerebrali). Il rischio non è, però, uguale per tutti i pazienti ma dipende dalle malattie già presenti e da altri fattori. Il suo medico è in grado di calcolare il suo rischio personale e di stabilire il trattamento più adatto a lei sia per quanto riguarda l’aritmia sia per quanto riguarda il rischio di embolia.

In questo studio saranno solo esaminate le modalità con cui i pazienti vengono gestiti e curati, senza che questo comporti alcun cambiamento rispetto alla normale pratica clinica; in particolare, saranno raccolte informazioni sul trattamento anticoagulante volto ad evitare gli episodi ischemici, specialmente gli episodi ischemici cerebrali. L’analisi di questi dati renderà possibile individuare le eventuali aree di potenziale miglioramento nella cura dei pazienti affetti da fibrillazione atriale. Al termine dello studio Lei sarà informato sui risultati dello stesso.

L’iniziativa si propone di rilevare dati senza interferire in alcun modo con la condotta clinica di ciascun Centro; in particolare non prevede la somministrazione di farmaci sperimentali né l’esecuzione di esami diversi da quelli abitualmente effettuati su
pazienti come Lei. Le verrà richiesto, semplicemente, di presentarsi per una prima visita di controllo fra 6 mesi e successivamente dopo altri 6 mesi. In tali visite, che hanno lo scopo di controllare la sua situazione clinica, Le verrà eseguito un elettrocardiogramma.
Al momento dell’arruolamento e nel corso della visita di controllo a 12 mesi, Le verrà inoltre chiesto di compilare due brevi questionari per valutare cosa Lei pensa della Sua salute.
I dati verranno raccolti in forma rigorosamente anonima su una scheda specifica e trasmessi al database in conformità con le leggi in vigore e tutto lo studio verrà condotto in accordo alla dichiarazione di Helsinki ed alle norme di buona pratica clinica. Lo studio è stato approvato dal Comitato Etico di riferimento di questo Ospedale.
La Sua partecipazione a questo studio è volontaria. Lei può ritirare in qualsiasi momento la Sua adesione alla partecipazione allo studio ATA-AF, senza che questo condizioni in alcun modo la possibilità di essere adeguatamente seguito e curato presso questa struttura.
Per qualsiasi altro dubbio o per ogni chiarimento si rivolga al Dott._________________presso questo centro.
Consenso alla partecipazione allo Studio e al Sottoprogetto

Study Title: AntiThrombotic Agents in Atrial Fibrillation (ATA-AF)
Routine Management of Atrial Fibrillation: a Survey in Italian routine practice

Titolo dello Studio: Uso degli antitrombotici nella fibrillazione Atriale (ATA-AF)
Gestione della Fibrillazione Atriale: survey sulla pratica clinica in Italia

Io sottoscritto _______________________ ho ricevuto le informazioni relative al progetto ed ho letto quanto scritto nell’informativa. Accetto di prendere parte allo studio ATA-AF. Autorizzo lo staff di questa struttura a visionare le mie cartelle cliniche ed a compararne i dati con quelli raccolti sulla scheda raccolta dati del progetto.
Sono consapevole che i dati raccolti potranno essere utilizzati solo per scopi scientifici.
Dichiaro inoltre che mi è stata data l’opportunità di rivolgere domande e richieste di chiarimenti e di aver ricevuto riposte chiare e esaustive.
Confermo che mi è stata consegnata copia sia del documento informativo che di consenso.

Acconsento/non acconsento inoltre ad informare il mio medico curante della mia partecipazione al presente progetto.

____________________________________  __________________________
Nome e Cognome del paziente                  Firma Paziente

________________________________________  __________________________
Nome e Cognome del legale rappresentante del paziente
(se previsto)                                    Firma legale rappresentante

____________________________________  __________________________
Nome e Cognome del medico che raccoglie il consenso

Data __/___/______
Informativa e Consenso Informato – Privacy – Studio e Sottoprogetto

Study Title: AntiThrombotic Agents in Atrial Fibrillation (ATA-AF)
Routine Management of Atrial Fibrillation: a Survey in Italian routine practice

Titolo dello Studio: Uso degli antitrombotici nella fibrillazione Atriale (ATA-AF)

TITOLARI DEL TRATTAMENTO E RELATIVE FINALITÀ
Il nostro Centro e la Fondazione Italiana per la Lotta alle Malattie Cardiovascolari-ONLUS, che ha commissionato lo studio che Le è stato descritto, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme della buona pratica clinica (decreto-legge n. 211/2003), tratteranno i Suoi dati personali, in particolare quelli sulla salute e, soltanto nella misura in cui sono indispensabili in relazione all’obiettivo dello studio, altri dati relativi alla Sua origine e ai Suoi stili di vita, esclusivamente in funzione della realizzazione dello studio e a fini di farmacovigilanza.

A tal fine i dati indicati saranno raccolti dal Centro partecipante e trasmessi alla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari.

Il trattamento dei dati personali relativi alla sua condizione clinica è indispensabile allo svolgimento dello studio: il rifiuto di conferirli non Le consentirà di parteciparvi.

NATURA DEI DATI
Il medico che La seguirà nello studio La identificherà con un codice: i dati che La riguardano raccolti nel corso dello studio, ad eccezione del Suo nominativo, saranno trasmessi alla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari, registrati, elaborati e conservati unitamente a tale codice, alla Sua data di nascita, al sesso, e ai dati relativi alla sua condizione clinica. Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo.

MODALITÀ DEL TRATTAMENTO
I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Sua partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale della Fondazione Italiana per la Lotta alle Malattie Cardiovascolari o i collaboratori della stessa che eseguono per conto della prima il monitoraggio e la verifica dello studio, il Comitato etico e le autorità sanitarie italiane potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.
Esercizio dei diritti
Potrà esercitare i diritti di cui all’art. 7 del D.Lgs. 196/2003 (es. accedere ai Suoi dati personali, integrarli, aggiornarli, rettificarli, opporsi al loro trattamento per motivi legittimi, ecc.) rivolgendosi direttamente al Dott. ____________________ presso il nostro centro, per il suo tramite, alla Fondazione Italiana per la Lotta alle Malattie Cardiovascolari.
Potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio. Non saranno in tal caso raccolti ulteriori dati che La riguardano, ferma restando l’utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

Consenso
Sottoscrivendo questo modulo acconsento al trattamento dei miei dati personali per gli scopi della ricerca nei limiti e con le modalità indicate nell’informativa fornitami con il presente documento.

Dichiaro che mi sono state preventivamente fornite, al momento iniziale della raccolta dati, le prescritte informazioni circa le caratteristiche, le finalità e le modalità del trattamento dei dati personali, esplicitate per iscritto nel documento allegato (informativa per il paziente).

Nome e Cognome dell’interessato (in stampatello) ________________________________
Firma dell’interessato ________________________________
Data ______________________

Nome e Cognome del legale rappresentante del paziente (se previsto) ____________
Firma legale rappresentante ________________________________

Nome e cognome del referente dello studio che raccoglie il consenso____________
Firma di chi raccoglie il consenso ________________________________
Data ______________________
APPENDIX III – Recommendations for antithrombotic therapy in atrial fibrillation

Recommendations for antithrombotic therapy in Atrial Fibrillation/Flutter


<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Recommended long term therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors</td>
<td>Aspirin 81 to 325 mg daily</td>
</tr>
<tr>
<td>One moderate risk factor</td>
<td>Aspirin 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)</td>
</tr>
</tbody>
</table>
| Any high risk factor or more than 1 moderate risk factor| Warfarin (INR 2.0 to 3.0, target 2.5) 

<table>
<thead>
<tr>
<th>Less validate or weaker risk factors</th>
<th>Moderate risk factors</th>
<th>High risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>Age ≥75 years</td>
<td>Previous stroke, TIA, embolism</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>Hypertension</td>
<td>Mitral stenosis</td>
</tr>
</tbody>
</table>
| Coronary artery disease             | Heart Failure         | Prosthetic heart valve 

Thyrotoxicosis LV ejection fraction ≤35% Diabetes mellitus

INR=international normalized ratio; LV=left ventricular; TIA=transient ischemic attack

*a if mechanical valve, target international normalized ratio (INR) greater than 2.5
**Prescription of antithrombotic therapy for all patients with non valvular atrial fibrillation or atrial flutter according to risk stratification and 2006 guidelines**

1. Long term antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those with lone AF or contraindications (*Class I Level A*)

2. INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable (*Class I Level A*)

3. The selection of the antithrombotic agent should be based on the absolute risks of stroke and bleeding and the relative risk and benefit of a given patient. (*Level of Evidence: A*)

4. Long term aspirin 81-325 mg daily, is recommended as an alternative to vitamin K antagonists in low risk patients or in those with contraindications to oral anticoagulation (*Class I Level A*). The optimal dose of aspirin for patients with AF in unclear. The largest effect of aspirin was seen with 325 mg/die, however, generalizing from trials of aspirin for all antithrombotic indications and from physiologic studies, the guideline developers feel the best balance of efficacy and safety is achieved at low doses of aspirin (75 to 100 mg/die).

5. Timing to initiation of VKA therapy after an acute ischemic stroke involves balancing the risk of hemorrhagic conversion with short term risk of recurrent ischemic stroke.

6. For all recommendations of long-term therapy, “long term” means lifelong unless a contraindication emerges.

7. These recommendations apply to patients with persistent or paroxysmal AF and not to patients with a single brief episode of AF due to a reversible cause, such as an acute pulmonary infection, pericarditis, pulmonary embolism ecc.

**Valvular heart disease and Atrial Fibrillation**

1. For patients with AF and mitral stenosis, long term anticoagulation with an oral VKA such as warfarin (target INR 2.5; range 2.0 to 3.0) is recommended (*Grade 1B*)

2. For patients with AF and prosthetic heart valves, the guidelines developers recommend long term anticoagulation with an oral VKA, such as warfarin, at intensity appropriate for the specific type of prosthesis (*Grade 1B*)

**Anticoagulation for elective cardioversion of Atrial Fibrillation**

1. For patients with AF of ≥ 48 hours or of unknown duration for whom pharmacological or electrical cardioversion is planned, the guideline developers recommend anticoagulation with an oral VKA, such as warfarin, at a target INR of 2.5 (range 2.0 to 3.0) for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained (*Grade 1C*)
2. For patients with AF of $\geq 48$ hours or of unknown duration who are undergoing pharmacological or electrical cardioversion, immediate anticoagulation with intravenous unfractioned heparin (UFH) target Partial Thromboplastin Time (PTT), 60 s; range 50 to 70, or low molecular weight heparin (LMWH) at full deep vein thrombosis (DVT) treatment doses or at least 5 days of warfarin (INR target 2.5; range 2.0 to 3.0) at the time of cardioversion, are recommended. A performance of a screening multiplane transesophageal echocardiography (TEE) is also recommended. If no thrombus is seen on TEE, cardioversion is successful and sinus rhythm is maintained the guideline developers recommend anticoagulation (same INR target) for at least 4 weeks. If a thrombus is seen on TEE then cardioversion should be postponed and anticoagulation should be continued indefinitely (Grade 1B).

3. For patients with AF of known duration $< 48$ hours the cardioversion may be performed without prolonged anticoagulation (Grade 2C). However, in patients without contraindications to anticoagulation the guidelines developers suggest beginning IV heparin (target PTT, 60s; range 50 to 70) or LMWH (at full DVT treatment doses) at presentation (Grade 2C).

4. For emergency cardioversion in the hemodynamically unstable patients, the guidelines developers suggest that IV UFH (target PTT of 60 s with a target range of 50 to 70) or LMWH (at full DVT treatment doses) be started as soon as possible, followed by at least 4 weeks of anticoagulation with an oral VKA, such as warfarin (target INR of 2.5; range 2.0 to 3.0) if cardioversion is successful and sinus rhythm is maintained (Grade 2C).
Stroke risk in patients with non valvular atrial fibrillation not treated with anticoagulation according to the CHADS$_2$ index

*Gage BF et al JAMA 2001;285:2864*

<table>
<thead>
<tr>
<th>CHADS$_2$ risk criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior stroke or TIA</td>
<td>2</td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Heart Failure or impaired left ventricular systolic function (≤40%)</td>
<td>1</td>
</tr>
</tbody>
</table>

CHADS$_2$ = Cardiac Failure, Hypertension, Age, Diabetes, Stroke (Doubled)
Appendix IV – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION
DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community
leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or

- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from
it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.