Faculté de Médecine
Aix*Marseille Université

Aspirine, statines et réduction du risque embolique dans l'endocardite infectieuse.

T H È S E A R T I C L E

Présentée et publiquement soutenue devant

LA FACULTÉ DE MÉDECINE DE MARSEILLE

Le 31 Octobre 2018

Par Monsieur Jason VEYRIER

Né le 21 octobre 1990 à Carpentras (84)

Pour obtenir le grade de Docteur en Médecine

D.E.S. de CARDIOLOGIE ET MALADIES VASCULAIRES

Membres du Jury de la Thèse :

Monsieur le Professeur HABIB Gilbert	**Président**
Monsieur le Professeur AMBROSI Pierre	**Assesseur**
Monsieur le Professeur THUNY Franck	**Assesseur**
Monsieur le Docteur PANSIERI Michel	**Assesseur**

Faculté de Médecine
Aix*Marseille Université

Aspirine, statines et réduction du risque embolique dans l'endocardite infectieuse.

T H È S E A R T I C L E

Présentée et publiquement soutenue devant

LA FACULTÉ DE MÉDECINE DE MARSEILLE

Le 31 Octobre 2018

Par Monsieur Jason VEYRIER

Né le 21 octobre 1990 à Carpentras (84)

Pour obtenir le grade de Docteur en Médecine

D.E.S. de CARDIOLOGIE ET MALADIES VASCULAIRES

Membres du Jury de la Thèse :

Monsieur le Professeur HABIB Gilbert	**Président**
Monsieur le Professeur AMBROSI Pierre	**Assesseur**
Monsieur le Professeur THUNY Franck	**Assesseur**
Monsieur le Docteur PANSIERI Michel	**Assesseur**

AIX-MARSEILLE UNIVERSITE

Président : Yvon BERLAND

FACULTE DE MEDECINE

Doyen : Georges LEONETTI

Vice-Doyen aux Affaires Générales : Patrick DESSI
Vice-Doyen aux Professions Paramédicales : Philippe BERBIS

Assesseurs :
* aux Etudes : Jean-Michel VITON
* à la Recherche : Jean-Louis MEGE
* aux Prospectives Hospitalo-Universitaires : Frédéric COLLART
* aux Enseignements Hospitaliers : Patrick VILLANI
* à l'Unité Mixte de Formation Continue en Santé : Fabrice BARLESI
* pour le Secteur Nord : Stéphane BERDAH
* aux centres hospitaliers non universitaires : Jean-Noël ARGENSON

Chargés de mission :
* 1er cycle : Jean-Marc DURAND et Marc BARTHET
* 2ème cycle : Marie-Aleth RICHARD
* 3eme cycle DES/DESC : Pierre-Edouard FOURNIER
* Licences-Masters-Doctorat : Pascal ADALIAN
* DU-DIU : Véronique VITTON
* Stages Hospitaliers : Franck THUNY
* Sciences Humaines et Sociales : Pierre LE COZ
* Préparation à l'ECN : Aurélie DAUMAS
* Démographie Médicale et Filiarisation : Roland SAMBUC
* Relations Internationales : Philippe PAROLA
* Etudiants : Arthur ESQUER

Chef des services généraux : * Déborah ROCCHICCIOLI

Chefs de service :
* Communication : Laetitia DELOUIS
* Examens : Caroline MOUTTET
* Logistique : Joëlle FRAVEGA
* Maintenance : Philippe KOCK
* Scolarité : Christine GAUTHIER

DOYENS HONORAIRES

M. Yvon BERLAND
M. André ALI CHERIF
M. Jean-François PELLISSIER

PROFESSEURS HONORAIRES

MM AGOSTINI Serge
ALDIGHIERI René
ALESSANDRINI Pierre
ALLIEZ Bernard
AQUARON Robert
ARGEME Maxime
ASSADOURIAN Robert
AUFFRAY Jean-Pierre
AUTILLO-TOUATI Amapola
AZORIN Jean-Michel
BAILLE Yves
BARDOT Jacques
BARDOT André
BERARD Pierre
BERGOIN Maurice
BERNARD Dominique
BERNARD Jean-Louis
BERNARD Pierre-Marie
BERTRAND Edmond
BISSET Jean-Pierre
BLANC Bernard
BLANC Jean-Louis
BOLLINI Gérard
BONGRAND Pierre
BONNEAU Henri
BONNOIT Jean
BORY Michel
BOTTA Alain
BOURGEADE Augustin
BOUVENOT Gilles
BOUYALA Jean-Marie
BREMOND Georges
BRICOT René
BRUNET Christian
BUREAU Henri
CAMBOULIVES Jean
CANNONI Maurice
CARTOUZOU Guy

CHAMLIAN Albert
CHARREL Michel
CHAUVEL Patrick
CHOUX Maurice
CIANFARANI François
CLEMENT Robert
COMBALBERT André
CONTE-DEVOLX Bernard
CORRIOL Jacques
COULANGE Christian
DALMAS Henri
DE MICO Philippe
DELARQUE Alain
DEVIN Robert
DEVRED Philippe
DJIANE Pierre
DONNET Vincent
DUCASSOU Jacques
DUFOUR Michel
DUMON Henri
FARNARIER Georges
FAVRE Roger
FIECHI Marius

MM FIGARELLA Jacques
FONTES Michel
FRANCOIS Georges
FUENTES Pierre
GABRIEL Bernard
GALINIER Louis
GALLAIS Hervé
GAMERRE Marc
GARCIN Michel
GARNIER Jean-Marc
GAUTHIER André
GERARD Raymond
GEROLAMI-SANTANDREA André
GIUDICELLI Roger
GIUDICELLI Sébastien
GOUDARD Alain
GOUIN François
GRISOLI François
GROULIER Pierre
HADIDA/SAYAG Jacqueline
HASSOUN Jacques
HEIM Marc
HOUEL Jean
HUGUET Jean-François
JAQUET Philippe
JAMMES Yves
JOUVE Paulette
JUHAN Claude
JUIN Pierre
KAPHAN Gérard
KASBARIAN Michel
KLEISBAUER Jean-Pierre
LACHARD Jean
LAFFARGUE Pierre
LAUGIER René
LEVY Samuel
LOUCHET Edmond
LOUIS René
LUCIANI Jean-Marie
MAGALON Guy
MAGNAN Jacques
MALLAN- MANCINI Josette
MALMEJAC Claude
MATTEI Jean François
MERCIER Claude
METGE Paul
MICHOTEY Georges
MILLET Yves
MIRANDA François
MONFORT Gérard
MONGES André
MONGIN Maurice
MONTIES Jean-Raoul
NAZARIAN Serge
NICOLI René
NOIRCLERC Michel
OLMER Michel
OREHEK Jean
PAPY Jean-Jacques
PAULIN Raymond
PELOUX Yves
PENAUD Antony

MM PENE Pierre
PIANA Lucien
PICAUD Robert
PIGNOL Fernand
POGGI Louis
POITOUT Dominique
PONCET Michel
POUGET Jean
PRIVAT Yvan
QUILICHINI Francis
RANQUE Jacques
RANQUE Philippe
RICHAUD Christian
ROCHAT Hervé
ROHNER Jean-Jacques
ROUX Hubert
ROUX Michel
RUFO Marcel
SAHEL José
SALAMON Georges
SALDUCCI Jacques
SAN MARCO Jean-Louis
SANKALE Marc
SARACCO Jacques
SARLES Jean-Claude
SASTRE Bernard
SCHIANO Alain
SCOTTO Jean-Claude
SEBAHOUN Gérard
SERMENT Gérard
SERRATRICE Georges
SOULAYROL René
STAHL André
TAMALET Jacques
TARANGER-CHARPIN Colette
THOMASSIN Jean-Marc
UNAL Daniel
VAGUE Philippe
VAGUE/JUHAN Irène
VANUXEM Paul
VERVLOET Daniel
VIALETTES Bernard
WEILLER Pierre-Jean

PROFESSEURS HONORIS CAUSA

1967

MM. les Professeurs — DADI (Italie)
CID DOS SANTOS (Portugal)

1974

MM. les Professeurs — MAC ILWAIN (Grande-Bretagne)
T.A. LAMBO (Suisse)

1975

MM. les Professeurs — O. SWENSON (U.S.A.)
Lord J.WALTON of DETCHANT (Grande-Bretagne)

1976

MM. les Professeurs — P. FRANCHIMONT (Belgique)
Z.J. BOWERS (U.S.A.)

1977

MM. les Professeurs — C. GAJDUSEK-Prix Nobel (U.S.A.)
C.GIBBS (U.S.A.)
J. DACIE (Grande-Bretagne)

1978

M. le Président — F. HOUPHOUET-BOIGNY (Côte d'Ivoire)

1980

MM. les Professeurs — A. MARGULIS (U.S.A.)
R.D. ADAMS (U.S.A.)

1981

MM. les Professeurs — H. RAPPAPORT (U.S.A.)
M. SCHOU (Danemark)
M. AMENT (U.S.A.)
Sir A. HUXLEY (Grande-Bretagne)
S. REFSUM (Norvège)

1982

M. le Professeur — W.H. HENDREN (U.S.A.)

1985

MM. les Professeurs — S. MASSRY (U.S.A.)
KLINSMANN (R.D.A.)

1986

MM. les Professeurs — E. MIHICH (U.S.A.)
T. MUNSAT (U.S.A.)
LIANA BOLIS (Suisse)
L.P. ROWLAND (U.S.A.)

1987

M. le Professeur — P.J. DYCK (U.S.A.)

1988

MM. les Professeurs — R. BERGUER (U.S.A.)
W.K. ENGEL (U.S.A.)
V. ASKANAS (U.S.A.)
J. WEHSTER KIRKLIN (U.S.A.)
A. DAVIGNON (Canada)
A. BETTARELLO (Brésil)

1989

M. le Professeur — P. MUSTACCHI (U.S.A.)

1990

MM. les Professeurs — J.G. MC LEOD (Australie)
J. PORTER (U.S.A.)

1991

MM. les Professeurs — J. Edward MC DADE (U.S.A.)
W. BURGDORFER (U.S.A.)

1992

MM. les Professeurs — H.G. SCHWARZACHER (Autriche)
D. CARSON (U.S.A.)
T. YAMAMURO (Japon)

1994

MM. les Professeurs — G. KARPATI (Canada)
W.J. KOLFF (U.S.A.)

1995

MM. les Professeurs — D. WALKER (U.S.A.)
M. MULLER (Suisse)
V. BONOMINI (Italie)

1997

MM. les Professeurs — C. DINARELLO (U.S.A.)
D. STULBERG (U.S.A.)
A. MEIKLE DAVISON (Grande-Bretagne)
P.I. BRANEMARK (Suède)

1998

MM. les Professeurs — O. JARDETSKY (U.S.A.)

1999

MM. les Professeurs — J. BOTELLA LLUSIA (Espagne)
D. COLLEN (Belgique)
S. DIMAURO (U. S. A.)

2000

MM. les Professeurs — D. SPIEGEL (U. S. A.)
C. R. CONTI (U.S.A.)

2001

MM. les Professeurs — P-B. BENNET (U. S. A.)
G. HUGUES (Grande Bretagne)
J-J. O'CONNOR (Grande Bretagne)

2002

MM. les Professeurs — M. ABEDI (Canada)
K. DAI (Chine)

2003

M. le Professeur — T. MARRIE (Canada)
Sir — G.K. RADDA (Grande Bretagne)

2004

M. le Professeur — M. DAKE (U.S.A.)

2005

M. le Professeur — L. CAVALLI-SFORZA (U.S.A.)

2006

M. le Professeur — A. R. CASTANEDA (U.S.A.)

2007

M. le Professeur — S. KAUFMANN (Allemagne)

EMERITAT

2008

M. le Professeur	LEVY Samuel	31/08/2011
Mme le Professeur	JUHAN-VAGUE Irène	31/08/2011
M. le Professeur	PONCET Michel	31/08/2011
M. le Professeur	KASBARIAN Michel	31/08/2011
M. le Professeur	ROBERTOUX Pierre	31/08/2011

2009

M. le Professeur	DJIANE Pierre	31/08/2011
M. le Professeur	VERVLOET Daniel	31/08/2012

2010

M. le Professeur	MAGNAN Jacques	31/12/2014

2011

M. le Professeur	DI MARINO Vincent	31/08/2015
M. le Professeur	MARTIN Pierre	31/08/2015
M. le Professeur	METRAS Dominique	31/08/2015

2012

M. le Professeur	AUBANIAC Jean-Manuel	31/08/2015
M. le Professeur	BOUVENOT Gilles	31/08/2015
M. le Professeur	CAMBOULIVES Jean	31/08/2015
M. le Professeur	FAVRE Roger	31/08/2015
M. le Professeur	MATTEI Jean-François	31/08/2015
M. le Professeur	OLIVER Charles	31/08/2015
M. le Professeur	VERVLOET Daniel	31/08/2015

2013

M. le Professeur	BRANCHEREAU Alain	31/08/2016
M. le Professeur	CARAYON Pierre	31/08/2016
M. le Professeur	COZZONE Patrick	31/08/2016
M. le Professeur	DELMONT Jean	31/08/2016
M. le Professeur	HENRY Jean-François	31/08/2016
M. le Professeur	LE GUICHAOUA Marie-Roberte	31/08/2016
M. le Professeur	RUFO Marcel	31/08/2016
M. le Professeur	SEBAHOUN Gérard	31/08/2016

2014

M. le Professeur	FUENTES Pierre	31/08/2017
M. le Professeur	GAMERRE Marc	31/08/2017
M. le Professeur	MAGALON Guy	31/08/2017
M. le Professeur	PERAGUT Jean-Claude	31/08/2017
M. le Professeur	WEILLER Pierre-Jean	31/08/2017

2015

M. le Professeur	COULANGE Christian	31/08/2018
M. le Professeur	COURAND François	31/08/2018
M. le Professeur	FAVRE Roger	31/08/2016
M. le Professeur	MATTEI Jean-François	31/08/2016
M. le Professeur	OLIVER Charles	31/08/2016
M. le Professeur	VERVLOET Daniel	31/08/2016

2016

M. le Professeur	BONGRAND Pierre	31/08/2019
M. le Professeur	BOUVENOT Gilles	31/08/2017
M. le Professeur	BRUNET Christian	31/08/2019
M. le Professeur	CAU Pierre	31/08/2019
M. le Professeur	COZZONE Patrick	31/08/2017
M. le Professeur	FAVRE Roger	31/08/2017
M. le Professeur	FONTES Michel	31/08/2019
M. le Professeur	JAMMES Yves	31/08/2019
M. le Professeur	NAZARIAN Serge	31/08/2019
M. le Professeur	OLIVER Charles	31/08/2017
M. le Professeur	POITOUT Dominique	31/08/2019
M. le Professeur	SEBAHOUN Gérard	31/08/2017
M. le Professeur	VIALETTES Bernard	31/08/2019

2017

M. le Professeur	ALESSANDRINI Pierre	31/08/2020
M. le Professeur	BOUVENOT Gilles	31/08/2018
M. le Professeur	CHAUVEL Patrick	31/08/2020
M. le Professeur	COZZONE Pierre	31/08/2018
M. le Professeur	DELMONT Jean	31/08/2018
M. le Professeur	FAVRE Roger	31/08/2018
M. le Professeur	OLIVER Charles	31/08/2018
M. le Professeur	SEBBAHOUN Gérard	31/08/2018

PROFESSEURS DES UNIVERSITES - PRATICIENS HOSPITALIERS

AGOSTINI FERRANDES Aubert
ALBANESE Jacques
ALIMI Yves
AMABILE Philippe
AMBROSI Pierre
ANDRE Nicolas
ARGENSON Jean-Noël
ASTOUL Philippe
ATTARIAN Shahram
AUDOUIN Bertrand
AUQUIER Pascal
AVIERINOS Jean-François
AZULAY Jean-Philippe
BAILLY Daniel
BARLESI Fabrice
BARLIER-SETTI Anne
BARTHET Marc
BARTOLI Jean-Michel
BARTOLI Michel
BARTOLIN Robert Surnombre
BARTOLOMEI Fabrice
BASTIDE Cyrille
BENSOUSSAN Laurent
BERBIS Philippe
BERDAH Stéphane
BERLAND Yvon Surnombre
BERNARD Jean-Paul
BEROUD Christophe
BERTUCCI François
BLAISE Didier
BLIN Olivier
BLONDEL Benjamin
BONIN/GUILLAUME Sylvie
BONELLO Laurent
BONNET Jean-Louis
BOTTA/FRIDLUND Danielle
BOUBLI Léon
BOYER Laurent
BREGEON Fabienne
BRETELLE Florence
BROUQUI Philippe
BRUDER Nicolas
BRUE Thierry
BRUNET Philippe
BURTEY Stéphane
CARCOPINO-TUSOLI Xavier
CASANOVA Dominique
CASTINETTI Frédéric
CECCALDI Mathieu
CHABOT Jean-Michel
CHAGNAUD Christophe
CHAMBOST Hervé
CHAMPSAUR Pierre
CHANEZ Pascal
CHARAFFE-JAUFFRET Emmanuelle
CHARREL Rémi
CHARPIN Denis Surnombre
CHAUMOITRE Kathia
CHIARONI Jacques
CHINOT Olivier
CHOSSEGROS Cyrille
CLAVERIE Jean-Michel Surnombre
COLLART Frédéric
COSTELLO Régis
COURBIERE Blandine
COWEN Didier
CRAVELLO Ludovic
CUISSET Thomas
CURVALE Georges
DA FONSECA David
DAHAN-ALCARAZ Laetitia
DANIEL Laurent
DARMON Patrice
D'ERCOLE Claude
D'JOURNO Xavier
DEHARO Jean-Claude
DELPERO Jean-Robert
DENIS Danièle
DESSEIN Alain Surnombre
DESSI Patrick
DISDIER Patrick
DODDOLI Christophe
DRANCOURT Michel
DUBUS Jean-Christophe
DUFFAUD Florence
DUFOUR Henry
DURAND Jean-Marc
DUSSOL Bertrand
ENJALBERT Alain Surnombre
EUSEBIO Alexandre
FAKHRY Nicolas
FAUGERE Gérard Surnombre
FELICIAN Olvier
FENOLLAR Florence
FIGARELLA/BRANGER Dominique
FLECHER Xavier
FOURNIER Pierre-Edouard
FRANCES Yves Surnombre
FUENTES Stéphane
GABERT Jean
GAINNIER Marc
GARCIA Stéphane
GARIBOLDI Vlad
GAUDART Jean
GAUDY-MARQUESTE Caroline
GENTILE Stéphanie
GERBEAUX Patrick
GEROLAMI/SANTANDREA René
GILBERT/ALESSI Marie-Christine
GIORGI Roch
GIOVANNI Antoine
GIRARD Nadine
GIRAUD/CHABROL Brigitte
GONCALVES Anthony
GORINCOUR Guillaume
GRANEL/REY Brigitte
GRANVAL Philippe
GREILLIER Laurent
GRILLO Jean-Marie Surnombre
GRIMAUD Jean-Charles
GROB Jean-Jacques
GUEDJ Eric
GUIEU Régis
GUIS Sandrine
GUYE Maxime
GUYOT Laurent
GUYS Jean-Michel
HABIB Gilbert
HARDWIGSEN Jean
HARLE Jean-Robert
HOFFART Louis
HOUVENAEGHEL Gilles
JACQUIER Alexis
JOURDE-CHICHE Noémie
JOUVE Jean-Luc
KAPLANSKI Gilles
KARSENTY Gilles
KERBAUL François
KRAHN Martin
LAFFORGUE Pierre
LAGIER Jean-Christophe
LAMBAUDIE Eric
LANCON Christophe
LA SCOLA Bernard
LAUNAY Franck
LAVIEILLE Jean-Pierre
LE CORROLLER Thomas
LE TREUT Yves-Patrice Surnombre
LECHEVALLIER Eric
LEGRE Régis
LEHUCHER-MICHEL Marie-Pascale
LEONE Marc
LEONETTI Georges
LEPIDI Hubert
LEVY Nicolas
MACE Loïc
MAGNAN Pierre-Edouard
MARANINCHI Dominique Surnombre
MARTIN Claude Surnombre
MATONTI Frédéric
MEGE Jean-Louis
MERROT Thierry
METZLER/GUILLEMAIN Catherine
MEYER/DUTOUR Anne
MICCALEF/ROLL Joëlle
MICHEL Fabrice
MICHEL Gérard
MICHELET Pierre
MILH Mathieu
MOAL Valérie
MONCLA Anne
MORANGE Pierre-Emmanuel
MOULIN Guy
MOUTARDIER Vincent
MUNDLER Olivier Surnombre
NAUDIN Jean
NICOLAS DE LAMBALLERIE Xavier
NICOLLAS Richard
OLIVE Daniel

OUAFIK L'Houcine
PAGANELLI Franck
PANUEL Michel
PAPAZIAN Laurent
PAROLA Philippe
PARRATTE Sébastien
PELISSIER-ALICOT Anne-Laure
PELLETIER Jean
PETIT Philippe
PHAM Thao
PIERCECCHI/MARTI Marie-Dominique
PIQUET Philippe
PIRRO Nicolas
POINSO François
RACCAH Denis
RAOULT Didier
REGIS Jean
REYNAUD/GAUBERT Martine
REYNAUD Rachel
RICHARD/LALLEMAND Marie-Aleth
RIDINGS Bernard Surnombre
ROCHE Pierre-Hugues
ROCH Antoine
ROCHWERGER Richard
ROLL Patrice
ROSSI Dominique
ROSSI Pascal
ROUDIER Jean
SALAS Sébastien
SAMBUC Roland Surnombre
SARLES Jacques
SARLES/PHILIP Nicole
SCAVARDA Didier
SCHLEINITZ Nicolas
SEBAG Frédéric
SEITZ Jean-François
SIELEZNEFF Igor
SIMON Nicolas
STEIN Andréas
TAIEB David
THIRION Xavier
THOMAS Pascal
THUNY Franck
TREBUCHON-DA FONSECA Agnès
TRIGLIA Jean-Michel
TROPIANO Patrick
TSIMARATOS Michel
TURRINI Olivier
VALERO René
VAROQUAUX Arthur Damien
VELLY Lionel
VEY Norbert
VIDAL Vincent
VIENS Patrice
VILLANI Patrick
VITON Jean-Michel
VITTON Véronique
VIEHWEGER Heide Elke
VIVIER Eric
XERRI Luc

PROFESSEUR DES UNIVERSITES

ADALIAN Pascal
AGHABABIAN Valérie
BELIN Pascal
CHABANNON Christian
CHABRIERE Eric
FERON François
LE COZ Pierre
LEVASSEUR Anthony
RANJEVA Jean-Philippe
SOBOL Hagay

PROFESSEUR CERTIFIE

BRANDENBURGER Chantal

PRAG

TANTI-HARDOUIN Nicolas

PROFESSEUR ASSOCIE DE MEDECINE GENERALE *A MI-TEMPS*

ADNOT Sébastien
FILIPPI Simon

PROFESSEUR ASSOCIE *A TEMPS PARTIEL*

BURKHART Gary

MAITRE DE CONFERENCES DES UNIVERSITES - PRATICIENS HOSPITALIERS

ACHARD Vincent (disponibilité)
ANGELAKIS Emmanouil
ATLAN Catherine (disponibilité)
BARTHELEMY Pierre
BARTOLI Christophe
BEGE Thierry
BELIARD Sophie
BERBIS Julie
BERGE-LEFRANC Jean-Louis
BEYER-BERJOT Laura
BIRNBAUM David
BONINI Francesca
BOUCRAUT Joseph
BOULAMERY Audrey
BOULLU/CIOCCA Sandrine
BUFFAT Christophe
CAMILLERI Serge
CARRON Romain
CASSAGNE Carole
CHAUDET Hervé
COZE Carole
DADOUN Frédéric (disponibilité)
DALES Jean-Philippe
DAUMAS Aurélie
DEGEORGES/VITTE Joëlle
DEL VOLGO/GORI Marie-José
DELLIAUX Stéphane
DESPLAT/JEGO Sophie
DEVEZE Arnaud Disponibilité
DUBOURG Grégory
DUFOUR Jean-Charles
EBBO Mikaël
FABRE Alexandre
FOLETTI Jean- Marc
FOUILLOUX Virginie
FROMONOT Julien
GABORIT Bénédicte
GASTALDI Marguerite
GELSI/BOYER Véronique
GIUSIANO Bernard
GIUSIANO COURCAMBECK Sophie
GONZALEZ Jean-Michel
GOURIET Frédérique
GRAILLON Thomas
GRISOLI Dominique
GUENOUN MEYSSIGNAC Daphné
GUIDON Catherine
HAUTIER/KRAHN Aurélie
HRAIECH Sami
KASPI-PEZZOLI Elise
L'OLLIVIER Coralie
LABIT-BOUVIER Corinne
LAFAGE/POCHITALOFF-HUVALE Marina
LAGIER Aude (disponibilité)
LAGOUANELLE/SIMEONI Marie-Claude
LEVY/MOZZICONACCI Annie
LOOSVELD Marie
MANCINI Julien
MARY Charles
MASCAUX Céline
MAUES DE PAULA André
MILLION Matthieu
MOTTOLA GHIGO Giovanna
NGUYEN PHONG Karine
NINOVE Laetitia
NOUGAIREDE Antoine
OLLIVIER Matthieu
OUDIN Claire
OVAERT Caroline
PAULMYER/LACROIX Odile
PERRIN Jeanne
RANQUE Stéphane
REY Marc
ROBERT Philippe
SABATIER Renaud
SARI-MINODIER Irène
SARLON-BARTOLI Gabrielle
SAVEANU Alexandru
SECQ Véronique
TOGA Caroline
TOGA Isabelle
TROUSSE Delphine
TUCHTAN-TORRENTS Lucile
VALLI Marc
VELY Frédéric
VION-DURY Jean
ZATTARA/CANNONI Hélène

MAITRES DE CONFERENCES DES UNIVERSITES

(mono-appartenants)

ABU ZAINEH Mohammad
BARBACARU/PERLES T. A.
BERLAND/BENHAIM Caroline
BOUCAULT/GARROUSTE Françoise
BOYER Sylvie
COLSON Sébastien
DEGIOANNI/SALLE Anna
DESNUES Benoît
MARANINCHI Marie
MERHEJ/CHAUVEAU Vicky
MINVIELLE/DEVICTOR Bénédicte
POGGI Marjorie
RUEL Jérôme
STEINBERG Jean-Guillaume
THOLLON Lionel
THIRION Sylvie
VERNA Emeline

MAITRE DE CONFERENCES DES UNIVERSITES DE MEDECINE GENERALE

GENTILE Gaëtan

MAITRES DE CONFERENCES ASSOCIES DE MEDECINE GENERALE à MI-TEMPS

BARGIER Jacques
BONNET Pierre-André
CALVET-MONTREDON Céline
GUIDA Pierre
JANCZEWSKI Aurélie

MAITRE DE CONFERENCES ASSOCIE à MI-TEMPS

REVIS Joana

MAITRE DE CONFERENCES ASSOCIE à TEMPS-PLEIN

TOMASINI Pascale

PROFESSEURS DES UNIVERSITES et MAITRES DE CONFERENCES DES UNIVERSITES - PRATICIENS HOSPITALIERS
PROFESSEURS ASSOCIES, MAITRES DE CONFERENCES DES UNIVERSITES mono-appartenants

ANATOMIE *4201*

CHAMPSAUR Pierre (PU-PH)
LE CORROLLER Thomas (PU-PH)
PIRRO Nicolas (PU-PH)

GUENOUN-MEYSSIGNAC Daphné (MCU-PH)
LAGIER Aude (MCU-PH) disponibilité

THOLLON Lionel (MCF) (60ème section)

ANATOMIE ET CYTOLOGIE PATHOLOGIQUES *4203*

CHARAFE/JAUFFRET Emmanuelle (PU-PH)
DANIEL Laurent (PU-PH)
FIGARELLA/BRANGER Dominique (PU-PH)
GARCIA Stéphane (PU-PH)
XERRI Luc (PU-PH)

DALES Jean-Philippe (MCU-PH)
GIUSIANO COURCAMBECK Sophie (MCU PH)
LABIT/BOUVIER Corinne (MCU-PH)
MAUES DE PAULA André (MCU-PH)
SECQ Véronique (MCU-PH)

ANESTHESIOLOGIE ET REANIMATION CHIRURGICALE ; MEDECINE URGENCE *4801*

ALBANESE Jacques (PU-PH)
BRUDER Nicolas (PU-PH)
KERBAUL François (PU-PH)
LEONE Marc (PU-PH)
MARTIN Claude (PU-PH) Surnombre
MICHEL Fabrice (PU-PH)
MICHELET Pierre (PU-PH)
VELLY Lionel (PU-PH)

GUIDON Catherine (MCU-PH)

ANGLAIS *11*

BRANDENBURGER Chantal (PRCE)

BURKHART Gary (PAST)

BIOLOGIE ET MEDECINE DU DEVELOPPEMENT ET DE LA REPRODUCTION ; GYNECOLOGIE MEDICALE *5405*

METZLER/GUILLEMAIN Catherine (PU-PH)

PERRIN Jeanne (MCU-PH)

BIOPHYSIQUE ET MEDECINE NUCLEAIRE *4301*

GUEDJ Eric (PU-PH)
GUYE Maxime (PU-PH)
MUNDLER Olivier (PU-PH) Surnombre
TAIEB David (PU-PH)

BELIN Pascal (PR) (69ème section)
RANJEVA Jean-Philippe (PR) (69ème section)

CAMMILLERI Serge (MCU-PH)
VION-DURY Jean (MCU-PH)

BARBACARU/PERLES Téodora Adriana (MCF) (69ème section)

BIOSTATISTIQUES, INFORMATIQUE MEDICALE ET TECHNOLOGIES DE COMMUNICATION *4604*

CLAVERIE Jean-Michel (PU-PH) Surnombre
GAUDART Jean (PU-PH)
GIORGI Roch (PU-PH)

CHAUDET Hervé (MCU-PH)
DUFOUR Jean-Charles (MCU-PH)

ANTHROPOLOGIE *20*

ADALIAN Pascal (PR)

DEGIOANNI/SALLE Anna (MCF)
VERNA Emeline (MCF)

BACTERIOLOGIE-VIROLOGIE ; HYGIENE HOSPITALIERE *4501*

CHARREL Rémi (PU PH)
DRANCOURT Michel (PU-PH)
FENOLLAR Florence (PU-PH)
FOURNIER Pierre-Edouard (PU-PH)
NICOLAS DE LAMBALLERIE Xavier (PU-PH)
LA SCOLA Bernard (PU-PH)
RAOULT Didier (PU-PH)

ANGELAKIS Emmanouil (MCU-PH)
DUBOURG Grégory (MCU-PH)
GOURIET Frédérique (MCU-PH)
NOUGAIREDE Antoine (MCU-PH)
NINOVE Laetitia (MCU-PH)

CHABRIERE Eric (PR) (64ème section)
LEVASSEUR Anthony (PR) (64ème section)
DESNUES Benoit (MCF) (65ème section)
MERHEJ/CHAUVEAU Vicky (MCF) (87ème section)

BIOCHIMIE ET BIOLOGIE MOLECULAIRE *4401*

BARLIER/SETTI Anne (PU-PH)
ENJALBERT Alain (PU-PH) Surnombre
GABERT Jean (PU-PH)
GUIEU Régis (PU-PH)
OUAFIK L'Houcine (PU-PH)

BUFFAT Christophe (MCU-PH)
FROMONOT Julien (MCU-PH)
MOTTOLA GHIGO Giovanna (MCU-PH)
SAVEANU Alexandru (MCU-PH)

BIOLOGIE CELLULAIRE *4403*

ROLL Patrice (PU-PH)

GASTALDI Marguerite (MCU-PH)
KASPI-PEZZOLI Elise (MCU-PH)
LEVY-MOZZICONNACCI Annie (MCU-PH)

CARDIOLOGIE *5102*

AVIERINOS Jean-François (PU-PH)
BONELLO Laurent (PU PH)
BONNET Jean-Louis (PU-PH)
CUISSET Thomas (PU-PH)
DEHARO Jean-Claude (PU-PH)
FRANCESCHI Frédéric (PU-PH)
HABIB Gilbert (PU-PH)
PAGANELLI Franck (PU-PH)
THUNY Franck (PU-PH)

CHIRURGIE DIGESTIVE *5202*

BERDAH Stéphane (PU-PH)
HARDWIGSEN Jean (PU-PH)
LE TREUT Yves-Patrice (PU-PH) Surnombre
SIELEZNEFF Igor (PU-PH)

BEYER-BERJOT Laura (MCU-PH)

CHIRURGIE GENERALE *5302*

GIUSIANO Bernard (MCU-PH)
MANCINI Julien (MCU-PH)

ABU ZAINEH Mohammad (MCF) (5ème section)
BOYER Sylvie (MCF) (5ème section)

CHIRURGIE ORTHOPEDIQUE ET TRAUMATOLOGIQUE *5002*

ARGENSON Jean-Noël (PU-PH)
BLONDEL Benjamin (PU-PH)
CURVALE Georges (PU-PH)
FLECHER Xavier (PU PH)
PARRATTE Sébastien (PU-PH)
ROCHWERGER Richard (PU-PH)
TROPIANO Patrick (PU-PH)

OLLIVIER Matthieu (MCU-PH)

CANCEROLOGIE ; RADIOTHERAPIE *4702*

BERTUCCI François (PU-PH)
CHINOT Olivier (PU-PH)
COWEN Didier (PU-PH)
DUFFAUD Florence (PU-PH)
GONCALVES Anthony PU-PH)
HOUVENAEGHEL Gilles (PU-PH)
LAMBAUDIE Eric (PU-PH)
MARANINCHI Dominique (PU-PH) Surnombre
SALAS Sébastien (PU-PH)
VIENS Patrice (PU-PH)

SABATIER Renaud (MCU-PH)

CHIRURGIE THORACIQUE ET CARDIOVASCULAIRE *5103*

COLLART Frédéric (PU-PH)
D'JOURNO Xavier (PU-PH)
DODDOLI Christophe (PU-PH)
GARIBOLDI Vlad (PU-PH)
MACE Loïc (PU-PH)
THOMAS Pascal (PU-PH)

FOUILLOUX Virginie (MCU-PH)
GRISOLI Dominique (MCU-PH)
TROUSSE Delphine (MCU-PH)

CHIRURGIE VASCULAIRE ; MEDECINE VASCULAIRE *5104*

ALIMI Yves (PU-PH)
AMABILE Philippe (PU-PH)
BARTOLI Michel (PU-PH)
MAGNAN Pierre-Edouard (PU-PH)
PIQUET Philippe (PU-PH)

SARLON-BARTOLI Gabrielle (MCU PH)

HISTOLOGIE, EMBRYOLOGIE ET CYTOGENETIQUE *4202*

GRILLO Jean-Marie (PU-PH) Surnombre
LEPIDI Hubert (PU-PH)

ACHARD Vincent (MCU-PH) disponibilité
PAULMYER/LACROIX Odile (MCU-PH)

DERMATOLOGIE - VENEREOLOGIE *5003*

BERBIS Philippe (PU-PH)
GAUDY/MARQUESTE Caroline (PU-PH)
GROB Jean-Jacques (PU-PH)
RICHARD/LALLEMAND Marie-Aleth (PU-PH)

DUSI

COLSON Sébastien (MCF)

ENDOCRINOLOGIE ,DIABETE ET MALADIES METABOLIQUES ; GYNECOLOGIE MEDICALE *5404*

BRUE Thierry (PU-PH)
CASTINETTI Frédéric (PU-PH)

EPIDEMIOLOGIE, ECONOMIE DE LA SANTE ET PREVENTION *4601*

AUQUIER Pascal (PU-PH)
BOYER Laurent (PU-PH)
CHABOT Jean-Michel (PU-PH)
GENTILE Stéphanie (PU-PH)
SAMBUC Roland (PU-PH) Surnombre
THIRION Xavier (PU-PH)

DELPERO Jean-Robert (PU-PH)
MOUTARDIER Vincent (PU-PH)
SEBAG Frédéric (PU-PH)
TURRINI Olivier (PU-PH)

BEGE Thierry (MCU-PH)
BIRNBAUM David (MCU-PH)

CHIRURGIE INFANTILE *5402*

GUYS Jean-Michel (PU-PH)
JOUVE Jean-Luc (PU-PH)
LAUNAY Franck (PU-PH)
MERROT Thierry (PU-PH)
VIEHWEGER Heide Elke (PU-PH)

CHIRURGIE MAXILLO-FACIALE ET STOMATOLOGIE *5503*

CHOSSEGROS Cyrille (PU-PH)
GUYOT Laurent (PU-PH)

FOLETTI Jean-Marc (MCU-PH)

CHIRURGIE PLASTIQUE,

RECONSTRUCTRICE ET ESTHETIQUE ; BRÛLOLOGIE *5004*

CASANOVA Dominique (PU-PH)
LEGRE Régis (PU-PH)

HAUTIER/KRAHN Aurélie (MCU-PH)

GASTROENTEROLOGIE ; HEPATOLOGIE ; ADDICTOLOGIE *5201*

BARTHET Marc (PU-PH)
BERNARD Jean-Paul (PU-PH)
BOTTA-FRIDLUND Danielle (PU-PH)
DAHAN-ALCARAZ Laetitia (PU-PH)
GEROLAMI-SANTANDREA René (PU-PH)
GRANDVAL Philippe (PU-PH)
GRIMAUD Jean-Charles (PU-PH)
SEITZ Jean-François (PU-PH)
VITTON Véronique (PU-PH)

GONZALEZ Jean-Michel (MCU-PH)

GENETIQUE *4704*

BEROUD Christophe (PU-PH)
KRAHN Martin (PU-PH)
LEVY Nicolas (PU-PH)
MONCLA Anne (PU-PH)
SARLES/PHILIP Nicole (PU-PH)

NGYUEN Karine (MCU-PH)
TOGA Caroline (MCU-PH)
ZATTARA/CANNONI Hélène (MCU-PH)

GYNECOLOGIE-OBSTETRIQUE ; GYNECOLOGIE MEDICALE *5403*

AGOSTINI Aubert (PU-PH)
BOUBLI Léon (PU-PH)
BRETELLE Florence (PU-PH)
CARCOPINO-TUSOLI Xavier (PU-PH)
COURBIERE Blandine (PU-PH)
CRAVELLO Ludovic (PU-PH)
D'ERCOLE Claude (PU-PH)

BERBIS Julie (MCU-PH)
LAGOUANELLE/SIMEONI Marie-Claude (MCU-PH)

MINVIELLE/DEVICTOR Bénédicte (MCF)(06ème section)
TANTI-HARDOUIN Nicolas (PRAG)

IMMUNOLOGIE *4703*

KAPLANSKI Gilles (PU-PH)
MEGE Jean-Louis (PU-PH)
OLIVE Daniel (PU-PH)
VIVIER Eric (PU-PH)

FERON François (PR) (69ème section)

BOUCRAUT Joseph (MCU-PH)
DEGEORGES/VITTE Joëlle (MCU-PH)
DESPLAT/JEGO Sophie (MCU-PH)
ROBERT Philippe (MCU-PH)
VELY Frédéric (MCU-PH)

BOUCAULT/GARROUSTE Françoise (MCF) 65ème section)

MALADIES INFECTIEUSES ; MALADIES TROPICALES *4503*

BROUQUI Philippe (PU-PH)
LAGIER Jean-Christophe (PU-PH)
PAROLA Philippe (PU-PH)
STEIN Andréas (PU-PH)

MILLION Matthieu (MCU-PH)

MEDECINE INTERNE ; GERIATRIE ET BIOLOGIE DU VIEILLISSEMENT ; MEDECINE GENERALE ; ADDICTOLOGIE *5301*

BONIN/GUILLAUME Sylvie (PU-PH)
DISDIER Patrick (PU-PH)
DURAND Jean-Marc (PU-PH)
FRANCES Yves (PU-PH) Surnombre
GRANEL/REY Brigitte (PU-PH)
HARLE Jean-Robert (PU-PH)
ROSSI Pascal (PU-PH)
SCHLEINITZ Nicolas (PU-PH)

EBBO Mikael (MCU-PH)

GENTILE Gaëtan (MCF Méd. Gén. Temps plein)

ADNOT Sébastien (PR associé Méd. Gén. à mi-temps)
FILIPPI Simon (PR associé Méd. Gén. à mi-temps)

BARGIER Jacques (MCF associé Méd. Gén. À mi-temps)
BONNET Pierre-André (MCF associé Méd. Gén à mi-temps)
CALVET-MONTREDON Céline (MCF associé Méd. Gén. à temps plein)
GUIDA Pierre (MCF associé Méd. Gén. à mi-temps)
JANCZEWSKI Aurélie (MCF associé Méd. Gén. À mi-temps)

NUTRITION *4404*

DARMON Patrice (PU-PH)
RACCAH Denis (PU-PH)
VALERO René (PU-PH)

ATLAN Catherine (MCU-PH) disponibilité
BELIARD Sophie (MCU-PH)

MARANINCHI Marie (MCF) (66ème section)

ONCOLOGIE 65 (BIOLOGIE CELLULAIRE)

CHABANNON Christian (PR) (66ème section)
SOBOL Hagay (PR) (65ème section)

OPHTALMOLOGIE *5502*

DENIS Danièle (PU-PH)
HOFFART Louis (PU-PH)
MATONTI Frédéric (PU-PH)
RIDINGS Bernard (PU-PH) Surnombre

HEMATOLOGIE ; TRANSFUSION *4701*

BLAISE Didier (PU-PH)
COSTELLO Régis (PU-PH)
CHIARONI Jacques (PU-PH)
GILBERT/ALESSI Marie-Christine (PU-PH)
MORANGE Pierre-Emmanuel (PU-PH)
VEY Norbert (PU-PH)

GELSI/BOYER Véronique (MCU-PH)
LAFAGE/POCHITALOFF-HUVALE Marina (MCU-PH)
LOOSVELD Marie (MCU-PH)

POGGI Marjorie (MCF) (64ème section)

MEDECINE LEGALE ET DROIT DE LA SANTE *4603*

LEONETTI Georges (PU-PH)
PELISSIER/ALICOT Anne-Laure (PU-PH)
PIERCECCHI/MARTI Marie-Dominique (PU-PH)

BARTOLI Christophe (MCU-PH)
TUCHTAN-TORRENTS Lucile (MCU-PH)

BERLAND/BENHAIM Caroline (MCF) (1ère section)

MEDECINE PHYSIQUE ET DE READAPTATION *4905*

BENSOUSSAN Laurent (PU-PH)
VITON Jean-Michel (PU-PH)

MEDECINE ET SANTE AU TRAVAIL *4602*

LEHUCHER/MICHEL Marie-Pascale (PU-PH)

BERGE-LEFRANC Jean-Louis (MCU-PH)
SARI/MINODIER Irène (MCU-PH)

NEPHROLOGIE *5203*

BERLAND Yvon (PU-PH) Surnombre
BRUNET Philippe (PU-PH)
BURTEY Stépahne (PU-PH)
DUSSOL Bertrand (PU-PH)
JOURDE CHICHE Noémie (PU PH)
MOAL Valérie (PU-PH)

NEUROCHIRURGIE *4902*

DUFOUR Henry (PU-PH)
FUENTES Stéphane (PU-PH)
REGIS Jean (PU-PH)
ROCHE Pierre-Hugues (PU-PH)
SCAVARDA Didier (PU-PH)

CARRON Romain (MCU PH)
GRAILLON Thomas (MCU PH)

NEUROLOGIE *4901*

ATTARIAN Sharham (PU PH)
AUDOIN Bertrand (PU-PH)
AZULAY Jean-Philippe (PU-PH)
CECCALDI Mathieu (PU-PH)
EUSEBIO Alexandre (PU-PH)
FELICIAN Olivier (PU-PH)
PELLETIER Jean (PU-PH)

PEDOPSYCHIATRIE; ADDICTOLOGIE *4904*

DA FONSECA David (PU-PH)
POINSO François (PU-PH)

OTO-RHINO-LARYNGOLOGIE *5501*

DESSI Patrick (PU-PH)
FAKHRY Nicolas (PU-PH)
GIOVANNI Antoine (PU-PH)
LAVIEILLE Jean-Pierre (PU-PH)
NICOLLAS Richard (PU-PH)
TRIGLIA Jean-Michel (PU-PH)

DEVEZE Arnaud (MCU-PH) Disponibilité

REVIS Joana (MAST) (Orthophonie) (7ème Section)

PARASITOLOGIE ET MYCOLOGIE *4502*

DESSEIN Alain (PU-PH) Surnombre

CASSAGNE Carole (MCU-PH)
L'OLLIVIER Coralie (MCU-PH)
MARY Charles (MCU-PH)
RANQUE Stéphane (MCU-PH)
TOGA Isabelle (MCU-PH)

PEDIATRIE *5401*

ANDRE Nicolas (PU-PH)
CHAMBOST Hervé (PU-PH)
DUBUS Jean-Christophe (PU-PH)
GIRAUD/CHABROL Brigitte (PU-PH)
MICHEL Gérard (PU-PH)
MILH Mathieu (PU-PH)
REYNAUD Rachel (PU-PH)
SARLES Jacques (PU-PH)
TSIMARATOS Michel (PU-PH)

COZE Carole (MCU-PH)
FABRE Alexandre (MCU-PH)
OUDIN Claire (MCU-PH)
OVAERT Caroline (MCU-PH)

PSYCHIATRIE D'ADULTES ; ADDICTOLOGIE *4903*

BAILLY Daniel (PU-PH)
LANCON Christophe (PU-PH)
NAUDIN Jean (PU-PH)

'CHOLOGIE - PSYCHOLOGIE CLINIQUE, PCYCHOLOGIE SOCIALE 16

AGHABABIAN Valérie (PR)

RADIOLOGIE ET IMAGERIE MEDICALE *4302*

BARTOLI Jean-Michel (PU-PH)
CHAGNAUD Christophe (PU-PH)
CHAUMOITRE Kathia (PU-PH)
GIRARD Nadine (PU-PH)
GORINCOUR Guillaume (PU-PH)
JACQUIER Alexis (PU-PH)
MOULIN Guy (PU-PH)
PANUEL Michel (PU-PH)
PETIT Philippe (PU-PH)
VAROQUAUX Arthur Damien (PU-PH)
VIDAL Vincent (PU-PH)

REANIMATION MEDICALE ; MEDECINE URGENCE *4802*

GAINNIER Marc (PU-PH)
GERBEAUX Patrick (PU-PH)
PAPAZIAN Laurent (PU-PH)
ROCH Antoine (PU-PH)

HRAIECH Sami (MCU-PH)

RHUMATOLOGIE *5001*

GUIS Sandrine (PU-PH)
LAFFORGUE Pierre (PU-PH)
PHAM Thao (PU-PH)
ROUDIER Jean (PU-PH)

PHARMACOLOGIE FONDAMENTALE - PHARMACOLOGIE CLINIQUE; ADDICTOLOGIE *4803*

BLIN Olivier (PU-PH)
FAUGERE Gérard (PU-PH) Surnombre
MICALLEF/ROLL Joëlle (PU-PH)
SIMON Nicolas (PU-PH)

BOULAMERY Audrey (MCU-PH)
VALLI Marc (MCU-PH)

PHILOSPHIE *17*

LE COZ Pierre (PR) (17ème section)

PHYSIOLOGIE *4402*

BARTOLOMEI Fabrice (PU-PH)
BREGEON Fabienne (PU-PH)
MEYER/DUTOUR Anne (PU-PH)
TREBUCHON/DA FONSECA Agnès (PU-PH)

BARTHELEMY Pierre (MCU-PH)
BONINI Francesca (MCU-PH)
BOULLU/CIOCCA Sandrine (MCU-PH)
DADOUN Frédéric (MCU-PH) (disponibilité)
DEL VOLGO/GORI Marie-José (MCU-PH)
DELLIAUX Stéphane (MCU-PH)
GABORIT Bénédicte (MCU-PH)
REY Marc (MCU-PH)

LIMERAT/BOUDOURESQUE Françoise (MCF) (40ème section) Retraite 1/5/2018
RUEL Jérôme (MCF) (69ème section)
STEINBERG Jean-Guillaume (MCF) (66ème section)
THIRION Sylvie (MCF) (66ème section)

PNEUMOLOGIE; ADDICTOLOGIE *5101*

ASTOUL Philippe (PU-PH)
BARLESI Fabrice (PU-PH)
CHANEZ Pascal (PU-PH)
CHARPIN Denis (PU-PH) Surnombre
GREILLIER Laurent (PU PH)
REYNAUD/GAUBERT Martine (PU-PH)

MASCAUX Céline (MCU-PH)

TOMASINI Pascale (Maitre de conférences associé des universités)

THERAPEUTIQUE; MEDECINE D'URGENCE; ADDICTOLOGIE *4804*

AMBROSI Pierre (PU-PH)
BARTOLIN Robert (PU-PH) Surnombre
VILLANI Patrick (PU-PH)

DAUMAS Aurélie (MCU-PH)

UROLOGIE *5204*

BASTIDE Cyrille (PU-PH)
KARSENTY Gilles (PU-PH)
LECHEVALLIER Eric (PU-PH)
ROSSI Dominique (PU-PH)

A Monsieur le Professeur Gilbert HABIB

Je vous remercie de m'avoir confié ce travail, de l'avoir dirigé, corrigé et d'en présider le jury. Je mesure la chance d'avoir pu évoluer dans votre service, de profiter de vos connaissances, de votre clairvoyance et de votre expertise clinique.
Merci de m'offrir la possibilité de continuer cet apprentissage.

Veuillez recevoir ici le témoignage de ma sincère reconnaissance.

A Monsieur le Professeur Franck THUNY

Vous me faites l’honneur de critiquer ce travail.

Je vous remercie pour votre simplicité, votre gentillesse, la qualité de votre enseignement dès les premières années de notre cursus et reste admiratif de votre relation au patient.

A Monsieur le Professeur Pierre AMBROSI

Je vous remercie d’avoir accepté de juger ce travail.

Je vous remercie pour votre implication dans notre formation scientifique, le développement de notre esprit critique et le partage de vos connaissances.

A Monsieur le Docteur Michel PANSIERI

Merci d’avoir accepté de siéger dans ce jury de cardiologie non interventionnelle.

Je vous suis reconnaissant pour la qualité de l’accueil et la confiance qui m’a été accordée par votre équipe ainsi que d’avoir œuvré pour que je puisse y revenir me former.

Au Professeur Laurence CAMOIN

Ce fût un plaisir de faire votre connaissance, d'échanger et de rédiger ce travail à vos côtés. Merci pour votre grande implication, votre disponibilité et votre patience. Je vous exprime ici mes sincères remerciements.

Au Professeur Jean François AVIERINOS

Je vous suis reconnaissant pour votre bienveillance et vous remercie pour votre pédagogie, la transmission de votre rigueur et de votre vision de la cardiologie.
J'ai plaisir à pouvoir travailler à vos côtés dans les mois à venir et ainsi continuer à bénéficier de vos enseignements.

A Madame Noémie RESSEGUIER qui a réalisé le travail statistique nécessaire à ce travail.

A Johan, Benjamin, tous les brillants internes (Clémence, Laurie Anne, Guillaume, Baptiste, Lory…) et Monsieur Alberto RIBERI qui m'ont transmis l'appétence pour la cardiologie, sans oublier Virginie et Estelle qui étaient là pour guider mon choix vers cette spécialité.

A tous les services qui m'ont accueilli

A commencer par l'Hôpital Nord, Monsieur PAGANELLI, Laurent, Michael, Marc et les supers mamans Jennifer et Chloé qui ont permis à Anne Sophie ''casse pied'' et moi de débuter cet internat dans un véritable cocon. A tous nos co-internes d'époque.

Au service de chirurgie cardiaque du Pr Collart, à Alexis, Virginie et tous les chirurgiens pour leur bienveillance. A Florent et Flora compagnons d'astreintes et de contrôles péricardiques.

A l'assurance tout risque Dr Mouret, aux supers assistants Erwan et Ludivine, à la formidable équipe infirmière des vétustes soins intensifs, à Hélène ''Marcelino'' (obligé de dire que tu râles beaucoup), aux copains du staff : Marion, Laura et Jean Charles et à Cindy la maman gâteaux.

A la cardiologie avignonnaise, Stéphane, Pierre, Olivier, Marc, Falah, Jean Paul, Saida, ''la machine'' Mathieu, Oana, Bassem et tous les autres, sans oublier tous les infirmiers que l'on envie au CHU. Aux voisins d'internat : Thibault, Hugo et Benoit, partenaires du petit dej' au soleil.

Au service du 10em étage, au plaisir d'apprendre aux cotés de Sébastien et Sandrine, à Julie et Anne Claire qui vont laisser un vide et aux compagnons de galère Elisabeth et Floriane.

A la cardiologie pédiatrique, Caroline, Philippe, Fedoua, Florent, l'équipe chirurgicale pour cette immersion en terre inconnue, aux deux mamans Elisa et Lucie qui m'ont permis de faire fortune et à Gaëlle infatigable pédiatre toujours garante de la bonne humeur.

Au service de rythmologie du Pr DEHARO, au Pr FRANCESCHI, à Linda, à Jérôme et ses meurs douteuses, à Nicolas adepte du ''moto-cross avec papa'' sans oublier Blandine, Francine, Pauline … et Lilith élue unanimement meilleure co-interne. A Julien ''Bertoto'' dont la gentillesse et la patience semblent venues d'un autre monde. A l'entrain et la curiosité de Sarah.

Enfin au service de vasculaire du Pr Piquet, à l'ensemble des chirurgiens et internes qui réalisent des prises charges haute couture et à Magali, la référence de l'écho vasculaire. A Olivier et Clem avec qui on ''dopplérise'' à tout va entre deux ''brainstormings'' dans ce lumineux bureau qui aura vu naître tant d'avancées scientifiques. A nos complices Benoit et Narimène.

Aux coronarographistes de la Timone, au Pr BONNET, à Thomas, Stéphanie, Marc, Pierre sans oublier Olivier C. pour partager votre science et venir exercer vos talents à toute heure du jour et de la nuit.

A tous les co-internes : les plus vieux trop forts (Anissa, Eléonore, Marie, Thibault, Chloé, Mélanie, Morgane…), les plus jeunes passionnés et motivés (Jérôme, Antoine, Maxime, Noémie, Vassili, Cédric, Mary, Aliénor, Alexandra, Florence, Camille, Arnaud, Hilla, Claire, Henitsoa, Marie, Jérémy…) sans oublier la folie de Marine, le calme de Charlène, la sérénité d'Olivier M. et les deux nordistes Florian et Thibault.

A mes amis :

A ceux avec qui j'ai appris à colorier :

A toi le pâtissier londonien, j'ai plaisir à te voir aussi passionné et fier de te voir te donner autant de mal, mais même si maintenant tu récoltes des étoiles je n'oublierai pas les pates sans eau.

A Flo, tu sais très bien que je freine toujours plus tard et que si je te leste tu ne verras plus que le derrière du kart. A toutes ces manettes de PlayStation qu'on a usé.

A cet homme qui m'a supporté sur la chaise d'à cotés pendant tant d'heures jusqu'à partir là où je ne le suivrais pas, non pas en classe prépa mais à Paris. Content de te voir trouver ton bonheur même si j'ai toujours pas bien compris ce que tu faisais de tes journées.

A ceux que j'ai connus à l'époque des deux roues :

Au tchécoslovaque indien naturalisé marocain,

Au normand conquérant, reconnaissant pour ton amitié, je te dois autant que je t'apprécie, garde ton génie et ta curiosité, garde Marie aussi, je ne suis pas témoin pour rien.

A Benoît avec beaucoup de respect pour la passion que tu mets dans ton travail, j'espère qu'il y aura encore beaucoup de dégustations à l'aveugle et surtout je te souhaite le meilleur pour ta petite famille.

A cette folle équipe de montiliens, aux deux plus élégants Zouzou et Manou, aux pecs de Keke, aux gros bras de Paulo, à Perrine, Mooky, Thomas et tous les autres, merci pour ces soirées d'insouciance, même si je me suis un peu ‘'autistisé'' ces dernières années je garde en mémoire tellement de bons souvenirs. A Baptiste qui me doit toujours une vitre et à Mae qui a tout pour devenir une grande urgentiste.

A ceux connu autour d'un verre :

A Thomas, s'il ne devait en rester qu'un après 10 ans c'est bien toi, en plus j'ai l'impression que tu triches moins et que tu acceptes presque de perdre depuis que Hugo est là. J'admire tes qualités humaines et ta générosité. Pour info après deux déménagements le troisième est offert, beaucoup de bonheur à vous trois.

A Sylvain, si tu ne te dépêches pas, on va finir dans les foires aux célibataires du centre de la France.

A Benjamin et Simon qui partent toujours plus loin.

A Dawei, je suis tellement content de te voir réussir, il va me falloir trouver un nouveau DU pour venir te voir. Je t'ai promis une côte de bœuf, en attendant je te souhaite toute la réussite que tu mérites et espère du mieux dans ces moments délicats.

A Chloé et Boris, hâte que vous rentriez de Toulouse, on a encore de la bière à boire. On devait être dans le juste avec ces sous-colles, vu le résultat. La prochaine invitation à Bratislava, promis je dis oui.

A ma famille :

A ma superbe maman, à mon athlétique papa, je n'ai jamais manqué de rien y compris d'engueulades et je vous en remercie, sachez comme je suis fier de vous.

A ma sœur, même si avant chaque chef d'œuvre il y a un brouillon, la seconde version a quand même beaucoup perdu en charme. Evite de te mettre une armée de tueurs à dos mais tu sais que je serais là. En attendant, prépare-toi, j'arrive avec toute une animalerie.

Aux oncles, tantes et amis qui ont pris soins de moi.

Aux plus anciens, à ceux qui ne sont plus là et à celui qui m'a tant transmis.

Table des matières

ABSTRACT 2

RESUME 3

INTRODUCTION 4

METHODS 5
- **Data sources** 5
- **Variables** 5
- **End points** 5
- **Outcomes** 6
- **Statistical analyses** 6

RESULTS 7
- **I. Patient Characteristics on Admission** 7
- **II. Embolic events** 7
  - **EE according to ASA and ST therapy** 7
- **III. Secondary end points** 8
  - **Micro bacteriological results** 8
  - **Cerebral embolism** 8
  - **Hemorrhagic complications** 9
  - **30 days mortality** 9

DISCUSSION 10

LIMITS 12

CONCLUSION 13

BIBLIOGRAPHY 14

ANNEXES 18

Both aspirin and statin therapy reduce embolic events in patients with infective endocarditis

Jason Veyrier, Laurence Camoin-Jau, Noémie Resseguier, Cécile Lavoute, Julie Haentjens, Anne-Claire Casalta, Julie Pradier, Sébastien Renard, Sandrine Hubert, Jean-François Avierinos, Erwan Salaun, Gilbert Habib.

Corresponding author :
Gilbert Habib, Cardiology Department, la Timone Hospital, AP-HM, boulevard Jean-Moulin, Aix Marseille Univ, IRD, APHM, MEPHI, IHU Méditerranée infection, 13005 Marseille, France. Courriel : Gilbert.HABIB@ap-hm.fr

Word counts: 2897

Conflict of interest statement : None. The authors report no relationships with industry.

ABSTRACT

Background:

Embolic events (EE) are major complications of infective endocarditis (IE). Animal models have demonstrated the benefit of aspirin (ASA) and statins (ST) in their prevention, but clinical studies gave conflicting results. The aim of our study was to evaluate the benefit of prior ASA and/or ST therapy on embolic risk in patients with IE.

Methods:

In a retrospective study from 2010 to 2016, the impact of daily ASA or ST therapy on outcome of patients with IE was assessed. The primary end point was EE. The secondary end points were cerebral emboli, EE according to causative bacteria, hemorrhagic events and 30-day mortality.

Results:

Among 529 patients with IE, 135 (25%) were treated by ASA, 130 (24%) by ST, and 66 (12%) by both therapies at the time of hospitalization. EE occurred in 264 (50%) patients.

As compared with 330 patients with no therapy, the 66 patients treated with combined ASA and ST presented with less frequent EE (23 (34%) vs 179 (54%), OR=0.46 [0.26-0.78] p=0.004) and less cerebral hemorrhage (2 (3%) vs 38 (11%), OR 0.29 [0.06-0.91] p=0.03).

EE were significantly reduced by ASA in *Staphylococcus coagulase* negative (0R=0.23 [0.06-0.73] p=0.01) and *Streptococcus gallolyticus* IE (OR=0.26 [0.05-0.95] p=0.04), and by ST in *Staphyloccus aureus* IE (0R=0.46 [0.2-0.99] p=0.046).

By multivariate analysis, only combined therapy was protective against EE (OR=0.3 [0.06- 0.96]).

Conclusions:

Prior aspirin combined to statin therapy reduces embolic events and hemorrhagic complications in patients with IE. Additional prospective studies are warranted to assess the benefits of both treatments in reducing morbidity and mortality in IE.

Key words

Infective endocarditis, aspirin, statin, emboli.

Aspirine, statines et réduction du risque embolique dans l'endocardite infectieuse.

RESUME

Introduction

Les évènements emboliques (EE) représentent la complication majeure de l'endocardite infectieuse (EI). Le bénéfice d'un traitement par aspirine (ASA) et statines (ST) a été démontré par des études animales, mais les conclusions des études cliniques sont discordantes. Le but de cette étude était d'évaluer le bénéfice d'une préexposition à l'aspirine et/ou aux statines sur le risque embolique chez des patients présentant une EI.

Méthode

Dans une étude rétrospective menée de 2010 à 2016, nous avons évalué l'impact d'un traitement quotidien par ASA ou ST sur les complications liées à l'EI. Le critère de jugement principal était les EE. Les critères secondaires étaient les emboles cérébraux, les EE en fonction de la bactérie impliquée, les évènements hémorragiques et la mortalité à 30 jours.

Résultats

Parmi 529 patients porteurs d'une endocardite infectieuse, à l'admission 135 (23%) patients étaient traités par ASA, 130 (24%) par ST, et 66 (12%) recevaient la combinaison des deux. Au total, 264 (50%) patients ont présenté un EE.

En comparant aux 330 patients non traités, les 66 patients recevant la combinaison ASA et ST présentaient moins d'EE (23 (34%) vs 179 (54%), OR=0.46 [0.26-0.78] p=0.004) et moins d'hémorragies cérébrales (2 (3%) vs 38 (11%), OR 0.29 [0.06-0.91] p=0.03).

Les EE étaient significativement réduits par l'ASA dans les EI à *Staphylocoque coagulase* négative (0R=0.23 [0.06-0.73] p=0.01) et les EI à *Streptocoque gallolyticus* (OR=0.26 [0.05-0.95] p=0.04), et par les ST dans les EI à *Staphylocoque aureus* (0R=0.46 [0.2-0.99] p=0.046).

En analyse multivariée, seule la thérapie combinée était protectrice contre les EE (OR=0.3 [0.06- 0.96]).

Conclusions

Une préexposition à un traitement combiné par aspirine et statine réduit les évènements emboliques ainsi que les complications hémorragiques dans l'endocardite infectieuse. Des études supplémentaires sont requises pour établir le bénéfice de ces deux traitements en termes de morbidité et de mortalité dans l'endocardite infectieuse.

Introduction

Embolic events (EE) are a major complication of Infective Endocarditis (IE) (1-2) with a high mortality and morbidity since death is the result in a quarter of patients (3-4). The incidence of systemic embolism in endocarditis ranges from 13% to 49% and remains high despite improvement in medical and surgical treatment (5-6).

Early antibiotic and surgical therapy in specific subgroups are effective in preventing embolism (7). The embolic risk is correlated to the presence and the length of vegetations. (8-9)

Since vegetation is made up of an aggregation of fibrin and platelets (10-12), it has been suggested that aspirin used early in the disease have a beneficial effect in reducing embolic events (13). Animal models have demonstrated the benefit of aspirin (ASA) in this indication. (14-15) However clinical studies have given conflicting results (16-23).

Statin (ST) therapy has pleiotropic effects, including inhibition of platelet activation and anti-inflammatory properties (24-28) and may theoretically be useful to reduce embolic risk, but data on their use in IE are very scarce. (22)

In addition, the risk of embolism may differ according to the pathogen (5), but the effect of ASA or ST according to different microorganisms has never been studied.

To evaluate the benefit of prior ASA and/or ST therapy on embolic risk, we undertook a retrospective study of a large cohort of patients with a diagnosis of IE

Methods

Data sources

This retrospective observational study was performed at La Timone Hospital, Marseille, France, in our endocarditis reference center database of IE, including adult patients hospitalized from 01/01/2010 to 31/12/2106 with a diagnosis of IE according to the modified Duke criteria (29). Diagnosis of IE was based on clinical assessment, blood cultures, causative pathogen serology, transthoracic and transesophageal echocardiography, nuclear imaging and cerebrothoracoabdominal CT scans or magnetic resonance. Antibiotic therapy was started as soon as the diagnosis of IE was suspected. The choice of antibiotic treatments (ATB) was made at the judgement of the infectious disease specialists. From the medical records, demographic information, data on pre-existing comorbidities, risk factors for IE (prosthetic valves, other cardiac abnormalities, use of injection drugs), pathogens, clinical, laboratory and echocardiographic findings, treatment (medical, surgical), chronic ASA and ST therapy, cardiac and extracardiac complications and mortality were recorded in the database by research engineers. In this study, patients with left-sided, right-sided, prosthetic valve or intracardiac device-associated IE were included but only if they were due to Staphylococcus aureus, Staphylococcus coagulase negative (S. co-neg), Streptococci or Enterococcus in the idea to carry out the bacterial analysis on sufficient size samples.

Variables

ASA therapy and ST therapy were defined as daily use of aspirin and statin, respectively, prior to admission. From this database, no information on the dosage or duration of ASA and ST therapy was available. ST therapy included atorvastatin, pravastatin, simvastatin, fluvastatin or rosuvastatin.

Embolism was defined as one or more of coronary, cerebral, splenic, renal, mesenteric, peripheral and pulmonary embolism, either symptomatic or not. A stroke consisted of a neurological deficit lasting more than 24 hours and presumed of vascular origin. (30) Hemorrhagic complications involved intracranial hemorrhages only. In-hospital mortality was defined as death occurring during the 30 first days from the start of antibiotic therapy.

End points

The Primary end point was embolic events (EE) occurring before or during hospitalization for EI. Secondary end points were cerebral emboli, the occurrence of a hemorrhagic event, 30 days mortality among the global population, and EE according to the pathogen.

Outcomes

During hospitalization all patients were observed daily in the cardiology unit by cardiologists, infectious disease specialists and had additional consultations when indicated. CT scan, systematically performed during the first week of hospitalization, was subsequently repeated if clinically indicated. Patients were systematically reviewed at one month after discharge for a follow-up consultation.

Statistical analyses

First a descriptive analysis of clinical, echocardiographic, therapeutic and biological characteristics of the included patients was performed. Quantitative variables were described as means ± standard deviations. Qualitative variables were described as numbers and percentages. These characteristics were also described and compared according to treatment groups. Quantitative variables were compared using Student t test (or Mann-Whitney test depending on the conditions of application) and qualitative variables were compared using chi-square test (or Fisher test depending on the conditions of application).

Then a bivariate analysis between these clinical and biological characteristics and the various endpoints was performed using bivariate logistic regression. Crude odds ratios were estimated with their 95% confidence intervals. Firth's (31-32) correction was applied by performing penalized-likelihood logistic regression to take into account small numbers when necessary. Finally, a multivariate analysis was performed to assess the independent associations of clinical and biological characteristics and the various endpoints. Multivariate logistic regression models were built using prognostic factors identified according to literature, and therapeutic regimen which was systematically forced in the models. Adjusted odds ratios were estimated with their 95% confidence intervals.

An exploratory analysis was performed according to the type of germ identified, by estimating crude odds ratios between therapeutic regimen and the endpoint.

All statistical analyses were performed using R software. All tests were two-sided. A value of $p<0.05$ was considered as significant.

Results

I. Patient Characteristics on Admission

From 01/01/2010 to 31/12/2106, 529 patients with a definite diagnosis of IE were included. Patient baseline characteristics are detailed in Table 1. Mean age was 65.2 ± 15 years (range 16 to 91 years) and 26% of patients were females. Left sided EI occurred in 478 patients (88.7%). A vegetation was identified in 417 patients (78.8%), it was superior to 10 mm in 252 (46.7%) patients. 135 patients (25.5%) were treated by ASA, 130 (24.5%) by ST, and 66 (12%) by both. Patients receiving ASA or ST or both therapies were older, more frequently men, with a higher incidence of hypertension, diabetes and history of myocardial infarction or prosthetic valve implantation. *Staphylococcus aureus* was the most frequently observed microorganism (Table 1), without difference according to ASA, ST or combined therapy groups. Compared with non-treated patients, ASA, ST and combined therapy were associated with significantly less valvular injury (perforation and severe regurgitation) and fewer mitral and/or tricuspid vegetations.

II. Embolic events

EE occurred in 264 (50%) patients including 242 events (46%) before and 45 (8.5%) after initiation of ATB therapy (Figure 1 and Table 3).

S. aureus infection, presence of vegetation and vegetation length > 10 mm are associated with significant higher incidence of EE (Table 2). Similarly, an history of stroke, right sided IE and IV drug use was associated with an increased embolic risk.

Conversely, older age, diabetes, atrial fibrillation, and previous myocardial infarction were paradoxically associated with a lower risk of embolism. Use of VKA was also associated with a reduced embolic risk (Table 2).

EE according to ASA and ST therapy

As compared with the 394 patients without prior ASA therapy, the 135 patients treated by ASA presented with less frequent EE (53 (39%) vs 211 (54%), OR 0.56 [0.38-0.83] p=0.004), (Table 3).

Similarly, the 130 patients treated by ST presented with less frequent EE (55 (42%) vs 209 (52%), OR 0.67 [0.45-0.99] p= 0.04) compared with the 399 patients without previous ST therapy.

The benefit was even more significant in patients with combined therapy. Since as compared with 330 patients without ST and without ASA, the 66 patients presented with less frequent EE (23 (34%) vs 179 (54%), OR 0.46 [0.26-0.78] p=0.004) (Table 3).

By multivariate analysis, only combined therapy (OR 0.5 [0.28-0.89] p=0.018) was protective against EE (Table 4).

EE occurring after initiation of ATB therapy (45/529, 8.5%) were not reduced by ASA, ST or combined therapy (Table 3 and Figure 1).

III. Secondary end points

Micro bacteriological results

In 176 patients with *Staphylococcus aureus* IE, EE occurred in 100 (56.8%) of them. Significant reduced risk of EE (OR 0.34 [0.17-0.67] p=0.002) and cerebral emboli (0R 0.46 [0.20-0.99] p=0.046) was observed in patients treated by ST. Combined therapy was also associated with less EE (OR 0.36 [0.15-0.83] p=0.02). Conversely, ASA therapy was not associated with a significant decrease of EE (OR 0.76 [0.40-1.44] p=0.4).

In 61 patients with Staphylococcus coagulase negative IE, EE occurred in 25 (40,9%) of them. ASA and combined therapy induced a significant decrease in EE, (respectively, 0R 0.23 [0.06-0.73] p=0.01 and OR 0.24 [0.04-0.98] p=0.046). Conversely, ST therapy did not induce a significant decrease in EE (OR 0,65 [0.20-1.96] p=0.4).

In 30 (38.5%) patients with *Streptococcus gallolyticus* IE, only ASA therapy induced a benefit through a significant decrease of EE (OR 0.26 [0.05-0.95] p=0.04).

Among patients with Enterococcus or Streptococcus viridans associated IE, EE occurred in 48% and 62 % of them. Surprisingly, prevalence of EE with *S. viridans* and in a lesser extend with Enterococcus was not decreased whatever the therapy (Table 5 and Figure 2).

Cerebral embolism

Among the global population, 134 (25.3%) patients had presented a cerebral embolism. History of stroke, left heart IE, vegetation length, and valvular or annular complications (valve perforation, severe regurgitation or abscess) were associated with an increased risk of cerebral embolism (Table 6). Only the combined therapy was associated with a significant decrease of cerebral emboli rate: 9/66 (13%) with combined therapy group compared to 82/330 (24%) without therapy group (0R 0.50 [0.23-0.99]) p=0.0046) (Table 3 and 6). However, this significance could not be maintained by multivariate analysis (OR 0.51 [0.23-1.04] p=0.064).

Hemorrhagic complications

Among the 529 patients, cerebral hemorrhage occurred in 53 (10%) patients. Compared with the 394 patients without prior ASA therapy, the 135 patients treated by ASA presented a trend toward a complication rate reduction (8 (5.9%) vs 45 (11.4%), OR 0.51 [0.22-1.04] p=0.06). Patients treated by ST had similar hemorrhagic complications compared with patients without previous ST therapy (9 (7%) vs 44 (11%) OR 0.62 [0.28-1.24] p=0.19).

Patients with combined therapy had significantly less hemorrhagic complications compared with patients without ST and without ASA therapy (2 (3%) vs 38 (11.5%), OR 0.29 [0.06-0.91]) p=0.03) in univariate analysis (Table 3 and 6) confirmed by multivariate analysis (Table 7). Unexpectedly, age, diabetes and use of VKA are associated with a decrease in risk of cerebral hemorrhages (Table 6).

30 days mortality

30 days after admission, 489 patients were still alive, 40 (7.6%) were died. There are no significant association with prior ASA therapy (OR 1.0 [0.46-2.01] p=0.99), prior ST therapy (OR 1.21 [0.57-2.40] p=0.6) or combined therapy (OR 1.08 [0.38-2.56] p=0.87) (Table 3). Prosthetic valve as use of VKA was associated with an increased mortality (Table 6).

Discussion

The exact role of aspirin and to a lesser extent statin in IE has been largely debated and past studies gave conflicting results. The present study was initiated to assess the association between prior therapy by ASA, ST or both with embolic events, cerebral bleeding and mortality in patients with IE. The present study although retrospective, clearly demonstrates that daily combined ASA and ST therapy prior to EI diagnosis is associated with a reduction of EE and related complications as cerebral hemorrhages.

Vegetation consists of an aggregation of fibrin, platelet and bacteria on endothelial lesions (10-12). Besides their hemostatic role, platelets have other functions, particularly in innate immunity, host defense against infection and inflammatory process (14-15) (33-34). Regarding the key role of platelets in vegetation, the effect of ASA has been evaluated through animal models and clinical trials (12). Numerous *in vitro* models have demonstrated that ASA had pleiotropic effects on platelet-bacteria interactions (35). In parallel, animal models have demonstrated the benefit of ASA trough reducing of weight vegetations and their sterilization (12) (16) (36-37). However, experimental models differed according to the studies notably the dose used.

The supposed benefits of ST therapy include a combination of immunomodulatory, anti-inflammatory and antiplatelet effects. It is established that statins, as a manifestation of their pleiotropic effects, exert an antiplatelet effect (24). Indeed, ST use is associated with a reduced thrombosis burden and diminished platelet activity, which have been demonstrated in both animal models and in vitro studies (25-26). Moreover, statin has been shown to inhibit the inflammatory response to *Staphylococcus aureus* toxin in rats and clinical trials in atherosclerosis have demonstrated a positive influence of statins on endothelial function (38-40).

In a retrospective cohort of patients with a diagnosis of IE, Anavekar et al also demonstrated that EE occurred significantly less among those who had received daily aspirin prior IE diagnosis (18). By opposite, Pepin et al observed in a small retrospective study that chronic antiplatelet therapy was not associated with a significantly lower risk of major embolism (19). Surprisingly, Anavekar et al did not confirm in a second study the benefit of ASA on native valves (22). The authors explained this discrepancy through many hypothesis notably aspirin resistance and higher proportion of patients with severe comorbidities. In another model of clinical trial, Chan et al excluded all patients with prior ASA therapy and

demonstrated that once the diagnosis is made, late adjunctive ASA therapy are not associated with less EE according with animal models of experimental endocarditis in which antiplatelet therapy was started prior to infection onset (12).

Our study failed to show the effectiveness of ASA, ST or combined therapy once the antibiotic beginning, may be by a lack of power or by the underlying physiopathological mechanism and need additional data (figure 1).

Another main result of this study is the benefit of ST therapy prior IE. Although patients treated by ST were older and presented more comorbidity, EE were significantly less frequent compared to patients without ST. The benefit of ST in embolisms prevention has already been demonstrated on native valves (22). In another clinical settings, statin has demonstrated their interest (28). Indeed, ST presented anti-inflammatory, anti-platelets and anti-infectious effect (24-27) (38-39).

For the first time, we demonstrated that patients treated by ASA and ST presented a lower risk of embolic events notably cerebral embolisms with a decrease in cerebral bleeding. Furthermore, our results demonstrated that reduction of EE induced by therapies such as ASA or ST differs according to causative microorganisms. Indeed, best results seemed to be achieved on the *Staphylococcus aureus* for the statin therapy and on the *Staphylococcus coagulase* negative and *Strepococcus gallolyticus* for the ASA therapy. Strengthening the Pepin's report that "the effect of chronic antiplatelet therapy appears to be more pronounced in patients infected with pathogen other than *Staphylococcus aureus*" (19). Hence we could imagine an adaptation of treatment according to microbiologic findings.

Although TAHA, then SNYGG-MARTIN found a decrease of vegetation growth in response to ASA, we did not confirm these observation in our study (16)(23). More precisely, we had not evaluated the growth of length vegetation but the maximal size of vegetation which was similar between all groups of patients whatever the treatment.

We choose to include both native and prosthetic valve endocarditis in this trial. Indeed, the risk of excessive bleeding associated with the combined use of anticoagulants and aspirin in patients with mechanical heart valves may be different than native valve. Despite that, cerebral hemorrhages were not increased in patients treated as well by aspirin or statin. It is even necessary to underline once again a significant decrease of the risk associated to combined therapy according to Eisen data, which showed a negative association between

hemorrhagic strokes and chronic ASA therapy (OR 0.43, [0.18-1.01], p=0.05) (21). Otherwise, in term of safety, extensive clinical trial data have previously demonstrated that the risks of major bleeding episodes that are attributable to low-dose aspirin therapy are only 2.6% (41-42).

Although aspirin and statin reduced significantly embolic events and cerebral hemorrhages, we did not demonstrate a reduction of mortality at 30 days. This can be explained, in part, by an increased number of comorbid conditions that characterized patients who received these therapies. Administration of combined therapy was more common among older patients and those with various comorbidities that are themselves strongly associated with mortality. This absence of benefit was also observed by Anavekar during the first 6 months after diagnostic of IE whatever the treatment (18) (22).

Limits

This study had several limitations. First, it is a retrospective observational study. Our findings are based on data collected in a data-base and accuracy of the patient, as drug compliance cannot be guaranteed. Second, this was a single-center study. Unfortunately our study was limited by a lack of specific information on either the dose or duration of ASA therapy in patients prior to and after their diagnosis of IE, but a higher dose than 160mg/day was rarely indicated in clinical practice. We did not realize an assessment of the differential effects of aspirin, statin or both in native versus prosthetic valve endocarditis regarding the modest sample size. Finally, outcomes were measured only during the hospital period and at one month during the follow-up consultation, without long-term follow up assessment.

Conclusion

Our study was the first to evaluate the association of ASA and ST in patients with IE. Our results highlighted the benefit of this bi-therapy through a significant reduction of EE, less cerebral embolism, less cerebral hemorrhages and a similar mortality. Moreover, we defined the interest of treatment according to species.

Low-dose aspirin with statin therapy to prevent embolic morbi-mortality in infective endocarditis merits further evaluation. A definitive answer on efficacy would require a large multicenter clinical trial. The question remains open whether immediate administration of low-dose ASA and ST after EI diagnosis, when vegetations and valvular damages are already present, will still be beneficial. Finally, the type of offending organism may have different properties and these observational data call additional studies.

Bibliography

1. Netzer RO, Zollinger E, Seiler C, Cerny A. Infective endocarditis: clinical spectrum, presentation and outcome. An analysis of 212 cases 1980-1995. Heart Br Card Soc. 2000; 84: 25-30.

2. Castillo JC, Anguita MP, Ramírez A, Siles JR, Torres F, Mesa D, et al. Long term outcome of infective endocarditis in patients who were not drug addicts: a 10 year study. Heart Br Card Soc. 2000; 83: 525-30.

3. Delahaye JP, Poncet P, Malquarti V, Beaune J, Garé JP, Mann JM. Cerebrovascular accidents in infective endocarditis: role of anticoagulation. Eur Heart J. 1990; 11: 1074-8.

4. Heiro M, Nikoskelainen J, Engblom E, Kotilainen E, Marttila R, Kotilainen P. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med. 2000; 160: 2781-7.

5. Thuny F, Di Salvo G, Disalvo G, Belliard O, Avierinos J-F, Pergola V, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. Circulation. 2005; 112: 69-75.

6. Hoen B, Alla F, Selton-Suty C, Béguinot I, Bouvet A, Briançon S, et al. Changing profile of infective endocarditis: results of a 1-year survey in France. JAMA. 2002; 288: 75-81.

7. Dickerman SA, Abrutyn E, Barsic B, Bouza E, Cecchi E, Moreno A, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J.2007 ; 154: 1086-94.

8. Di Salvo G, Habib G, Pergola V, Avierinos JF, Philip E, Casalta JP, et al. Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol. 2001; 37: 1069-76.

9. Sanfilippo AJ, Picard MH, Newell JB, Rosas E, Davidoff R, Thomas JD, et al. Echocardiographic assessment of patients with infectious endocarditis: prediction of risk for complications. J Am Coll Cardiol. 1991; 18: 1191-9.

10. Calderone RA, Rotondo MF, Sande MA. Candida albicans endocarditis: ultrastructural studies of vegetation formation. Infect Immun. 1978; 20: 279-89.

11. Bayer AS, Sullam PM, Ramos M, Li C, Cheung AL, Yeaman MR. Staphylococcus aureus induces platelet aggregation via a fibrinogen-dependent mechanism which is independent of principal platelet glycoprotein IIb/IIIa fibrinogen-binding domains. Infect Immun. 1995; 63: 3634-41.

12. Kupferwasser LI, Yeaman MR, Shapiro SM, Nast CC, Sullam PM, Filler SG, et al. Acetylsalicylic acid reduces vegetation bacterial density, hematogenous bacterial dissemination, and frequency of embolic events in experimental Staphylococcus aureus endocarditis through antiplatelet and antibacterial effects. Circulation. 1999; 99: 2791-7.

13. Homma S, Grahame-Clarke C. Toward reducing embolic complications from endocarditis. J Am Coll Cardiol. 2003; 42: 781-3.

14. Kupferwasser LI, Yeaman MR, Nast CC, Kupferwasser D, Xiong Y-Q, Palma M, et al. Salicylic acid attenuates virulence in endovascular infections by targeting global regulatory pathways in *Staphylococcus aureus*. J Clin Invest. 2003; 112: 222-33.

15. Nicolau DP, Tessier PR, Nightingale CH. Beneficial effect of combination antiplatelet therapy on the development of experimental Staphylococcus aureus endocarditis. Int J Antimicrob Agents. 1999; 11: 159-61.

16. Taha TH, Durrant SS, Mazeika PK, Nihoyannopoulos P, Oakley CM. Aspirin to prevent growth of vegetations and cerebral emboli in infective endocarditis. J Intern Med. 1992; 231: 543-6.

17. Chan K-L, Dumesnil JG, Cujec B, Sanfilippo AJ, Jue J, Turek MA, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. J Am Coll Cardiol. 2003; 42: 775-80.

18. Anavekar NS, Tleyjeh IM, Anavekar NS, Mirzoyev Z, Steckelberg JM, Haddad C, et al. Impact of prior antiplatelet therapy on risk of embolism in infective endocarditis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2007; 44: 1180-6.

19. Pepin J, Tremblay V, Bechard D, Rodier F, Walker C, Dufresne D, et al. Chronic antiplatelet therapy and mortality among patients with infective endocarditis. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2009; 15: 193-9.

20. Chan K-L, Tam J, Dumesnil JG, Cujec B, Sanfilippo AJ, Jue J, et al. Effect of long-term aspirin use on embolic events in infective endocarditis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008; 46: 37-41.

21. Eisen DP, Corey GR, McBryde ES, Fowler VG, Miro JM, Cabell CH, et al. Reduced valve replacement surgery and complication rate in *Staphylococcus aureus* endocarditis patients receiving acetyl-salicylic acid. J Infect. 2009; 58: 332-8.

22. Anavekar NS, Schultz JC, De Sa DDC, Thomas JM, Lahr BD, Tleyjeh IM, et al. Modifiers of symptomatic embolic risk in infective endocarditis. Mayo Clin Proc. 2011; 86: 1068-74.

23. Snygg-Martin U, Rasmussen RV, Hassager C, Bruun NE, Andersson R, Olaison L. The relationship between cerebrovascular complications and previously established use of antiplatelet therapy in left-sided infective endocarditis. Scand J Infect Dis. 2011; 43: 899-904.

24. Serebruany VL, Miller M, Pokov AN, Malinin AI, Lowry DR, Tanguay J-F, et al. Effect of statins on platelet PAR-1 thrombin receptor in patients with the metabolic syndrome (from the PAR-1 inhibition by statins [PARIS] study). Am J Cardiol. 2006; 97: 1332-6.

25. Schäfer K, Kaiser K, Konstantinides S. Rosuvastatin exerts favourable effects on thrombosis and neointimal growth in a mouse model of endothelial injury. Thromb Haemost. 2005; 93: 145-52.

26. Undas A, Brozek J, Musial J. Anti-inflammatory and antithrombotic effects of statins in the management of coronary artery disease. Clin Lab. 2002; 48: 287-96.

27. Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. Nat Rev Drug Discov. 2005; 4: 977-87.

28. Tleyjeh IM, Kashour T, Hakim FA, Zimmerman VA, Erwin PJ, Sutton AJ, et al. Statins for the prevention and treatment of infections: a systematic review and meta-analysis. Arch Intern Med. 2009; 169: 1658-67.

29. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2000; 30:633-8.

30. Hatano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ. 1976; 54: 541-53.

31. Firth D. 'Bias reduction of maximum likelihood estimates'. Biometrika. 1995; 82: 667-667.

32. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med. 2002; 21:2409-19.

33. Farber BF, Wolff AG. The use of nonsteroidal antiinflammatory drugs to prevent adherence of Staphylococcus epidermidis to medical polymers. J Infect Dis. 1992; 166:861-5.

34. Polonio RE, Mermel LA, Paquette GE, Sperry JF. Eradication of biofilm-forming Staphylococcus epidermidis (RP62A) by a combination of sodium salicylate and vancomycin. Antimicrob Agents Chemother. 2001; 45: 3262-6.

35. Herrmann M. Salicylic acid: an old dog, new tricks, and staphylococcal disease. J Clin Invest. 2003;112: 149-51.

36. Johnson CE, Dewar HA. Effect of sulphinpyrazone on the development of experimental endocardial vegetations. Cardiovasc Res. 1982; 16: 657-62.

37. Nicolau DP, Marangos MN, Nightingale CH, Quintiliani R. Influence of aspirin on development and treatment of experimental Staphylococcus aureus endocarditis. Antimicrob Agents Chemother. 1995; 39: 1748-51.

38. Pruefer D, Makowski J, Schnell M, Buerke U, Dahm M, Oelert H, et al. Simvastatin inhibits inflammatory properties of Staphylococcus aureus alpha-toxin. Circulation. 2002;106: 2104-10.

39. Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. Blood. 1998; 91: 3527-61.

40. Laufs U, Liao JK. Post-transcriptional regulation of endothelial nitric oxide synthase mRNA stability by Rho GTPase. J Biol Chem. 1998; 273:24266-71.

41. Dutch TIA Trial Study Group, van Gijn J, Algra A, Kappelle J, Koudstaal PJ, van Latum A. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. N Engl J Med. 1991; 325:1261-6.

42. Weinberger J. Adverse effects and drug interactions of antithrombotic agents used in prevention of ischaemic stroke. Drugs. 2005; 65: 461-71.

ANNEXES

Table 1 : Baseline characteristics in 529 cases of IE, with and without ASA therapy, ST therapy and combined therapy.

	Global population (n=529)	ASA user (n=135)	ASA non users (n=394)	P	ST users (n=130)	ST non users (n=399)	P	ASA&ST users (n=66)	ASA&ST non users (n=463)	P
Clinical data										
Female sex (n, %)	136(25.7%)	13.3%	29.9%	**.00**	19.2%	27.8%	.05	12.1%	30.6%	**.00**
Age(Y) mean	65 ±15	67±11	64±16	**.02**	70±10	63±16	**.00**	69±9	63±17	**.03**
Weight (kg)	72±16	76±16	70±16	**.00**	77±16	71±18 p	**.00**	82±17	70±16	**.00**
Diabetes (n, %)	114(21.5%)	29.8%	18.9%	**.01**	37.5%	16.5%	**.00**	38.5%	15.5%	**.00**
Smoking (n, %)	178(33%)	50%	42%	.1	45.1%	43.8%	.08	56.6%	43.9%	.1
Hemodialysis	16(3%)	5.2%	2.3%	.1	0.8%	3.8%	.1	1.5%	2.7%	.9
Myocardial infarct	56(10.6%)	29.6%	4.1%	**.00**	26.9%	5.3%	**.00**	37.9%	1.8%	**.00**
History of stroke	38(7.2%)	8.9%	6.6%	**.04**	6.9%	7.3%	.9	4.6%	6.1%	.8
HTA	222(42%)	59.9%	36%	**.00**	68.5%	33.3%	**.00**	68.2%	29.7%	**.00**
Atrial fibrillation	151(28.5%)	31.3%	30.5%	.9	39%	27.5%	**.02**	31.8%	27.3%	.5
Hist. of malignancy	90(17%)	16.3%	17.3%	.08	19.2%	16.4%	.4	16.6%	16.4%	.9
IV drug use	49(9.2%)	2.9%	11.4%	**.00**	0.8%	12%	**.00**	1.5%	13.6%	**.01**
Localization										
Ao valve invol.	267(50.4%)	50.4%	50.5%	.9	50.8%	50.4%	.09	47%	49.7%	.7
Mi valve invol.	211(39.9%)	30.4%	43.1%	**.01**	30%	43.1%	**.01**	22.2%	44.6%	**.00**
Tric valve invol.	50(9.4%)	9.6%	9.4%	.09	6.1%	10.5%	.14	7.6%	10.3%	.5
Prosthetic valve	144(27.2%)	43.7%	21.6%	**.00**	30%	26.3%	.4	31.8%	20.3%	**.04**
Echocardiography										
Vegetation	417(78.8%)	74.1%	80.5%	.1	76.9%	79.5%	.5	72.7%	80.3%	.2
Ao veget (n, %)	187(35.3%)	34.8%	35.5%	.9	32%	36.3%	.4	28.8%	35.4%	.3
Mi veget(n, %)	165(31.2%)	30.4%	43.1%	**.02**	24.6%	33.3%	.06	18.2%	34.6%	**.01**
Tri veget (n, %)	40(7.6%)	5.2%	8.4%	.2	2.3%	9.3%	**.01**	3%	9.7%	**.01**
Veget lenght (mm)										
Aortic valve	11±6	9.4±5	12±7	**.02**	11±6	11±6	.07	10±5	12±7	.2
Mitral valve	14±8	15±8	14±8	.4	15±8	13.±7	.2	17±9	14±8	.1
Tricupsid valve	20±8	24±8	19±8	.2	23±10	19±8	.6	27±11	19±9	.2
LVEF %	58±11	54±13	59±9	**.00**	54±13	59±10	**.00**	52±14	60±9	**.00**
Severe regurgitat.	257(48.5%)	32.6%	54.1%	**.00**	36.9%	52.4%	**.00**	28.8%	55.7%	**.00**
Valve perforation	147(27.8%)	14.8%	32.4%	**.00**	18.6%	30.9%	**.01**	13.6%	34%	**.00**
Abscess	24(4.5%)	6.7%	3.8%	.2	6.1%	4%	.3	4.6%	3%	.5
Complete AV block	29(5.5%)	6.1%	5.5%	.08	7.1%	5.2%	.4	9.5%	5.6%	**.03**
Treatment										
Use of VKA	139(26.5%)	25.8%	26.8%	.8	37%	23.7%	**.00**	28.1%	23.1%	.4
Use of aspirin	135(25.5%)				50.8%	17.3%	**.00**			
Use of statin	130(24.5%)	12%	7.2%	**.00**						
Biology										
Hemoglobin (g/L)	108±18	111±17	107±18	.4	111±17	108±18	**.04**	111±15	107±18	**.04**
Platelets (G/L)	250±121	248±118	251±121	.8	236±106	255±125	.1	245±112	256±125	.5
CRP (mg/L)	112±97	109±101	113±96	.7	113±102	111±95	.8	121±111	114±97	.6
Creatinin (µmol.L)	131±116	157±137	122±107	**.00**	136±84	129±125	.5	152±88	122±112	**.04**
BNP (ng.L)	546±921	639±1106	514±848	.2	648±1149	512±890	.2	716±1420	501±856	.1
Bacteriology										
Staph aureus	176(33.2%)	38.5%	31.5%	.1	35.4%	35.6%	.6	40.5%	31.8%	.1
Staph CoNeg	61(11.5%)	15.6%	10.1%	.1	13.9%	10.8%	.6	18.2%	10.3%	.1
Strepto Gallolyticus	78(14.7%)	10.4%	16.2%	.1	14.6%	14.8%	.6	10.6%	15.8%	.1
Strepto Viridans	87(16.4%)	8.9%	19%	.1	12.3%	18.8%	.6	9.1%	19.7%	.1
Other strepto	23(4.9%)	4.4%	4.3%	.1	3.1%	4.8%	.6	3.1%	4.6%	.1
Enterococcus	104(19.6%)	22.2%	18.8%	.1	20.8%	19.3%	.6	18.2%	17.9%	.1

HTA = high blood pressure, IV = intra-veinous, Ao = aortic, Mi = mitral, Tric = tricuspid, LVEF = left ventricular ejection fraction, AV = atrio-ventricular, VKA = vitamin k antagonist, CRP = C-reactive protein, BNP = B-type Natriuretic Peptide.

Table 2 clinical, echocardiographic and laboratory findings in 529 cases of IE with and without EE

	Global pop. (n=529)	EE (n=264)	no EE (n=265)	IC 95%	OR	P
Clinical data (n, %)						
Female sex	136(25.7%)	28.8%	22.6%	0.49-1.07	0.3	0.1
Age (Y), mean**± SD**	65±15	62±16	68±13	0.96-0.98	0.97	**0.000**
Diabetes	114(21.5%)	17.9%	25.4%	0.42-0.98	0.64	**0.038**
Smoking	178(33%)	47.7%	40.9%	0.89-1.95	1.32	0.17
Hemodialysis	16(3%)	4.2%	1.9%	0.80-6.54	2.15	0.13
Myocardial infarct	56(10.6%)	7.6%	13.6%	0.29-0.92	0.53	**0.025**
History of stroke	38(7.2%)	9.8%	4.5%	1.1-4.66	2.25	**0.018**
HTA	222(42%)	38.6%	45.2%	0.54-1.08	0.76	0.12
Atrial fibrillation	151(28.5%)	23.4%	37.9%	0.34-0.74	0.50	**0.000**
IV drug use	49(9.2%)	13.3%	5.3%	1.45-5.22	2.68	**0.001**
Localization (n, %)						
Ao valve invol.	267(50.4%)	53.4%	47.5%	0.90-1.78	1.26	0.18
Mi valve invol.	211(39.9%)	41.3%	38.5%	0.79-1.59	1.12	0.51
Tric valve invol.	50(9.4%)	14.0%	4.9%	1.65-6.09	3.08	**0.000**
Prosthetic valve	144(27.2%)	22.7%	31.7%	0.43-0.93	0.64	**0.020**
Echocardiograph (n, %)						
Vegetation	417(78.8%)	86.7%	79.9%	1.72-4.17	2.66	**0.000**
Veget lenght						
10 to 15mm	11±6	22.4%	17.7%	1.31-3.21	2.04	**0.001**
>15mm	14±8	36.2%	15.1%	2.5-6.0	3.84	**0.000**
LVEF %	58±11	59±9	56±12	1.01-1.05	1.03	**0.000**
Treatment (n, %)						
Use of VKA	139(26.5%)	21.4%	31.7%	0.40-0.87	0.59	**0.007**
Use of aspirin	135(25.5%)	20.1%	30.9%	0.38-0.83	0.56	**0.004**
Use of statin	130(24.5%)	20.8%	28.3%	0.45-0.99	0.67	**0.046**
Aspirin and statin	66(12.5%)	8.71%	16.23%	0.26-0.78	0.46	**0.004**
Biology						
Hemoglobin (g/L)	108±18	105±17	111±19	0.97-0.99	0.98	**0.000**
Platelets (G/L)	250±121	246±126	254±115	1.00-1.00	1.00	0.47
CRP (mg/L)	112±97	128±97	96±94	1.00-1.00	1.00	**0.002**
S. aureus (n, %)	176(33.2%)	37.9%	28.7%	1.05-2.18	1.51	**0.024**

EE= embolic events before or during hospitalization, HTA = high blood pressure, IV = intra-venous, Ao = aortic, Mi = mitral, Tric = tricuspid, LVEF = left ventricular ejection fraction, VKA = vitamin k antagonist, CRP = C-reactive protein.

Table 3 : Complications in 529 cases of IE , with and without ASA, ST and combined therapy

	ASA				ST				ASA+ST			
	No (n=394)	**Yes (n=135)**	**p**	**OR (IC) 95%**	**No (n=399)**	**Yes (n=130)**	**p**	**OR (IC) 95%**	**No (n=330)**	**Yes (n=66)**	**p**	**OR (IC) 95%**
EE before ATB therapy (n-%)	197-50%	45-33%	**0.001**	0.5 (0.33-0.75)	193-48.4%	49-37.6 %	**0.033**	0.65 (0.43-0.97)	169-51.2 %	21-31.8 %	**0.004**	0.45 (0.25-0.78)
EE after beginning of ATB therapy (n-%)	37-9.4 %	8-5.9%	0.2	0.63 (0.29-1.35)	38-9.5 %	7-5.4 %	0.1	0.55 (0.25-1.23)	32-9.7 %	2-3%	0.1	0.30 (0.07-1.28)
Total emboli (n-%)	211-54%	53-39.2%	**0.004**	0.56 (0.38-0.83)	209-52.4%	55-42.3%	**0.046**	0.67 (0.45-0.99)	179-54%	23-34 %	**0.004**	0.46 (0.26-0.78)
Cerebral emboli (n- %)	102-25.9%	32-23%	0.6	0.90 (0.56-1.40)	105-26%	29-22%	0.37	0.81 (0.50-1.28)	82-24%	9-13%	**0.0046**	0.50 (0.23-0.99)
Cerebral hemorrhages (n- %)	45-11%	8-6%	0.06	0.51 (0.22-1.04)	44-11%	9-7%	0.18	0.62 (0.28-1.24)	38-11.5%	2-3%	**0.003**	0.29 (0.06-0.91)
30 Day mortality (n-%)	30-7.6%	10-7.4%	0.99	1 (0.46-2.0)	29-7.3%	11-8.4%	0.60	1.2 (0.57-2.4)	24-7.8%	5-7.6%	0.82	1.12 (0.38-2.75)

ATB = antibiotic

Table 4: EE by multivariate analysis

	OR	IC 95%	p
AGE	0.98	0.97-0.99	**.002**
VEGET LENGTH (10 to 15mm)	1.88	1.19-2.99	**.01**
VEGET LENGHT (> 15mm)	3.51	2.25-5.55	**.0000**
STAPH AUREUS	1.34	0.91-2.00	.1
AF	0.74	0.47-1.16	.2
ASA only (n=69)	0.74	0.42-1.27	.3
ST only (n=64)	1.08	0.62-1.89	.8
ASA and ST (n=66)	0.50	0.28-0.89	**.018**

AF = atrial fibrillation

Table 5: Association between ASA,ST or combined therapy and EE according to causative bacteria.

	N	EE	%	OR	IC	P
STAPH AUREUS IE						
No ASA + No ST	105	66	62.9%	1		
ASA	52	27	51.9%	0.76	0.39-1.44	0.4
ST	46	17	36.9%	0.34	0.17-1.67	**0.002**
COMBINED THERAPY	27	10	37.0%	0.36	0.15-0.83	**0.017**
STAPH COAG NEG IE						
No ASA + No ST	34	17	50.0%			
ASA	21	4	19.0%	0.23	0.06-0.73	**0.012**
ST	18	6	33.3%	0.65	0.20-1.96	0.5
COMBINED THERAPY	12	2	16.7%	0.24	0.04-0.98	**0.047**
STRETPO GALLOLYTICUS IE						
No ASA + No ST	52	22	42.3%	1		
ASA	14	2	14.3%	0.26	0.05-0.95	**0.041**
ST	19	8	42.1%	1.23	0.43-3.44	0.7
COMBINED THERAPY	7	2	28.6%	0.62	0.10-2.83	0.5
STREPTO VIRIDANS IE						
No ASA + No ST	65	40	61.5%	1		
ASA	12	8	66.7%	1.20	0.36-4.48	0.8
ST	16	10	62.5%	1.00	0.34-3.10	0.9
COMBINED THERAPY	6	4	66.7%	1.13	0.23-6.89	0.9
ENTEROCOCCUS IE						
No ASA + No ST	59	30	50.1%	1		
ASA	30	11	36.7%	0.53	0.22-1.24	0.1
ST	27	13	48.1%	1.01	0.42-2.39	0.9
COMBINED THERAPY	12	4	33.3%	0.51	0.13-1.73	0.3

TABLE 6: secondary outcomes and baseline characteristics

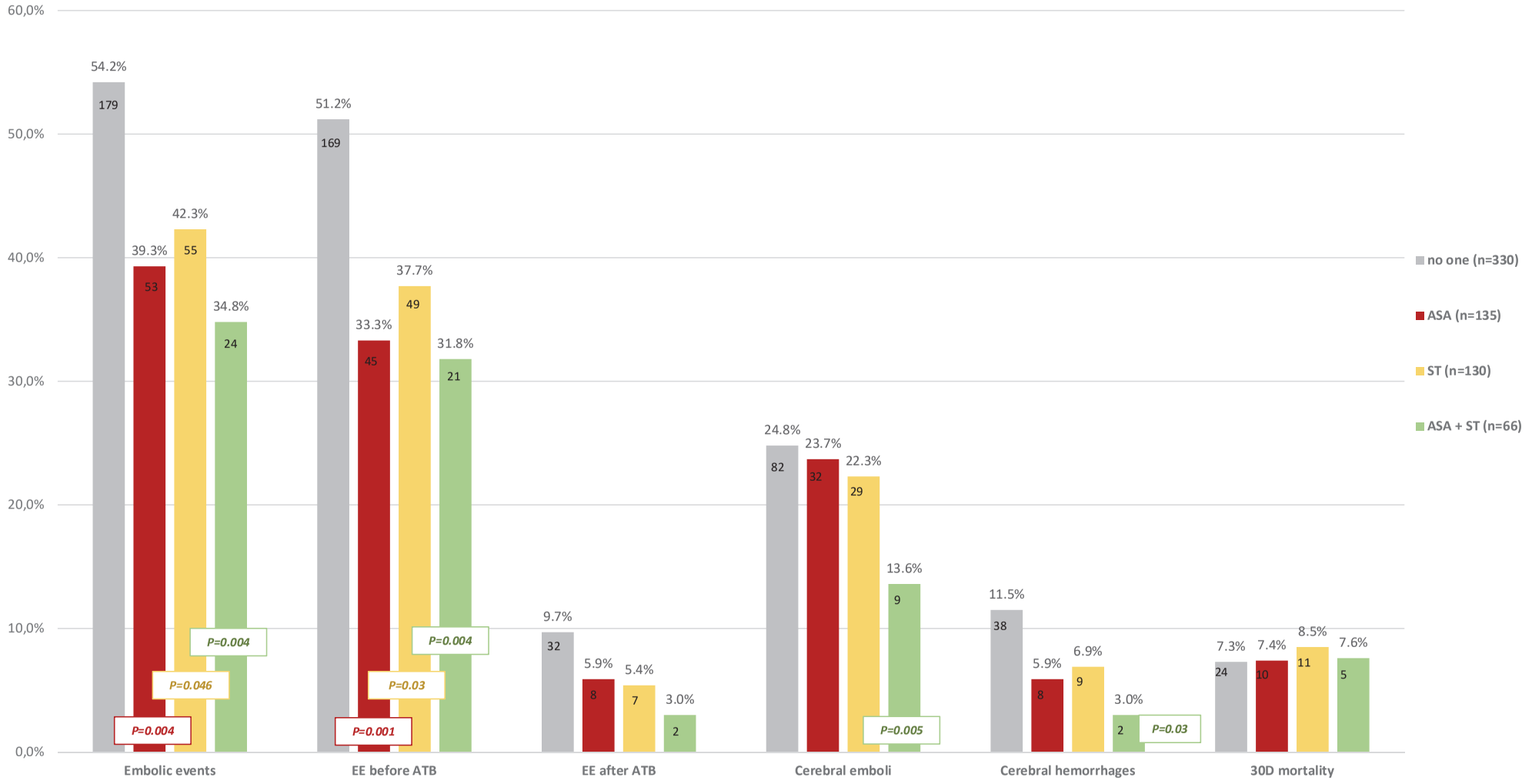
	Cerebral emboli N=134			**Hemorrhagic complications N=53**			**30D mortality N=40**		
Clinical data	IC	OR	p	IC	OR	P	IC	OR	P
Female sex	0.54-1.29	0.83	0.41	0.42-1.45	0.77	0.40	0.40-1.61	0.78	0.48
Age mean	0.98-1.01	0.99	0.28	0.97-1.00	0.98	**0.047**	1.00-1.05	1.02	0.07
Diabetes	0.51-1.35	0.84	9.48	0.10-0.72	0.30	**0.005**	0.79-3.25	1.65	0.17
Smoking	0.50-1.28	0.8	0.35	0.39-1.45	0.76	0.41	0.37-1.56	0.78	0.48
Hemodialysis	0.46-3.85	1.42	0.51	0.00-1.98	0.26	0.24	0.41-7.30	2.13	0.33
Myocardial infarct	0.25-1.10	0.56	0.09	0.15-1.48	0.055	0.26	0.62-3.76	1.64	0.29
History of stroke	1.49-5.65	2.91	**0.002**	0.52-3.61	1.50	0.42	0.50-4.21	1.63	0.38
HTA	0.64-1.41	0.95	0.81	0.38-1.24	0.69	0.22	0.93-3.37	1.76	0.08
Atrial fibrillation	0.65-1.57	1.01	0.95	0.40-1.49	0.79	0.48	0.99-3.76	1.94	0.05
Hist of malignancy	0.56-1.59	0.96	0.87	0.19-1.19	0.52	0.13	0.29-1.72	0.73	0.49
IV drug use	0.20-1.03	0.49	0.061	0.52-3.09	1.36	0.50	0.38-3.06	1.20	0.07
Localization									
Ao valve invol.	1.11-1.45	1.64	**0.013**	1.23-4.11	2.21	**0.007**	0.71-2.60	1.35	0.36
Mi valve invol.	1.32-2.92	1.97	**0.001**	0.55-1.76	0.99	0.98	0.73-2.66	1.40	0.30
Tric valve invol.	0.24-1.14	0.56	0.11	0.03-0.95	0.25	**0.039**	0.023-2.39	0;87	0.81
Prosthetic valve	0.77-1.83	1.20	0.42	0.56-1.98	1.08	0.81	1.22-4.51	2.36	**0.011**
Echocardiography									
Vegetation	1.35-4.19	2.31	**0.001**	0.73-3.44	1.50	0.28	0.66-3.83	1.47	0.36
Veget lenght									
10 to 15mm	1.25-3.45	2.09	**0.05**	0.62-2.80	1.36	0.43	0.11-1.18	0.42	0.10
>15mm	1.66-4.18	2.63	**0.000**	0.99-3.57	1.88	0.05	0.86-3.36	1.71	0.13
LVEF	1.00-1.04	1.02	**0.02**	0.99-1.06	1.02	0.14	0.96-1.01	0.98	0.17
Severe regurgitat.	1.35-4.19	1.68	**0.01**	1.47-4.97	2.64	**0.001**	0.36-1.32	0.69	0.26
Valve perforation	1.05-2.44	1.61	**0.02**	1.01-3.24	1.82	**0.047**	0.41-1.76	1.71	0.73
Absess	1.15-5.95	2.64	**0.02**	0.90-6.76	2.66	0.07	0.85-7.65	2.82	0.08
Complete AVB	0.73-3.53	1.65	0.22	0.05-1.75	0.44	0.28	0.99-7.35	2.94	0.05
Treatment									
Use of VKA	0.43-1.54	0.99	0.97	0.21-0.99	0.48	**0.045**	1.18-4.44	2.31	**0.014**
Use of aspirin	0.56-1.40	0.90	0.64	0.22-1.04	0.51	0.06	0.46-2.01	1.00	0.99
Use of statin	0.50-1.28	0.81	0.37	0.00-1.68	0.22	0.19	0.57-2.40	1.21	0.60
Aspirin and statin	0.23-0.99	0.50	**0.046**	0.06-0.91	0.29	**0.031**	0.38-2.75	1.12	0.82
Biology									
Hemoglobin	0.98-1.00	0.99	0.13	0.98-1.02	1.00	0.96	0.99-1.03	1.01	0.22
Platelets	1.00-1.00	1.00	**0.027**	1.00-1.00	1.00	0.15	1.00-1.00	1.00	0.54
CRP	1.00-1.00	1.00	**0.006**	1.00-1.00	1.00	0.19	1.00-1.01	1.01	**0.000**
Creatinin	1.00-1.00	1.00	0.37	0.99-1.00	1.00	0.12	1.00-1.00	1.00	0.12
BNP	1.00-1.00	1.00	0.67	1.00-1.00	1.00	0.40	1.00-1.00	1.00	**0.003**
S. aureus	1.05-2.36	1.58	**0.028**	1.18-3.69	2.09	**0.01**	0.89-3.27	1.72	0.10

HTA = high blood pressure, IV = intra venous, Ao = aortic, Mi = mitral, Tric = tricuspid, LVEF = left ventricular ejection fraction,
AV = atrioventricular, VKA = vitamin k antagonist, CRP = C-reactive protein, BNP = B-type Natriuretic Peptide.

Table 7: 53 cerebral hemorrhagic complications: multivariate analysis

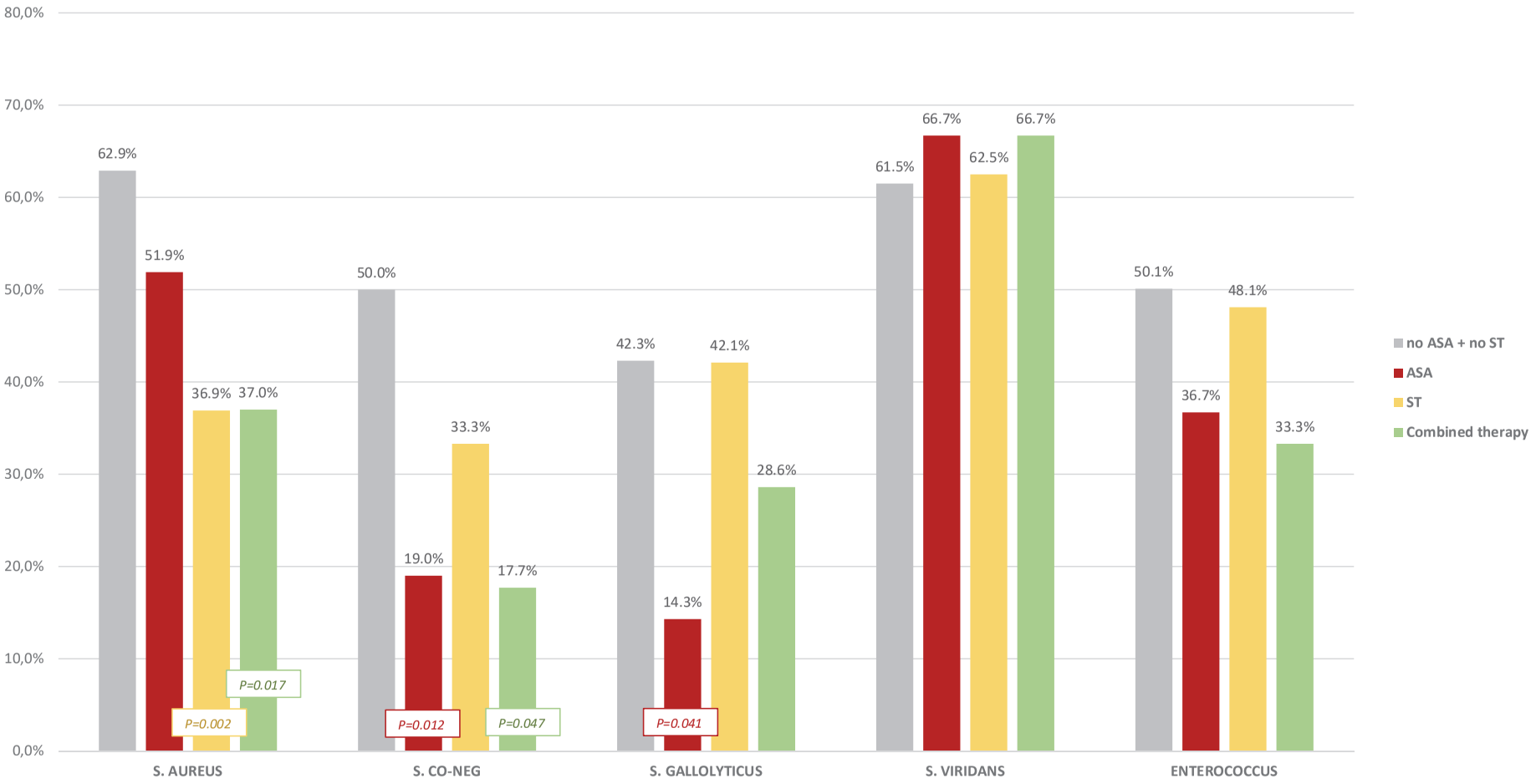
	OR	IC 95%	p
AGE	0.99	0.97-1.01	0.25
VEGETATION LENGTH : 10 to 15 mm	1.29	0.59-2.70	0.51
VEGETATION LENGTH : sup 15 mm	1.62	0.83-3.12	0.16
STAPH AUREUS	1.91	1.06-3.44	**0.033**
ATRIAL FIBRILLATION	1.21	0.57-2.45	0.62
ST or ASA	0.94	0.46-1.80	0.85
ST and ASA	0.30	0.06-0.96	**0.041**

Figure 1 . Outcomes according to medical therapy



Embolic events = total emboli, ASA = aspirin, ST = statin, (Chi square test or fisher test)

Figure 2. EE according to causative bacteria and treatment by ASA, ST or combined therapy.



ASA = aspirin, ST = statin, (Chi square test or fisher test)

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les moeurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

ORDRE NATIONAL DES MÉDECINS
Conseil National de l'Ordre

RESUME

Introduction

Les évènements emboliques (EE) représentent la complication majeure de l'endocardite infectieuse (EI). Le bénéfice d'un traitement par aspirine (ASA) et statines (ST) a été démontré par des études animales, mais les conclusions des études cliniques sont discordantes. Le but de cette étude était d'évaluer le bénéfice d'une préexposition à l'aspirine et/ou aux statines sur le risque embolique chez des patients présentant une EI.

Méthode

Dans une étude rétrospective menée de 2010 à 2016, nous avons évalué l'impact d'un traitement quotidien par ASA ou ST sur les complications liées à l'EI. Le critère de jugement principal était les EE. Les critères secondaires étaient les emboles cérébraux, les EE en fonction de la bactérie impliquée, les évènements hémorragiques et la mortalité à 30 jours.

Résultats

Parmi 529 patients porteurs d'une endocardite infectieuse, à l'admission 135 (23%) patients étaient traités par ASA, 130 (24%) par ST, et 66 (12%) recevaient la combinaison des deux. Au total, 264 (50%) patients ont présenté un EE.

En comparant aux 330 patients non traités, les 66 patients recevant la combinaison ASA et ST présentaient moins d'EE (23 (34%) vs 179 (54%), OR=0.46 [0.26-0.78] p=0.004) et moins d'hémorragies cérébrales (2 (3%) vs 38 (11%), OR 0.29 [0.06-0.91] p=0.03).

Les EE étaient significativement réduits par l'ASA dans les EI à *Staphylocoque coagulase* négative (0R=0.23 [0.06-0.73] p=0.01) et les EI à *Streptocoque gallolyticus* (OR=0.26 [0.05-0.95] p=0.04), et par les ST dans les EI à *Staphylocoque aureus* (0R=0.46 [0.2-0.99] p=0.046).

En analyse multivariée, seule la thérapie combinée était protectrice contre les EE (OR=0.3 [0.06- 0.96]).

Conclusions

Une préexposition à un traitement combiné par aspirine et statine réduit les évènements emboliques ainsi que les complications hémorragiques dans l'endocardite infectieuse. Des études supplémentaires sont requises pour établir le bénéfice de ces deux traitements en termes de morbidité et de mortalité dans l'endocardite infectieuse.

ABSTRACT

Background

Embolic events (EE) are major complications of infective endocarditis (IE). Animal models have demonstrated the benefit of aspirin (ASA) and statins (ST) in their prevention, but clinical studies gave conflicting results. The aim of our study was to evaluate the benefit of prior ASA and/or ST therapy on embolic risk in patients with IE.

Methods

In a retrospective study from 2010 to 2016, the impact of daily ASA or ST therapy on outcome of patients with IE was assessed. The primary end point was EE. The secondary end points were cerebral emboli, EE according to causative bacteria, hemorrhagic events and 30-day mortality.

Results

Among 529 patients with IE, 135 (25%) were treated by ASA, 130 (24%) by ST, and 66 (12%) by both therapies at the time of hospitalization. EE occurred in 264 (50%) patients.

As compared with 330 patients with no therapy, the 66 patients treated with combined ASA and ST presented with less frequent EE (23 (34%) vs 179 (54%), OR=0.46 [0.26-0.78] p=0.004) and less cerebral hemorrhage (2 (3%) vs 38 (11%), OR 0.29 [0.06-0.91] p=0.03).

EE were significantly reduced by ASA in *Staphylococcus coagulase* negative (0R=0.23 [0.06-0.73] p=0.01) and *Streptococcus gallolyticus* IE (OR=0.26 [0.05-0.95] p=0.04), and by ST in *Staphyloccus aureus* IE (0R=0.46 [0.2-0.99] p=0.046).

By multivariate analysis, only combined therapy was protective against EE (OR=0.3 [0.06- 0.96]).

Conclusions

Prior aspirin combined to statin therapy reduces embolic events and hemorrhagic complications in patients with IE. Additional prospective studies are warranted to assess the benefits of both treatments in reducing morbidity and mortality in IE.

Keywords: Infective endocarditis, aspirin, statin, emboli.