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

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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

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PIRRO Nicolas (PU-PH)

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

THOLLON Lionel (MCF) (60ème section)

ANATOMIE ET CYTOLOGIE PATHOLOGIQUES *4203*

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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*

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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)

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GAUDART Jean (PU-PH)
GIORGI Roch (PU-PH)

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

ANTHROPOLOGIE *20*

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

BACTERIOLOGIE-VIROLOGIE ; HYGIENE HOSPITALIERE *4501*

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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)

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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*

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

CARDIOLOGIE *5102*

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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*

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

BEYER-BERJOT Laura (MCU-PH)

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MANCINI Julien (MCU-PH)

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

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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*

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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*

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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*

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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*

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LEPIDI Hubert (PU-PH)

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

DERMATOLOGIE - VENEREOLOGIE *5003*

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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*

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

CHIRURGIE MAXILLO-FACIALE ET STOMATOLOGIE *5503*

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GUYOT Laurent (PU-PH)

FOLETTI Jean-Marc (MCU-PH)

CHIRURGIE PLASTIQUE,

RECONSTRUCTRICE ET ESTHETIQUE ; BRÛLOLOGIE *5004*

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LEGRE Régis (PU-PH)

HAUTIER/KRAHN Aurélie (MCU-PH)

GASTROENTEROLOGIE ; HEPATOLOGIE ; ADDICTOLOGIE *5201*

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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*

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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*

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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*

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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*

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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)

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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*

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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)

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Table des matières

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

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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.

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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

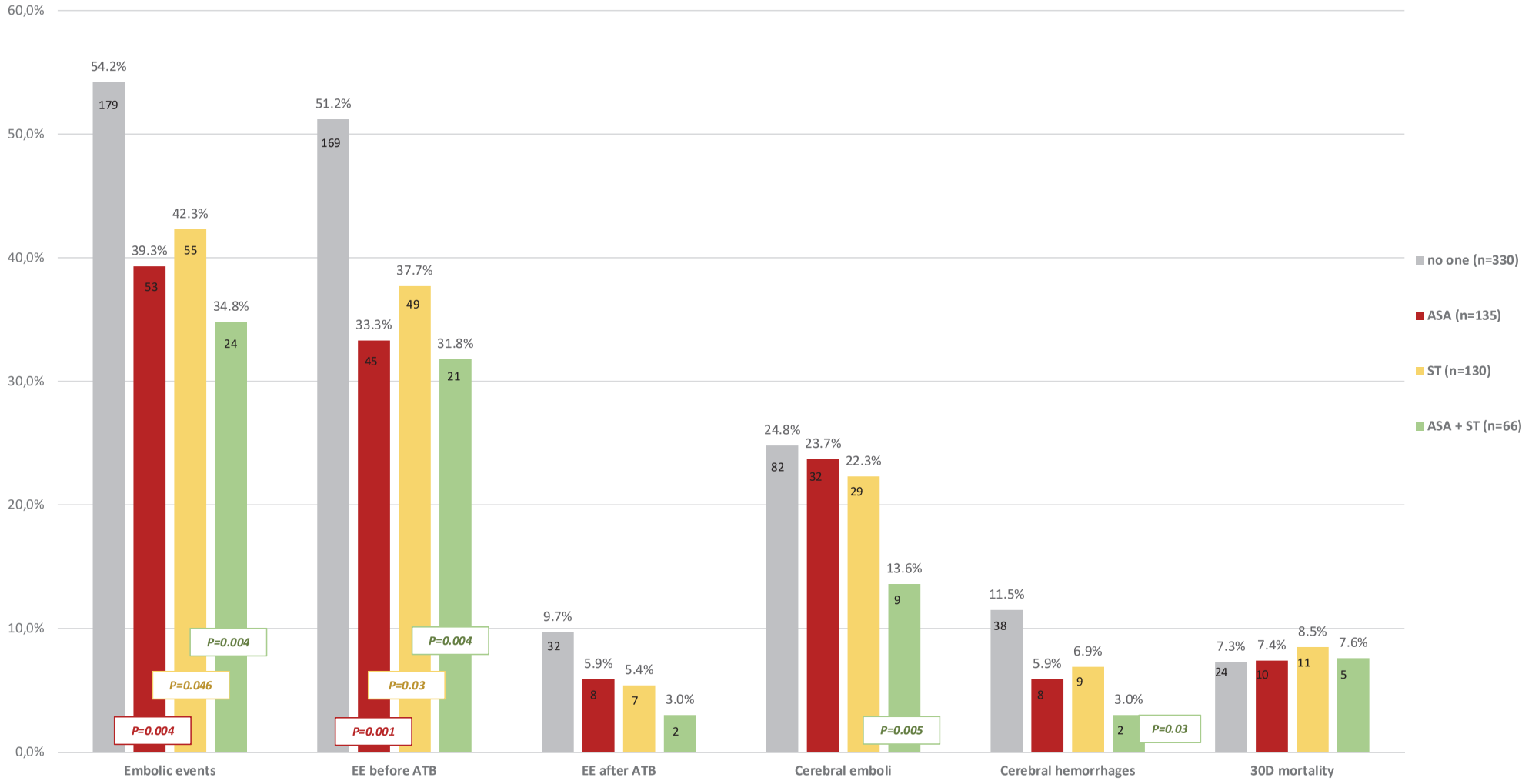
	Cerebral emboli N=134			**Hemorrhagic complications N=53**			**30D mortality N=40**		
Clinical data	IC	OR	p	IC	OR	P	IC	OR	P
Female sex	0.54-1.29	0.83	0.41	0.42-1.45	0.77	0.40	0.40-1.61	0.78	0.48
Age mean	0.98-1.01	0.99	0.28	0.97-1.00	0.98	**0.047**	1.00-1.05	1.02	0.07
Diabetes	0.51-1.35	0.84	9.48	0.10-0.72	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

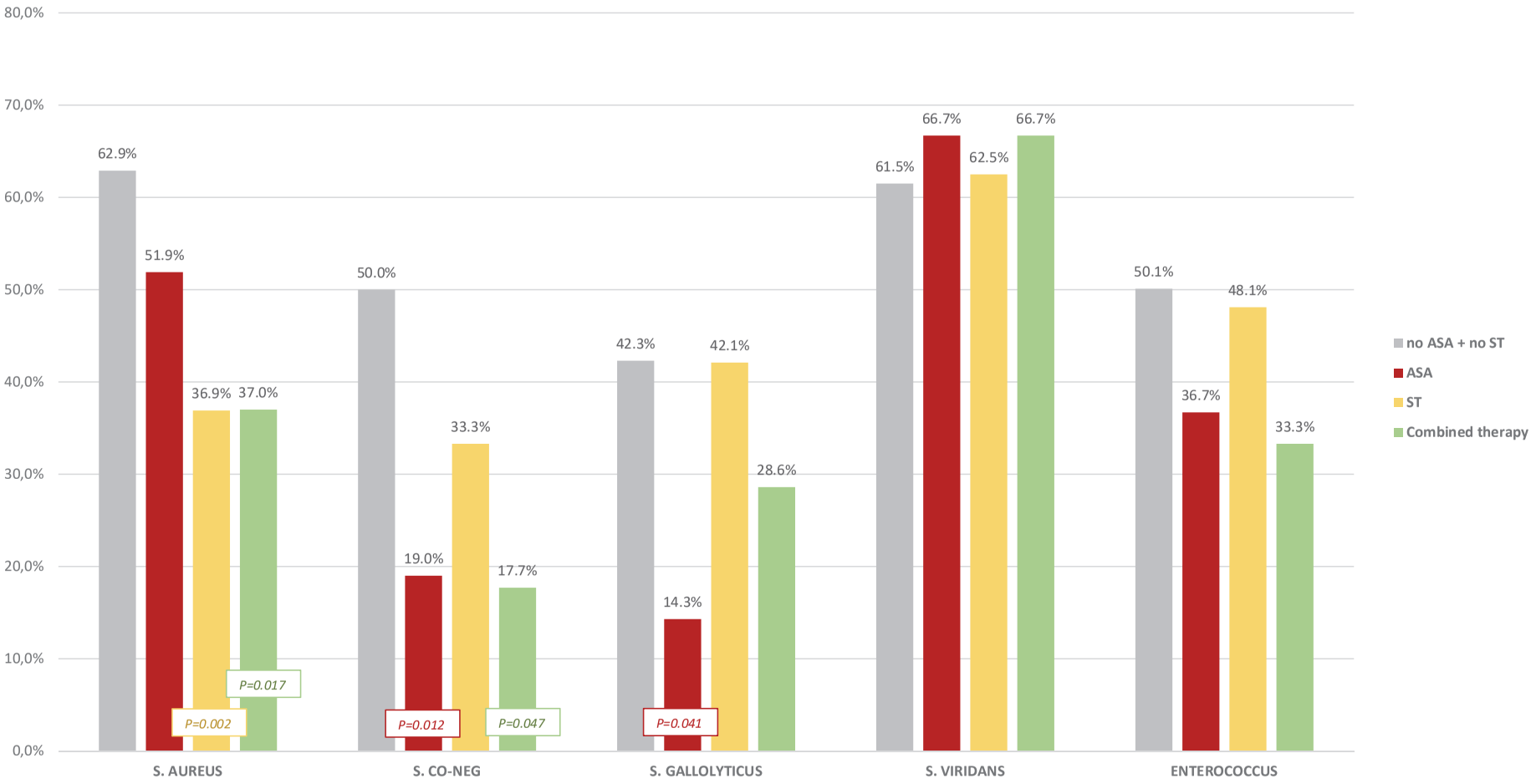
	OR	IC 95%	p
AGE	0.99	0.97-1.01	0.25
VEGETATION LENGTH : 10 to 15 mm	1.29	0.59-2.70	0.51
VEGETATION LENGTH : sup 15 mm	1.62	0.83-3.12	0.16
STAPH AUREUS	1.91	1.06-3.44	**0.033**
ATRIAL FIBRILLATION	1.21	0.57-2.45	0.62
ST or ASA	0.94	0.46-1.80	0.85
ST and ASA	0.30	0.06-0.96	**0.041**

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.

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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.