STATINS IN STROKE

Essay

Submitted for partial fulfillment of Master Degree in
General Intensive Care

By

Ahmed Abdel Hakiem Abdel Hafiz
M.B.B.Ch.
Faculty of Medicine – Assuit University

Under Supervision of

Professor Doctor/ Naglaa Mohamed Ali
Professor of Anesthesiology & Intensive Care & Pain Management
Faculty of Medicine – Ain Shams University

Doctor/ Mahmoud Hassan Mohamed
Lecturer of Anesthesiology & Intensive Care & Pain Management
Faculty of Medicine - Ain Shams University

Doctor/ Ahmad Nabil Mohammad Hamdy
Lecturer of Anesthesiology, Intensive Care & Pain Management
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2014

First of all, I would like to thank Allah who granted me the strength to accomplish this work.

Words do fail to express deepest gratitude and appreciation to **Prof. Dr. Naglaa Mohamed Ali,** Professor of Anesthesiology & Intensive Care & Pain Management Faculty of Medicine – Ain Shams University for her excellent guidance and powerful support .

My deepest thanks and appreciation go to **Dr. Mahmoud Hassan Mohamed,** Lecturer of Anesthesiology & Intensive Care & Pain Management Faculty of Medicine – Ain Shams University for his valuble instructions and support.

My deepest thanks and gratitude go to **Dr. Ahmad Nabil Mohammad Hamdy,** Lecturer of Anesthesiology & Intensive Care & Pain Management Faculty of Medicine – Ain Shams University for his guidance and advices throughout this work.

I would also like to truly thank each and every person who gave me a hand in accomplishing this work.

Last but not least, my true affection and love goes to all my family, who were and will always be by my side and without whom I would have never been able to accomplish this work. Their love, patience and support are most appreciated.

Ahmed Abdel Hakiem Abdel Hafiz

LIST OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Akt ..... Protein Kinase B.

AMPA…….Alpha-amino-3-hydroxy-5-methyl-4-isoxanole propionate.

ASCOT-LLA…….The Anglo-Scandinavian Coronary Outcomes Trial-Lipid Lowering Arm.

AT1 …… Angiotensin receptor 1.

ATP…….Adenosine triphosphate.

AUC ..... .Area under plasma statin concentration- time curve.

BBB ……... Blood brain barrier.

BI ……... Barthel index.

C3-5…… Carbon atom 3-5.

Ca^{++} ..... Ionized calcium.

CAD ……...Coronary artery disease.

CADASIL..... Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

CARE …….The Cholesterol and Recurrent Event.

CBF ..... .Cerebral blood flow.

CCL2,7,13,18 ..... .Chemokine (C-C motif) ligand 2,7,13,18.

CD40,80,86 ..... .Cluster of differentiation 40,80,86.

CD8/CD4 ..... Cluster of differentiation 8/ cluster of differentiation 4.

cdk……...Cyclin-dependent kinases.

cGMP …….Cyclic guanine monophosphate.

CHD ……...Coronary heart disease.

CNS..... Central nervous system.

CRP ……....C- reactive protein.

CSF ..... Cerebrospinal fluid.

CT .....Computerized tomography.

CXCL1..... Chemokine (C-X-C motif) ligand 1.

CYP…… Cytochrome P450.

CYP3A4……..Cytochrome P450, family 3, subfamily A, polypeptide 4.

CYP2C8,9,19……. Cytochrome P450, family 2, subfamily C, polypeptide 8,9,19.

DNA ..... Deoxyribonucleic acid.

eNOS..... Endothelial nitric oxide synthase.

EPCs ……..Endothelial progenitor cells.

ES..... Embolic stroke.

FMD..... Fibromuscular dysplasia.

FPP..... Farnesylpyrophosphate.

GC ……. guanylate cyclase.

G-CSF..... Granulocyte colony-stimulating factor.

GDP ..... Guanosine diphosphate.

GGPP..... Geranylgeranylpyrophosphate.

G1/S……A stage in the cell cycle at the boundary between the G1 phase and the S phase.

GTP..... Guanosine triphosphate.

GTPase ..... Guanosine triphosphatase.

HDL ……...High density lipoprotein.

HI ..... Hemorrhagic infarction.

HIV ..... Human immunodeficiency virus.

HMG-CoA..... 3-hydroxy-3-methyl-glutaryl-CoA.

HMG-R..... 3-hydroxy-3-methyl-glutaryl-CoA reductase enzyme.

HPS ……...Heart protection study.

ICAM-1 ..... Intracellular adhesion molecule-1.

ICP..... Intracranial pressure.

IFN..... Interferon.

IL-1,6,8 ..... Interleukin 1,6,8.

IMT …….. Intima media thickness.

IP..... Ischemic penumbra.

LDL..... Low density lipoprotein.

LDL-C ..... Low density lipoprotein cholesterol.

LDL/TC …… Low density lipoprotein/ total cholesterol ratio.

LFA-1..... Lymphocyte function-associated antigen-1.

LIPID ……Long-term Intervention with Pravastatin in Ischemic Disease.

L-NAME ……...L-NG-Nitroarginine Methyl Ester.

MAP……...Mean arterial pressure.

MCA ……..Middle cerebral artery.

MHC……...Major histocompatibility complex.

MIRACL…….. .Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering.

MRFIT……...Multiple Risk Factor Intervention Trial**.**

MRI…….……Magnetic resonance imaging.

mRNA ……... Messenger ribonucleic acid.

MRS …….. Modified Rankin scale.

NADH ..... Nicotinamide adenine dinucleotide.

NF-B..... Nuclear factor-B.

NMDA ..... N-methy1-D-asapartate.

NO..... Nitric oxide.

NSAIDs..... Nonsteroidal anti-inflammatory drugs.

NXY-059..... Disufenton sodium.

OAT3 ..... Organic anion transporter 3.

OATP..... Organic anion transporting polypeptides.

OATP1B1 ..... Organic anion transporting polypeptide family, member 1B1.

PaCO2 ..... Partial pressure of arterial carbon dioxide.

PAI-1..... Plasminogen activator inhibitor-1.

PaO2 ..... Partial pressure of arterial oxygen.

PDGF ..... Platelet-derived growth factor.

P-gp..... P-glycoprotein.

PI3K..... Phosphatidylinositol 3-kinase.

PROVE IT-TIMI…In pravastatin or atorvastatin evaluation and infection therapy thrombolysis in myocardial infarction.

PSC ……Prospective study collaboration.

Rac1 ……...Rho family, small GTP binding protein.

Ras …….Small GTP responsible for cell growth regulation.

Rb……Retinoblastoma protein.

Rho ……..…Small GTP responsible for organization of the cytoskeleton

ROS..... Reactive oxygen species.

4S …….. The Scandinavian Simvastatin Survival Study.

SAH..... Subarachnoid hemorrhage.

SLCO..... Solute carrier organic anion transporter family.

SMCs ..... Smooth muscle cells.

SPARCL ……Stroke Prevention by Aggressive Reduction in Cholesterol Level.

STAT4,6…….Signal Transducer and Activator of Transcription protein 4,6.

Th1,2……...T helper cells 1,2.

TIA ..... Transient ischemic attacks.

T-cell..... T lymphocytes.

TGF-1 ..... Transforming growth factor-1.

Tmax..... Peak plasma concentration.

TNT……Treating to New Targets.

TXA2…….Thromboxane A2.

VEGF ……Vascular endothelial growth factor.

INTRODUCTION

Stroke is the third most common cause of death and the leading cause of neurological disability in the world. While some risk factors for stroke, such as hypertension and cigarette smoking, are well defined. However, numerous studies have shown that medications that reduce cholesterol via 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibiton (statins) reduce incidence of ischemic stroke in patients who are known to have or be at high risk of coronary artery disease. In addition statins may have benefits in neuroprotection and recovery after stroke. The mechanisms by which statins protect against, and improve outcome after, stroke probably extend beyond lipid lowering ***(Jeffery & David, 2006)***.

Large clinical trials have demonstrated that statins decrease the incidence of myocardial infarctions and ischemic strokes in hypercholesterolemic and atherosclerotic individuals ***(Amarenco et al., 2004)***.

These agents inhibit an early step in cholesterol biosynthesis by blocking the conversion of HMG-CoA to mevalonate. Because serum cholesterol level is strongly associated with coronary atherosclerotic disease it has been generally assumed that cholesterol reduction by statins is the predominant, if not the only

mechanism, underlying their beneficial effects in cardiovascular diseases ***(Stancu & Sima, 2001)***.

Statins is attributable to pleiotropic effects; they not only exhibit cholesterol lowering, but also direct effects on endothelial function and antithrombotic and anti-inflammatory activity ***(Liao & Laufs, 2005).***

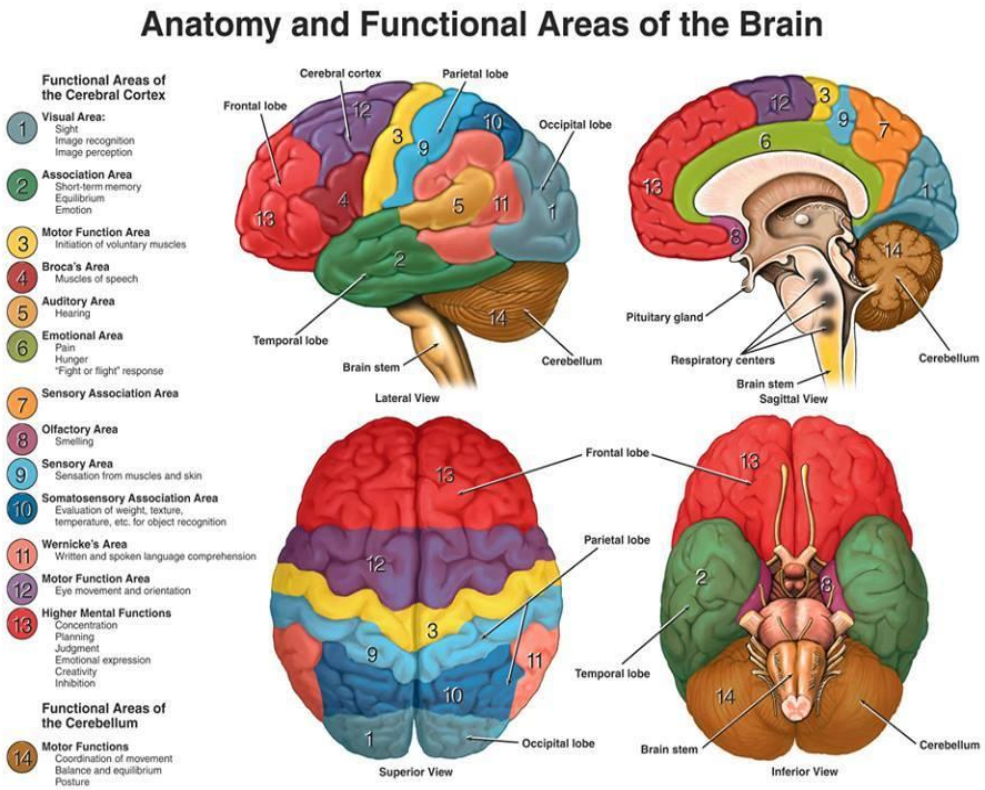
Statins up-regulate endothelial nitric oxide synthase and landmark trials demonstrated that they reduce the risk of myocardial infarction and stroke ***(Wagner et al., 2000)***.

However, patients with normal lipid levels also received the benefit of stroke reduction with statin therapy. This extensive experience clearly indicates that statins are highly effective in the long-term prevention of stroke, and suggests that this benefit may be partially independent of the cholesterol-lowering effect of the drugs ***(Crouse et al., 2007)***.

PATHOPHYSIOLOGY OF STROKE

Structure and function of the brain

The brain is the body's control centre. It constantly receives and interprets nerve signals from the body and responds based on this information. Different parts of the brain control movement, speech, emotions, consciousness and internal body functions, such as heart rate, breathing and body temperature ***(Loukas et al., 2011).***



Figure(1): Anatomy and Functional Area of the Brain ***(Loukas et al., 2011).***

The brain has 3 main parts: cerebrum, cerebellum and brain stem.

Cerebrum

The cerebrum is the largest part of the brain. It is divided into 2 parts (halves) called the left and right cerebral hemispheres. The 2 hemispheres are connected by a bridge of nerve fibres called the corpus callosum.

The outer surface of the cerebrum is called the cerebral cortex or grey matter and the inner area is called the white matter.

The right half of the cerebrum (right hemisphere) controls the left side of the body. The left half of the cerebrum (left hemisphere) controls the right side of the body, each hemisphere consists of four lobes: frontal, parietal, temporal and occipital lobe. Each lobe has different functions:

The frontal lobe controls movement, speech, behaviour, memory, emotions and intellectual functioning, such as thought processes, reasoning, problem solving, decision making and planning.

The parietal lobe controls sensations, such as touch, pressure, pain and temperature. It also controls spatial orientation (understanding of size, shape and direction).

The temporal lobe controls hearing, memory and emotions. The left temporal lobe also controls speech.

The occipital lobe controls vision ***(Toro et al., 2008)***.

Cerebellum

The cerebellum is the next largest part of the brain. It is located under the cerebrum at the back of the brain. It is divided into 2 parts or hemispheres and has grey and white matter, much like the cerebrum.

The cerebellum is responsible for:

Movement, posture, balance, reflexes, complex actions (walking, talking) and collecting sensory information from the body ***(Edwards* et al., *2008)***.

Brain stem

The brain stem is a bundle of nerve tissue at the base of the brain. It connects the cerebrum to the spinal cord and sends messages between different parts of the body and the brain.

The brain stem has 3 areas:

Midbrain, pons and medulla oblongata.

The brain stem controls:

Breathing, body temperature, blood pressure, heart rate, hunger and thirst ***(Kandel et al., 2011)***.

Other important parts of the brain:

Meninges

The brain and spinal cord are covered and protected by 3 thin layers of tissue (membranes) called the meninges:

- dura mater – thickest outer layer.
- arachnoid layer – middle, thin membrane.
- pia mater – inner, thin membrane.

Cerebrospinal fluid (CSF) flows in the space between the arachnoid layer and the pia mater. This space is called the subarachnoid space **(Loukas *et al.*, 2011)**.

Thalamus

The thalamus is a structure in the middle of the brain that has 2 lobes or sections. It acts as a relay station for almost all information that comes and goes between the brain and the rest of the nervous system in the body ***(Sherman, 2006)***.

Hypothalamus

The hypothalamus is a small structure in the middle of the brain below the thalamus. It plays a part in controlling body temperature, hormone secretion, blood pressure, emotions, appetite, and sleep patterns ***(Herrero et al., 2002)***.