THE IMPACT OF PREVENTIVE MEDICATIONS AND FACTORS RELATED TO ACUTE ISCHEMIC STROKE ON OUTCOMES: MULTIMODAL PREVENTIVE MEDICATION APPROACH

BY

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DEDICATION

I would like to dedicate my thesis for my beloved family.

To my husband "Sa'ed" who stands beside me, reduces my stress and accompanies me working through down periods and maintaining a positive attitude

To my lovely daughter "Sima" who brings the happiness to our life

To my father and mother

Allah says in the Holy Quran

"And say: "Work (righteousness): Soon will Allah observe your work, and His Messenger, and the Believers"

Surat-at-Tawbah (9), ayah 105

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TABLE OF CONTENTS

Title	Page
DEDICATION…….....	ii
ACKNOWLEDGEMENTS …….	iii
TABLE OF CONTENTS……..	vi
LIST OF TABLES……	xvi
LIST OF FIGURES…….....…	xxiii
LIST OF ABBREVIATIONS……...	xxv
LIST OF APPENDICES……...	xxix
ABSTRAK…….....	xxx
ABSTRACT……..	xxxiii
CHAPTER 1 – INTRODUCTION	1
1.1 Stroke: general background...…….....	1
1.1.1 Stroke: background and global disease burden …….....	1
1.1.2 Stroke: the Malaysian situation....…….....	3
1.2 Definition of stroke.....……...	4
1.3 Pathophysiology of acute ischemic stroke.....	4
1.3.1 Mechanisms of ischemia.....	4
1.3.2 Cellular pathophysiology.....	6
1.4 Classification, clinical diagnosis and syndromes of acute ischemic stroke.....	9
1.5 Risk factors of acute ischemic stroke.…….....	13
1.5.1 Modifiable risk factors.....…….....	14
1.5.1.1 Hypertension ….....…….....	14
1.5.1.2 Diabetes mellitus.....……..	15
1.5.1.3 Ischemic heart disease…....……...	16
1.5.1.4 Atrial fibrillation…....……...	16
1.5.1.5 Dyslipidemia…....…….	17
1.5.1.6 Renal impairment…....……..	17
1.5.1.7 Heart failure…....……..	18
1.5.1.8 Smoking……..	18
1.5.1.9 Left ventricular hypertrophy…....…….	19
1.5.1.10 Obesity …….	19

Title **Page**

1.5.1.11 Carotid artery stenosis 20
1.5.1.12 Elevated Lipoprotein(a)....…....…….. 20
1.5.1.13 Von Willebrand factor (vWF) …....…… 21
1.5.1.14 C-reactive protein (CRP) …....……... 21
1.5.1.15 Homocysteine …….. 21
1.5.1.16 Alcohol abuse..... 22
1.5.2 Non-modifiable risk factors ……... 22
1.5.2.1 Age …… 22
1.5.2.2 Gender ……... 23
1.5.2.3. Ethnic group ……. 24
1.6 Treatment of acute ischemic stroke …… 24
1.6.1 Current management strategy ……... 24
1.6.2 Control of physiological variables ……..... 25
1.6.2.1 Control of blood pressure …….. 25
1.6.2.2 Hyperglycemia …….. 26
1.6.2.3 Fever …….. 27
1.6.3 Antiplatelet therapy ……..... 27
1.6.4 Anticoagulant therapy ……... 28
1.6.5 Thrombolysis ……. 28
1.6.6 Neuroprotective agents..... 29

CHAPTER 2 – LITERATURE REVIEW 33
2.1 Ischemic stroke prevention ……..... 33
2.1.1 Primary and secondary prevention of ischemic stroke: general measures..... 33
2.1.1.1 Blood pressure management..... 34
2.1.1.2 Lipid lowering treatment..... 35
2.1.1.3 Antiplatelet therapy..... 37
2.2 Impact of preventive medications on mortality after ischemic stroke..... 38
2.2.1 Impact of previous ACEI use on mortality after ischemic stroke... 39
2.2.2 Impact of previous antiplatelet use on mortality after ischemic stroke..... 40

Title **Page**

2.2.3 Impact of previous statin use on mortality after ischemic stroke..... 41

2.3 Impact of preventive medications on functional status at discharge after ischemic stroke..... 42

2.3.1 Impact of previous ACEI use on functional status at discharge after ischemic stroke..... 42

2.3.2 Impact of previous antiplatelet use on functional status at discharge after ischemic stroke..... 44

2.3.3 Impact of previous statin use on functional status at discharge after ischemic stroke..... 45

2.4 Impact of preventive medications on the occurrence of complications after ischemic stroke..... 47

2.4.1 Complications after ischemic stroke: classification and associated factors..... 47

2.4.1.1 Pneumonia..... 47

2.4.1.2 Gastrointestinal complications: dysphagia..... 49

2.4.1.3 Gastrointestinal complications: gastrointestinal bleeding.. 49

2.4.1.4 Gastrointestinal complications: fecal incontinence and constipation..... 50

2.4.1.5 Genitourinary complications: urinary tract infections..... 51

2.4.1.6 Genitourinary complications: urinary incontinence..... 51

2.4.1.7 Deep vein thrombosis..... 52

2.4.1.8 Fall and Hip fractures..... 53

2.4.1.9 Depression..... 54

2.4.1.10 Cardiac complications..... 55

2.4.1.11 Decubitus ulcers (bed sores)..... 56

2.4.1.12 Seizure…..…….... 56

2.4.2 Impact of complications after ischemic stroke on ischemic stroke outcomes..... 57

2.4.3 Impact of previous ACEI use on complications occurrence after ischemic stroke.....…… 58

Title **Page**

2.4.3.1 Impact of ACEI use on pneumonia..... 58

2.4.3.2 Impact of ACEI use on dysphagia..... 59

2.5 Impact of the previous use of antiplatelet, ACEI and statin combination therapy on ischemic stroke outcomes..... 60

2.6 Statement of the problem and rationale of the study..... 61

2.7 Significance and benefits of the study..... 63

2.8 Research questions..... 65

2.9 Research hypothesis..... 66

2.10 Objectives of the study..... 66

2.10.1 General objective..... 66

2.10.2 Specific objectives..... 66

CHAPTER 3 - MATERIALS AND METHODS 69

3.1 Study design..... 69

3.2 Study setting..... 70

3.3 Duration of the study..... 71

3.4 Study population and patient identification..... 71

3.4.1 Inclusion criteria..... 71

3.4.2 Exclusion criteria..... 72

3.5 Sampling procedure and sample size calculation..... 72

3.5.1 Sample size calculation for the univariate analysis..... 72

3.5.1.1 Sample size calculation for the impact of the previous ACEI use on in-hospital mortality rate..... 74

3.5.1.2 Sample size calculation for the impact of the previous antiplatelet use on in-hospital mortality rate..... 75

3.5.1.3 Sample size calculation for the impact of the previous statin use on in-hospital mortality rate..... 76

3.5.1.4 Sample size calculation for the impact of the previous ACEI use on functional status at discharge..... 77

3.5.1.5 Sample size calculation for the impact of the previous antiplatelet use on functional status at discharge..... 78

3.5.1.6 Sample size calculation for the impact of the previous statin use on functional status at discharge..... 79

Title **Page**

3.5.1.7 Sample size calculation for the impact of the previous ACEI use on the occurrence of post-stroke complications..... 80

3.5.1.8 Sample size calculation for the impact of the previous antiplatelet use or previous statin use on the occurrence of post-stroke complications..... 81

3.5.2 Sample size calculation for the binary logistic regression analysis 81

3.6 Ethical approval of the study..... 82

3.7 Data collection..... 82

3.7.1 Socio-demographic characteristics..... 86

3.7.2 Clinical characteristics..... 86

3.7.3 Risk factors and comorbid diseases..... 87

3.7.4 Medications classes..... 88

3.7.5 Ischemic stroke outcome: in-hospital mortality..... 90

3.7.6 Ischemic stroke outcome: functional status at discharge..... 90

3.7.7 Ischemic stroke outcome: post-stroke complications..... 91

3.8 Conceptual framework..... 93

3.9 Statistical data analysis..... 95

CHAPTER 4 – RESULTS 97

4.1 Description of the study patients..... 97

4.1.1 Demographic characteristics of acute ischemic stroke patients..... 97

4.1.2 Ischemic stroke subtypes and clinical characteristics upon admission..... 97

4.1.3 Risk factors and comorbid diseases..... 99

4.1.4 Medication classes used among patients prior to their current stroke and during hospitalization..... 99

4.1.5 Percentage of medication combinations of antiplatelet, ACEI and statin that were used prior to acute ischemic stroke..... 103

4.2 Acute ischemic stroke outcomes: in-hospital mortality..... 104

4.2.1 Impact of the pre-stroke use of angiotensin-converting enzyme inhibitor alone versus the additive effects of antiplatelet and statin on in-hospital mortality..... 104

Title **Page**

4.2.1.1 Baseline demographic and clinical characteristics and medications used among the 700 ischemic stroke patients evaluated, with or without previous ACEI use..... 105

4.2.1.2 The impact of the previous ACEI use on in-hospital mortality..... 106

4.2.1.3 The impact of the additive effects of antiplatelet and/or statin to ACEI on in-hospital mortality..... 112

4.2.2 Impact of pre-stroke use of antiplatelet medication alone versus the additive effect of ACEI and/or statin on in-hospital mortality..... 116

4.2.2.1 Baseline demographic and clinical characteristics and the medications used among the 637 ischemic stroke patients evaluated, with or without previous antiplatelet use..... 117

4.2.2.2 The impact of the previous antiplatelet use on in-hospital mortality..... 118

4.2.2.3 The impact of the additive effects of ACEI and/or statin to antiplatelet on in-hospital mortality..... 124

4.2.3 Impact of pre-stroke use of statin alone versus the additive effects of antiplatelet and/or ACEI on in-hospital mortality..... 128

4.2.3.1 Baseline demographic and clinical characteristics and medications used among the 622 ischemic stroke patients evaluated, with or without previous statin use..... 129

4.2.3.2 The impact of previous statin use on in-hospital mortality..... 130

4.2.3.3 The impact of the additive effects of antiplatelet and/or an ACEI to a statin medication on in-hospital mortality..... 136

4.2.4 Causes of death of acute ischemic stroke during hospitalization... 140

4.2.5 Independent factors associated with in-hospital mortality after acute ischemic stroke..... 141

4.2.6 Summary of the impact of ACEI, antiplatelet and statin on in-hospital mortality..... 148

4.3 Acute ischemic stroke outcomes: functional status at discharge..... 149

Title **Page**

4.3.1 Impact of pre-stroke use of an angiotensin-converting enzyme inhibitor alone versus the additive effects of antiplatelet and/or statin on functional status at discharge..... 149

4.3.1.1. Baseline demographic and clinical characteristics and medications used among the 593 ischemic stroke survivors evaluated, with or without previous ACEI use..... 150

4.3.1.2 The impact of previous ACEI use on functional status at discharge..... 151

4.3.1.3 The impact of the additive effects of antiplatelet and/or statin to ACEI medication on functional status at discharge..... 157

4.3.2 Impact of pre-stroke use of antiplatelet alone versus the additive effects of ACEI and/or statin on functional status at discharge..... 161

4.3.2.1 Baseline demographic and clinical characteristics and medications used among the 512 ischemic stroke survivors evaluated, with or without previous antiplatelet use..... 162

4.3.2.2 The impact of previous antiplatelet use on functional status at discharge..... 163

4.3.2.3 The impact of the additive effects of ACEI and/or statin to antiplatelet medication on functional status at discharge..... 170

4.3.3 Impact of pre-stroke use of statin alone versus the additive effects of antiplatelet and/or ACEI on functional status at discharge..... 174

4.3.3.1 Baseline demographic and clinical characteristics and medications used among the 520 ischemic stroke survivors evaluated, with or without previous statin use..... 175

4.3.3.2 The impact of previous statin use on functional status at discharge..... 176

4.3.3.3 The impact of the additive effects of antiplatelet and/or ACEI to statin medication on functional status at discharge..... 182

4.3.4 Independent factors associated with a good functional status of acute ischemic stroke survivors at discharge..... 186

4.3.5 Summary of the impact of ACEI, antiplatelet and statin on improving the functional status at discharge..... 194

Title **Page**

4.4 Acute ischemic stroke outcomes: post-stoke complications..... 195

4.4.1 Impact of pre-stroke use of angiotensin-converting enzyme inhibitor alone versus the additive effects of antiplatelet and/or statin on the occurrence of post-stroke complications..... 195

4.4.1.1 Baseline demographic and clinical characteristics and medications used among the 700 ischemic stroke patients evaluated, with or without previous ACEI use..... 196

4.4.1.2 The impact of the previous ACEI use on the occurrence of post-stroke complications..... 197

4.4.1.3 The impact of the additive effects of antiplatelet and/or statin to ACEI medication on the occurrence of post-stroke complications..... 203

4.4.2 Impact of pre-stroke use of antiplatelet medication alone versus the additive effects of ACEI and/or statin on the occurrence of post-stroke complications..... 206

4.4.2.1 Baseline demographic and clinical characteristics and medications used among the 637 ischemic stroke patients evaluated, with or without previous antiplatelet use..... 207

4.4.2.2 The impact of the previous antiplatelet medication use on the occurrence of post-stroke complications..... 208

4.4.2.3 The impact of the additive effects of ACEI and/or statin to antiplatelet medication on the occurrence of post-stroke complications..... 214

4.4.3 Impact of the pre-stroke use of statin medication alone versus the additive effect of antiplatelet and/or ACEI on the occurrence of post-stroke complications..... 218

4.4.3.1 Baseline demographic and clinical characteristics and medications used among the 622 ischemic stroke patients evaluated, with or without previous statin use…..…….... 219

4.4.3.2 The impact of the previous statin use on the occurrence of post-stroke complication…...…….....…..…….. 220

Title **Page**

4.4.3.3 The impact of the additive effects of antiplatelet and/or ACEI to statin medication on the occurrence of post-stroke complications ……..……..... 225

4.4.4 Frequency of post-stroke in-hospital complications…..... 229

4.4.5 Independent factors associated with the occurrence of post-stroke complications during hospitalization among acute ischemic stroke patients..... 230

4.4.6 Summary of the impact of ACEI, antiplatelet and statin on the occurrence of in-hospital post-stroke complications..... 239

CHAPTER 5 – DISCUSSION 240

5.1 Description of the study patients…....……..... 240

5.1.1 Demographic characteristics of acute ischemic stroke patients..... 241

5.1.2 Ischemic stroke subtypes and clinical characteristics upon admission..... 242

5.1.3 Risk factors and comorbid diseases..... 243

5.1.4 Medication classes used among patients prior their current stroke attack and during hospitalization..... 244

5.1.5 Proportion of medication combinations of antiplatelet, ACEI and statin that were used prior ischemic stroke.....…....…… 245

5.2 Acute ischemic stroke outcomes: in-hospital mortality….....……... 246

5.2.1 The impact of ACEI, antiplatelet and statin on in-hospital mortality…..... 247

5.2.2 Causes of death of acute ischemic stroke during hospitalization... 253

5.2.3 Independent factors associated with in-hospital mortality after acute ischemic stroke..... 253

5.3 Acute ischemic stroke outcomes: functional status at discharge..... 257

5.3.1 The impact of ACEI, antiplatelet and statins on improving the functional status at discharge..... 257

5.3.2 Independent factors associated with a good functional status of acute ischemic stroke survivors at discharge..... 265

5.4 Acute ischemic stroke outcomes: post-stroke complications..... 267

Title **Page**

5.4.1 The impact of ACEI, antiplatelet and statin on the occurrence of post-stroke in-hospital complications..... 267

5.4.2 Frequency of post-stroke in-hospital complications..... 271

5.4.3 Independent factors associated with the occurrence of post-stroke complications during hospitalization among acute ischemic stroke patients..... 273

CHAPTER 6 - CONCLUSIONS AND RECOMMENDATIONS 276

6.1 Conclusions…..……..... 276

6.2 Strengths of the study ……..... 279

6.3 Limitations of the study…...…….... 280

6.4 Recommendations…...……..... 281

REFERENCES……...…….. 283

APPENDICES……..……...……. 322

LIST OF TABLES

	Title	Page
Table 1.1	TOAST classification scheme of acute ischemic stroke	10
Table 1.2	OCSP classification scheme of acute ischemic stroke	11
Table 1.3	Modifiable and non-modifiable risk factors for ischemic stroke	14
Table 4.1	Previous ACEI use given by categories among 700 patients according to vital status at discharge	107
Table 4.2	Demographic, clinical characteristics and risk factors of 700 patients (who were either on ACEI or without any preventive medication) given by categories according to vital status at discharge	108
Table 4.3	Previous medications of 700 patients (who were either on ACEI or without any preventive medication) given by categories according to vital status at discharge	110
Table 4.4	Independent factors associated with in-hospital mortality in patients (who were either on ACEI or without any preventive medication) using binary logistic regression analysis	111
Table 4.5	Previous ACEI and its combinations given by categories according to vital status at discharge of 700 acute ischemic stroke patients	112
Table 4.6	Independent factors associated with in-hospital mortality of patients (who were either on different ACEI combinations or without any preventive medication) using binary logistic regression analysis	115
Table 4.7	Previous antiplatelet use among 637 patients given by categories according to vital status at discharge	118
Table 4.8	Demographic, clinical characteristics and risk factors of 637 patients (who were either on antiplatelet or without any preventive medication) given by categories according to vital status at discharge	120
Table 4.9	Previous medications of 637 patients (who were either on antiplatelet or without any preventive medication) given by categories according to vital status at discharge	122

	Title	Page
Table 4.10	Independent factors associated with in-hospital mortality in patients (who were either on antiplatelet or without any preventive medication) using binary logistic regression analysis	124
Table 4.11	Previous antiplatelet and its combinations among 637 patients given by categories according to vital status at discharge	125
Table 4.12	Independent factors associated with in-hospital mortality of patients (who were either on different antiplatelet combinations or without any preventive medication) using binary logistic regression analysis	127
Table 4.13	Previous statin use among 622 patients given by categories according to vital status at discharge	130
Table 4.14	Demographic, clinical characteristics and risk factors of 622 patients (who were either on statin or without any preventive medication) given by categories according to vital status at discharge	132
Table 4.15	Previous medications of 622 patients (who were either on statin or without any preventive medication) given by categories according to vital status at discharge	134
Table 4.16	Independent factors associated with in-hospital mortality of patients (who were either on statin or without any preventive medication) using binary logistic regression analysis	136
Table 4.17	Previous statin and its combinations among 622 patients given by categories according to vital status at discharge	137
Table 4.18	Independent factors associated with in-hospital mortality of patients (who were either on different statin combinations or without any preventive medication) using binary logistic regression analysis	139
Table 4.19	Demographic, clinical characteristics and risk factors of 854 acute ischemic stroke patients given by categories according to vital status at discharge	142
Table 4.20	Previous medications of 854 acute ischemic stroke patients given by categories according to vital status at discharge	144
Table 4.21	Previously used regimen of antiplatelet, ACEI and statin among 854 acute ischemic stroke patients given by categories according to vital status at discharge	145

	Title	Page
Table 4.22	Independent factors associated with in-hospital mortality of patients using binary logistic regression analysis	147
Table 4.23	Previous ACEI use among 593 patients given by categories according to functional status at discharge	152
Table 4.24	Demographic, clinical characteristics and risk factors of 593 patients (who were either on ACEI or without any preventive medication) given by categories according to functional status at discharge	153
Table 4.25	Previous medications of 593 patients (who were either on ACEI or without any preventive medication) given by categories according to functional status at discharge	155
Table 4.26	Independent factors associated with good functional status at discharge of patients (who were either on ACEI or without any preventive medication) using binary logistic regression analysis	156
Table 4.27	Previous ACEI and its combinations among 593 patients given by categories according to functional status at discharge	157
Table 4.28	Independent factors associated with good functional status at discharge of ischemic stroke survivors (who were either on different ACEI combinations or without any preventive medication) using binary logistic regression analysis	160
Table 4.29	Previous antiplatelet use among 512 patients given by categories according to functional status at discharge	163
Table 4.30	Demographic, clinical characteristics and risk factors of 512 patients (who were either on antiplatelet or without any preventive medication) given by categories according to functional status at discharge	165
Table 4.31	Previous medications of 512 patients (who were either on antiplatelet or without any preventive medication) given by categories according to functional status at discharge	167
Table 4.32	Independent factors associated with good functional status at discharge of patients (who were either on antiplatelet or without any preventive medication) using binary logistic regression analysis	169

	Title	Page
Table 4.33.	Previous antiplatelet and its combinations among 593 patients given by categories according to functional status at discharge	171
Table 4.34	Independent factors associated with good functional status at discharge of ischemic stroke patients (who were either on different antiplatelet combinations or without any preventive medication) using binary logistic regression analysis	173
Table 4.35	Previous statin use among 520 patients given by categories according to functional status at discharge	176
Table 4.36	Demographic, clinical characteristics and risk factors of 520 survivors (who were either on statin or without any preventive medication) given by categories according to functional status at discharge	178
Table 4.37	Previous medications of 520 survivors (who were either on statin or without any preventive medication) given by categories according to functional status at discharge	180
Table 4.38	Independent factors associated with good functional status at discharge of patients (who were either on statin or without any preventive medication) using binary logistic regression analysis	181
Table 4.39	Previous statin and its combinations among 593 survivors given by categories according to functional status at discharge	182
Table 4.40	Independent factors associated with good functional status at discharge of ischemic stroke patients (who were either on different statin combinations or without any preventive medication) using binary logistic regression analysis	185
Table 4.41	Demographic, clinical characteristics and risk factors of 708 acute ischemic stroke survivors given by categories according to functional status at discharge	187
Table 4.42.	Previous medications of 708 acute ischemic stroke survivors given by categories according to functional status at discharge	189
Table 4.43	Previously used regimen of antiplatelet, ACEI and statin among 708 acute ischemic stroke survivors given by categories according to functional status at discharge	190

	Title	Page
Table 4.44	Independent factors associated with good functional status at discharge of ischemic stroke patients using binary logistic regression analysis	193
Table 4.45	Previous ACEI use among 700 ischemic stroke patients given by categories according to the occurrence of post-stroke complications	198
Table 4.46	Demographic, clinical characteristics and risk factors of 700 patients (who were either on ACEI or without any preventive medication) given by categories according to the presence of post-stroke complication.	199
Table 4.47	Previous medications of the 700 patients (who were either on ACEI or without any preventive medication) given by categories according to the presence of post-stroke complication	201
Table 4.48	Independent factors associated with the occurrence of post-stroke complications of patients (who were either on ACEI or without any preventive medication) using binary logistic regression analysis	202
Table 4.49	Previous ACEI and its combinations among 700 ischemic stroke patients given by categories according to the presence of post-stroke complications	203
Table 4.50	Independent factors associated with the occurrence of post-stroke complications of patients (who were either on different ACEI combinations or without any preventive medication) using binary logistic regression analysis	205
Table 4.51	Previous antiplatelet use given by categories according to presence of post-stroke complications among 637 ischemic stroke patients	208
Table 4.52	Demographic, clinical characteristics and risk factors of 637 patients (who were either on antiplatelet or without any preventive medication) given by categories according to the presence of post-stroke complication	210
Table 4.53	Previous medications of 637 patients (who were either on antiplatelet or without any preventive medication) given by categories according to the presence of post-stroke complication	212

	Title	Page
Table 4.54	Independent factors associated with the occurrence of post-stroke complications of patients (who were either on antiplatelet or without any preventive medication) using binary logistic regression analysis	213
Table 4.55	Previous antiplatelet and its combinations among 637 ischemic stroke patients given by categories according to the presence of post-stroke complications	214
Table 4.56	Independent factors associated with the occurrence of post-stroke complications of patients (who were either on different antiplatelet combinations or without any preventive medication) using binary logistic regression analysis	217
Table 4.57.	Previous statin use among 622 patients given by categories according to the presence of post-stroke complication	220
Table 4.58	Demographic, clinical characteristics and risk factors of 622 patients (who were either on statin or without any preventive medication) given by categories according to the presence of post-stroke complication	222
Table 4.59	Previous medications of 622 patients (who were either on statin or without any preventive medication) given by categories according to the presence of post-stroke complication	223
Table 4.60	Independent factors associated with the occurrence of post-stroke complications of patients (who were either on statin or without any preventive medication) using binary logistic regression analysis	225
Table 4.61	Previous statin and its combinations of 622 patients given by categories according to the presence of post-stroke complications	226
Table 4.62	Independent factors associated with the occurrence of post-stroke complications of patients (who were either on different statin combinations or without any preventive medication) using binary logistic regression analysis	228
Table 4.63	In-hospital medical and neurological complication frequency after acute ischemic stroke	230
Table 4.64	Demographic, clinical characteristics and risk factors of 854 acute ischemic stroke patients given by categories according to the occurrence of in-hospital post-stroke complications	232

	Title	Page
Table 4.65	Previous medications of 854 acute ischemic stroke patients given by categories according to the occurrence of post-stroke in-hospital complications	234
Table 4.66	Previously used regimen of antiplatelet, ACEI and statin among 854 acute ischemic stroke patients given by categories according to occurrence of in-hospital post-stroke complications	235
Table 4.67	Independent factors associated with the occurrence of post-stroke complication during hospitalization among acute ischemic stroke patients using binary logistic regression analysis	238

LIST OF FIGURES

	Title	Page
Figure 1.1	Major pathways implicated in ischemic cell death	8
Figure 1.2	Major vascular territories of the brain and important anatomic structures	12
Figure 3.1	Conceptual framework depicting the evaluation of the impact of the preventive medications on acute ischemic stroke outcomes	94
Figure 4.1	Classification of acute ischemic stroke patients according to Oxfordshire Community Stroke Project (OCSP)	98
Figure 4.2	Percentage of risk factors and comorbid diseases in acute ischemic stroke patients	99
Figure 4.3	Percentage distribution of 345 ischemic stroke patients who used antiplatelet medication prior to the attack	100
Figure 4.4	Percentage distribution of 408 ischemic stroke patients who used angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker medication prior to the attack	101
Figure 4.5	Percentage distribution of 330 ischemic stroke patients who used statin medication prior to the attack	102
Figure 4.6	Percentage of patients who were on one preventive medication, two medications combination, and three medications combination of antiplatelet (AP), angiotensin-converting enzyme inhibitor (ACEI), and statins	103
Figure 4.7	Flow chart describing patients enrolled to study the impact of angiotensin-converting enzyme inhibitors and its combination on in-hospital mortality	105
Figure 4.8	Flow chart describing patients enrolled to study the impact of antiplatelet and its combination on in-hospital mortality	116
Figure 4.9	Flow chart describing patients enrolled to study the impact of statin and its combination on in-hospital mortality	128
Figure 4.10	The percentage distribution of the causes of death in acute ischemic stroke patients	140
Figure 4.11	Flow chart describing the enrolment of patients with ischemic stroke in the analysis of functional status at discharge	149
Figure 4.12	Flow chart describing the enrolment of patients with	150

	Title	Page
	ischemic stroke in the analysis of the impact of angiotensin-converting enzyme inhibitor and its combinations on functional status at discharge	
Figure 4.13	Flow chart describing the enrolment of patients with ischemic stroke in the analysis of antiplatelet and its combinations on functional status at discharge	161
Figure 4.14	Flow chart describing the enrolment of patients with ischemic stroke in the analysis of statin and its combination on the analysis of the functional status at discharge	174
Figure 4.15	Flow chart describing patients enrolled to study the impact of angiotensin-converting enzyme inhibitor and its combination on the incidence of post-stroke complications	196
Figure 4.16	Flow chart describing patients enrolled to study the impact of antiplatelet and its combination on the incidence of post-stroke complications	206
Figure 4.17	Flow chart describing patients enrolled to study the impact of statin and its combination on the incidence of post-stroke complications	218
Figure 4.18	The percentage of patients classified according to the number of post-stroke complication	229

LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
ACEI	Angiotensin converting enzyme inhibitors
ADL	Activities of daily living
AF	Atrial fibrillation
ARB	Angiotensin II receptor blocker
ATP	Adenosine triphosphate
BC	Before Christ
Bcl-2	B-cell lymphoma 2
BI	Barthel Index
CCB	Calcium channel blockers
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
DALY	Disability-Adjusted Life Years
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
DWI	Diffusion-weighted magnetic resonance imaging
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FOOD	Feed or Ordinary Diet
GABA	Gamma-aminobutyric acid
GCS	Glasgow Coma Scale
HDL	High density lipoprotein

HF	Heart failure
HMG-CoA	3-hydroxy-3-methyglutaryl coenzyme A
HOPE	Heart Outcomes Prevention Evaluation
HPP	Hospital Pulau Pinang
HSP70	Heat shock protein 70
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10^{th} Revision
IHD	Ischemic heart disease
INR	International normalized ratio
IST	International Stroke Trial
IV	Intravenous
JNC-7	the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
K^+	Potassium
LACI	Lacunar infarct
LDL	Low density lipoprotein
LIFE	Losartan Intervention For Endpoint
LVH	Left ventricular hypertrophy
MCA	Middle cerebral artery
Mg	Milligram
MI	Myocardial infarction
MOH	Ministry of Health
MOSES	Morbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid

Mrs	Modified Rankin Scale
Na^+	Sodium
NCBI	National Center for Biotechnology Information
NCEP	National Cholesterol Education Program
NIHSS	National Institutes of Health Stroke Scale
NMDA	N-methyl-D-aspartate
NOMASS	Northern Manhattan Stroke Study
OCSP	Oxfordshire Community Stroke Project
OR	Odds ratio
PACI	Partial anterior cerebral infarct
PCA	Posterior cerebral artery
PEG	Percutaneous endoscopic gastrostomy
PGH	Penang General Hospital
POCI	Posterior circulation infarct
PROGRESS	Perindopril Protection against Recurrent Stroke Study
PWI	Perfusion-weighted magnetic resonance imaging
Q1	Lower quartile
Q3	Upper quartile
RBG	Random blood glucose
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SALT	Swedish Aspirin Low-Dose Trial
Sc	Subcutaneous
SD	Standard deviation
SHEP	Systolic Hypertension in the Elderly Program

SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SPSS	Statistical Package for Social Sciences programme
TACI	Total anterior circulation infarct
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
Tpa	Tissue plasminogen activator
UK	United Kingdom
USA	United States of America
UTI	Urinary tract infection
VISTA	Virtual International Stroke Trials Archive
VWF	Von Willebrand factor
WBC	White blood cell
WHO	World health Organization

LIST OF APPENDICES

	Title	Page
Appendix A	National Institutes of Health Approval for Conducting Research in the Ministry of Health Malaysia	323
Appendix B	Medical Research and Ethics Committee of the Ministry of Health letter	325
Appendix C	Data collection form	327
Appendix D	Supplement materials	335
Appendix E	List of relevant original publications and communications	348

IMPAK UBAT-UBAT PENCEGAH DAN FAKTOR BERKAITAN STROK ISKEMIA TERHADAP HASIL RAWATAN: KAEDAH MULTIMODEL PENGUBATAN PENCEGAHAN

ABSTRAK

Strok iskemia akut adalah satu masalah kesihatan global dan merupakan antara punca utama morbiditi dan mortaliti. Oleh kerana pencegahan dianggap sebagai teras utama pengurusan strok iskemia akut, pengetahuan tentang bukti saintifik perlu ditekankan di sebalik penggunaan ubat-ubatan pencegahan dan kesannya keatas hasil rawatan pesakit. Objektif kajian adalah untuk mengkaji impak penggunaan terdahulu perencat enzim penukar-angiotensin (*angiotensin-converting enzyme inhibitor* [ACEI]), antiplatelet dan statin, sama ada secara bersendirian atau dalam kombinasi, terhadap mengurangkan kadar mortaliti di hospital, meningkatkan status fungsi sewaktu keluar hospital dan mengurangkan komplikasi selepas strok iskemia. Di samping itu, faktor-faktor lain yang dikaitkan dengan berlakunya hasil rawatan strok iskemia tersebut juga diselidiki.

Kajian pemerhatian dengan reka bentuk kohort retrospektif digunakan bagi semua pesakit strok iskemia yang dimasukkan ke Hospital Pulau Pinang dalam tempoh bermula dari 1 Januari 2008 sehingga 30 Jun 2009. Data termasuk ciri-ciri sosio-demografik, ciri-ciri klinikal, dan kelas ubat-ubatan terdahulu, dengan perhatian khusus diberikan kepada antiplatelet, ACEI dan statin. Impak penggunaan terdahulu ubat-ubatan tersebut terhadap hasil rawatan strok iskemia termasuklah: kadar mortaliti di hospital, status fungsi yang baik seperti yang ditakrifkan oleh Indeks Barthel (BI) $\geq$ 75, dan komplikasi pasca-strok, telah dinilai selepas mengawal lain-lain pembolehubah (iaitu sosio-demografik, ciri-ciri klinikal, faktor-faktor risiko dan ubat-ubatan lain) yang mungkin mempengaruhi kesan ubat-ubatan pencegahan itu terhadap kesudahan strok iskemia.

Secara keseluruhannya, 854 orang pesakit telah memenuhi kriteria penyertaan. Selepas mengawal semua pembolehubah yang mungkin mempengaruhi; penggunaan terdahulu ACEI secara bersendirian atau dalam kombinasi dengan antiplatelet dan/atau ubat-ubatan statin didapati mengurangkan risiko mortaliti dengan ketara semasa dirawat di hospital, dengan peluang tertinggi dalam mengurangkan mortaliti adalah dalam kalangan pesakit yang menggunakan kombinasi tiga-ubat. Selain itu, dalam kalangan mangsa strok yang terselamat, kombinasi dua-ubat "antiplatelet dan ACEI", "antiplatelet dan statin", atau "ACEI dan statin", atau kombinasi tiga-ubat boleh meningkatkan kemungkinan keluar dari hospital dengan status fungsi yang baik sebanyak kira-kira lima kali lebih tinggi berbanding dengan pesakit yang tidak mengambil ubat-ubatan pencegahan, dan mempunyai kemungkinan yang lebih baik berbanding pesakit yang hanya mengambil satu ubat daripada kumpulan-kumpulan berbeza. Tambahan pula, peluang lebih tinggi untuk mengurangkan risiko komplikasi pasca-strok didapati ketara dalam kalangan pesakit yang telah menggunakan ACEI. Penggunaan ACEI dan statin secara kombinasi, dan kombinasi tiga-ubat, secara ketara mempunyai kemungkinan yang tertinggi dalam mengurangkan terjadinya komplikasi. Berlakunya mortaliti di hospital, keluar hospital dengan status fungsi yang baik, atau pendedahan kepada komplikasi pasca-strok, mungkin boleh diramal daripada ciri-ciri klinikal yang spesifik, tanda-tanda penting semasa dimasukkan ke hospital, faktor-faktor risiko, dan tidak menggunakan ubat-ubatan pencegahan.

Kami menyimpulkan bahawa kemungkinan tertinggi bagi menambahbaik hasil fungsi dan mengurangkan kadar mortaliti serta komplikasi selepas strok iskemia diperhatikan pada pesakit yang mengambil kombinasi tiga-ubat antiplatelet, ACEI dan statin. Hasil kajian kelihatan mengesahkan penggunaan kombinasi ini dalam

individu-individu yang berisiko dan dalam pesakit yang didiagnos dengan strok iskemia dan juga untuk memulakan terapi kombinasi lebih awal selepas strok bagi memperbaiki hasil rawatan iskemia strok. Selain itu, peningkatan pengetahuan mengenai faktor-faktor bebas yang paling prediktif kepada hasil rawatan strok iskemia akut boleh membantu pengamal perubatan mengenalpasti pesakit-pesakit berisiko tinggi mengalami morbiditi dan mortaliti, dan seterusnya mungkin boleh mempengaruhi keputusan-keputusan pengurusan.

THE IMPACT OF PREVENTIVE MEDICATIONS AND FACTORS RELATED TO ACUTE ISCHEMIC STROKE ON OUTCOMES: MULTIMODAL PREVENTIVE MEDICATION APPROACH

ABSTRACT

Acute ischemic stroke is a global health problem and is among the leading causes of morbidity and mortality. As prevention is considered the mainstay of management for acute ischemic stroke, knowledge should be highlighted regarding the scientific evidence behind the use of preventive medications and their impact on patients' outcomes. The objective of the study is to evaluate the impact of the previous use of angiotensin-converting enzyme inhibitor (ACEI), antiplatelet and statin, either alone or in combinations on reducing in-hospital mortality rates, improving functional status at discharge and reducing complications after ischemic stroke. In addition, the independent factors associated with the occurrence of these ischemic stroke outcomes have been investigated.

An observational retrospective cohort design was used for all acute ischemic stroke patients admitted to Hospital Pulau Pinang during the period from January 1st 2008 to June 30th 2009. Data included socio-demographic characteristics, clinical characteristics, and previous medication classes, with particular attention being paid to antiplatelets, ACEIs and statins. Impact of the previous use of these medications on ischemic stroke outcomes included: the in-hospital mortality rate, a good functional status as defined by the Barthel Index (BI) $\geq$ 75, and post-stroke complications, was evaluated after controlling for other variables (i.e. socio-demographic, clinical characteristics, risk factors and other medications) that might have confounded the effects of these preventive medications on ischemic stroke outcomes.

Overall, 854 patients met the inclusion criteria. After controlling for possible confounders; the previous use of ACEI alone or in combination with antiplatelet

and/or statin medications was found to significantly reduce the risk of mortality during hospitalization, with the highest chance in reducing the mortality was among patients using the three-medication combination. In addition, among the stroke survivors, the two-medication combinations of “antiplatelet and ACEI”, “antiplatelet and statin”, or “ACEI and statin”, or the three-medication combination can increase the odds of discharge with a good functional status by approximately five times higher compared to patients who did not take preventive medications, and having higher odds compared to patients who took only one medication from different groups. Moreover, high chances of reducing the risk of post-stroke complications were significantly observed among the patients who were on ACEI. The use of ACEI and statin in combination, and the three-medication combination, had significantly the highest odds in reducing the occurrence of complications. The occurrence of in-hospital mortality, being discharged with good functional status, or the exposure to post-stroke complications, might be predicted from specific clinical characteristics, vital signs on admission, risk factors, and the non-use of preventive medications.

We conclude that the highest odds of improving functional outcome and reducing the rates of mortality and complications after ischemic stroke were observed in patients who were taking the three-medication combination of antiplatelet, ACEI and statin. The finding appear to endorse the use of this combination in individuals at risk and in patients diagnosed with ischemic stroke and for the early initiation of this combination therapy after stroke to improve ischemic stroke outcomes. Additionally, an increased knowledge of the most predictive variables of acute ischemic stroke outcomes can assist clinicians in identifying patients at higher risk of morbidity and mortality, and thus may influence management decisions.

CHAPTER 1

INTRODUCTION

1.1 Stroke: general background

Stroke (cerebrovascular disease) is a syndrome with several pathologies (Mant and Walker, 2011). The father of medicine, Hippocrates (460 to 370 BC), was the first to describe the event of sudden paralysis that is often associated with ischemia. In his writings, he used the word "*apoplexy*", a Greek word that means "struck down with violence", to describe the stroke event. The word "*stroke*" was used as a synonym for apoplectic seizure in approximately 1599. Later, in 1658, Johann Jacob Wepfer (1620-1695) identified the cause of hemorrhagic stroke when he suggested that people who had died because of apoplexy had a hemorrhage in their brains. Wepfer also identified the vertebral and carotid arteries, which are the main arteries supplying the brain, and the cause of ischemic stroke when he suggested that apoplexy might be caused by a blockage in these vessels (Gerber, 2003; Nilsen, 2010).

1.1.1 Stroke: background and global disease burden

Stroke is a global health problem and it is among the leading causes of morbidity and mortality worldwide. Annually, about 16 million first-ever strokes occur worldwide, with a death toll of approximately 5.7 million people per year (Strong *et al.*, 2007). Approximately more than half of all strokes occur in people older than 75 years of age, and although the incidence of stroke is declining in many developed countries, largely as a result of better risk factor control, the absolute number of strokes

continues to increase because populations are living longer (Brainin *et al.*, 2007; Feigin *et al.*, 2009). In addition, when stroke is considered separately from other cardiovascular diseases, it is ranked as the third most common cause of death behind heart diseases and cancer (Lloyd-Jones *et al.*, 2010). In addition, mortality data from 2006 indicated that stroke accounted for approximately 1 out of every 18 deaths in the United States of America (USA) during that year (Lloyd-Jones *et al.*, 2010). Furthermore, stroke is the leading cause of serious, long-term disability, which not only has a serious physical and emotional burden on the people affected, but also places a large economic burden on society (Lloyd-Jones *et al.*, 2010). Furthermore, stroke has dire consequences on patients, relatives and society and is associated with a vast economic burden. In the United Kingdom (UK) and other countries, stroke-related costs are on the rise and consistently consume around 5% of health-care resources (Martinez-Vila and Irimia, 2004). In the USA, the total estimated direct and indirect costs of stroke in 2010 came to $73.7 billion (Lloyd-Jones *et al.*, 2010).

Following the initial stroke, many patients suffer a further stroke, and recurrent strokes account for approximately 25% of stroke events, and it has been found that almost 1 in 10 hospitalized ischemic stroke patients was readmitted for a recurrent ischemic stroke within 1 year (Allen *et al.*, 2010). On the other hand, between 15 and 30% of stroke patients were found to have a history of transient ischemic attack (TIA) (Rothwell and Warlow, 2005); following TIA, the seventh-day risk of stroke can exceed 30% in high risk groups (Rothwell *et al.*, 2005b). Recent studies recommended the prompt evaluation and treatment of patients with TIA, as this can lower the expected risk of subsequent stroke events (Gallego *et al.*, 2009).

1.1.2 Stroke: the Malaysian situation

In 2002, the World Health Organization (WHO) reported that approximately 60% of the world's total mortality from stroke occurred in the East Asian region, which comprises South East Asia and the Western Pacific regions (WHO, 2004). In 2004, a study on disease burden using disability-adjusted life years (DALY) showed that the five leading diseases in Malaysia, in decreasing order, are ischemic heart disease (IHD), mental illness, cerebrovascular disease/stroke, road traffic injuries and cancer (WHO-Malaysia, 2009).

Furthermore, chronic non-communicable diseases and injuries are the leading causes of death in Malaysia. The Health Facts 2009 report showed that the leading causes of mortality in Ministry of Health (MOH) hospitals are heart diseases and pulmonary circulation diseases (ranked first), septicaemia (ranked second), malignant neoplasms (ranked third), pneumonia (ranked fourth) and cerebrovascular diseases (ranked fifth) (MOH Malaysia, 2010). In addition, the WHO statistical report of the level of mortality and the burden of diseases in the year 2004 showed that the number of deaths from cerebrovascular diseases in Malaysia was 43.2 per 100,000 population (WHO, 2009). Additionally, the third quarter 2010 Penang Statistical Report showed that cerebrovascular disease/stroke was the fourth principal cause of death in Penang Government Hospitals, with 366 (13.54%) deaths attributed to this cause in the year 2009 (SERI, 2010).

1.2 Definition of stroke

A stroke is defined by the WHO as a syndrome of rapidly developing clinical symptoms and/or signs of focal (or at times global) disturbance of cerebral functioning lasting more than 24 hours (unless interrupted by surgery or death), with no apparent cause other than being of vascular origin (Donnan *et al.*, 2008). This can be due to ischemia or hemorrhage (intracerebral hemorrhage or subarachnoid hemorrhage) (Warlow *et al.*, 2001). Ischemia results from an interruption of the blood supply, whereas a hemorrhage results from the rupture of a blood vessel or an abnormal vascular structure. Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhage and 3% are subarachnoid hemorrhage strokes (Lloyd-Jones *et al.*, 2010).

1.3 Pathophysiology of acute ischemic stroke

1.3.1 Mechanisms of ischemia

There are many etiologic mechanisms for acute ischemic stroke; however, the common pathway is the lack of sufficient blood flow to perfuse cerebral tissue that can lead to irreversible neuronal damage (Deb *et al.*, 2010). Ischemic stroke can manifest in the form of thrombotic stroke (large vessel and small vessel types), embolic stroke, systemic hypoperfusion or venous thrombosis (Donnan *et al.*, 2008; Deb *et al.*, 2010).

Thrombotic stroke is the most common type and occurs when a thrombus blocks the blood flow to parts of the brain. In large vessel thrombosis, the luminal part of atheromatous plaques may be degraded by metalloproteinases, leading to rupture and forming an ulcerated lesion with highly thrombogenic properties (Ay, 2010). In small vessel thrombosis, microatheromatosis results in lacunar infarcts, and in vessels less

than 200 micrometer in diameter the small lacunar infarcts formed are often asymptomatic (Labovitz *et al.*, 2007). Additionally, patients who develop heparin-induced thrombocytopenia due to abnormal antibody formation that leads to platelets activation (Salem *et al.*, 2010), thrombotic thrombocytopenic purpura (Lindblom *et al.*, 2009; Tsai, 2009) and patients with a hypercoaguable autoimmune antiphospholipid antibody syndrome in which antibodies are formed against the cell membrane phospholipids (Camargo *et al.*, 2011) may be at increased risk for both venous and arterial thrombosis.

On the other hand, embolic stroke occurs when an embolus carried by the bloodstream to the brain, where the larger arteries branch off into smaller vessels. This blood clot reaches a point where it cannot move further and effectively plugs a small cerebral artery, cutting off the blood supply to the brain (Allen and Bayraktutan, 2008; Massicotte and Bauman, 2011). Heart is the main source of the emboli that may reach the brain. Left atrial thrombus, left ventricular thrombus, atrial fibrillation (AF), sick sinus syndrome, sustained atrial flutter, rheumatic mitral or aortic valve disease, myocardial infarction (MI), infective or nonbacterial thrombotic endocarditis are examples of high risk sources for cerebral emboli (Doufekias *et al.*, 2008).

Systemic hypoperfusion is another main mechanism of ischemic stroke, which occurs due to a generalized loss of arterial pressure. The area of brain that tends to be predominantly affected is that called watershed region which is located at the most distal edges of the arterial tree of the main cerebral artery territories (Deb *et al.*, 2010). Additionally, another mechanism of ischemic stroke is cerebral venous

thrombosis that can lead to vascular congestion, impairment of forward flow, and eventually infarction (Vembu *et al.*, 2011).

1.3.2 Cellular pathophysiology

Low respiratory reserve and complete dependence on aerobic metabolism make the brain tissue particularly vulnerable to a compromised vascular supply to the brain that is called ischemia (Deb *et al.*, 2010). The brain's response to acute ischemia depends on the severity and duration of compromised vascular supply. It has been suggested that there are different ischemic thresholds for cerebral dysfunction and cell death. When blood flow drops from the normal value of 50 to 55 ml/100 gram/minute to about 18 ml/100 gram/minute, the brain has reached the threshold for synaptic transmission failure, however, these cells have the potential for recovery. Then, when blood flow drops to about 8 ml/100 gram/minute, cell death can result (Bandera *et al.*, 2006; Braeuninger and Kleinschnitz, 2009). However, due to the presence of collateral circulation, different degrees of severity can be observed in the affected region of the brain. Consequently, part of the brain parenchyma named the "core", undergoes immediate death, while other parts, the "penumbra", may be partially injured but still have the potential to recover (Deb *et al.*, 2010).

On the cellular level, the local depletion of oxygen or glucose leads to a failure of the mitochondria to produce high-energy phosphate compounds, such as adenosine triphosphate (ATP) that can trigger cell death. Although this energy failure does not immediately precipitate cell death, 5 to10 minutes of complete occlusion can lead to irreversible brain injury, and even a partial occlusion for a prolonged period can cause harmful effects (Karaszewski *et al.*, 2009). Furthermore, as approximately

70% of the metabolic demand in the brain is due to the Na^+/K^+ ATPase pump that maintains the ion gradient responsible for neuronal membrane potential, an inadequate energy supply leads to malfunctioning of the ion gradient, which results in a loss of potassium in exchange for sodium, chloride and calcium ions (Lo *et al.*, 2003; Deb *et al.*, 2010). This is accompanied by an inflow of water, resulting in rapid swelling of neurons and glia leading to cytotoxic edema (Kim *et al.*, 2011). An ischemic cascade also stimulates the release of excitatory neurotransmitters in the brain. An uncontrolled release of glutamate in ischemic area, for example, enhances the excitotoxic synaptic transmission that leads to further sodium and calcium ion influxes, which uses the already depleted ATP to maintain a calcium balance, and the disordered activation of protease, lipase, and nuclease enzymes ultimately leading to cell death (Lo *et al.*, 2003; Henson *et al.*, 2010), (Figure 1.1).

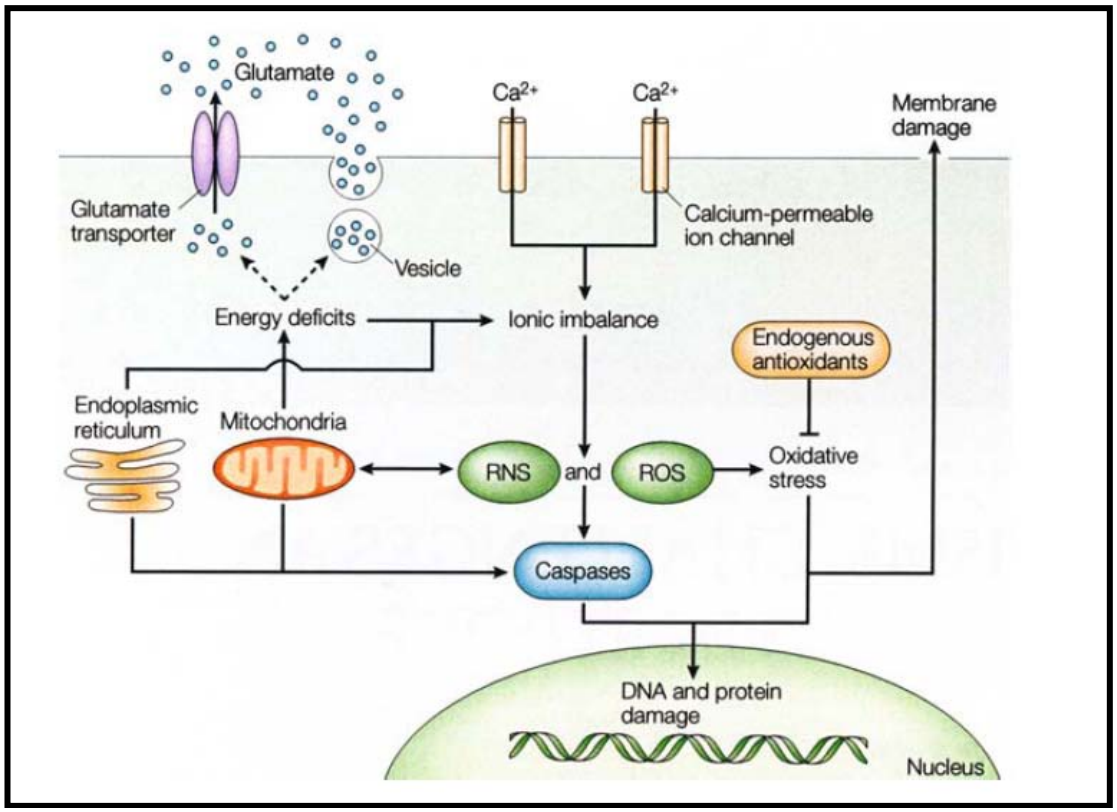

Figure 1.1: Major pathways implicated in ischemic cell death. (After ischemic onset, loss of energy substrates leads to mitochondrial dysfunction and the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Additionally, energy deficits lead to ionic imbalance and excitotoxic glutamate efflux and build up of intracellular calcium. Downstream pathways ultimately include direct free radical damage to membrane lipids, cellular proteins, and deoxyribonucleic acid (DNA)
(Reprinted by permission from Macmillan Publishers Ltd: [Nat Rev Neurosci] (Lo et al.,), copyright (2003).

On the other hand, an ischemic cascade also activates neuroprotective mechanisms as a defence against cell death (Liu *et al.*, 2009). The first protein to be released after ischemia is heat shock protein 70 (HSP70), and its messenger ribonucleic acid (mRNA) is expressed within 1 to 2 hours of ischemia. Studies on animals showed, that the HSP70 inducer is efficacious in limiting the infarct volume, and inhibiting monocyte/macrophage activation (Giffard and Yenari, 2004; Liu *et al.*, 2009).

Other neuroprotective mechanisms may be activated to compensate the effects of ischemia. Anti-apoptotic B-cell lymphoma 2 (Bcl-2) gene family members suppress the release of sequestered proteins and modulate calcium fluxes (Thomenius *et al.*, 2003). The prion protein may have a neuroprotective effect, it is up-regulated during hypoxia, and inhibits neuronal cell death (Weise *et al.*, 2006). In addition, neurotrophin-3 is the growth factor that is especially essential for the survival and maintenance of neurons, and its expression could play a role in neuronal survival after brain ischemia (Galvin and Oorschot, 2003). Interleukin-10 gene is another neuroprotective mechanism, its expression is elevated in most central nervous system diseases and aids in neuronal and glial cell survival via blocking the effects of pro-inflammatory cytokines and by promoting the expression of cell survival signals (Strle *et al.*, 2001).

1.4 Classification, clinical diagnosis and syndromes of acute ischemic stroke

Acute ischemic stroke classifications are largely based on clinical findings and pathophysiology. The most common schemes that have been developed to classify subtypes are the Trial of Org 10172 in Acute Stroke Treatment (TOAST) and the Oxfordshire Community Stroke Project (OCSP).

The TOAST classification system is mainly based on the etiology of the attack and includes five categories (Jackson and Sudlow, 2005; Kirshner, 2009). Moreover, the diagnoses are based on clinical features and on data collected by tests such as brain imaging by computed tomography (CT) or magnetic resonance imaging (MRI), cardiac imaging (echocardiography), duplex imaging of extracranial arteries,

arteriography, and laboratory assessments for a prothrombotic state (Adams *et al.*, 1993); (Table 1.1).

Table 1.1. TOAST classification scheme of acute ischemic stroke

Subtype classification	Subtype classification criteria
Large artery atherosclerosis	- Cortical, cerebellar, or brain stem dysfunction. - Cortical, cerebellar, or brain stem lesions > 1.5 cm upon brain imaging. - Diagnosis supported by > 50% stenosis of a major brain artery or branch cortical artery upon angiography or duplex imaging. - History of TIA in the same vascular territory, and/or exclusion of a cardioembolic source.
Cardioembolism	- Cortical, cerebellar, or brain stem dysfunction. - Cortical, cerebellar, or brain stem lesions > 1.5 cm upon brain imaging. - Identified source of cardioembolism (e.g., AF or valvular disease). - Previous TIAs in > 1 vascular territory.
Lacunar	- No evidence of cortical dysfunction. - Cortical, cerebellar, or brain stem lesions < 1.5 cm upon brain imaging. - Less than 50% stenosis of major brain artery or branch cortical artery upon angiography or duplex imaging. - Known lacunar syndrome. - History of diabetes or hypertension
Other determined aetiology	- Diagnosed nonatherosclerotic vasculopathy, hypercoagulable state, or hematologic disorder.
Undetermined aetiology	- Inability to classify after extensive evaluation. - Evidence of≥ 2 stroke subtypes (e.g., AF and stenosis > 50%).

Abbreviations: AF: Atrial fibrillation; TIA: Transient Ischemic Attack; TOAST: Trial of Org 10172 in Acute Stroke Treatment.

In addition, acute ischemic strokes are also categorized according to the OCSP classification system. The OCSP classification depends on the signs and symptoms present at the time of maximal deficit after a stroke attack, and it includes total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), lacunar infarct (LACI), and posterior circulation infarct (POCI) (Bamford *et al.*, 1991; Jackson and Sudlow, 2005). Additionally, this classification is a reasonably valid way of predicting the site and size of cerebral infarction, the functional recovery and rates of fatality after an attack. Therefore, it can be used very early after ischemic stroke onset, before the infarct appears on the scan (Bamford *et al.*, 1991); (Table 1.2).

Table 1.2. OCSP classification scheme of acute ischemic stroke

Subtype classification	Subtype classification criteria
TACI	- Charaterized by hemiparesis, dysphasia, and homonymous hemianopia. - Large cortical MCA infarct or > 50% of the MCA territory plus ACA or PCA territory. - Subcortical infarct > 1.5 cm
PACI	- Presentation with 2 of the following: hemiparesis, dysphasia, or homonymous hemianopia. - Isolated dysphagia. - Cortical MCA infarct < 50% of the MCA territory. - Border zone cortical infarct between ACA and MCA or PCA and MCA territories.
LACI	- Pure motor stroke, pure sensory stroke, sensorimotor stroke, or ataxic hemiparesis. - Subcortical infarct < 1.5 cm.
POCI	- Brainstem or cerebellar dysfunction and/or isolated homonymous hemianopia. - Cortical infarct in PCA territory. - Brainstem or cerebellar infarct.

Abbreviations: ACA: anterior cerebral artery; LACI: lacunar infarct; MCA: middle cerebral artery; OCSP: Oxfordshire Community Stroke Project; PACI: Partial anterior cerebral infarct; PCA: posterior cerebral artery; POCI: posterior circulation infarct; TACI: total anterior circulation infarct.

Ischemic stroke clinical symptoms depend on the area of the brain and the arterial territories affected (Figure 1.2). It is usually present with an acute loss of brain functions; these functions usually involve the area of motor, sensory, language, vision, visuo-spatial perception or consciousness. And the common signs of stroke include: acute hemiparesis or hemiplegia, acute hemisensory loss, complete or partial hemianopia, monocular or binocular visual loss, or diplopia, dysarthria or aphasia, ataxia, vertigo, or nystagmus, and sudden decrease in consciousness (Blumenfeld, 2002).

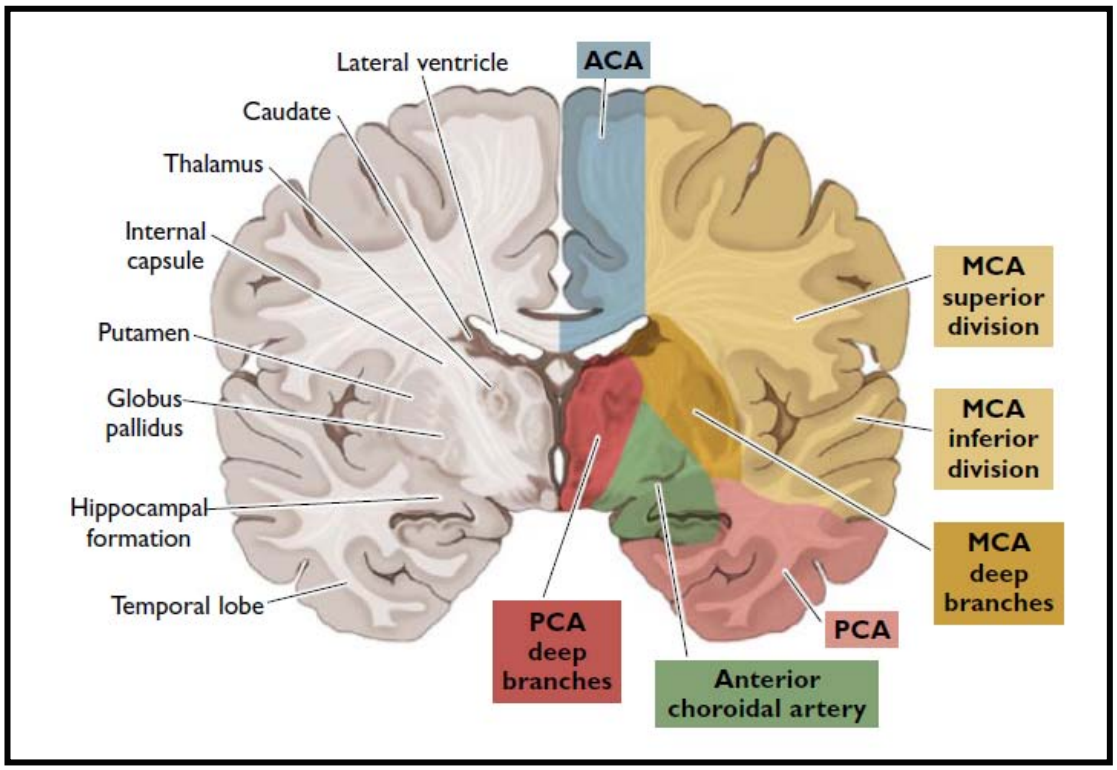

Figure 1.2. Major vascular territories of the brain and important anatomic structures.
Abbreviations: ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery.
(Adapted with permission from Blumenfeld HJ. Neuroanatomy through clinical cases. Sunderland [MA]: Sinauer Associates; 2002:375).

Motor weakness is the most frequent clinical manifestation of ischemic stroke. About two thirds of patients present with uniform hemiparesis involving face, hand, shoulder, foot, and hip. In addition, monoplegia, which occurs in approximately 19% of strokes, usually indicates small infarcts of the motor cortex or centrum semiovale. In majority of cases, faciobrachial weakness is caused by superficial middle cerebral artery (MCA) infarcts, and distal hemiparesis indicates cortical involvement (Blumenfeld, 2002). Furthermore, sensory abnormalities are the second most frequent manifestation of stroke that occur in 50% of stroke patients, and involve the hemiface, arm, trunk, and leg. Stroke is the most common cause of pure sensory loss. In addition, cortical strokes typically produce impairment of discriminative sensations with relative preservation of protopathic sensations (Sullivan and Hedman, 2008). Dysarthria occurs in nearly 8.7% of ischemic strokes. Pure dysarthria is frequently associated with cortical lesions, whereas dysarthria with other neurological signs is more frequently caused by pontine involvement (Kumral *et al.*, 2007).

1.5 Risk factors of acute ischemic stroke

Many risk factors have been identified for ischemic stroke that are associated with an increased risk of stroke attack. They are classified into modifiable and non-modifiable risk factors (Goldstein *et al.*, 2011), (Table 1.3). Modifiable risk factors include those resulting from lifestyle changes and the environment, which can be modified with the help of health-care professionals, treatment and continuing education. On the other hand, non-modifiable risk factors include factors that are related to hereditary or natural processes, which cannot be modified with the current technology and knowledge (Allen and Bayraktutan, 2008; Goldstein *et al.*, 2011).

Table 1.3 Modifiable and non-modifiable risk factors for ischemic stroke

Modifiable risk factors	Non-modifiable risk factors
Well-documented - Hypertension - Diabetes mellitus - Dyslipidemia - Ischemic heart disease - Heart failure - Asymptomatic carotid stenosis - Atrial fibrillation - Peripheral artery disease - Sickle cell disease - Renal impairment - Left ventricular hypertrophy - Postmenopausal hormone therapy - Obesity - Cigarette smoking **Less well-documented** - Alcohol abuse - Hyperhomocysteinemia - Hypercoagulability - Elevated Lipoprotein(a) - Elevated vWF - Oral contraceptive pills - Inflammation (e.g elevated CRP)	- Age - Gender - Race - Family history of stroke/TIA

Abbreviations: CRP: C-reactive protein; TIA: Transient ischemic attack; vWF: Von Willebrand factor.

1.5.1 Modifiable risk factors

1.5.1.1 Hypertension

Hypertension is the most prevalent modifiable risk factor for cerebral infarction. Arterial hypertension can result in multiple target organ damage and promotes atherosclerotic macroangiopathy, ensuing ischemic stroke; however, its treatment substantially reduces the risk of stroke (Fields *et al.*, 2004). The Framingham Heart Study found that the prevalence of hypertension is high and increasing, and that people who are normotensive at the age of 55 years have a 90% lifetime risk of

developing hypertension (Vasan *et al.*, 2002). Furthermore, more than two thirds of people older than 65 years of age are hypertensive (Chobanian *et al.*, 2003).

The relationship between blood pressure and stroke risk is strong, continuous, graded, independent, predictive and etiologically significant (Chobanian *et al.*, 2003). Furthermore, over the range of 115/75 to 185/115 mm Hg, each 20-mm Hg elevation in systolic blood pressure (or 10-mm Hg elevation in diastolic blood pressure) was found to roughly double the risk of death from stroke (Dahlof, 2008).

1.5.1.2 Diabetes mellitus

Diabetes mellitus (DM) is a clear risk factor for ischemic stroke. The risk of stroke is increased by 2- to 6- fold in patients with DM compared to non-diabetic individuals (Sander and Kearney, 2009). Case-controlled studies have shown that the odds ratio of lacunar stroke is increased by 2.3-fold in diabetic patients (You *et al.*, 1995). Diabetes mellitus not only significantly increases the risk of stroke, but it also affects outcomes following ischemic stroke. Diabetes mellitus also doubles the risk of stroke recurrence, which usually results in a poor outcome than the first stroke, and increases the risk of mortality after a stroke attack (Harmsen *et al.*, 2006; Hu *et al.*, 2006). In addition, approximately 20-40% of patients admitted with acute stroke are hyperglycemic. Some of them are known to be diabetic but a further 25-50% of patients have previously undiagnosed glucose tolerance abnormalities (Allen and Bayraktutan, 2008).

Moreover, stroke risk can be reduced in patients with diabetes. In the Steno-2 Study, patients with type 2 DM who are at high risk of vascular diseases; intensive intervention with multiple drug combinations of statin, angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), or antiplatelet drug as appropriate and behaviour modification showed sustained beneficial effects with regards to vascular complications. In addition, this intensive therapy was associated with a 57% lower risk of death from cardiovascular causes (Gaede *et al.*, 2008).

1.5.1.3 Ischemic heart disease

In the Atherosclerosis Risk in Communities study, a history of IHD was a risk factor for non-lacunar (6.5%) and cardioembolic strokes (5.8%) (Ohira *et al.*, 2006b). In addition, the risk of ischemic stroke has been found to gradually increase with increasing numbers of carotid plaques and an increase in the thickness of plaques (Amarenco *et al.*, 1994). The risk of ischemic stroke in subjects with severe plaques was found to be increased by 3-fold compared to subjects without plaques (Hollander *et al.*, 2002).

1.5.1.4 Atrial fibrillation

Even in the absence of other heart diseases, AF is associated with a 4- to 5-fold increased risk of ischemic stroke due to an embolism of stasis-induced thrombi forming in the left atrial appendage (Kannel and Benjamin, 2008). Moreover, one out of six strokes occurs in a patient with AF (Hart *et al.*, 2004). Moreover, other studies have indicated that ischemic stroke associated with AF is almost twice as likely to be fatal than strokes not associated with AF, and AF is an independent predictor of mortality or severe functional deficits among survivors of ischemic stroke attack

(Kannel and Wolf, 2006; Nedeltchev *et al.*, 2010). Furthermore, there is a vitally important opportunity for primary stroke prevention among patients with AF. For patients with AF who are classified as being at low risk of stroke, aspirin therapy alone is recommended; for patients at a high risk of stroke, an adjusted dose of warfarin, to the "target international normalized ratio (INR) range 2.0 to 3.0", or other anticoagulants can provide the greatest protection against stroke (Singer *et al.*, 2008).

1.5.1.5 Dyslipidemia

Dyslipidemia has long been recognized as a risk factor for IHD, but the risk of stroke has become increasingly apparent over the past decade (Lewis and Segal, 2010). Dyslipidemia is defined as elevated levels of low-density lipoproteins (LDL > 130 mg/dl) or triglycerides (>150 mg/dl), or decreased levels of high-density lipoproteins (HDL < 40 mg/dl) (Lloyd-Jones *et al.*, 2010). Moreover, a recent meta-analysis of 24 randomized trials that included 165,792 individuals showed that the reduction of LDL by 39 mg/dl led to a reduction in relative risk of stroke by 21.1% ($p = 0.009$) (Amarenco and Labreuche, 2009). This meta-analysis also showed that the incidence of all strokes was reduced by 18% by statin treatment ($p < 0.001$) (Amarenco and Labreuche, 2009).

1.5.1.6 Renal impairment

Patients with renal impairment were associated with a greater risk of developing ischemic stroke (Nakayama *et al.*, 2007; Kobayashi *et al.*, 2009). Moreover, renal impairment is an important predictor of mortality in patients with a variety of cardiovascular diseases, including stroke (MacWalter *et al.*, 2002; Sweileh, 2008). In

addition, a diagnosis of renal impairment has been linked to poorer medium-term and long-term outcomes following the occurrence of stroke, including increased rates of all-cause mortality (Tsagalis *et al.*, 2009). These findings suggest that there are mechanisms in the pathogenesis of stroke that warrant additional investigation.

1.5.1.7 Heart failure

Heart failure (HF) represents an important health problem. Its incidence approaches 10 per 1000 population after 65 years of age (Lloyd-Jones *et al.*, 2010). The reported stroke risk rate in HF varies according to the study and the length of patient follow-up: 1 to 29% of patients with dilated cardiomyopathy might have a stroke in 1 to 11 years of follow-up compared to 0.8% to 4% during hospitalization and up to 3 years of follow-up (Witt *et al.*, 2007). Moreover, pre-existing HF has been associated with a more severe type of ischemic stroke and with stroke mortality, both in the acute phase and in the first 3 months after the attack (Appelros *et al.*, 2002).

1.5.1.8 Smoking

The Framingham Heart Study was among the first studies that evaluated the relationship between smoking, including the number of cigarettes smoked, and the effect of stopping, and the type of stroke (Wolf *et al.*, 1988). This study identified cigarette smoking as a potent risk factor for ischemic stroke, and the relative risk of stroke in heavy smokers (> 40 cigarettes per day) was found to be twice than that of light smokers (< 10 cigarettes per day). Also, the reduction in the risk ratio was significant by 2 years after smoking cessation and it reached the level of a non-smoker at 5 years (Wolf *et al.*, 1988). Furthermore, smoking may contribute to increased stroke risk via both acute effects on generating a thrombus in

atherosclerotic arteries and chronic effects related to increased atherosclerosis (Burns, 2003). Impaired endogenous fibrinolysis, decreased blood flow in the brain, increased heart rate and increased blood pressure due to the vasoconstrictive effects of smoking are associated with lacunar stroke development (Jackson and Sudlow, 2005).

1.5.1.9 Left ventricular hypertrophy

The increased mass of left ventricle is independently associated with the risk of ischemic stroke (Bikkina *et al.*, 1994), although the mechanisms of the relationship between left ventricular hypertrophy (LVH) and ischemic stroke are not fully clear. One explanation is that large vessel disease promotes blood stasis in both the left ventricle and left atrium, increasing the chance of thrombus formation and the risk of embolic stroke (Allen and Bayraktutan, 2008).

1.5.1.10 Obesity

Abdominal obesity has been found to be an independent, potent risk factor for ischemic stroke, particularly the large vessel stroke subtype (Lu *et al.*, 2006; Ohira *et al.*, 2006b). Some studies have shown that abdominal obesity is related to endothelial dysfunction, a marker of atherosclerotic disease, and to hemorheological disorders such as hyperviscosity, hyperfibrinogenemia, reduced red cell deformability and erythrocyte aggregability (Carr and Brunzell, 2004; Wessel *et al.*, 2004).

1.5.1.11 Carotid artery stenosis

Carotid artery stenosis is a pathologic atherosclerotic narrowing of the extracranial carotid arteries (Smith *et al.*, 2001). Patients with more than 70% stenosis in the carotid artery and a history of stroke or TIA are 6 times more risk of developing a recurrent stroke on the side of the stenosis compared to asymptomatic patients (Fatahzadeh and Glick, 2006). On the other hand, significant reduction in the risk of stroke has been obtained by surgical intervention extracranial carotid stenosis (Sacco, 2001; Goldstein, 2003). In addition, aspirin therapy and modifications of risk factors are recommended for patients with asymptomatic carotid disease (Smith *et al.*, 2001).

1.5.1.12 Elevated lipoprotein (a)

Lipoprotein (a) is a low-density lipoprotein particle in which apolipoprotein B-100 is covalently linked to the glycoprotein apoprotein (a). Its structure is similar to LDL. Moreover, apoprotein (a) has a similar structure to plasminogen but it does not have its enzymatic activity. Therefore, it can inhibit fibrinolysis by binding to the catalytic complex of plasminogen, tissue plasminogen activator, and fibrin, leading to thrombosis (Hancock *et al.*, 2003; Marcovina and Koschinsky, 2003).

In addition, some population-based epidemiological studies found that lipoprotein (a) is associated with an increased risk of ischemic stroke (Milionis *et al.*, 2006; Ohira *et al.*, 2006a). It has been proposed that the use of niacin might prevent ischemic stroke in patients with high levels of lipoprotein (a), but its effectiveness has not been well established (Goldstein *et al.*, 2011).

1.5.1.13 Von Willebrand factor

The Von Willebrand factor (vWF) is a plasma glycoprotein and a mediator of platelet adhesion during endothelial insults via its spontaneous formation of strong bonds with the platelet glycoprotein 1b-IX-V complex, resulting in platelet aggregation and thrombus formation (Nishio *et al.*, 2004). It has been shown that vWF levels were significantly higher in ischemic stroke patients, especially in the acute phase of all stroke subtypes (Kozuka *et al.*, 2002).

1.5.1.14 C-reactive protein (CRP)

The C- reactive protein (CRP) is an acute-phase plasma protein produced by the liver and is considered as a molecular marker of the risk of stroke associated with inflammation (Elkind, 2010). The CRP has been demonstrated to predict disease progression and clinical adverse events in cerebrovascular circulation in apparently healthy subjects as well as in patients with established atherosclerosis. Moreover, CRP has also been shown to exacerbate ischemic necrosis (Rost *et al.*, 2001; Elkind, 2010).

1.5.1.15 Homocysteine

Homocysteine is a sulfur-containing amino acid derived from the conversion of methionine to cysteine (Kardesoglu *et al.*, 2011). Elevated levels of homocysteine are often a consequence of deficiencies in some B vitamins, some rare hereditary diseases, or they can be drug induced (Bostom *et al.*, 1999; Ntaios *et al.*, 2009). Evidence has been accumulated to support the concept that an elevation in plasma homocysteine is a strong predictor for the incidence of and mortality from atherosclerosis, cardiovascular disease and ischemic stroke, and this graded

association was found to be independent of other traditional risk factors (Bostom *et al.*, 1999; Tanne *et al.*, 2003).

1.5.1.16 Alcohol abuse

Alcohol abuse can lead to some medical complications, including stroke (Patra *et al.*, 2010; Hillbom *et al.*, 2011). It has been shown that heavy alcohol consumption can increase the relative risk of stroke subtypes, while light or moderate alcohol consumption may have a protective effect and reduce the risk of ischemic stroke (Patra *et al.*, 2010). Heavy alcohol intake can lead to hypertension, hypercoagulation, reduced cerebral blood flow, and a greater risk of AF (Djousse *et al.*, 2004; Mukamal, 2004). On the other hand, light to moderate alcohol intake can increase HDL, reduce platelet aggregation, and lower plasma fibrinogen concentration (Gaziano *et al.*, 1993; Britton *et al.*, 2009; Djousse *et al.*, 2009).

1.5.2 Non-modifiable risk factors

1.5.2.1 Age

Age is the most important non-modifiable risk factor for ischemic stroke (Rothwell *et al.*, 2005a). Although ischemic stroke can affect individuals of different ages, the incidence and prevalence of this condition sharply increase with age (Goldstein *et al.*, 2011). Moreover, the prevalence of cerebral infarction between the age of 55 and 64 years was found to be nearly 11%. This prevalence increases to 22% between 65 and 69 years of age, 28% between 70 and 74 years of age, 32% between 75 and 79 years of age, 40% between 80 and 85 years of age, and 43% at more than 85 years old (Lloyd-Jones *et al.*, 2010). Moreover, in the Northern Manhattan Stroke Study (NOMASS), which illustrated the relationship between age and ischemic stroke

subtypes, the majority of ischemic strokes in adult patients aged between 20 and 44 years were cryptogenic (55%). Other subtypes were less common: lacunar (18%), intracranial atherosclerosis (9%), cardioembolic (6%) and extracranial atherosclerosis (6%). On the other hand, the incidence of cardioembolic stroke was found to be much greater in an age group older than 45 years, and a decrease in the incidence of cryptogenic stroke was also observed (Jacobs *et al.*, 2002).

It has been estimated that by the year 2025, the global population aged above 60 years old may rise to 1.2 billion, which is double the number of people above that age in 1995 (Krug *et al.*, 2002). This growth in the elderly population, together with the influence of aging on stroke, suggests that the incidence and economic costs of this disease will increase (Chen *et al.*, 2010).

1.5.2.2 Gender

The incidence of stroke was found to be greater in males compared to females at younger ages, but not at very younger or much older ages (Kissela *et al.*, 2004; Lloyd-Jones *et al.*, 2010). Factors such as the use of oral contraceptives and pregnancy might contribute to the increased risk of stroke in young females (Baillargeon *et al.*, 2005), and the earlier cardiac-related deaths in males might contribute to the relatively greater risk of stroke in older females.

1.5.2.3 Ethnic group

Ethnic effects on disease risk can be difficult to be considered separately. Compared to European Americans, African Americans and some Hispanic Americans have higher rates of stroke incidence and mortality (White *et al.*, 2005; Borrell and Crawford, 2009). Possible reasons for the higher stroke incidence and mortality rates in blacks compared to whites include a higher prevalence of hypertension, DM and obesity among the black population (Kurian and Cardarelli, 2007). In addition, a previous study regarding the incidence of stroke in Chinese, Malays and Indians in Singapore found in females aged < 65 years, there was a significantly greater rate of stroke incidence among the Malays than the Chinese (Heng *et al.*, 2000). However, no significant differences regarding stroke prevalence among Singaporeans aged 50 years and older (Venketasubramanian *et al.*, 2005).

1.6 Treatment of acute ischemic stroke

1.6.1 Current management strategy

Once a patient has arrived at the hospital and diagnosed with acute ischemic stroke, management serves two purposes: to reduce the burden of disability and mortality after the attack and to reduce the risk of recurrent stroke, which is referred to as secondary prevention. Acute treatment of ischemic stroke involves the control of physiological variables, strategies to reperfuse the ischemic area, and protection of the vulnerable ischemic penumbra using neuroprotective therapy (Adams *et al.*, 2007).

All patients should be cared for in a dedicated acute stroke unit, which in itself saves lives and significantly improves functional outcomes (Langhorne *et al.*, 2010). Furthermore, all patients with suspected stroke should undergo emergency brain

imaging to help confirm the diagnosis. The main choices of brain imaging are CT and MRI. An immediate brain scan enables rapid treatment initiation and improves stroke outcomes (Wardlaw *et al.*, 2004). Non-contrast CT brain imaging is the most widely available test and has excellent sensitivity for detecting hemorrhage early after onset, while MRI has a similar sensitivity for detecting hemorrhage and a significantly greater sensitivity for detecting ischemia (Chalela *et al.*, 2007).

1.6.2 Control of physiological variables

1.6.2.1 Control of blood pressure

High blood pressure is found in nearly 80% of patients following acute stroke (Leonardi-Bee *et al.*, 2002), which may result from the stress of the stroke, pain, previous hypertension, a full bladder, a physiological response to hypoxia, or increased intracranial pressure (Adams *et al.*, 2007). It has been revealed that high blood pressure is independently associated with poor outcome (Willmot *et al.*, 2004). However, a blood pressure elevation directly after an attack could represent a protective response, and subsequent falls in blood pressure can lead to infarct expansion because of impaired cerebrovascular autoregulation following acute stroke (Sare *et al.*, 2009). The current guidelines suggest an early lowering of blood pressure in the presence of hypertensive encephalopathy, aortic dissection, severe cardiac failure and in cases where the blood pressure is extremely high (> 220 mmHg for systolic blood pressure or > 120 mmHg for diastolic blood pressure) (Chobanian *et al.*, 2003; Adams *et al.*, 2007; Goldstein *et al.*, 2011).

There are a growing number of pharmacological treatment choices for patients with hypertension. However, the choice of a certain antihypertensive drug class is affected by many factors, including the presence of co-morbid conditions (Chobanian *et al.*,