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3 **TITLE:** CALCIUM CHANNEL BLOCKERS IN SECONDARY CARDIOVASCULAR PREVENTION
4 AND RISK OF ACUTE EVENTS: REAL-WORLD EVIDENCE FROM NESTED CASE-CONTROL
5 STUDIES ON ITALIAN HYPERTENSIVE ELDERLY

6 **RUNNING HEAD:** CALCIUM CHANNEL BLOCKERS AND RISK OF ACUTE EVENTS

7

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28 “Acknowledgments' section”.

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33 **SUPPLEMENTARY MATERIAL**

34

35 **S1 text. List of ICDS-9 CM codes considered to identify CV events as inclusion criteria.** This material
36 reports all ICD-9 CM codes considered in primary or secondary fields of diagnosis, in order to identify all
37 patients hospitalized for CV events.

38 **S2 text. List of ICDS-9 CM codes considered to identify acute CV outcomes.** This material reports all
39 ICD-9 CM codes considered in primary field of diagnosis, in order to detect and stratify acute CV outcomes.

40 **S3 text. Identification of cardiovascular procedures from hospital discharge records.** This list reports all
41 ICD9-CM codes considered in primary or secondary diagnosis fields to identify cardiovascular procedures,
42 therefore allowing to assess the severity of the cardiovascular pathology.

43 **Table S1. Sensitivity analysis-** Odds Ratio of the acute CV outcomes and all-cause for current vs
44 past users of the different Calcium Channel Blockers classes, excluding from the analysis all
45 patients hospitalized for whichever cause in the 30 days before index.

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51 **S1 text- CV events considered as inclusion criteria**

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53 The following ICD9-CM codes were considered in either primary or secondary diagnosis fields:

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55 **1. ISCHEMIC HEART DISEASE**

56 The case selection algorithm includes the following ICD9CM codes in either primary or secondary diagnosis fields:

57

58 410.* Acute myocardial infarction

59 411.* Other acute and subacute forms of ischemic heart disease

60 412.* Old myocardial infarction

61 413.* Angina pectoris

62 414.* Other forms of chronic ischemic heart disease

63 It will be possible to distinguish different sub-populations:

64 1a. Acute Myocardial Infarction

65 Primary diagnosis = 410.*

66 OR

67 Primary diagnosis = codes compatible** with a diagnosis of acute myocardial infarction, including procedure-related complications, and secondary diagnosis = 410.*

68 **Codes compatible with a diagnosis of acute myocardial infarction

69 411.* Other acute and subacute forms of ischemic heart disease

70 413.* Angina pectoris

71 414.* Other forms of chronic ischemic heart disease

72 423.0 Hemopericardium

73 426.* Conduction disorders

74 427.* Cardiac dysrhythmias (excluding 427.5 Cardiac arrest)

75 428.* Heart failure

76 429.5 Rupture of chordae tendinae

77 429.6 Rupture of papillary muscle

78 429.71 Acquired cardiac septal defect

79 429.79 Other sequelae of myocardial infarction, not elsewhere classified (Mural thrombus (atrial, ventricular) acquired, following myocardial infarction)

80 429.81 Other disorders of papillary muscle

81 518.4 Acute edema of lung, unspecified

82 518.81 Acute respiratory failure

83 780.01 Coma

84 780.2 Syncope and collapse

85 785.51 Cardiogenic shock

86 799.1 Respiratory arrest

87 997.02 Iatrogenic cerebrovascular infarction or hemorrhage (postoperative stroke)

88 998.2 Accidental puncture or laceration during a procedure (accidental perforation by catheter)

89 1b. Subacute and chronic forms of ischemic heart disease

90 Subacute forms and angina pectoris

91 411.* Other acute and subacute forms of ischemic heart disease

92 413.* Angina pectoris

93 Chronic forms

94 412.* Old myocardial infarction

95 414.* Other forms of chronic ischemic heart disease

96 The following codes identify chronic forms when associated with codes 410.* or 414.* in secondary diagnosis fields:

97 429.2 Cardiovascular disease unspecified

98 429.3 Cardiomegaly

99 429.4 Functional disturbances following cardiac surgery

100 429.89 Other ill-defined heart diseases

101

102 **2. HEART FAILURE**

103

106 The case selection algorithm includes the following ICD9CM codes in either primary or secondary diagnosis
107 fields:

108 428.* Heart failure

109 398.91 Rheumatic heart failure (congestive)

110 402.01 Malignant hypertensive heart disease with heart failure

111 402.11 Benign hypertensive heart disease with heart failure

112 402.91 Unspecified hypertensive heart disease with heart failure

113 404.01 Malignant hypertensive heart and renal disease with heart failure

114 404.03 Malignant hypertensive heart and renal disease with heart failure and renal failure

115 404.11 Benign hypertensive heart and renal disease with heart failure

116 404.13 Benign hypertensive heart and renal disease with heart failure and renal failure

117 404.91 Unspecified hypertensive heart and renal disease with heart failure

118 404.93 Unspecified hypertensive heart and renal disease with heart failure and renal failure

119 The following codes identify heart failure when associated with code 428.* in secondary diagnosis fields:

120 425.4 Other primary cardiomyopathies

121 425.5 Alcoholic cardiomyopathy

122 425.7 Nutritional and metabolic cardiomyopathy

123 425.8 Cardiomyopathy in other diseases classified elsewhere

124 425.9 Secondary cardiomyopathy unspecified

125

126 **3. CARDIAC ARRHYTHMIA**

127 The case selection algorithm includes the following ICD9CM codes in either primary or secondary diagnosis
128 fields:

129 427.* Cardiac dysrhythmias

130 785.0 Tachycardia unspecified

131

132 **4. STROKE**

133 4a. Acute conditions

134 The case selection algorithm includes the following ICD9CM codes in primary diagnosis fields:

135 Haemorrhagic Stroke

136 430 Subarachnoid haemorrhage

137 431 Intracerebral haemorrhage

138 432.* Other and unspecified intracranial hemorrhage

139 Ischemic Stroke

140 433.*1 Occlusion and stenosis of precerebral arteries with cerebral infarction

141 434.* Occlusion of cerebral arteries

142 436 Acute but ill-defined cerebrovascular disease

143 Transient cerebral ischemia

144 435.* Transient cerebral ischemia

145 4b. Subacute, chronic and late effects of cerebrovascular disease

146 The case selection algorithm includes the following ICD9CM codes in primary and secondary diagnosis fields:

147 433.*0 Occlusion and stenosis of precerebral arteries without mention of cerebral infarction

148 437.0 Cerebral atherosclerosis

149 437.1 Other generalized ischemic cerebrovascular disease

150 438.* Late effects of cerebrovascular disease

151 **S2 text- CV events considered for outcomes evaluation**

152
153 The following ICD9-CM codes were considered in primary diagnosis:

154
155 **A. ACUTE MYOCARDIAL INFARCTION**

156 410.* OR Primary diagnosis = codes compatible* with a diagnosis of acute myocardial infarction, including
157 procedure-related complications, and secondary diagnosis
158 = 410.*

159 Codes compatible with a diagnosis of acute myocardial infarction

160 411.* Other acute and subacute forms of ischemic heart disease

161 413.* Angina pectoris

162 414.* Other forms of chronic ischemic heart disease

163 423.0 Hemopericardium

164 426.* Conduction disorders

165 427.* Cardiac dysrhythmias (excluding 427.5 Cardiac arrest)

166 428.* Heart failure

167 429.5 Rupture of chordae tendineae

168 429.6 Rupture of papillary muscle

169 429.71 Acquired cardiac septal defect

170 429.79 Other sequelae of myocardial infarction, not elsewhere classified (Mural thrombus (atrial) (ventricular)
171 acquired, following myocardial infarction)

172 429.81 Other disorders of papillary muscle

173 518.4 Acute edema of lung, unspecified

174 518.81 Acute respiratory failure

175 780.01 Coma

176 780.2 Syncope and collapse

177 785.51 Cardiogenic shock

178 799.1 Respiratory arrest

179 997.02 Iatrogenic cerebrovascular infarction or hemorrhage (postoperative stroke)

180 998.2 Accidental puncture or laceration during a procedure (accidental perforation by catheter)

181

182 **B. CARDIAC ARRHYTHMIA**

183 427.* Cardiac dysrhythmias

184 785.0 Tachycardia unspecified

185

186 **C. HEART FAILURE**

187 428.* Heart failure

188 402.01 Malignant hypertensive heart disease with heart failure

189 402.11 Benign hypertensive heart disease with heart failure

190 402.91 Unspecified hypertensive heart disease with heart failure

191 404.01 Malignant hypertensive heart and renal disease with heart failure

192 404.03 Malignant hypertensive heart and renal disease with heart failure and renal failure

193 404.11 Benign hypertensive heart and renal disease with heart failure

194 404.13 Benign hypertensive heart and renal disease with heart failure and renal failure

195 404.91 Unspecified hypertensive heart and renal disease with heart failure

196 404.93 Unspecified hypertensive heart and renal disease with heart failure and renal failure

197 **D. HEMORRHAGIC STROKE**

198 430 Subarachnoid hemorrhage

199 431 Intracerebral hemorrhage

200 432.* Other and unspecified intracranial hemorrhage

201

202 **E. ISCHEMIC STROKE**
203 433.*1 Occlusion and stenosis of precerebral arteries with cerebral infarction
204 434.* Occlusion of cerebral arteries

205
206 **F. TRANSIENT CEREBRAL ISCHEMIA**
207 435.* Transient cerebral ischemia

208

209

210 **S3 text. Identification of cardiovascular procedures from hospital discharge records.** This list reports all
211 ICD9-CM codes considered in primary or secondary diagnosis fields to identify cardiovascular procedures,
212 therefore allowing to assess the severity of the cardiovascular pathology.

213

214 **CORONARY ARTERY BYPASS SURGERY**

215 36.1* Bypass anastomosis for heart revascularization

216 V45.81 Postsurgical aortocoronary bypass status

217

218 **PTCA**

219 00.66 Percutaneous transluminal coronary angioplasty [ptca] or coronary atherectomy

220 36.0* Removal of coronary artery obstruction and insertion of stent(s)

221 V45.82 Percutaneous transluminal coronary angioplasty status

222

223 **CEREBRAL REVASCULARIZATION**

224 00.61 Percutaneous angioplasty or atherectomy of precerebral (extracranial) vessel(s)

225 00.62 Percutaneous angioplasty or atherectomy of extracranial vessel(s)

226 38.11 Endarterectomy, intracranial vessels

227 38.12 Endarterectomy, other vessels of head and neck

228 38.31 Resection of vessel with anastomosis, intracranial vessels

229 38.32 Resection of vessel with anastomosis, other vessels of head and neck

230

231 **OTHER HEART SURGERY PROCEDURES**

232 35.* Operations On Valves And Septa Of Heart

233 37.0 Pericardiocentesis

234 37.1* Cardiotomy and pericardiotomy

235 37.3* Pericardiectomy and excision of lesion of heart

236 37.4* Repair of heart and pericardium

237 37.5* Heart replacement procedures

238 37.6* Implantation of heart assist system

239 37.9* Other operations on heart and pericardium

240

241 **Table S1: Sensitivity analysis-** Odds Ratio of the acute CV outcomes and all-cause for current vs
 242 past users of the different Calcium Channel Blockers classes, excluding from the analysis all
 243 patients hospitalized for whichever cause in the 30 days before index.

244

	ACUTE CEREBRO- CARDIOVASCULAR OUTCOMES	ALL-CAUSE MORTALITY	245
			246
Number			247
Cases	11,672	8,427	
Controls	22,543	20,394	248
Odds Ratio [95% CI]			249
CCBs, overall	0.89 [0.85 – 0.92]	0.40 [0.38 – 0.43]	250
Among CCBs classes:			
Long-acting DHPs	0.87 [0.84 – 0.91]	0.46 [0.43 – 0.49]	251
Short-acting DHPs	1.75 [1.32 – 2.31]	1.40 [0.82 – 2.42]	252
Long-acting n-DHPs	1.02 [0.95 – 1.10]	0.52 [0.45 – 0.60]	
Short-acting n-DHPs	1.17 [1.07 – 1.28]	0.79 [0.67 – 0.94]	253

254

255 CCB=Calcium Channel Blockers; CI= Confidence Intervals; DHPs= Dihydropyridines; n-DHPs=non-
 256 Dihydropyridines

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