

# **SUPPLEMENTAL MATERIAL**

**Table S1.** Baseline characteristics of the studies.

Study, Ref.	Patients (N)	Age	Male	Diabetes	Hypertension	Hyperlipidemia	Smoking	Aspirin	P2Y12	β-Blockers	ACE-Inhib.	Statins
Abid <sup>1</sup>	Non-Obstr. (21) Obstr. (0)	45.0±14.9 -	19 (90.5) -	2 (9.5) -	5 (23.8) -	3 (14.3) -	18 (85.7) -	- -	- -	- -	- -	- -
Aldous <sup>2</sup>	Non-Obstr. (351) Obstr. (0)	54.9±20.7 -	166 (47.3) -	36 (10.3) -	139 (39.6) -	79 (22.5) -	105 (29.9) -	109 (31.1) -	215 (61.3) -	129 (36.8) -	- -	190 (54.1) -
Bugiardini <sup>3</sup>	Non-Obstr. (701) Obstr. (0)	57.2±11.7 -	329 (46.9) -	102 (14.6) -	322 (45.9) -	- -	213 (30.4) -	- -	- -	- -	- -	- -
Chan <sup>4</sup>	Non-Obstr. (0) Obstr. (8225)	- -	- 5664 (68.9)	- 2433 (29.6)	- 5604 (68.1)	- 4956 (60.3)	- 2875 (35.0)	- -	- 4798 (58.3)	- 7159 (87)	- 6032 (73.3)	- 6813 (82.8)
Cortell <sup>5</sup>	Non-Obstr. (64) Obstr. (440)	60.0±12.5 66.0±11.3	27 (42.2) 325 (73.9)	13 (20.3) 167 (38.0)	33 (51.6) 264 (60.0)	23 (35.9) 205 (46.6)	17 (32.3) 142 (32.3)	- -	- -	- -	- -	- -
Da Costa <sup>6</sup>	Non-Obstr. (91) Obstr. (91)	49.0±14.0 51.0±14.0	57 (62.6) 57 (62.6)	9 (9.9) 22 (24.2)	14 (15.4) 32 (35.2)	18 (19.8) 44 (48.4)	55 (62.6) 57 (62.6)	- -	- -	- -	- -	- -
Dey <sup>7</sup>	Non-Obstr. (2031) Obstr. (24724)	- -	- -	- -	- -	- -	- -	1919 (94.5) 23628 (95.6)	- -	1662 (81.8) 21692 (87.7)	1207 (59.4) 17205(69.6)	1324 (65.2) 18863 (76.3)
Dokainish <sup>8</sup>	Non-Obstr. (107) Obstr. (788)	59.0±12.5 62.4±10.7	50 (46.7) 529 (67.1)	17 (15.9) 237 (30.1)	70 (65.4) 510 (64.7)	46 (43) 512 (65)	27 (25.2) 235 (29.8)	- -	- -	- -	- -	- -
Dwyer <sup>9</sup>	Non-Obstr. (29) Obstr. (151)	59.0±2.0 66.0±1.0	19 (65.5) 123 (81.5)	6 (21.0) 35 (20.3)	11 (37.9) 61 (40.4)	- -	6 (20.7) 21 (13.9)	14 (48.3) 108 (71.5)	0 (0.0) 67 (44.4)	5 (17.2) 95 (62.9)	5 (17.2) 76 (50.3)	18 (62.1) 123 (81.5)
Golzio <sup>10</sup>	Non-Obstr. (53) Obstr. (351)	45.5±11.6 58.0±9.0	43 (81.1) 288 (82.1)	2 (3.8) 42 (12.0)	22 (41.5) 149 (42.5)	16 (30.2) 147 (41.9)	34 (64.2) 263 (74.9)	- -	- -	- -	- -	- -
Hamdan <sup>11</sup>	Non-Obstr. (11) Obstr. (113)	57.7±18.9 66.0±12.2	4 (36.4) 89 (78.8)	2 (18.2) 45 (39.8)	4 (36.4) 72 (63.7)	3 (27.3) 65 (57.5)	7 (63.6) 68 (60.2)	6 (54.5) 86 (76.1)	3 (27.3) 76 (67.3)	6 (54.5) 83 (73.5)	3 (27.3) 39 (34.5)	6 (54.5) 89 (78.8)
Hansen <sup>12</sup>	Non-Obstr. (1595) Obstr. (0)	62.1±12.5 -	5839 (44.3) -	- -	- -	- -	- -	- -	- -	- -	- -	- -
Harris <sup>13</sup>	Non-Obstr. (1170) Obstr. (0)	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -
Hung <sup>14</sup>	Non-Obstr. (19) Obstr. (0)	61.0±6.0 -	14 (73.7) -	- -	- -	- -	- -	- -	- -	- -	- -	- -
Johnston <sup>15</sup>	Non-Obstr. (13172) Obstr. (0)	63.0±11.6 -	5839 (44.3) -	1397 (10.6) -	4111 (31.2) -	5403 (41.0) -	1885 (14.3) -	- -	- -	- -	- -	- -

Kang <sup>16</sup>	Non-Obstr. (126)	59.0±12.9	77 (61.1)	19 (15.1)	49 (38.9)	7 (5.6)	65 (51.6)	-	-	-	-	-
	Obstr. (8238)	64.8±11.9	5940 (72.1)	2274 (27.6)	3987 (48.4)	1689 (20.5)	4910 (59.6)	-	-	-	-	-
Larsen <sup>17</sup>	Non-Obstr. (726)	53.8±15.4	442 (60.9)	69 (9.5)	299 (41.2)	249 (34.3)	307 (42.3)	-	-	-	-	-
	Obstr. (9071)	64.4±11.7	6821 (75.2)	4109 (45.3)	4536 (50)	1823 (20.1)	4381 (48.3)	-	-	-	-	-
Larson <sup>18</sup>	Non-Obstr. (187)	57.4±16.4	122 (65.2)	24 (12.8)	92 (49.2)	89 (47.6)	60 (32.1)	-	-	-	-	-
	Obstr. (1138)	62.8±14.1	828 (72.8)	172 (15.1)	626 (55)	619 (54.4)	470 (41.3)	-	-	-	-	-
Manfrini <sup>19</sup>	Non-Obstr. (350)	60.5±11.8	236 (67.4)	41 (11.7)	134 (38.3)	121 (34.6)	135 (38.6)	320 (91.4)	-	272 (77.7)	202 (57.7)	320 (91.4)
	Obstr. (1252)	71.5±12.1	811 (64.8)	233 (18.6)	550 (43.9)	506 (40.4)	349 (27.9)	991 (79.2)	-	793 (63.3)	831 (66.4)	991 (79.2)
Minha <sup>20</sup>	Non-Obstr. (163)	55.2±12.5	108 (66.3)	43 (26.4)	73 (44.8)	90 (55.2)	60 (36.8)	143 (87.7)	63 (38.7)	96 (58.9)	88 (54.0)	163 (68.7)
	Obstr. (3523)	60.7±12.4	2753 (78.1)	958 (27.2)	3515 (99.8)	2040 (57.9)	1585 (45.0)	3393 (96.3)	2945 (83.6)	2884 (81.9)	2677 (76.0)	3026 (85.9)
Ohlow <sup>21</sup>	Non-Obstr. (272)	61.9±14.0	138 (50.7)	76 (27.9)	204 (75)	119 (43.8)	62 (22.8)	-	-	-	-	-
	Obstr. (253)	65.4±12.0	180 (71.1)	73 (28.9)	173 (68.4)	76 (30.0)	70 (27.7)	-	-	-	-	-
Patel <sup>22</sup>	Non-Obstr. (3306)	59.0±16.3	1423 (43)	654 (19.8)	2019 (61.1)	1173 (35.5)	975 (29.5)	2432 (73.6)	856 (25.9)	1993 (60.3)	1209 (36.6)	3306 (36.5)
	Obstr. (34995)	64.0±14.8	22607 (64.6)	10131 (28.9)	22690 (64.8)	16708 (47.7)	12180 (34.8)	28239 (80.7)	20975 (59.9)	25630 (73.2)	13570(38.8)	17598 (50.3)
Pinheiro <sup>23</sup>	Non-Obstr. (220)	51.5±11.8	96 (43.6)	40 (18.2)	147 (66.8)	108 (49.1)	68 (30.9)	-	-	-	-	-
	Obstr. (1131)	60.6±11.4	675 (59.7)	323 (28.6)	819 (72.4)	693 (61.3)	406 (35.9)	-	-	-	-	-
Planer <sup>24</sup>	Non-Obstr. (197)	54.0±13.3	92 (46.7)	36 (18.3)	103 (52.3)	64 (32.5)	61 (31)	107 (54.3)	46 (23.4)	95 (48.2)	99 (50.3)	197 (49.7)
	Obstr. (2245)	60.6±13.3	1526 (68)	595 (26.5)	1308 (58.3)	980 (43.7)	825 (36.7)	1421 (63.3)	1506 (67.1)	1731 (77.1)	1194 (53.2)	1785 (79.5)
Ramanath <sup>25</sup>	Non-Obstr. (123)	58.7±15.4	57 (46.3)	29 (23.6)	75 (61)	59 (48)	27 (22.0)	108 (87.8)	44 (35.8)	91 (74)	77 (62.6)	123 (69.1)
	Obstr. (2141)	62.7±12.8	1473 (68.8)	601 (28.1)	1461 (68.2)	1374 (64.2)	558 (26.1)	2034 (95.0)	1567 (59.9)	1910 (89.2)	1404 (65.6)	1739 (81.2)
Raymond <sup>26</sup>	Non-Obstr. (74)	43.0±38.8	42 (56.8)	1 (1.4)	10 (13.5)	27 (36.5)	53 (71.6)	-	-	-	-	-
	Obstr. (74)	-	42 (56.8)	11 (14.9)	23 (31.1)	59 (79.7)	51 (68.9)	-	-	-	-	-
Rhew <sup>27</sup>	Non-Obstr. (100)	58.5±14.2	59 (59)	10 (10)	41 (41)	1 (1.0)	49 (49.0)	-	-	-	-	-
	Obstr. (1120)	63.4±12.2	808 (72.1)	323 (28.8)	527 (47.1)	55 (4.9)	711 (63.5)	-	-	-	-	-
Roe <sup>28</sup>	Non-Obstr. (696)	56.0±17.0	350 (50.3)	81 (11.6)	367 (52.7)	248 (35.6)	214 (30.7)	-	-	-	-	-
	Obstr. (5071)	63.0±11.1	3555 (70.1)	1212 (23.9)	2820 (55.6)	2358 (46.5)	1526 (30.1)	-	-	-	-	-
Rossini <sup>29</sup>	Non-Obstr. (318)	66.0±15.0	145 (45.6)	37 (11.6)	185 (58.2)	141 (44.3)	73 (23.0)	276 (86.8)	183 (57.5)	204 (64.2)	167 (52.5)	236 (74.2)
	Obstr. (888)	63.0±12	697 (78.5)	229 (25.8)	526 (59.2)	603 (67.9)	64 (7.2)	883 (99.4)	882 (99.3)	763 (85.9)	634 (71.4)	801 (90.2)
Shishehbor <sup>30</sup>	Non-Obstr. (0)	-	-	-	-	-	-	-	-	-	-	-
	Obstr. (1240)	65.4±12.0	796 (64.2)	390 (31.5)	-	-	291 (23.5)	1162 (93.7)	979 (79.0)	572 (77.1)	275 (22.2)	1069 (86.2)
Sun <sup>31</sup>	Non-Obstr. (51)	57.2±10.8	31 (60.8)	8 (15.7)	27 (52.9)	10 (19.6)	13 (25.5)	-	-	-	-	-
	Obstr. (678)	60.3±10.8	483 (71.2)	200 (29.5)	432 (63.7)	137 (20.2)	274 (40.4)	-	-	-	-	-

Terefe <sup>32</sup>	Non-Obstr. (58)	55.0±13.0	27 (46.6)	10 (17.2)	43 (74.1)	13 (22.4)	28(48.3)	-	-	-	-	-
	Obstr. (56)	56.6±11.0	39 (69.6)	11 (19.6)	40 (71.4)	33 (58.9)	33 (58.9)	-	-	-	-	-
von Korn <sup>33</sup>	Non-Obstr. (127)	60.3±15.4	60 (81.1)	26 (20.5)	88 (69.3)	55 (43.3)	32 (25.2)	-	-	-	-	-
	Obstr. (509)	78.0±2.8	344 (67.6)	198 (38.9)	451 (88.6)	309 (60.7)	124 (24.4)	-	-	-	-	-

Non-Obstr. = Non-obstructive; Obstr. = Obstructive. Data are presented as means±SD or numbers (%).

**Table S2.** Methodological quality: study scores according to the Newcastle-Ottawa scale.

Quality categories	Selection (Max score 4)	Comparability (max score 2)	Outcome (max score 3)
<i>Studies included in all meta-analyses</i>			
Raymond <sup>26</sup>	4	0	2
Roe <sup>28</sup>	4	1	1
Da Costa <sup>6</sup>	4	2	3
Dokainish <sup>8</sup>	4	0	1
Larsen <sup>17</sup>	4	0	2
Pinheiro <sup>23</sup>	4	0	0
Patel <sup>22</sup>	4	1	0
Larson <sup>18</sup>	4	0	2
Terefe <sup>32</sup>	4	0	3
Dey <sup>7</sup>	4	1	1
Dwyer <sup>9</sup>	4	0	3
von Korn <sup>33</sup>	4	0	3
Cortell <sup>5</sup>	3	1	1
Kang <sup>16</sup>	4	0	1
Ramanath <sup>25</sup>	4	0	1
Hamdan <sup>11</sup>	4	0	0
Rhew <sup>27</sup>	4	1	3
Sun <sup>31</sup>	4	0	3
Rossini <sup>29</sup>	3	2	2
Manfrini <sup>19</sup>	4	0	1
Minha <sup>21</sup>	4	0	1
Planer <sup>24</sup>	4	2	2
<i>Studies included only in the meta-analyses of event rates by single group **</i>			
Harris <sup>13</sup>	3	--	2
Hung <sup>14</sup>	2	--	2
Golzio <sup>10</sup>	3	--	3
Bugiardini <sup>3</sup>	3	--	3
Shishehbor <sup>30</sup>	3	--	3
Chan <sup>4</sup>	3	--	3
Hansen <sup>12</sup>	3	--	3
Abid <sup>1</sup>	2	--	3
Aldous <sup>2</sup>	2	--	3
Johnston <sup>15</sup>	3	--	3
Ohlow <sup>21</sup>	3	--	2

\* The total "Selection" score is given by the sum of the scores (stars) of the single items (a) representativeness of the exposed cohort; (b) selection of the non exposed cohort; (c) ascertainment of exposure; (d) demonstration that outcome of interest was not present at start of study. The "Comparability" score is referred to the item "Comparability of cohorts on the basis of the design or analysis" (and could not be evaluated in single-arm studies). The total "Outcome" score is given by the sum of the scores (stars) of the single items: (a) assessment of outcome; (b) Was follow-up long enough for outcomes to occur; (c) adequacy of follow-up of cohorts. \*\* The item "Selection of the non exposed cohort (in the section "Selection"), and the item "Comparability" inevitably scored 0, as there was no control group in these studies.

**Table S3.** Results of the meta-analyses estimating the rates of several baseline patient characteristics (and the mean age) among Non-obstructive coronary artery disease (NObCAD) and Obstructive coronary artery disease (ObCAD) patients, separately.

	<b>Non-obstructive CAD (0%-50% stenosis)</b>	<b>Obstructive CAD (&gt;50% stenosis)</b>
<i>Proportion of Males</i>		
N. studies (n/N)	28 (15,892 / 34,856)	24 (57,330 / 83,631)
Estimated % (95% CI)	53.0 (50.5-55.6)	70.3 (68.0-72.5)
<i>Proportion of Diabetics</i>		
N. studies (n/N)	26 (2784 / 21,665)	24 (24,989 / 83,631)
Estimated % (95% CI)	14.6 (12.4-17.0)	27.5 (24.8-30.3)
<i>Proportion of hypertensive subjects</i>		
N. studies (n/N)	26 (8676 / 21,665)	23 (51,115 / 82,391)
Estimated % (95% CI)	48.0 (41.2-54.8)	61.5 (54.5-68.2)
<i>Proportion of dyslipidemic subjects</i>		
N. studies (n/N)	25 (8165 / 20,694)	23 (35,991 / 82,391)
Estimated % (95% CI)	33.0 (29.4-36.8)	46.9 (39.6-54.3)
<i>Proportion of current smokers</i>		
N. studies (n/N)	26 (4643 / 21,665)	24 (32,448 / 83,631)
Estimated % (95% CI)	37.2 (31.3-43.2)	40.3 (35.5-45.2)
<i>Proportion of STACS</i>		
N. studies (n/N)	13 (2256 / 13,168)	11 (14382 / 19627)
Estimated % (95% CI)	14.7 (11.1-18.6)	73.8 (70.2-77.3)
<i>Proportion of ACE-inhibitors users</i>		
N. studies (n/N)	10 (43,861 / 79,346)	8 (3052 / 6499)
Estimated % (95% CI)	57.4 (45.0-69.3)	51.5 (41.6-61.4)
<i>Proportion of beta-blockers users</i>		
N. studies (n/N)	10 (63,217 / 79,346)	9 (4548 / 6850)
Estimated % (95% CI)	77.5 (70.8-83.6)	62.6 (51.7-73.0)
<i>Proportion of statins users</i>		
N. studies (n/N)	10 (52,774 / 79,346)	9 (3579 / 6850)
Estimated % (95% CI)	79.7 (69.3-88.3)	63.7 (49.3-76.9)
<i>Proportion of aspirin users</i>		
N. studies (n/N)	10 (69,516 / 79,346)	9 (5420 / 6850)
Estimated % (95% CI)	89.5 (82.8-94.6)	76.3 (62.1-88.0)
<i>Proportion of P2Y12 inhibitors users</i>		
N. studies (n/N)	8 (33,728 / 53,370)	7 (1410 / 4469)
Estimated % (95% CI)	75.6 (66.5-83.7)	39.0 (25.6-53.3)
<i>Age in years</i>		
N. studies (N patients)	28 (23,279)	22 (75,332)
Estimated mean (95% CI)	56.9 (55.4-58.5)	63.2 (60.6-65.8)

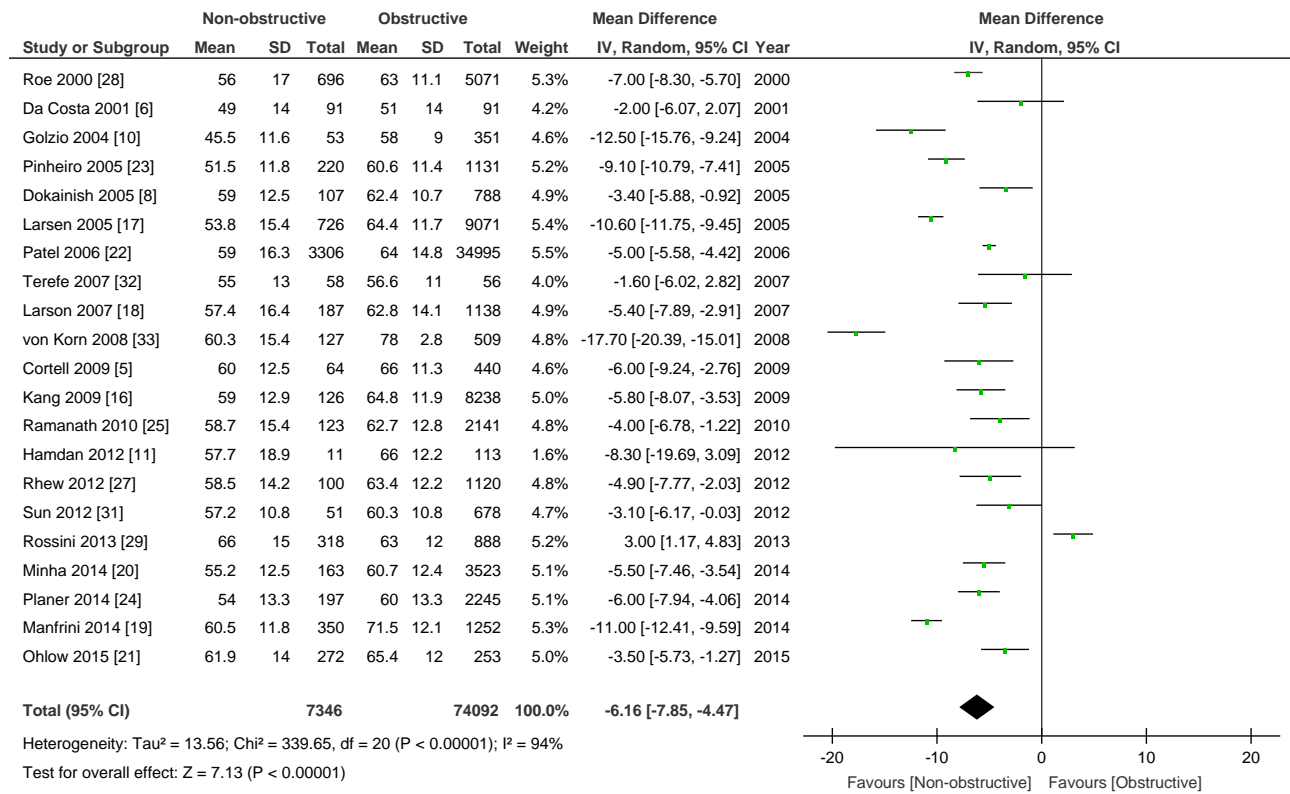
**Table S4.** Diagnostic methods and rate of other diseases of non-obstructive CAD patients, for each included study.

<b>Study, <sup>Ref.</sup></b>	<b>Methods for differential diagnosis in NObCAD</b>	<b>N. of patients with other diagnoses (%)</b>
<b><i>Studies included in all meta-analyses</i></b>		
Raymond <sup>26</sup>	Coronary angiography Intracoronary ergonovine test	5 (6.8%) with coronary spasm
Roe <sup>28</sup>	Coronary angiography	
Da Costa <sup>6</sup>	Coronary angiography Intravenous ergonovine test Coagulation test	11 (12.5%) with coronary spasm 9 (10.2%) with coagulation disorder
Dokainish <sup>8</sup>	Coronary angiography	
Larsen <sup>17</sup>	Coronary angiography	
Pinheiro <sup>23</sup>	Coronary angiography	
Patel <sup>22</sup>	Coronary angiography	
Larson <sup>18</sup>	Coronary angiography	17 (9.1%) with stress cardiomyopathy
	Left ventricular angiography	15 (8.0%) with myocarditis
	Cardiac magnetic resonance	4 (2.1%) with vasospasm
	Computed tomographic pulmonary angiography	2 (1.1%) with pulmonary embolus
Terefe <sup>32</sup>	Coronary angiography	16 (28.6%) with coagulation disorder
	Left ventricular angiography	6 (10.7%) with cocaine abuse
	Coagulation test	5 (8.9%) with stress cardiomyopathy
	Drug test	
Dey <sup>7</sup>	Coronary angiography	
Dwyer <sup>9</sup>	Coronary angiography	
Von Korn <sup>33</sup>	Coronary angiography	10 (7.9%) with stress cardiomyopathy
	Left ventricular angiography	10 (7.9%) with myocarditis
	Cardiac magnetic resonance	5 (3.9%) with muscular bridge
Cortell <sup>5</sup>	Coronary angiography	
	Cardiac MRI in 15 subjects	
Kang <sup>16</sup>	Coronary angiography	
Ramanath <sup>25</sup>	Coronary angiography	
Hamdan <sup>11</sup>	Coronary angiography	
Rhew <sup>27</sup>	Coronary angiography	
Sun <sup>32</sup>	Coronary angiography	
Rossini <sup>29</sup>	Coronary angiography	
Manfrini <sup>19</sup>	Coronary angiography	
Minha <sup>20</sup>	Coronary angiography	
Planer <sup>24</sup>	Coronary angiography	
<b><i>Studies included only in the meta-analyses of event rates by single group</i></b>		
Harris <sup>13</sup>	Coronary angiography	
Hung <sup>14</sup>	Coronary angiography	1 (5.2%) with coronary spasm

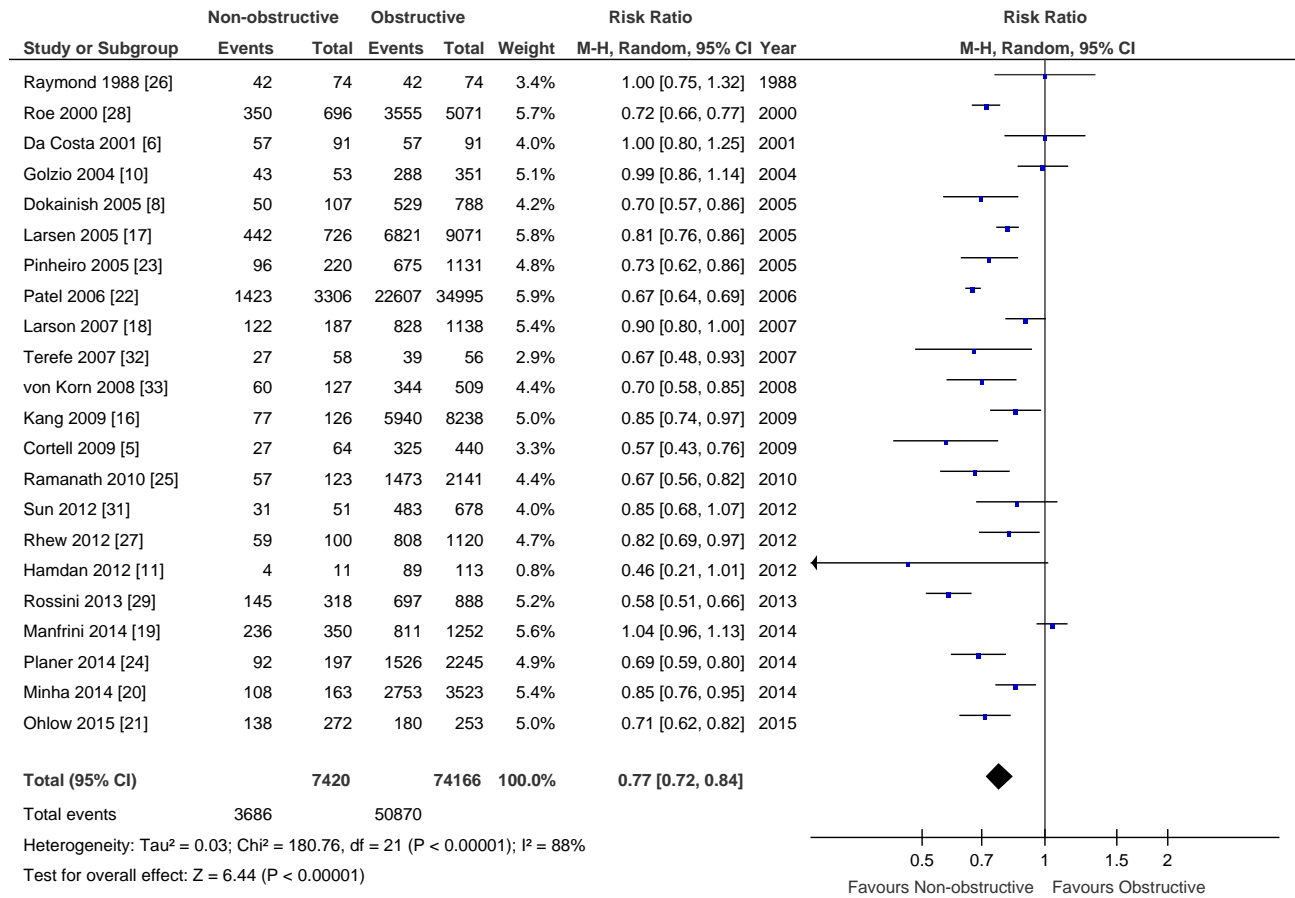
	Intracoronary ergon ovine test	
Golzio <sup>10</sup>	Coronary angiography	
Bugiardini <sup>3</sup>	Coronary angiography	
Shishehbor <sup>30</sup>	Coronary angiography	
Chan <sup>4</sup>	Coronary angiography	
Hansen <sup>12</sup>	Coronary angiography	
Abid <sup>1</sup>	Coronary angiography	
	Intracoronary ergonovine test	7 (33.3%) with coronary spasm
	Intracoronary isosorbide dinitrate test	1 (4.6%) with coagulation disorder
	Coagulation test	
Aldous <sup>2</sup>	Coronary angiography	The authors excluded other causes of NObACS
Johnston <sup>15</sup>	Coronary angiography	
Ohlow <sup>21</sup>	Coronary angiography	39 (19.1%) with stress cardiomyopathy
	Left ventricular angography	78 (38.2%) with myocarditis
	Intracoronary isosorbide dinitrate test	1 (0.5%) with coronary spasm
<b><i>Studies included in meta-analyses of single groups on the baseline proportion of STE-ACS only</i></b>		
Hochman <sup>34</sup>	Coronary angiography	
Germing <sup>35</sup>	Coronary angiography	
Ong <sup>36</sup>	Coronary angiography	42 (30.4%) with coronary spasm
	Acetylcholine test	
Chokshi <sup>37</sup>	Coronary angiography	



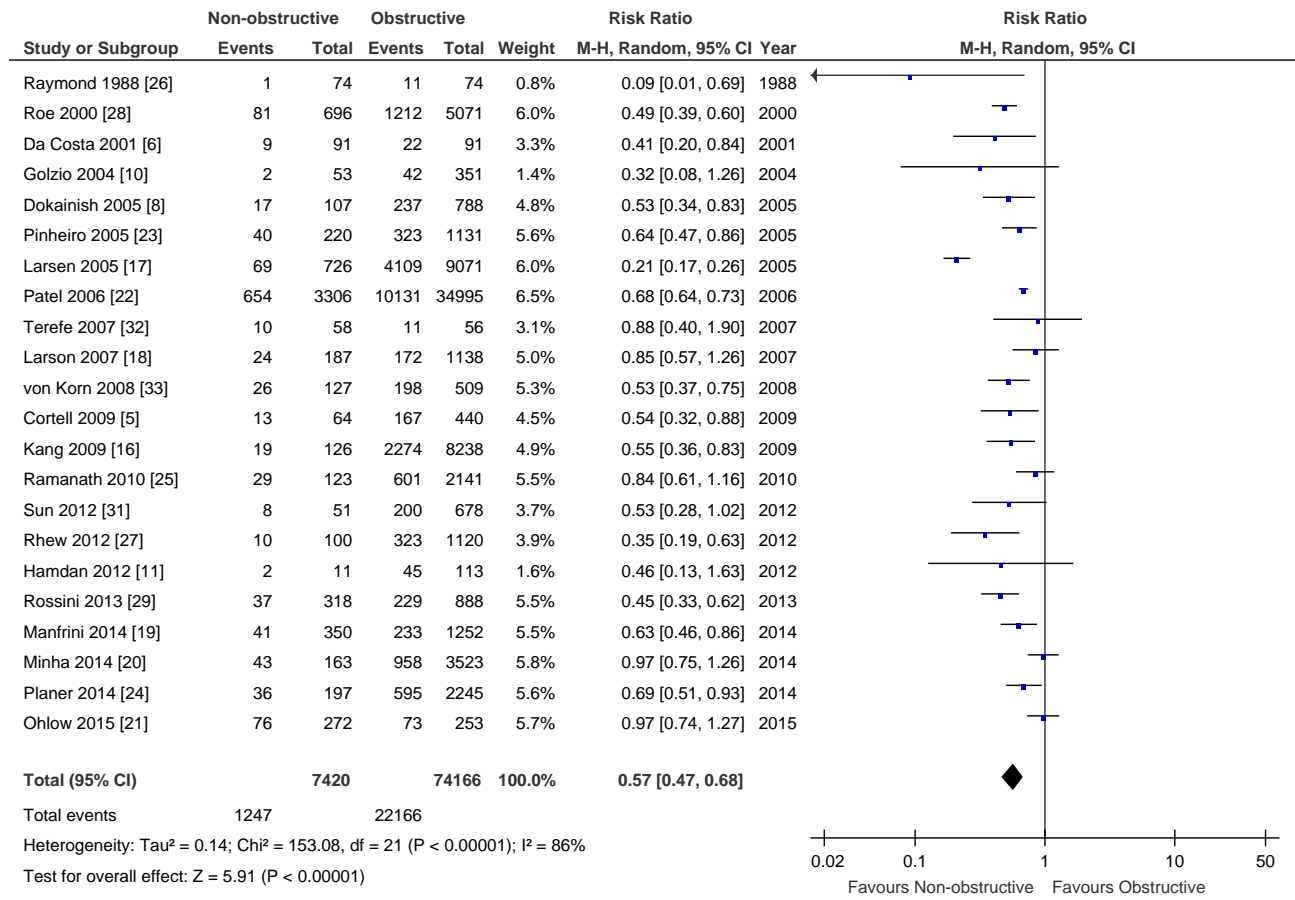
**Figure S1.** Meta-analysis comparing the mean age at baseline between non-obstructive vs obstructive CAD patients.



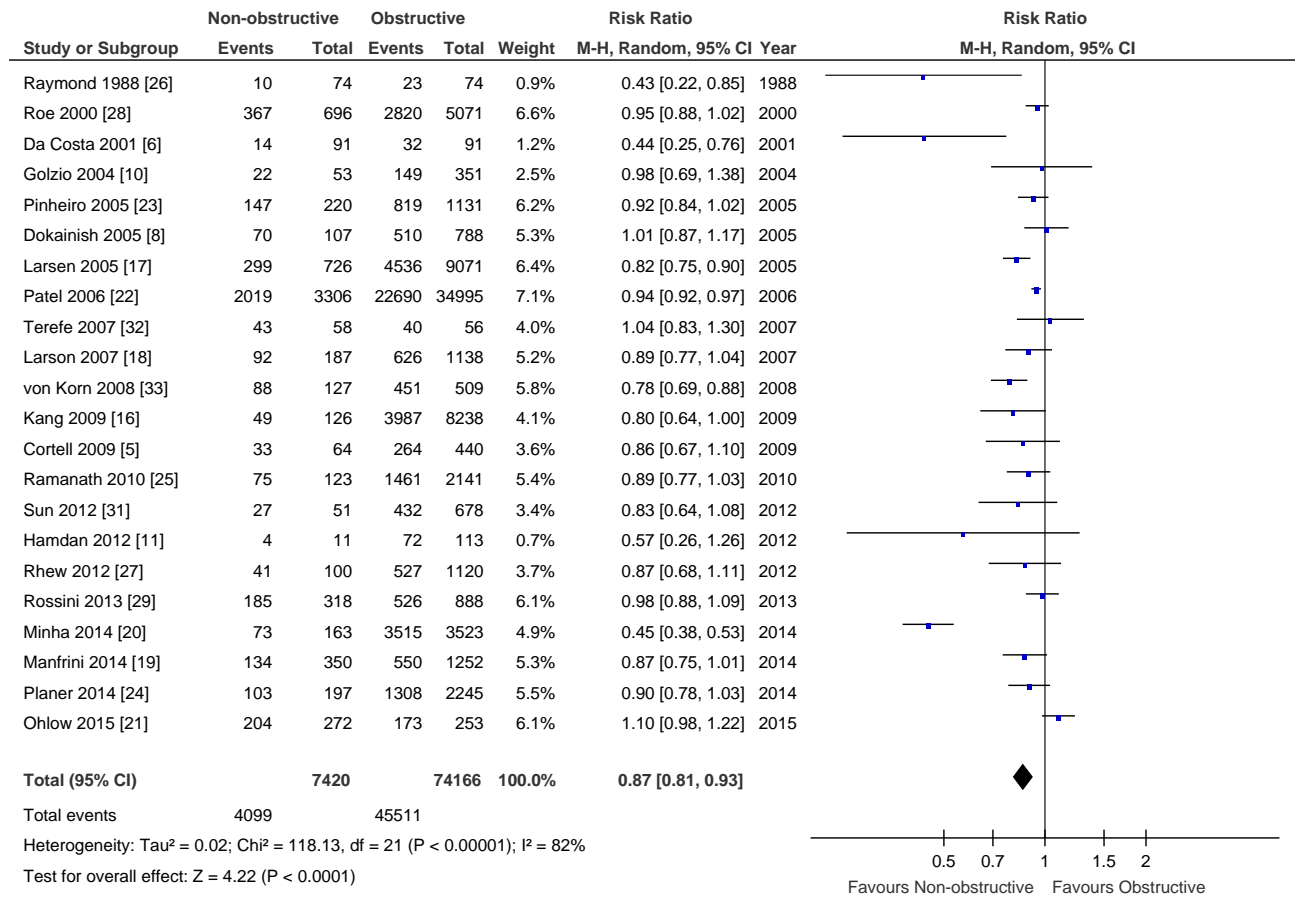
**Figure S2.** Meta-analysis comparing the baseline likelihood of male gender of non-obstructive vs obstructive CAD patients.



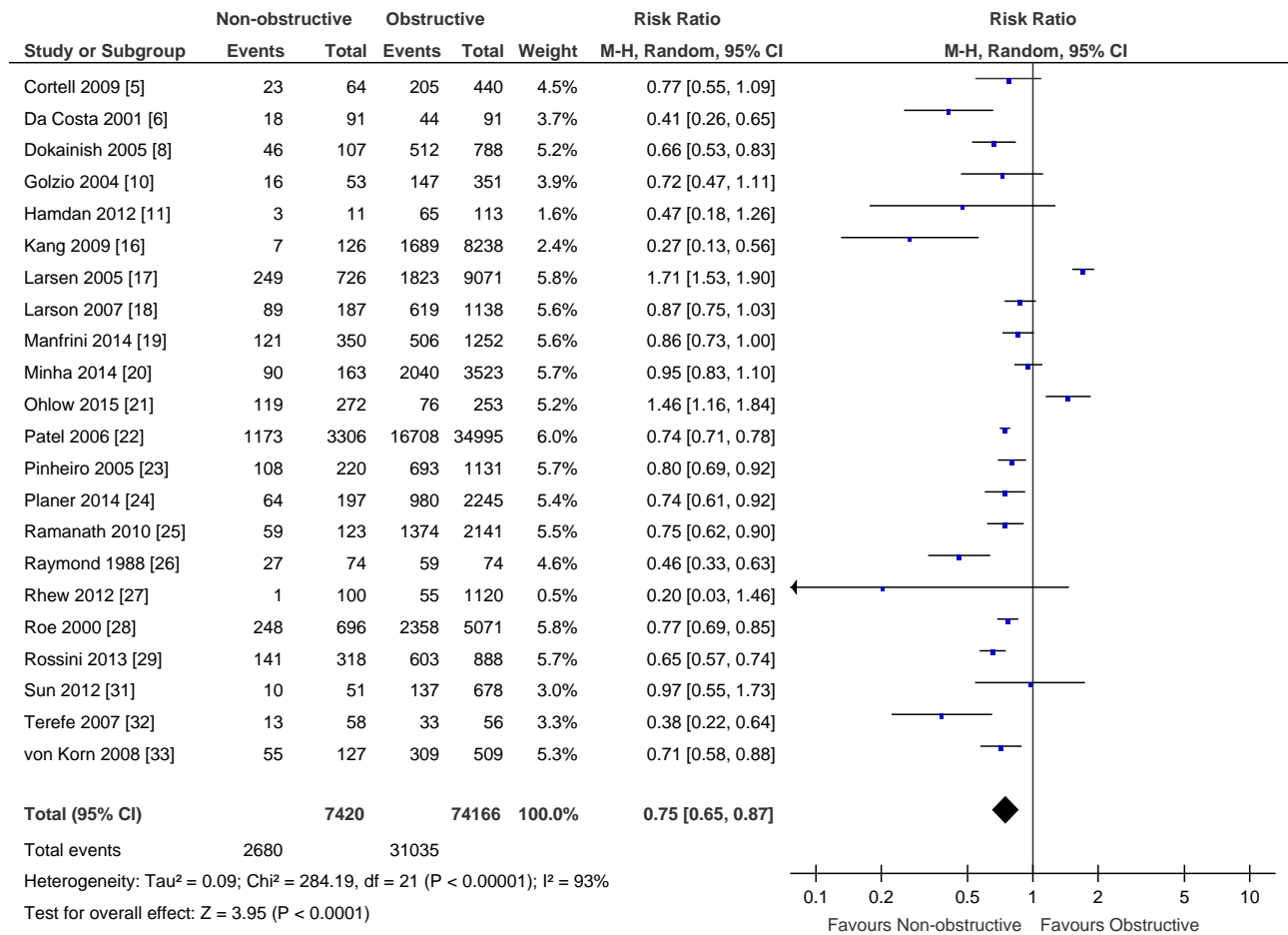
**Figure S3.** Meta-analysis comparing the baseline likelihood of diabetes of non-obstructive vs obstructive CAD patients.



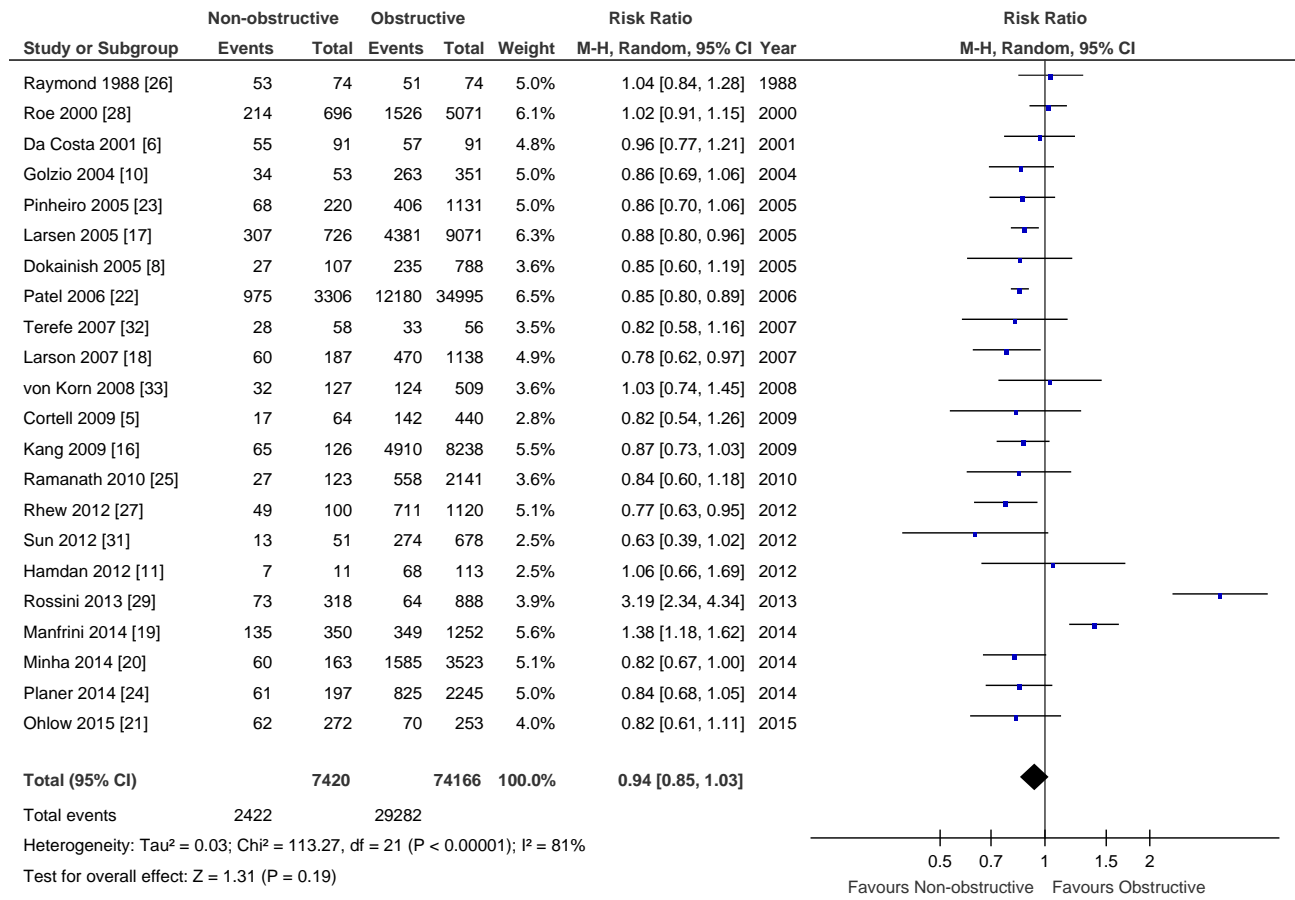
**Figure S4.** Meta-analysis comparing the baseline likelihood of hypertension of non-obstructive vs obstructive CAD patients.



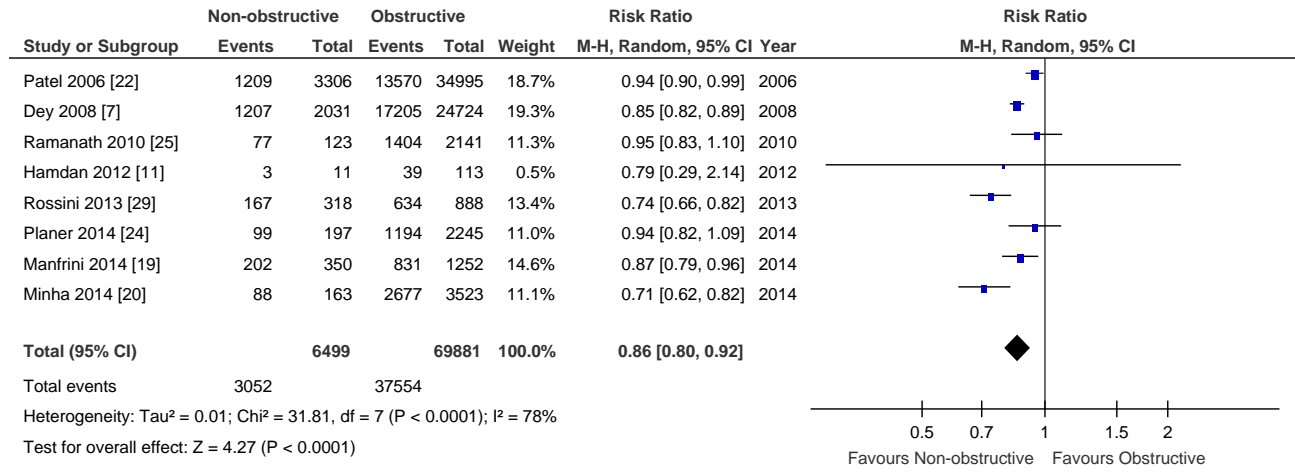
**Figure S5.** Meta-analysis comparing the baseline likelihood of dyslipidemia of non-obstructive vs obstructive CAD patients.



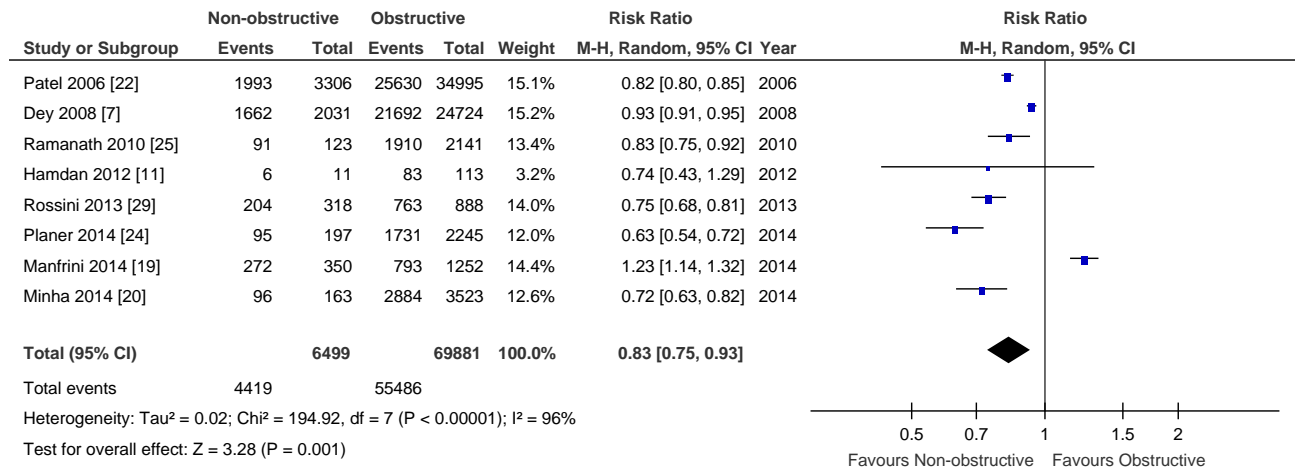
**Figure S6.** Meta-analysis comparing the baseline likelihood of current cigarette smoking of non-obstructive vs obstructive CAD patients.



**Figure S7.** Meta-analysis comparing the baseline likelihood of ACE-inhibitors use of non-obstructive vs obstructive CAD patients.

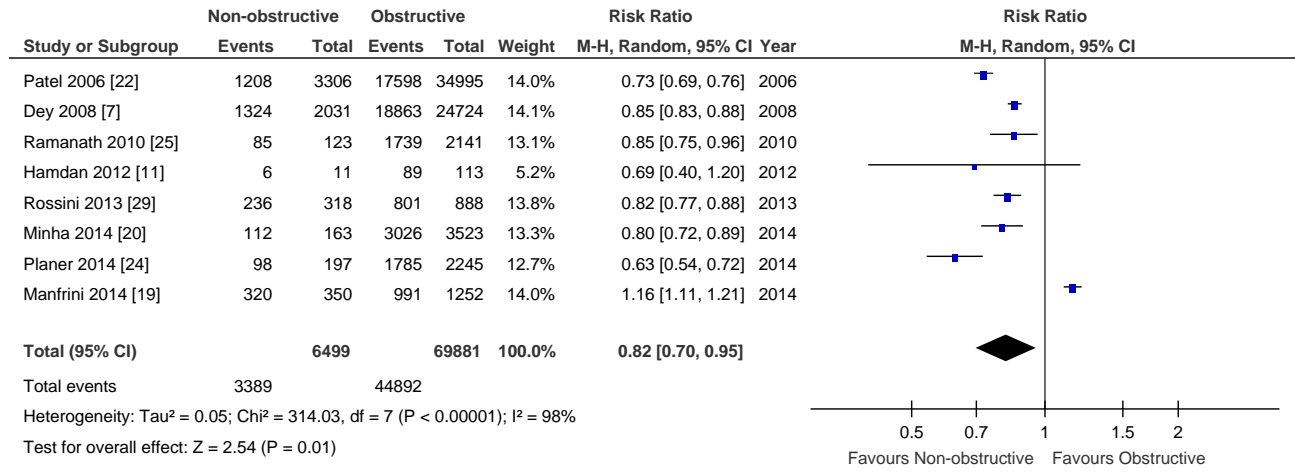


**Figure S8.** Meta-analysis comparing the baseline likelihood of beta-blockers use of non-obstructive vs obstructive CAD patients.

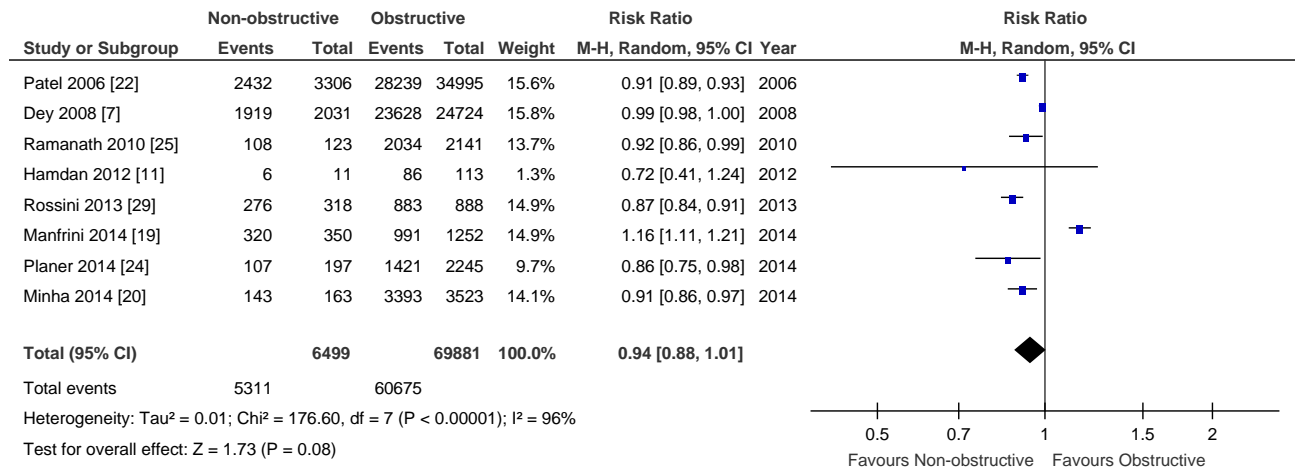




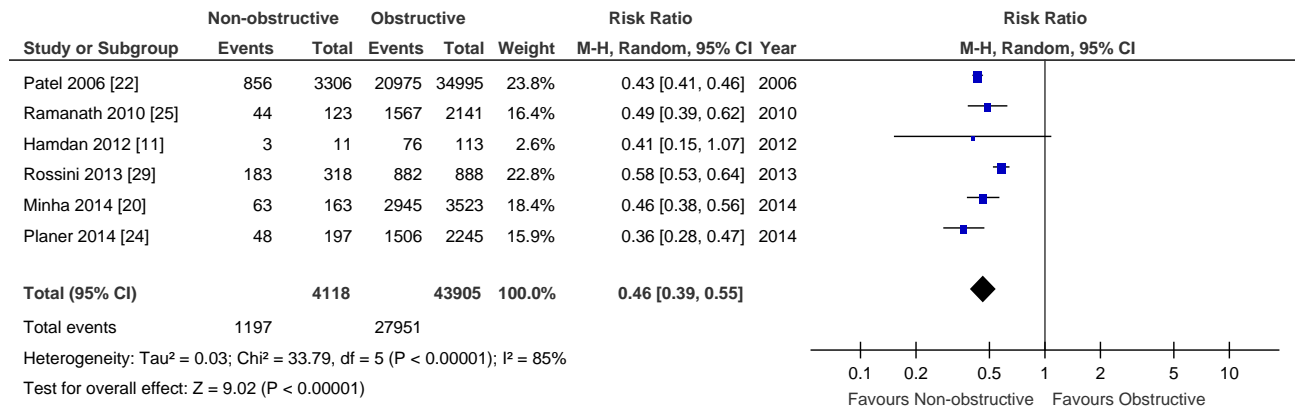
**Figure S9.** Meta-analysis comparing the baseline likelihood of statins use of non-obstructive vs obstructive CAD patients.



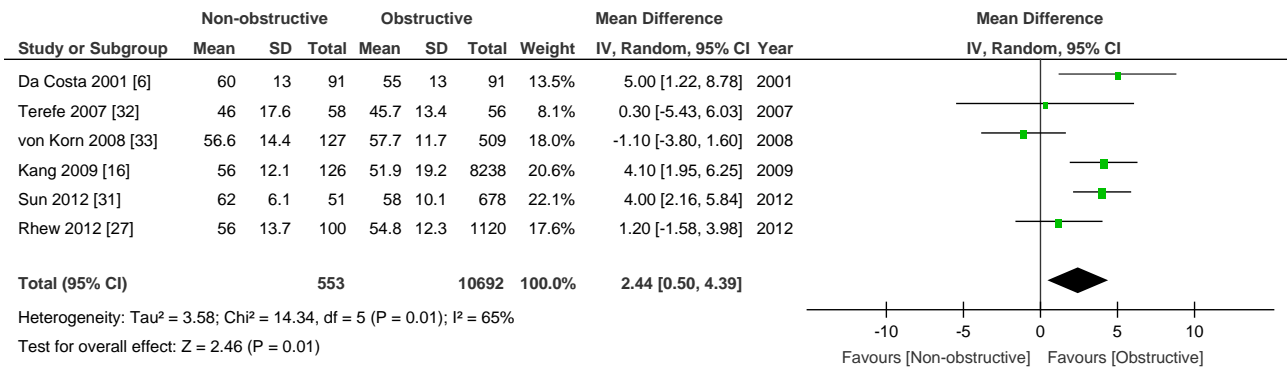
**Figure S10.** Meta-analysis comparing the baseline likelihood of aspirin use of non-obstructive vs obstructive CAD patients.



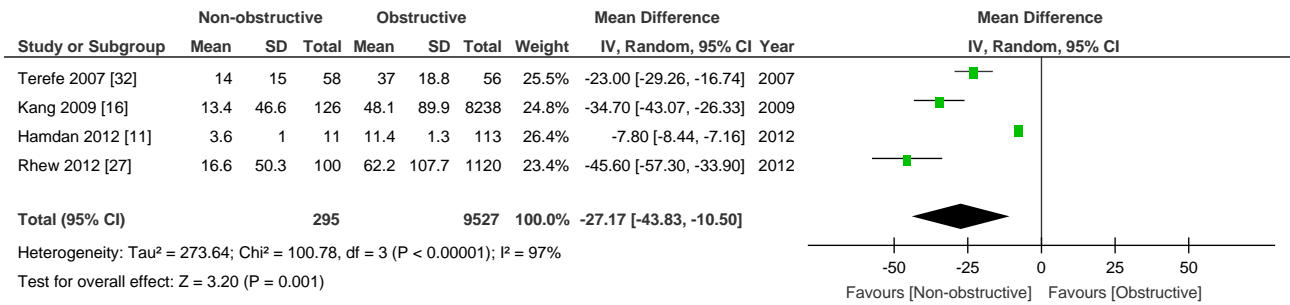
**Figure S11.** Meta-analysis comparing the baseline likelihood of P2Y12 inhibitors use of non-obstructive vs obstructive CAD patients.



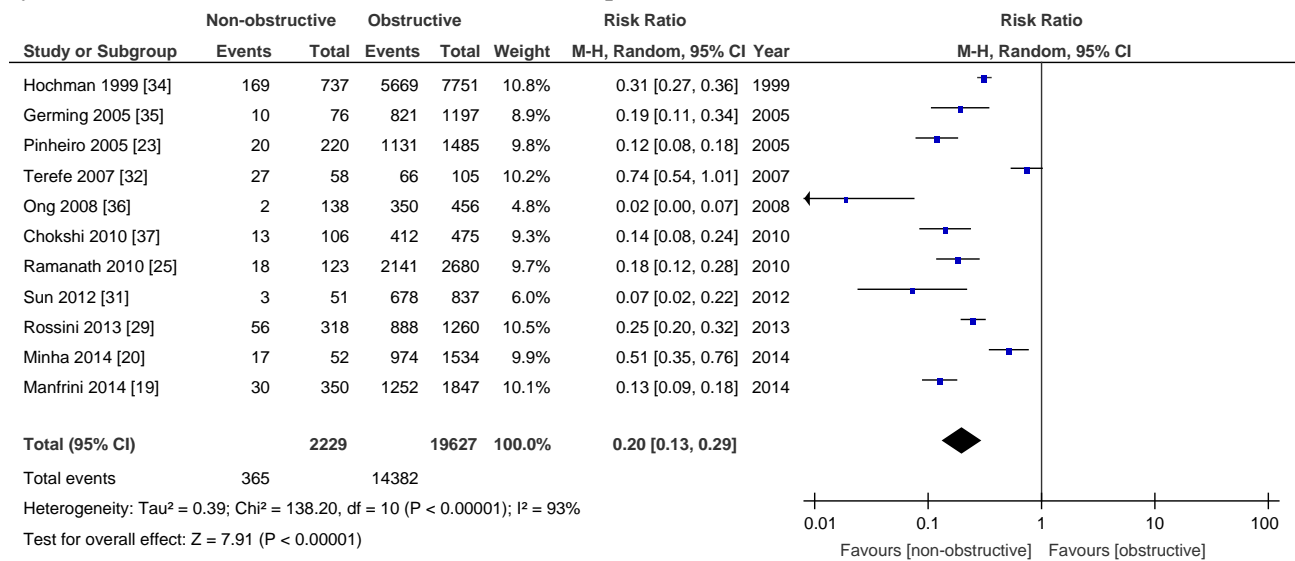
**Figure S12.** Meta-analysis comparing the mean left ventricular ejection fraction (LVEF) at baseline between non-obstructive vs obstructive CAD patients.



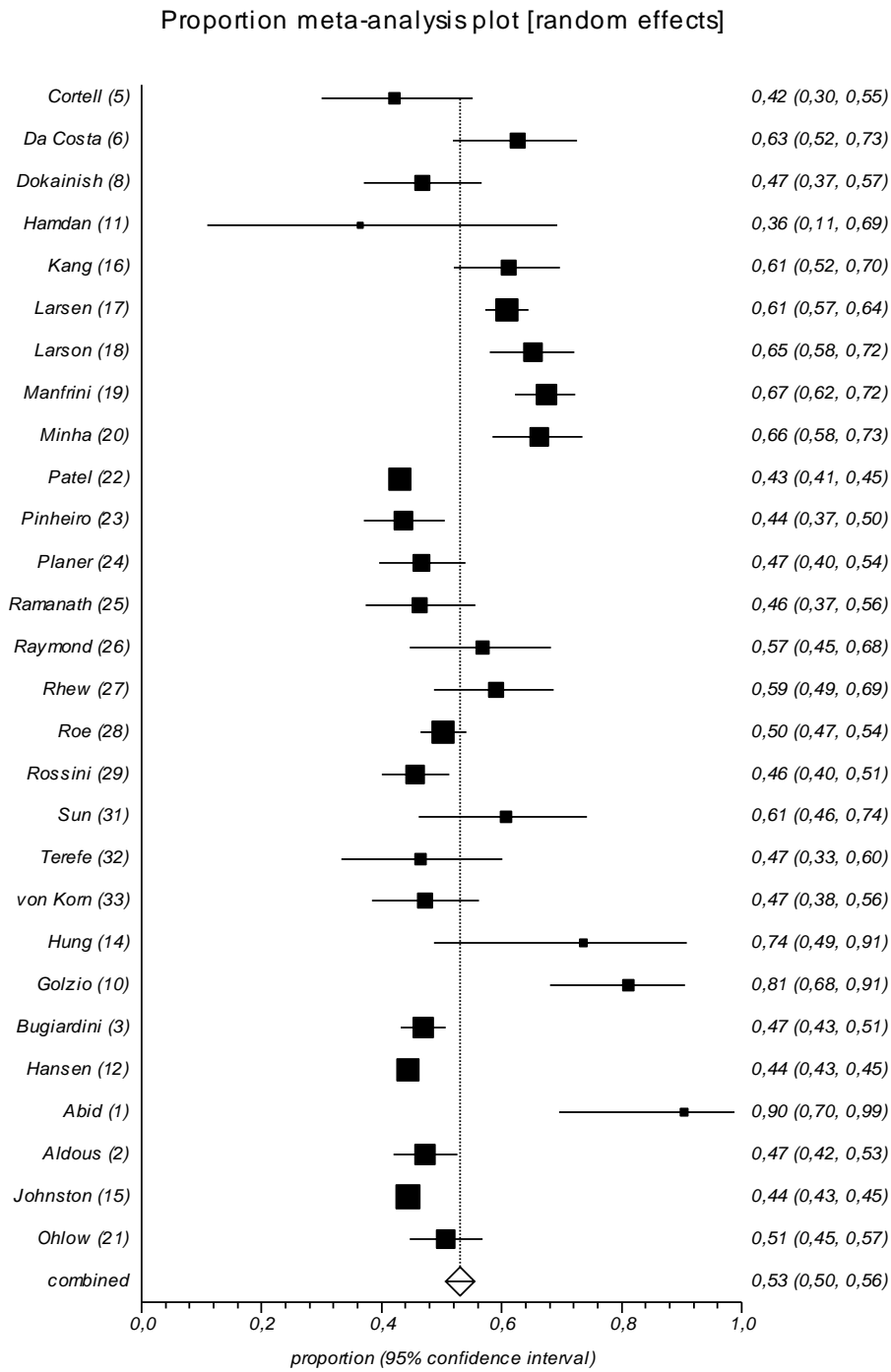
**Figure S13.** Meta-analysis comparing the mean troponin level at baseline between non-obstructive vs obstructive CAD patients.



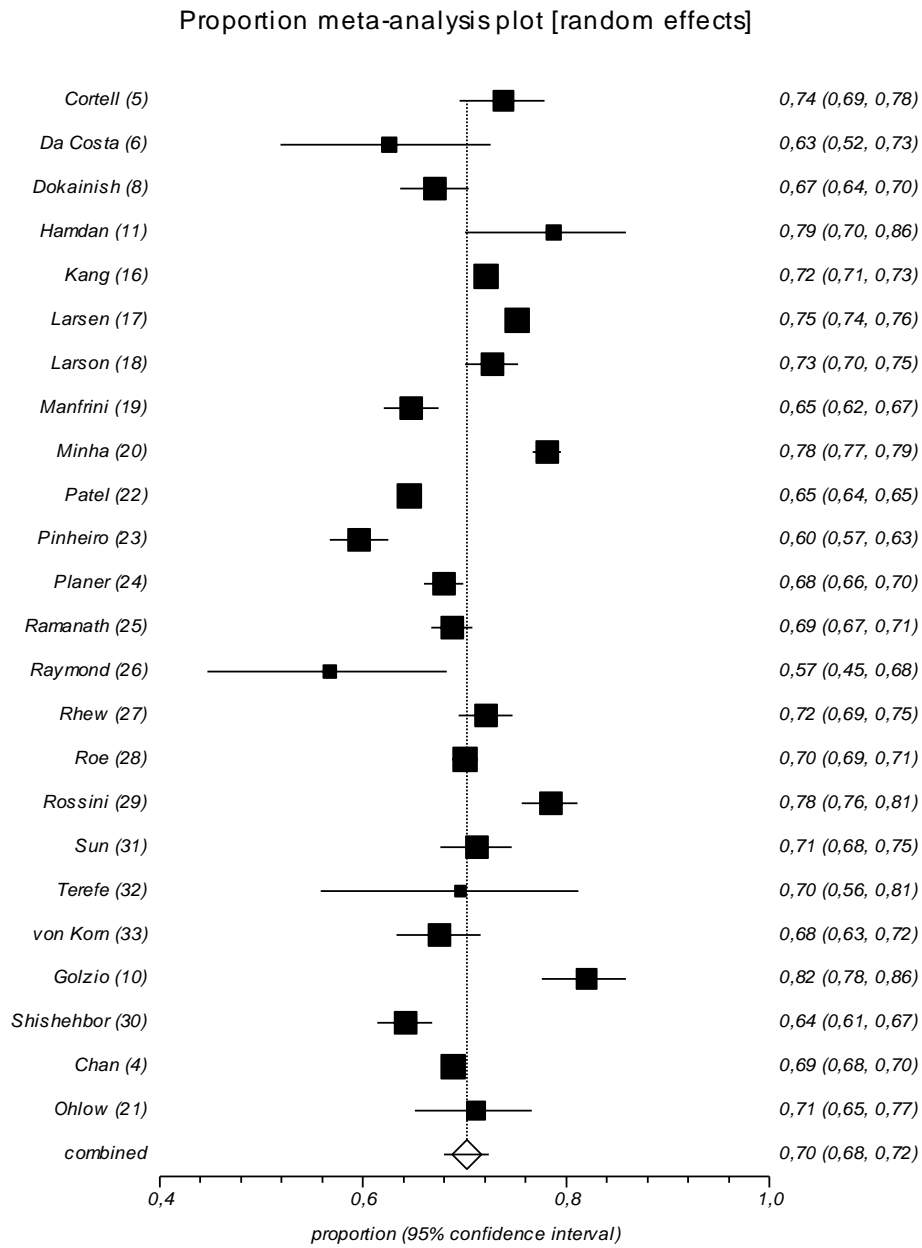
**Figure S14.** Meta-analysis comparing the baseline likelihood of STACS (ST-elevation Acute coronary syndrome) of non-obstructive vs obstructive CAD patients.



**Figure S15.** Meta-analysis estimating the baseline proportion of males among non-obstructive CAD patients.

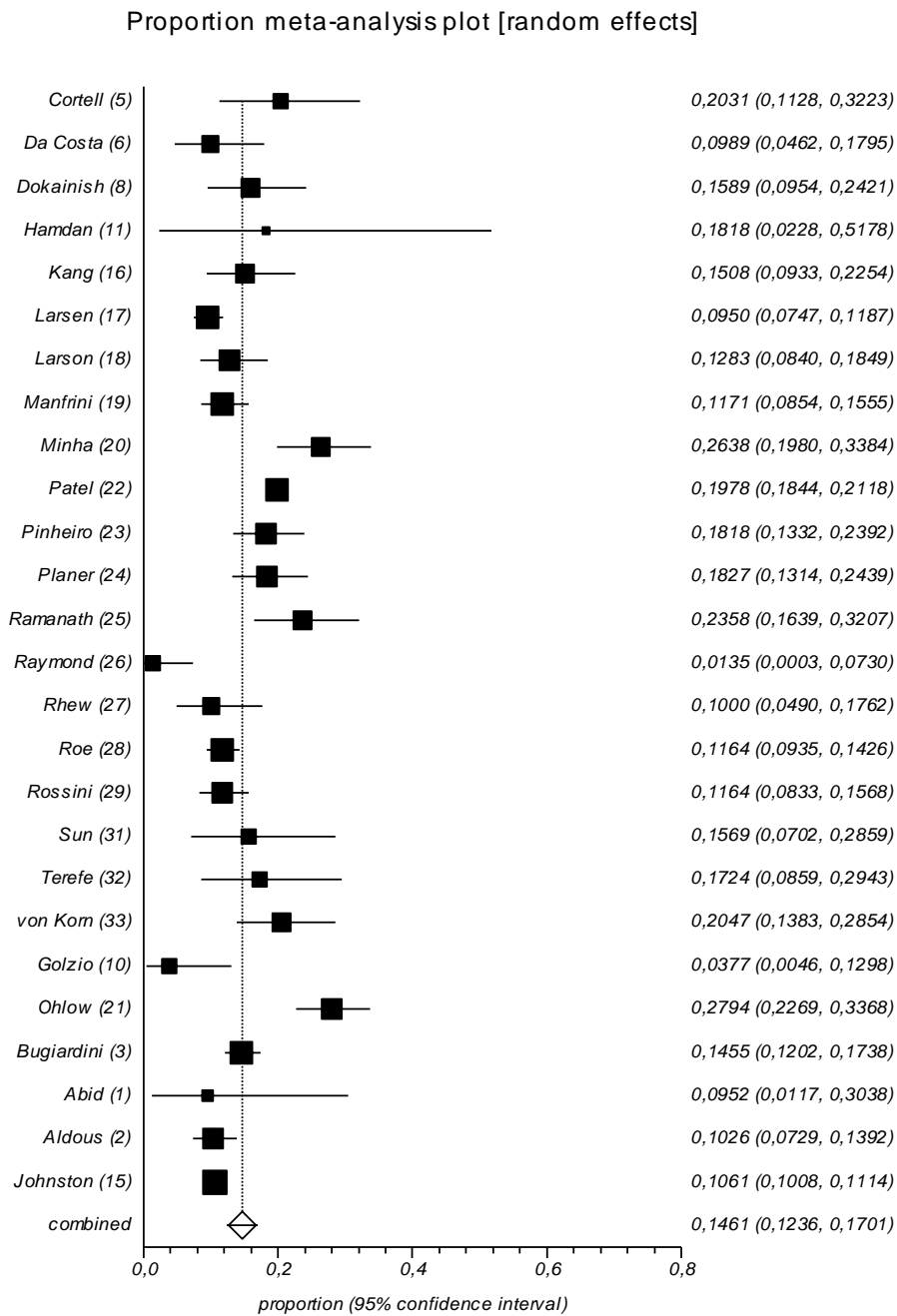


**Figure S16.** Meta-analysis estimating the baseline proportion of males among obstructive CAD patients.

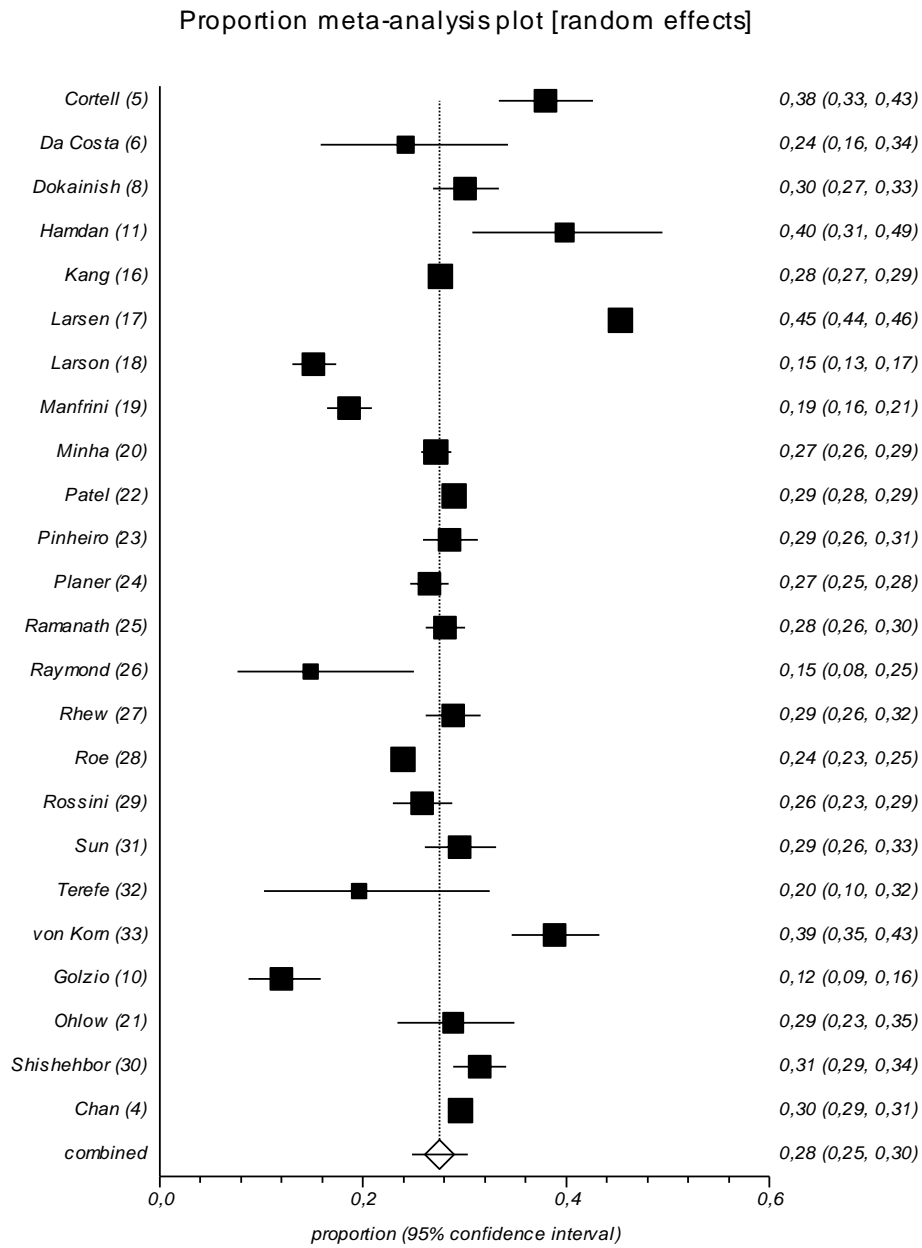




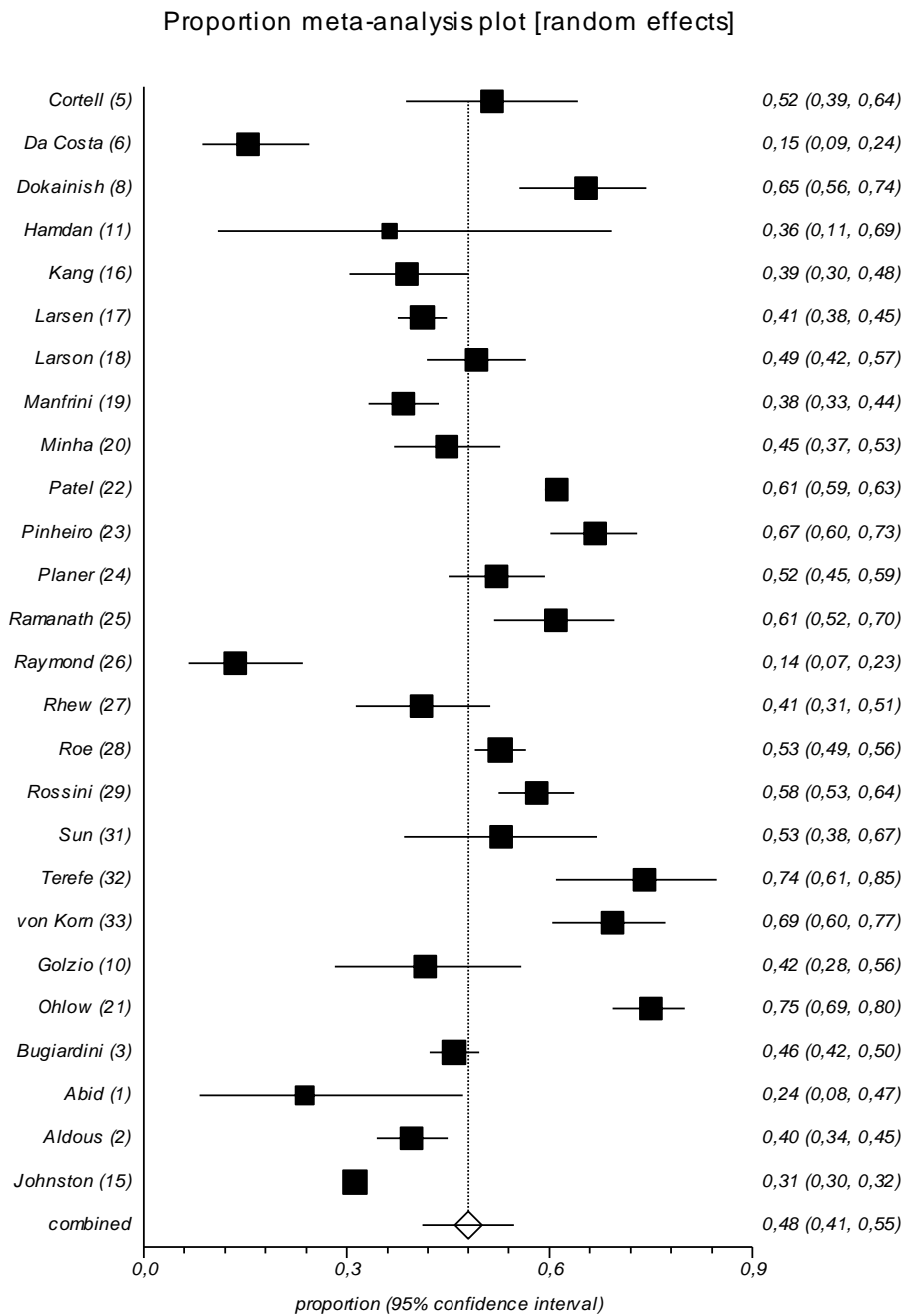
**Figure S17.** Meta-analysis estimating the baseline proportion of diabetics among non-obstructive CAD patients.



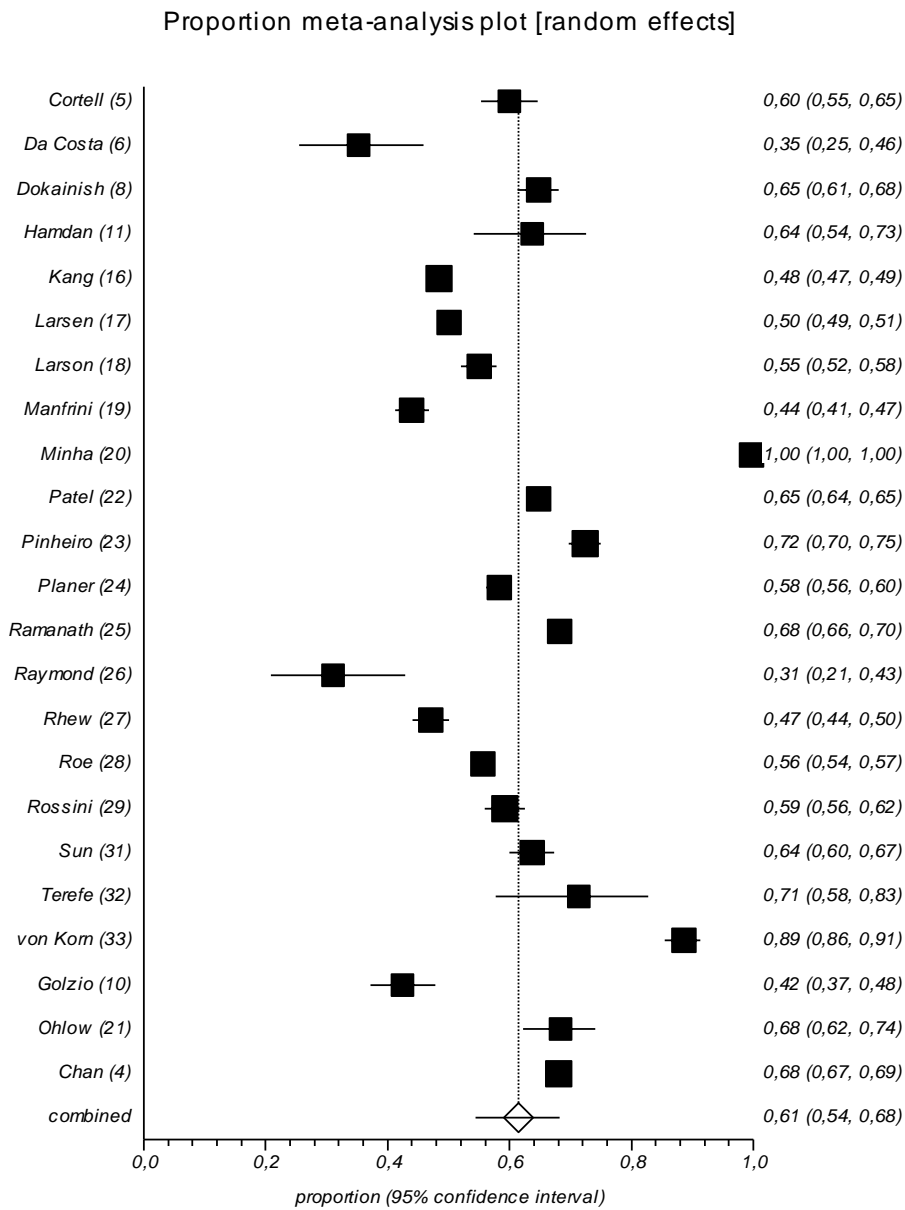
**Figure S18.** Meta-analysis estimating the baseline proportion of diabetics among obstructive CAD patients.



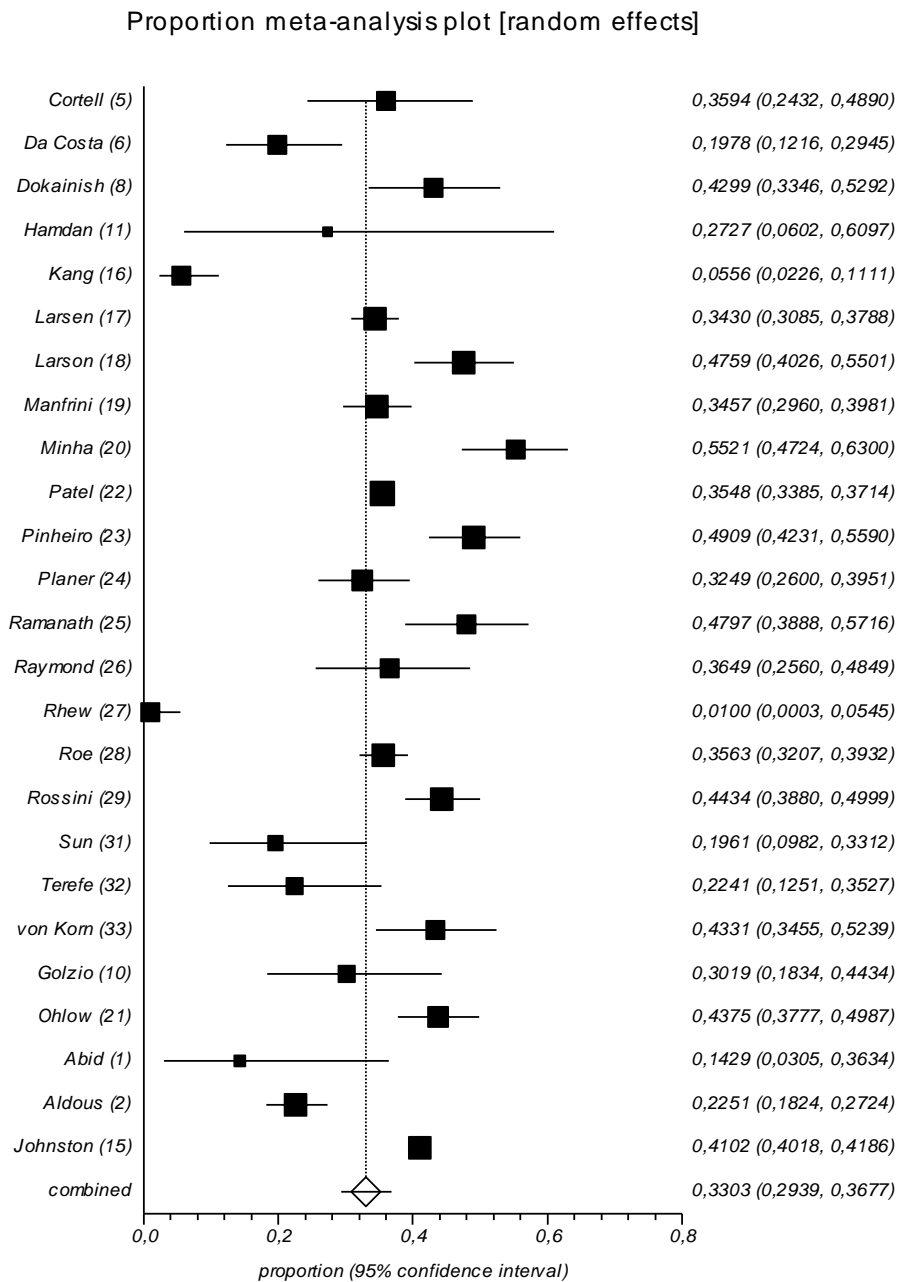
**Figure S19.** Meta-analysis estimating the baseline proportion of hypertensive subjects among non-obstructive CAD patients.



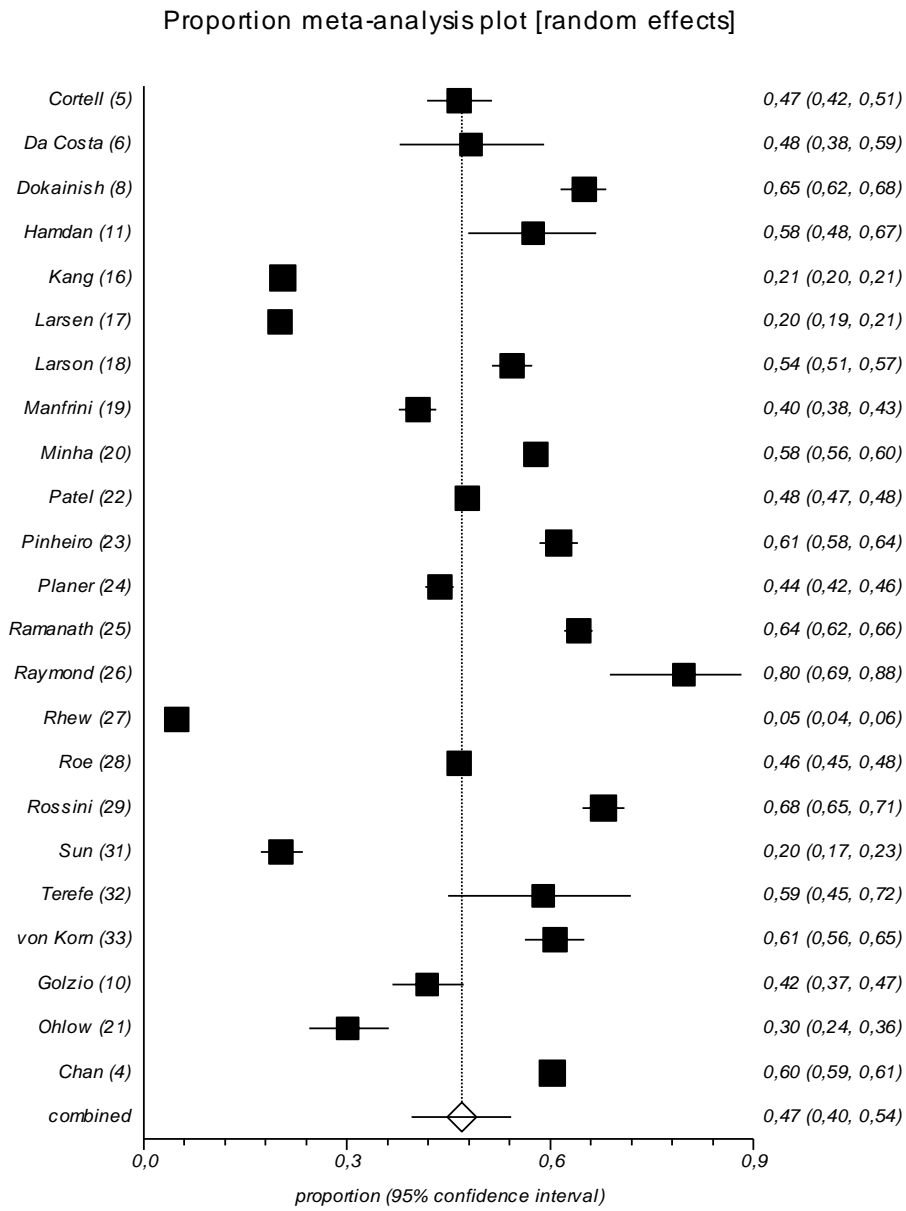
**Figure S20.** Meta-analysis estimating the baseline proportion of hypertensive subjects among obstructive CAD patients.



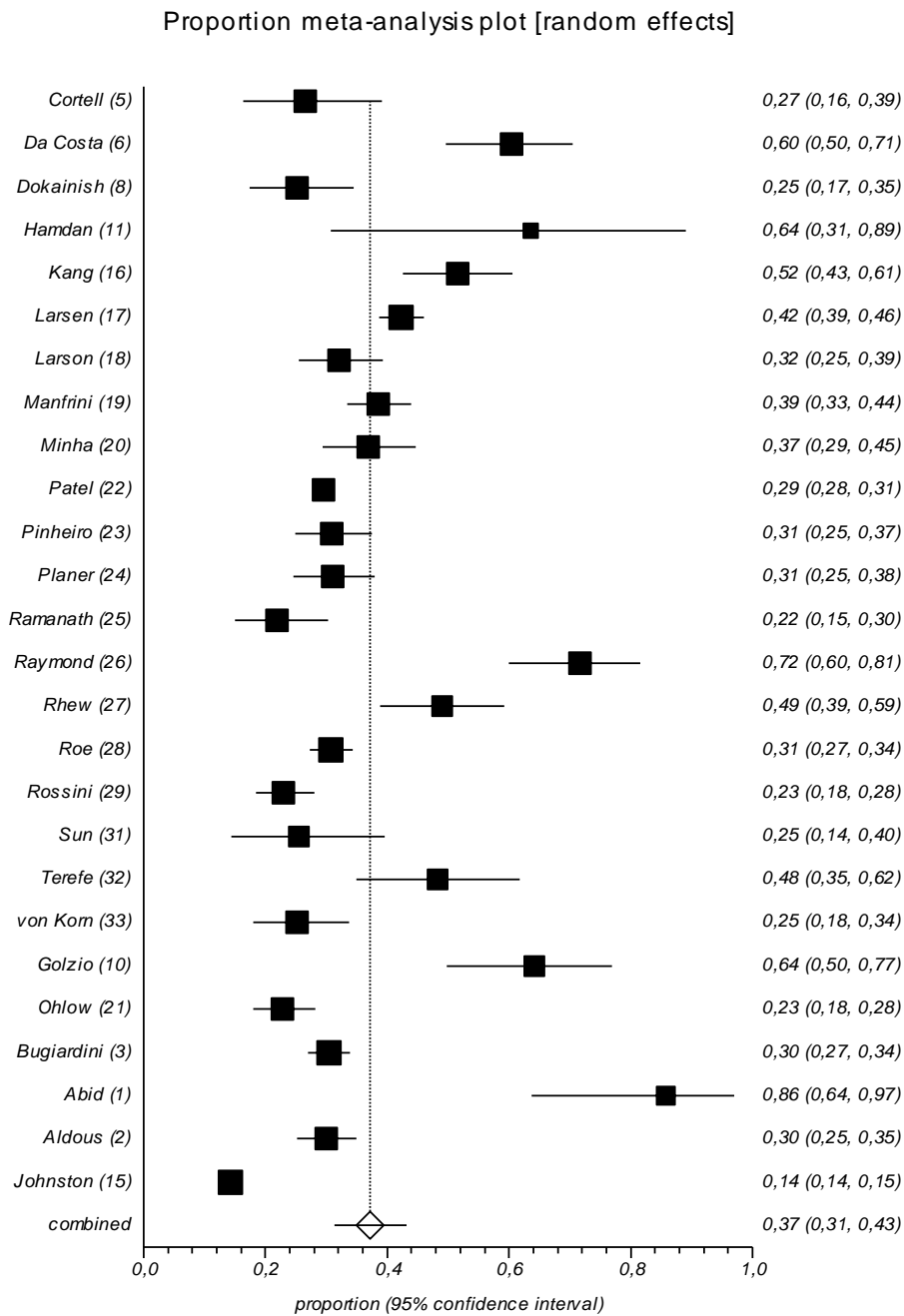
**Figure S21.** Meta-analysis estimating the baseline proportion of dyslipidemic subjects among non-obstructive CAD patients.



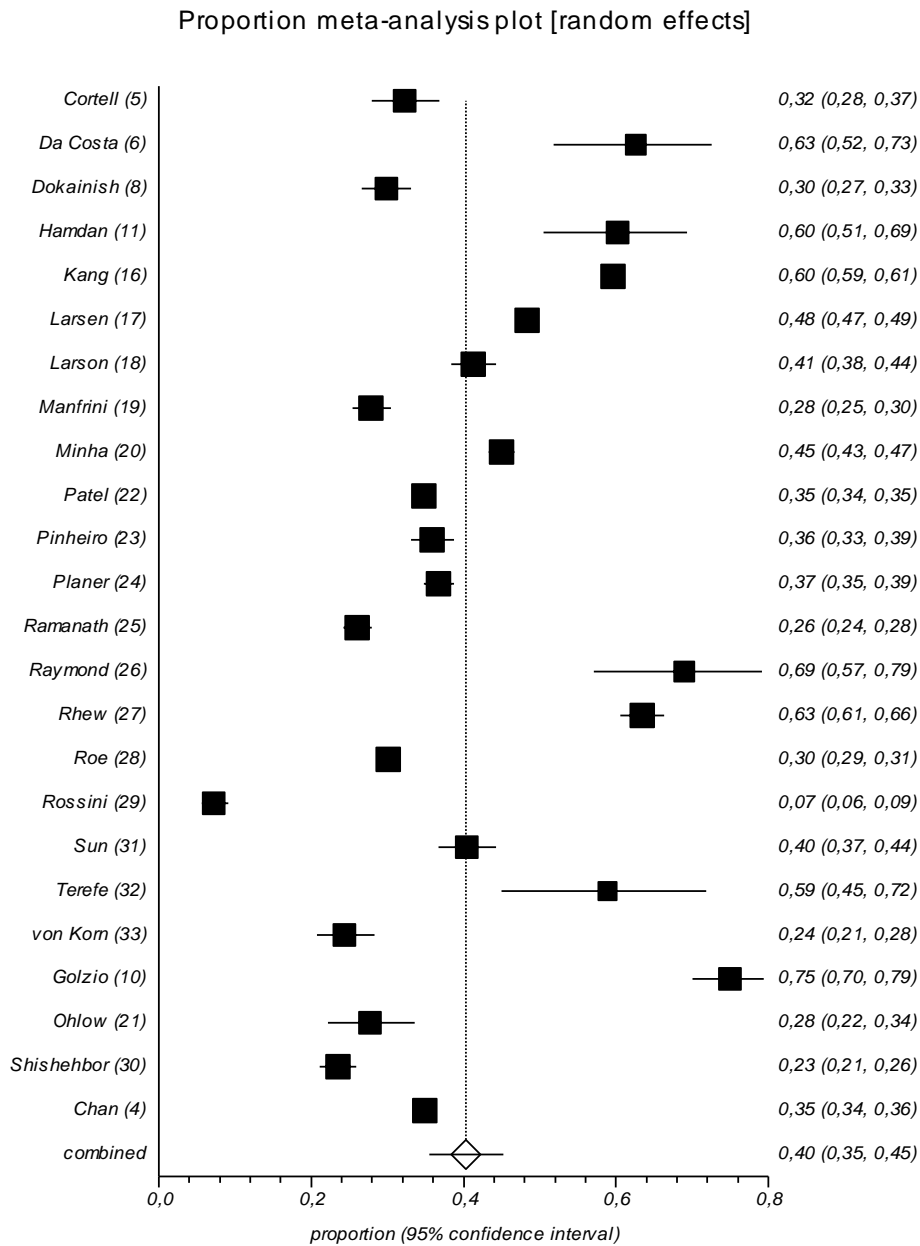
**Figure S22.** Meta-analysis estimating the baseline proportion of dyslipidemic subjects among obstructive CAD patients.



**Figure S23.** Meta-analysis estimating the baseline proportion of current smokers among non-obstructive CAD patients.

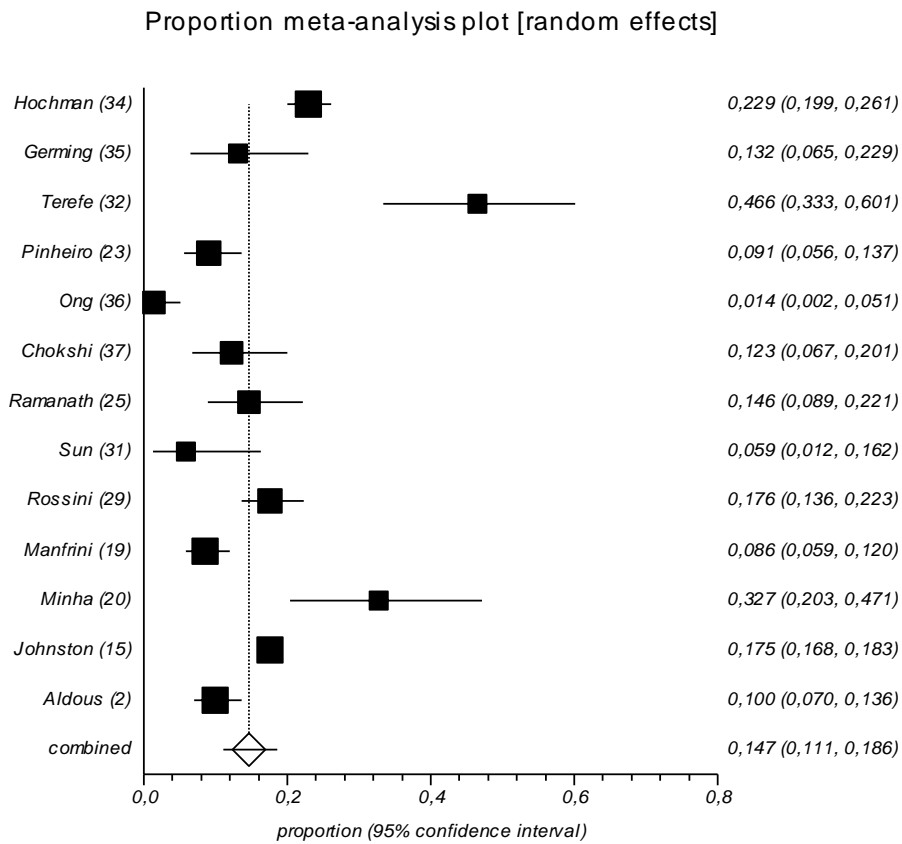


**Figure S24.** Meta-analysis estimating the baseline proportion of current smokers among obstructive CAD patients.

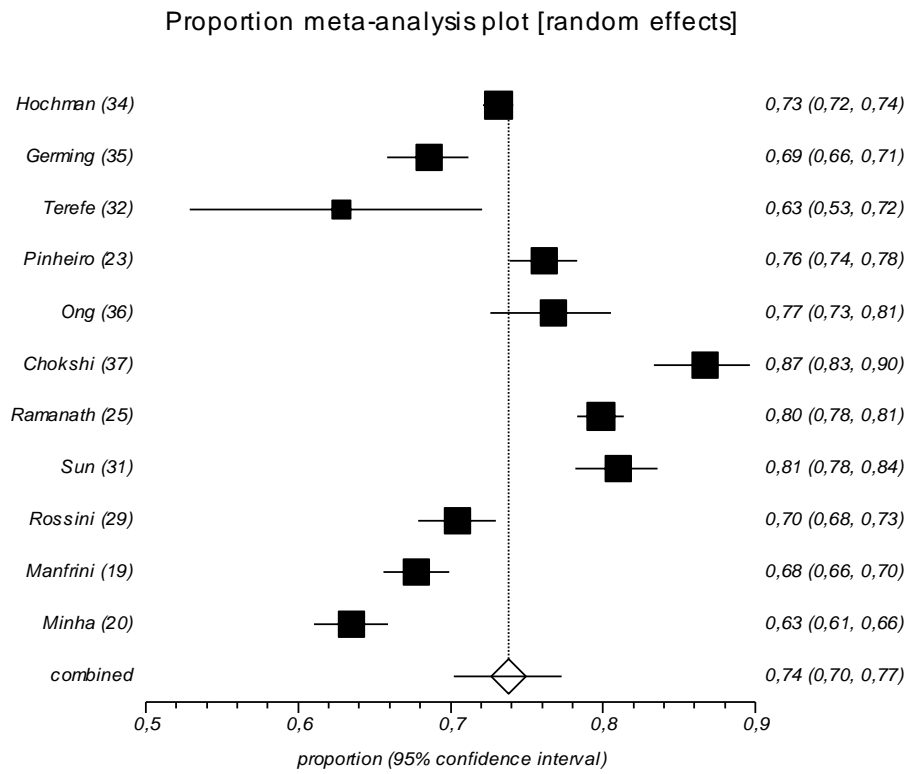




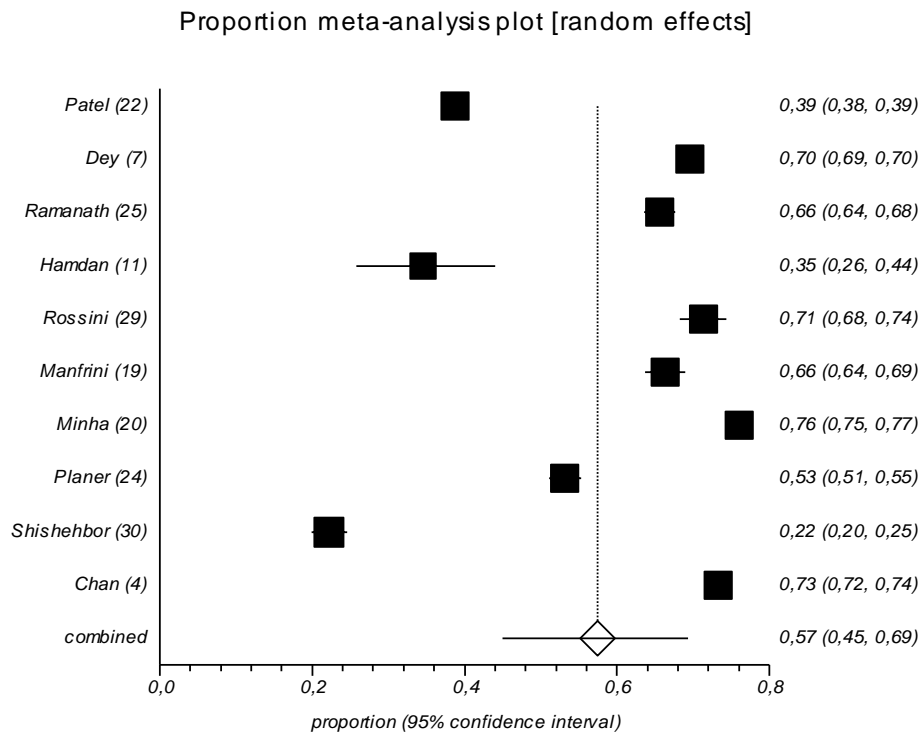
**Figure S25.** Meta-analysis estimating the baseline proportion of STACS (ST elevation acute coronary syndrome) among non-obstructive CAD patients.



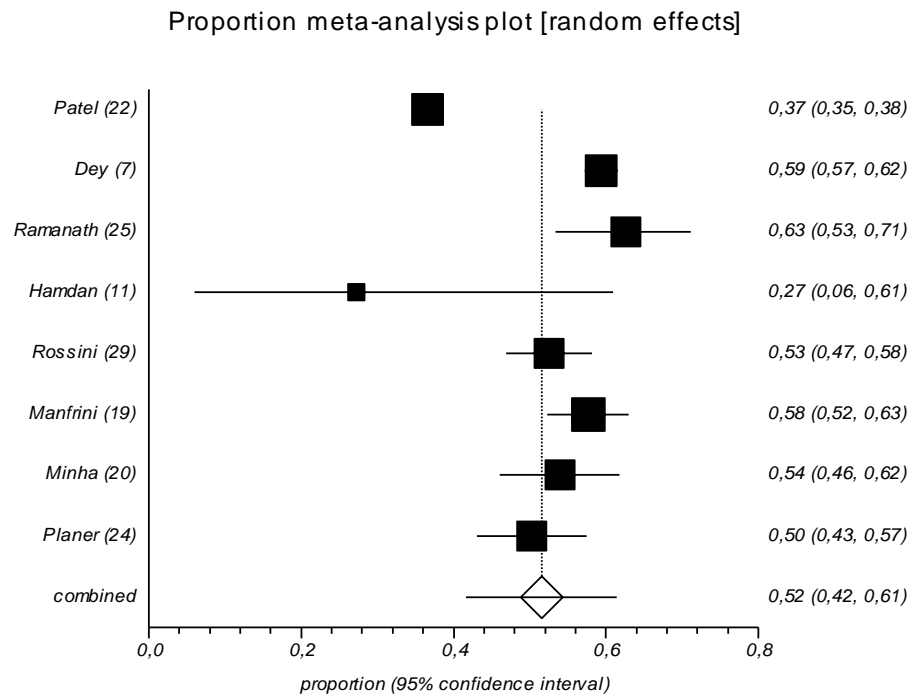
**Figure S26.** Meta-analysis estimating the baseline proportion of STACS (ST elevation acute coronary syndrome) among obstructive CAD patients.



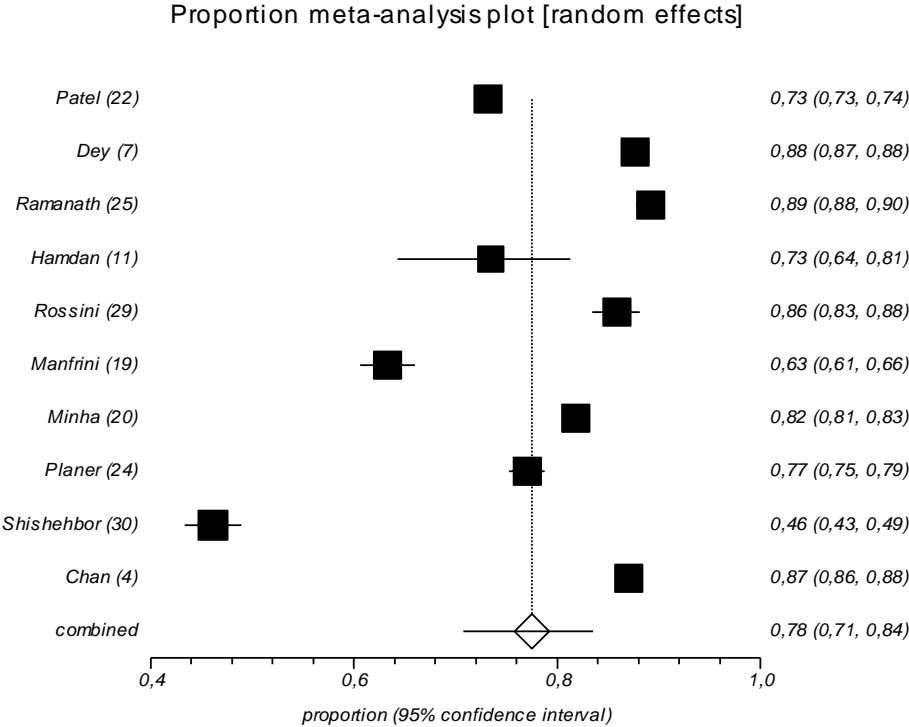
**Figure S27.** Meta-analysis estimating the baseline proportion of ACE inhibitors users among non-obstructive CAD patients.



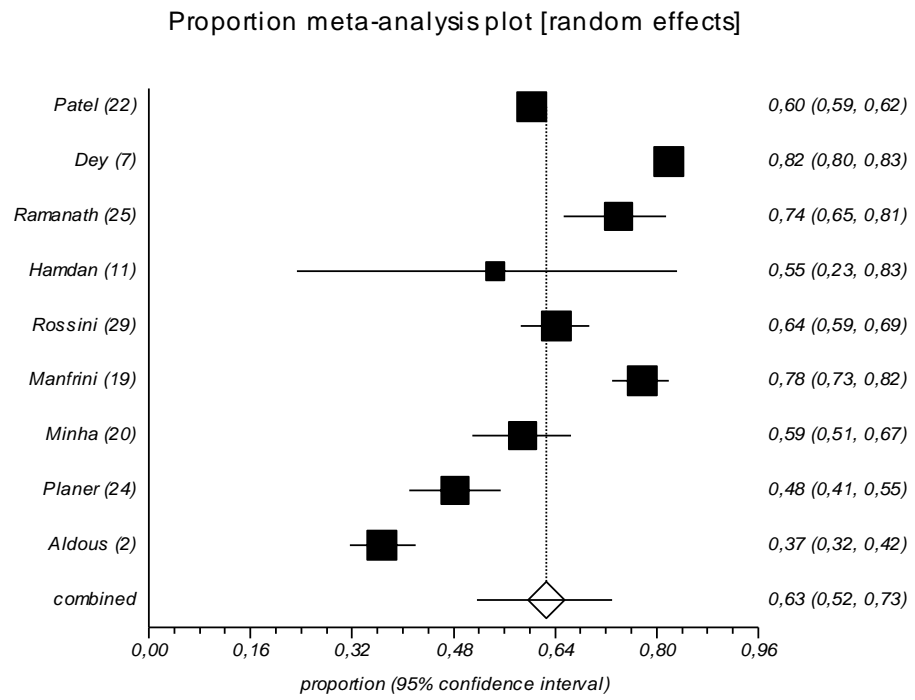
**Figure S28.** Meta-analysis estimating the baseline proportion of ACE inhibitors users among obstructive CAD patients.



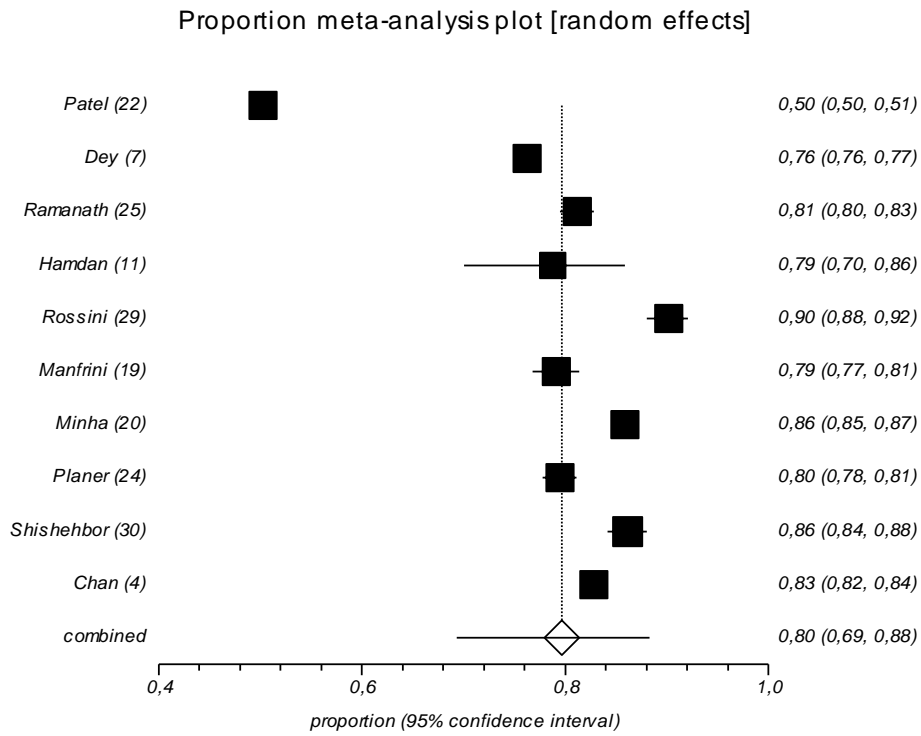
**Figure S29.** Meta-analysis estimating the baseline proportion of beta-blockers users among non-obstructive CAD patients.



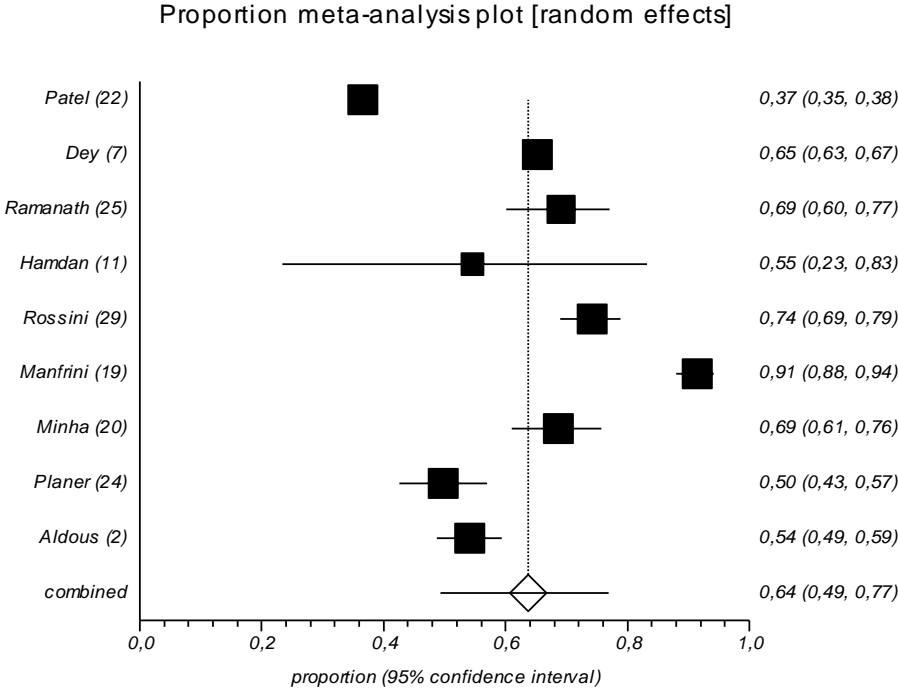
**Figure S30.** Meta-analysis estimating the baseline proportion of beta-blockers users among obstructive CAD patients.



**Figure S31.** Meta-analysis estimating the baseline proportion of statin users among non-obstructive CAD patients.

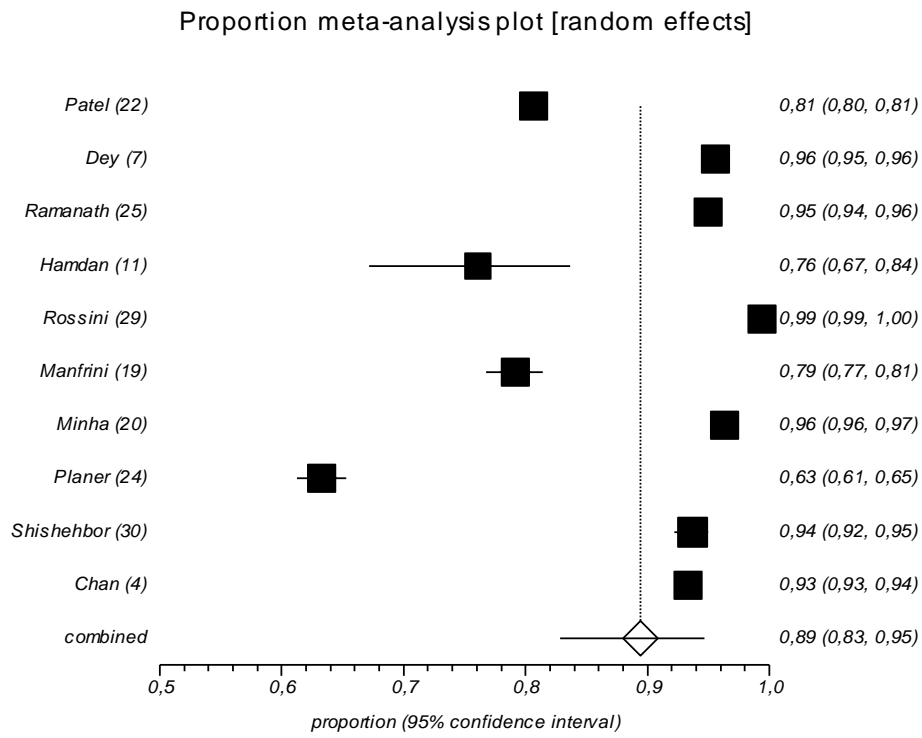


**Figure S32.** Meta-analysis estimating the baseline proportion of statin users among obstructive CAD patients.

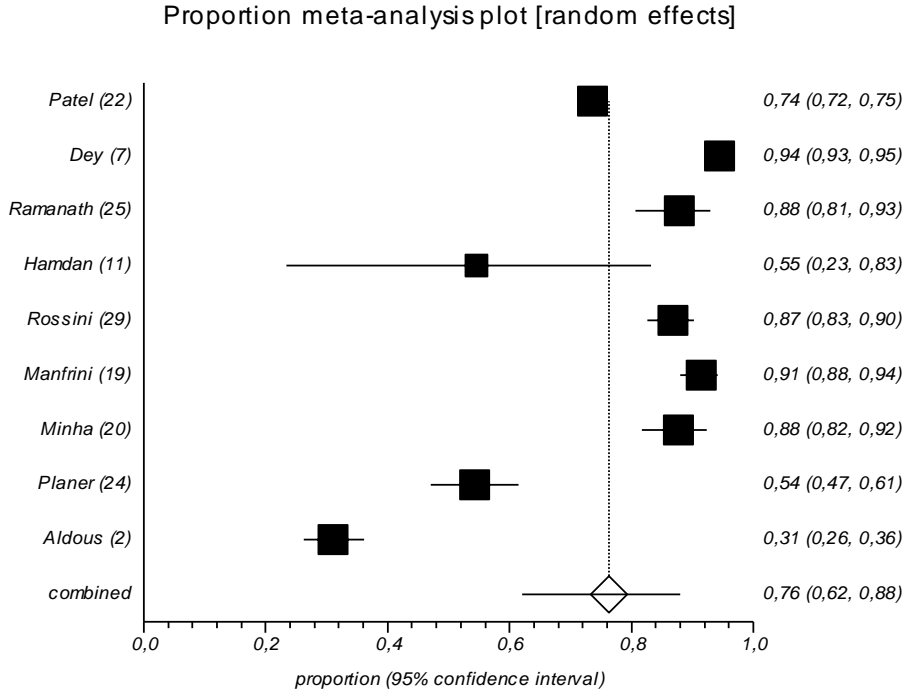




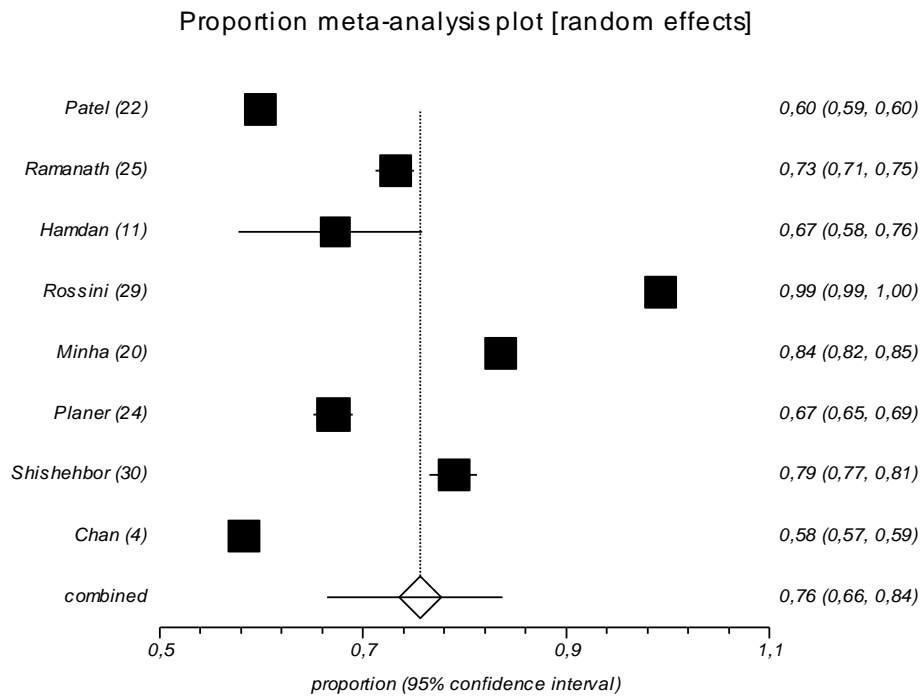
**Figure S33.** Meta-analysis estimating the baseline proportion of aspirin users among non-obstructive CAD patients.



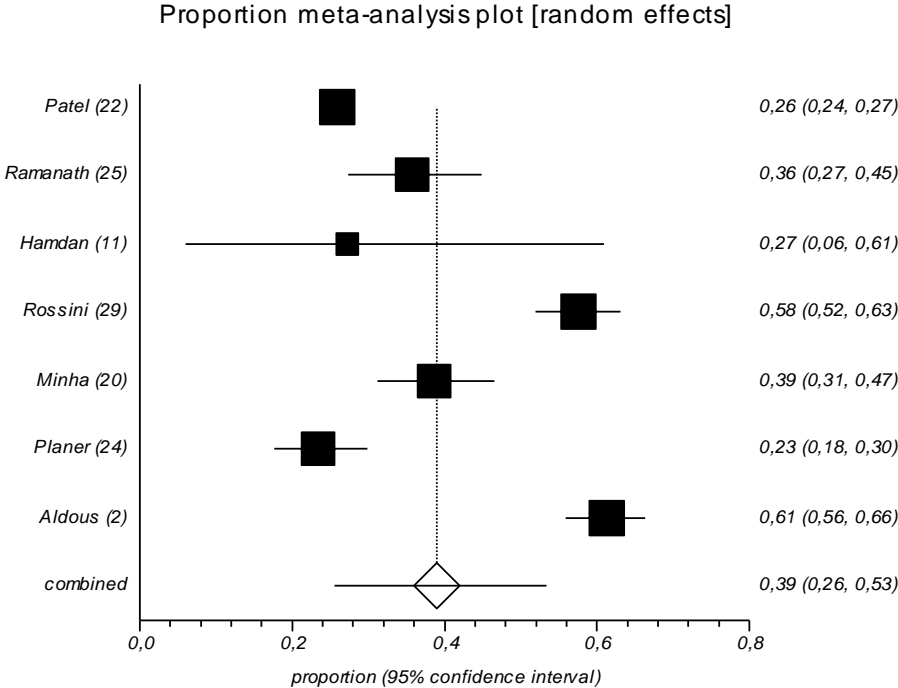
**Figure S34.** Meta-analysis estimating the baseline proportion of aspirin users among obstructive CAD patients.



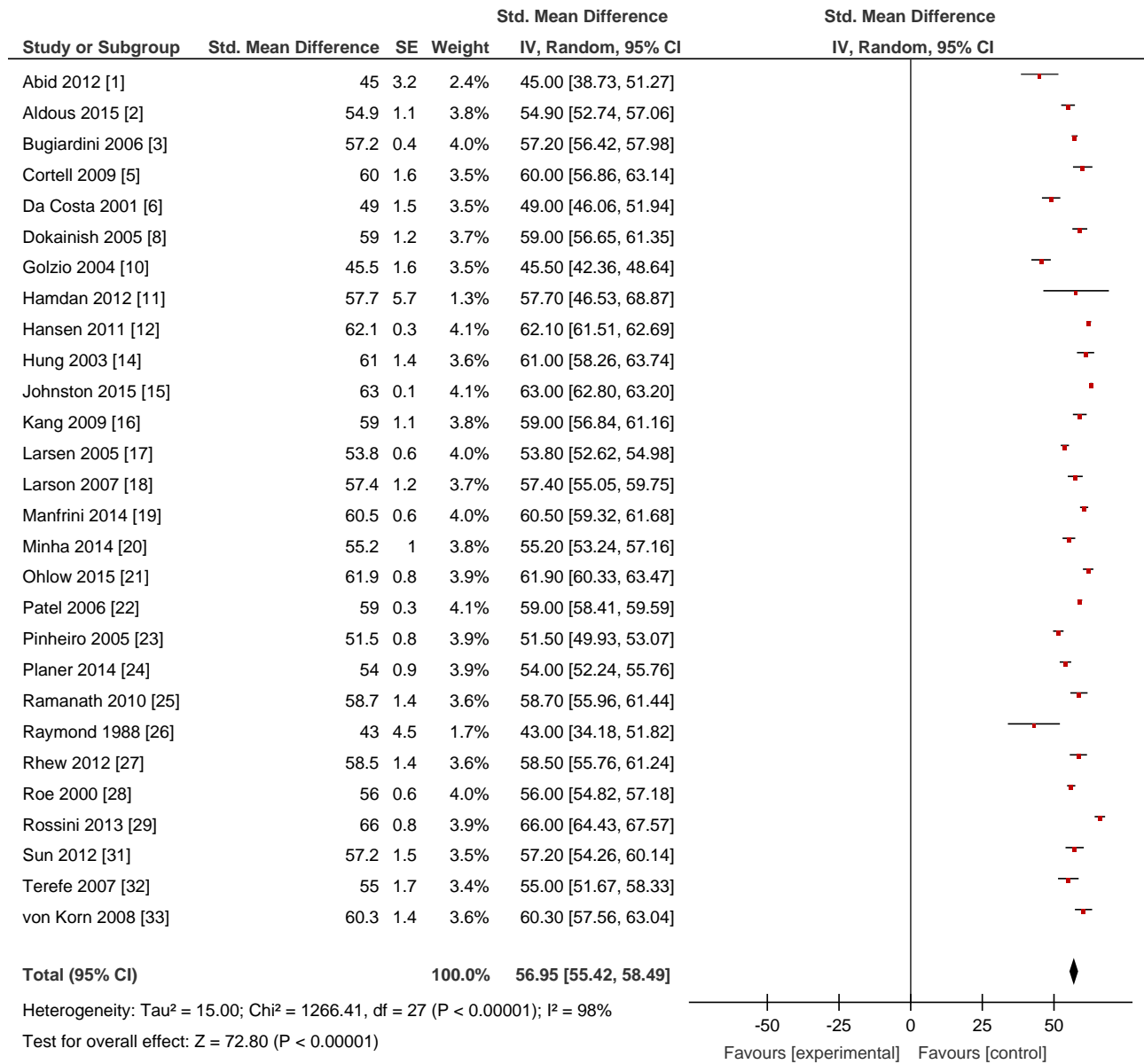
**Figure S35.** Meta-analysis estimating the baseline proportion of P2Y12 inhibitors users among non-obstructive CAD patients.



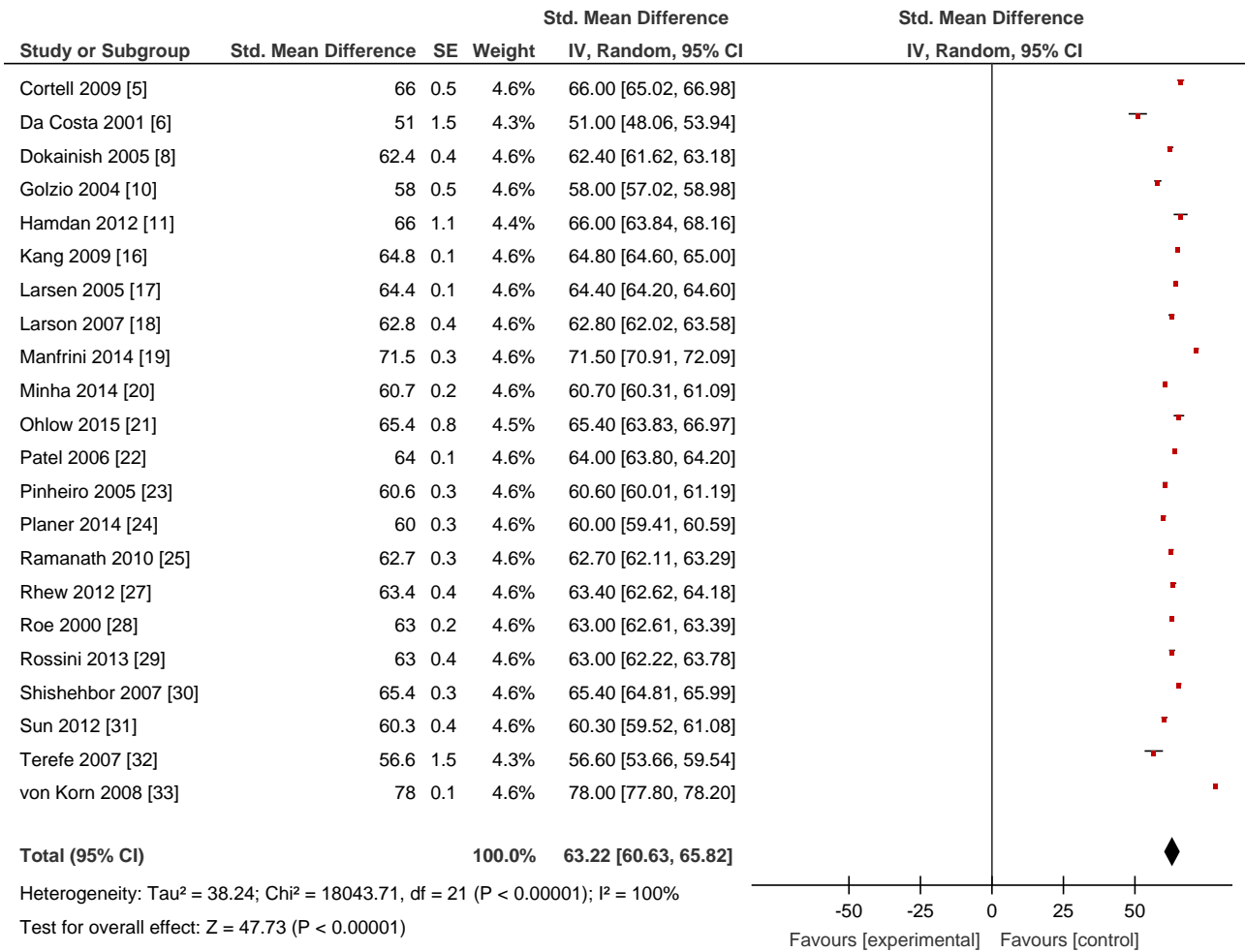
**Figure S36.** Meta-analysis estimating the baseline proportion of P2Y12 inhibitors users among obstructive CAD patients.



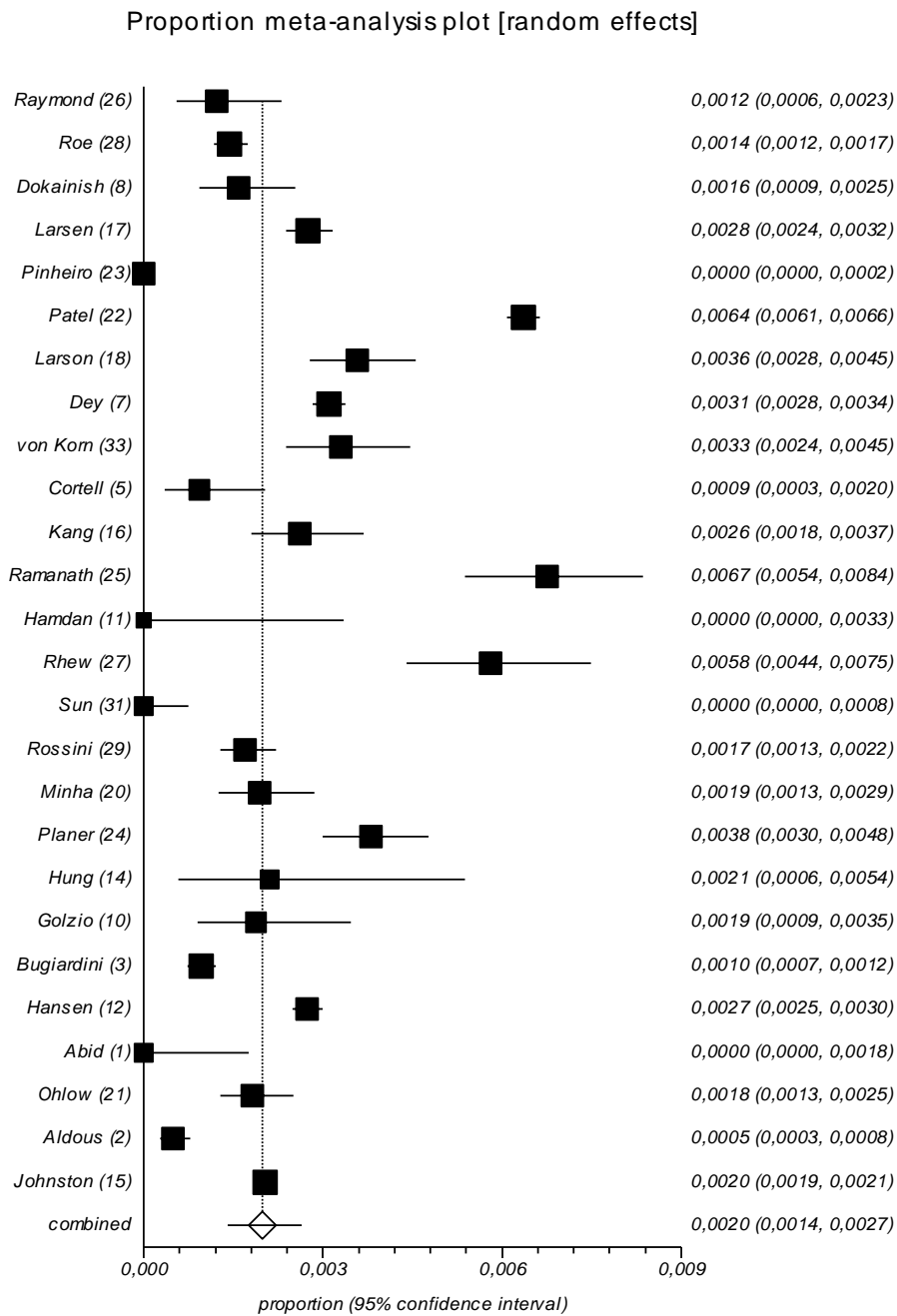
**Figure S37.** Meta-analysis estimating the mean age at baseline of non-obstructive CAD patients.



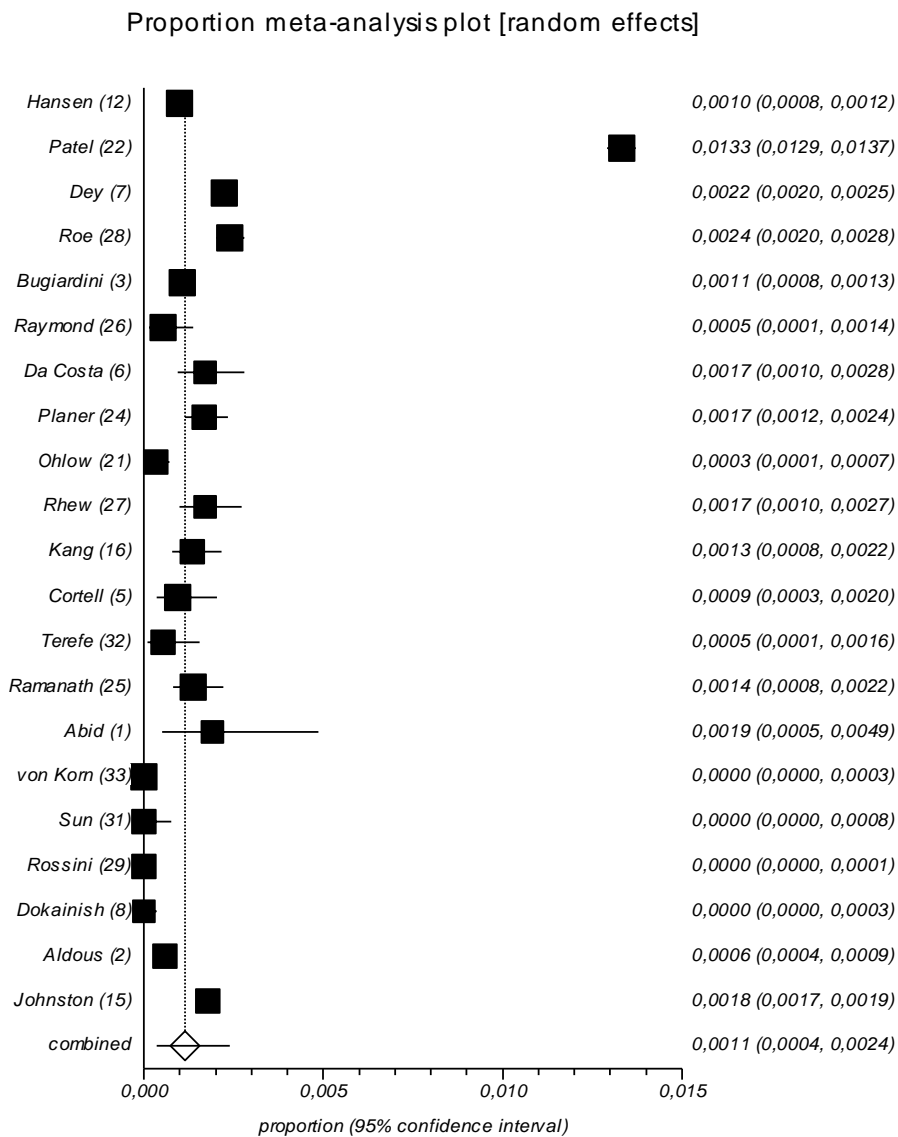
**Figure S38.** Meta-analysis estimating the mean age at baseline of obstructive CAD patients.



**Figure S39.** Meta-analysis estimating the monthly rates of all-cause death among non-obstructive CAD patients.

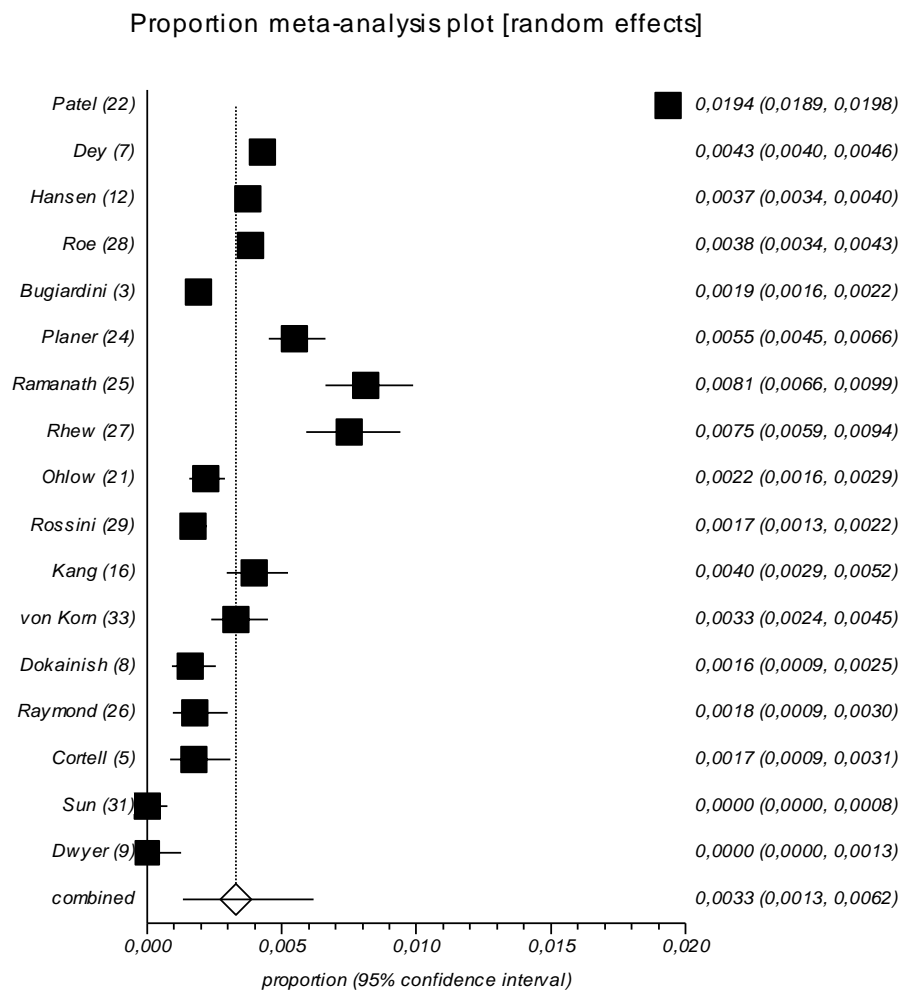


**Figure S40.** Meta-analysis estimating the monthly rates of re-infarction among non-obstructive CAD patients.

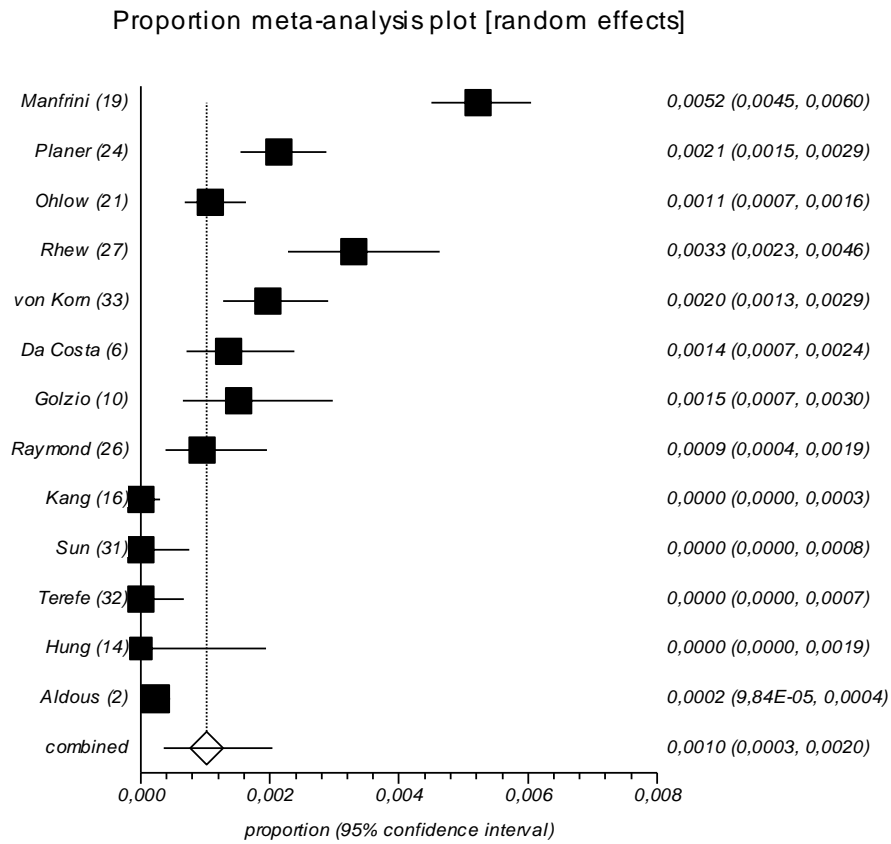




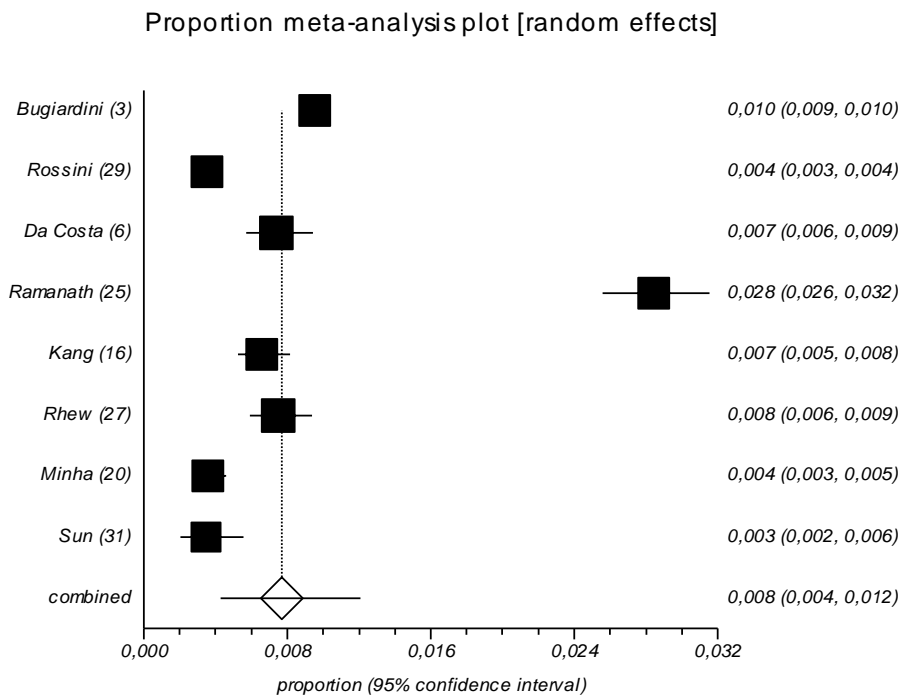
**Figure S41.** Meta-analysis estimating the monthly rates of all-cause death + re-infarction among non-obstructive CAD patients.



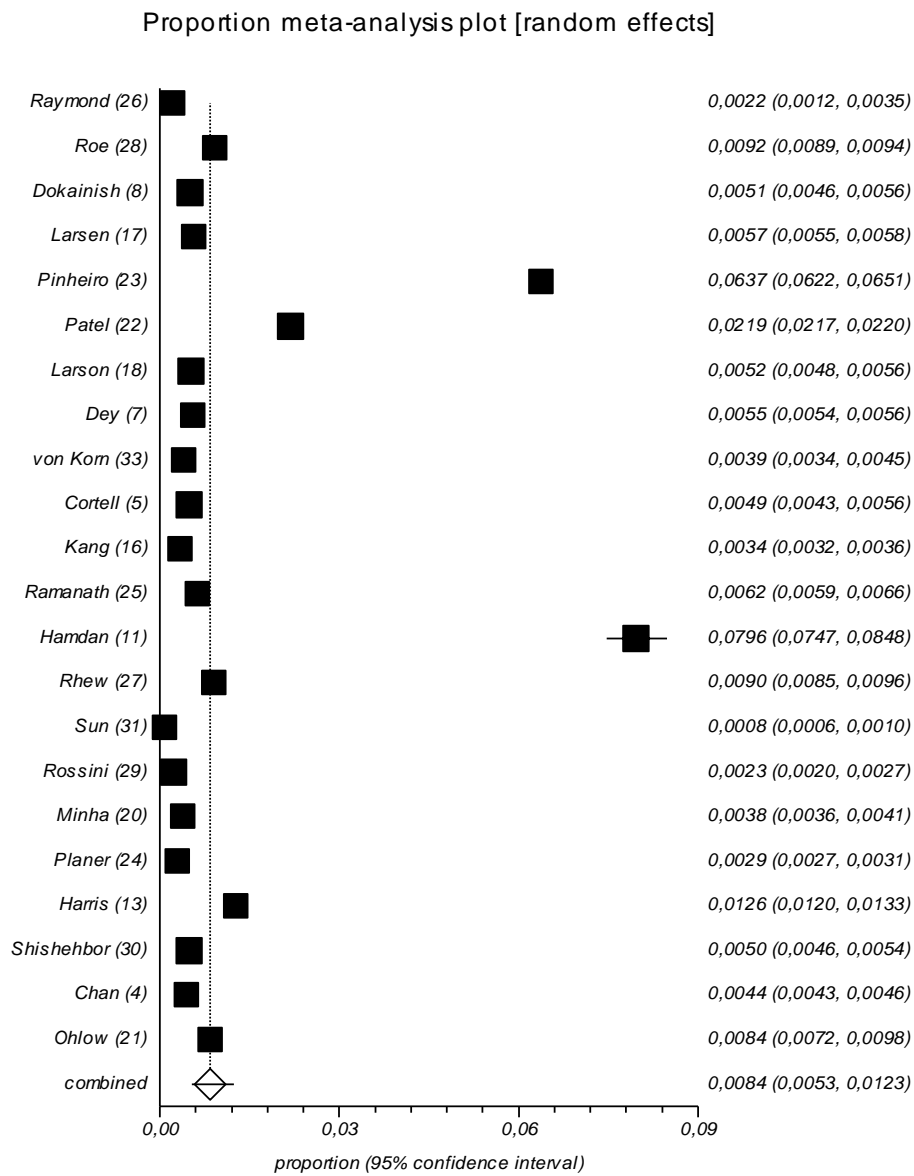
**Figure S42.** Meta-analysis estimating the monthly rates of cardiac death among non-obstructive CAD patients.



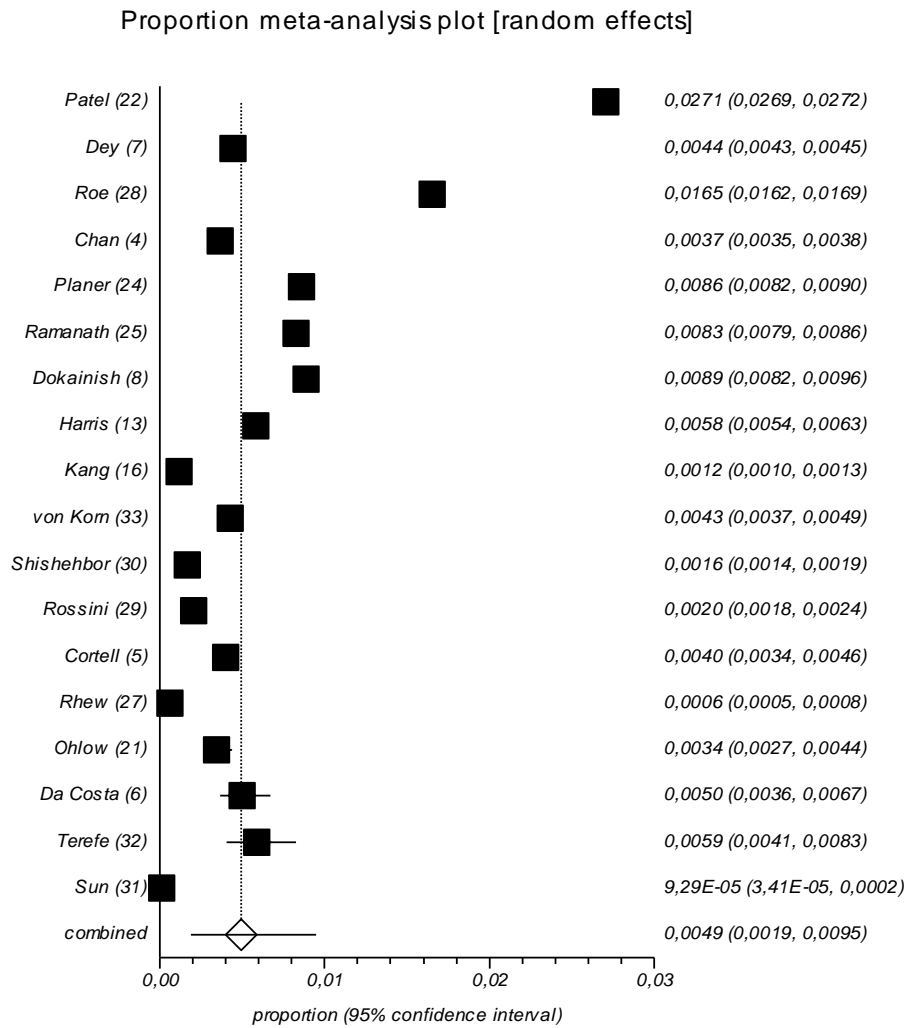
**Figure S43.** Meta-analysis estimating the monthly rates of MACE (major cardiovascular adverse events) among non-obstructive CAD patients.



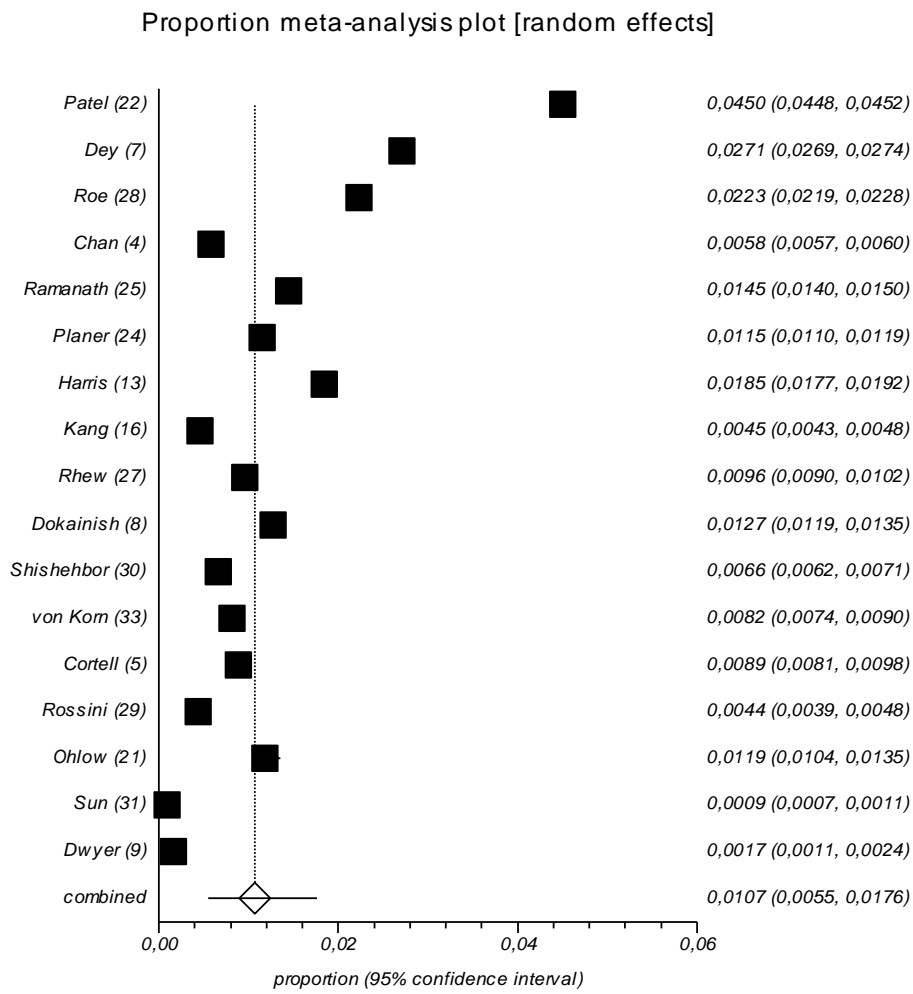
**Figure S44.** Meta-analysis estimating the monthly rates of all-cause death among obstructive CAD patients.



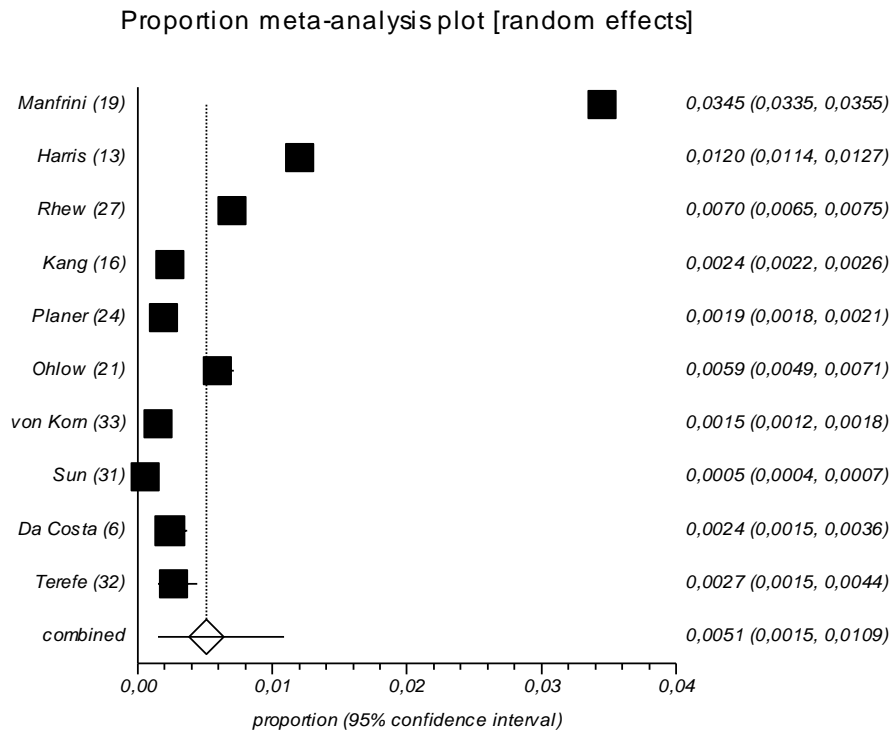
**Figure S45.** Meta-analysis estimating the monthly rates of re-infarction among obstructive CAD patients.



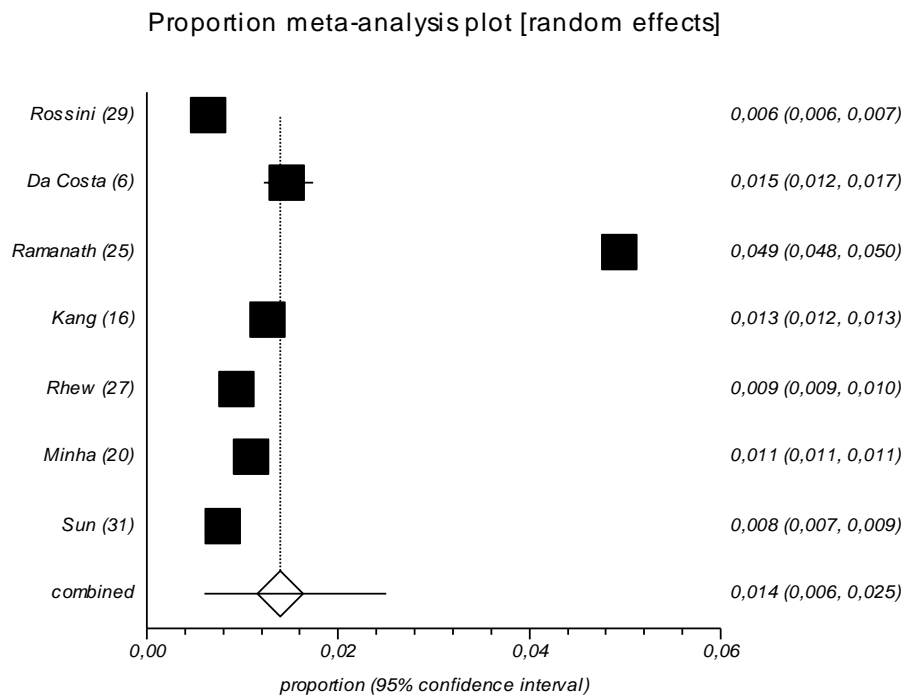
**Figure S46.** Meta-analysis estimating the monthly rates of all-cause death + re-infarction among obstructive CAD patients.



**Figure S47.** Meta-analysis estimating the monthly rates of cardiac death among obstructive CAD patients.

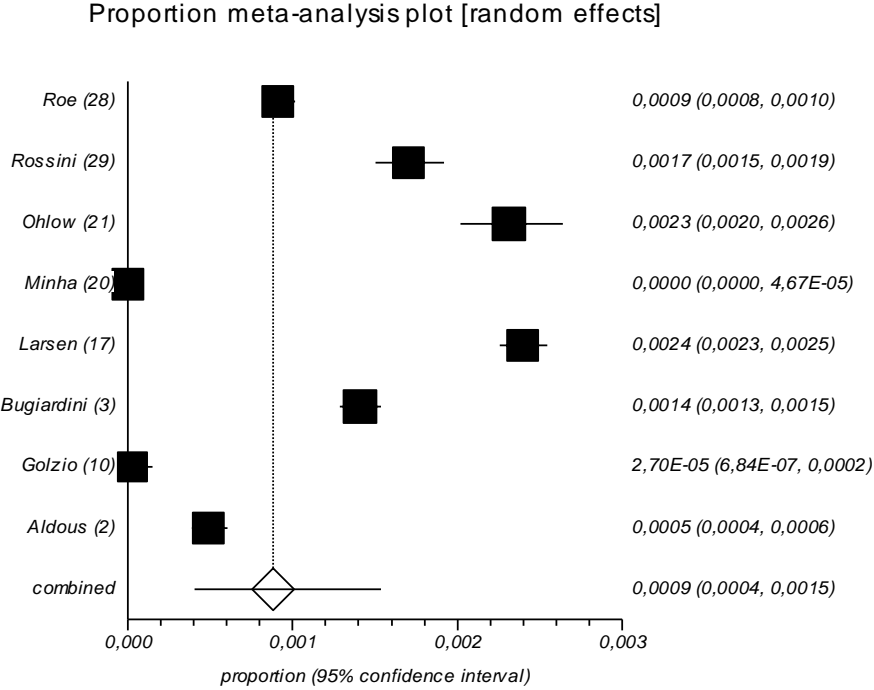


**Figure S48.** Meta-analysis estimating the monthly rates of MACE (major cardiovascular adverse events) among obstructive CAD patients.

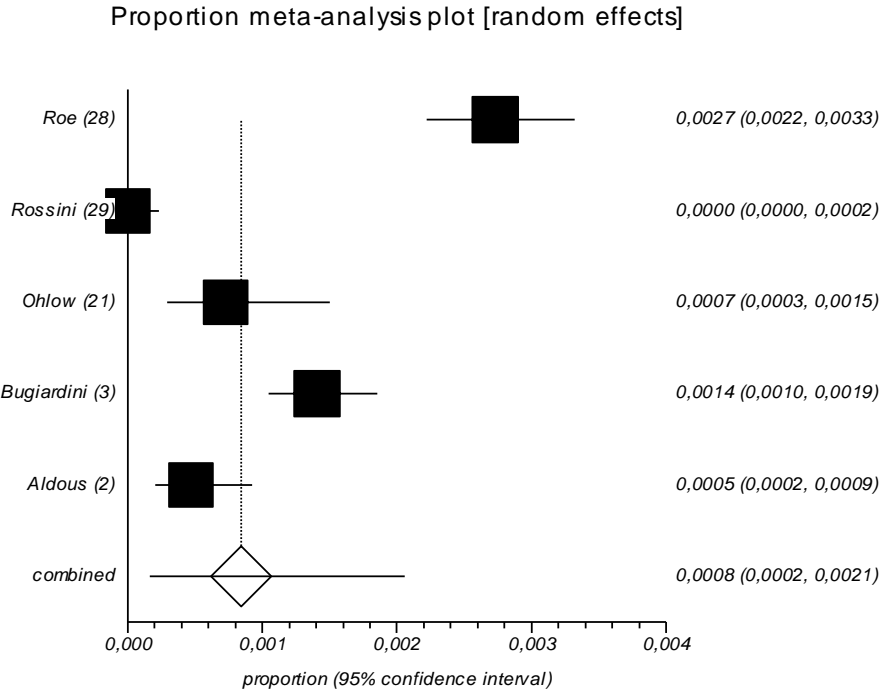




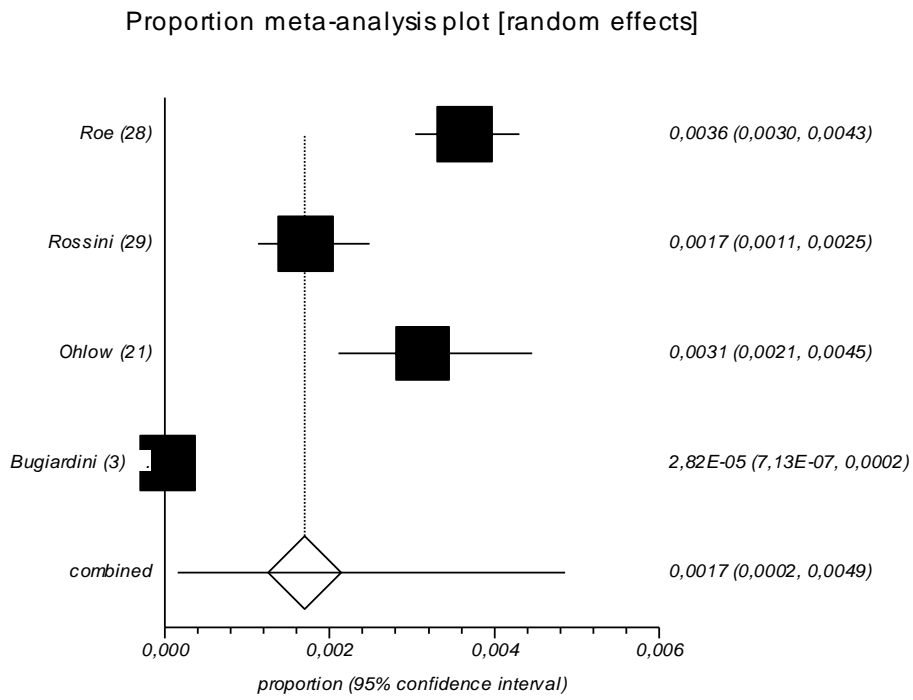
**Figure S49.** Meta-analysis estimating the monthly rates of all-cause death among mildly-obstructive CAD patients (1% -50% stenosis).



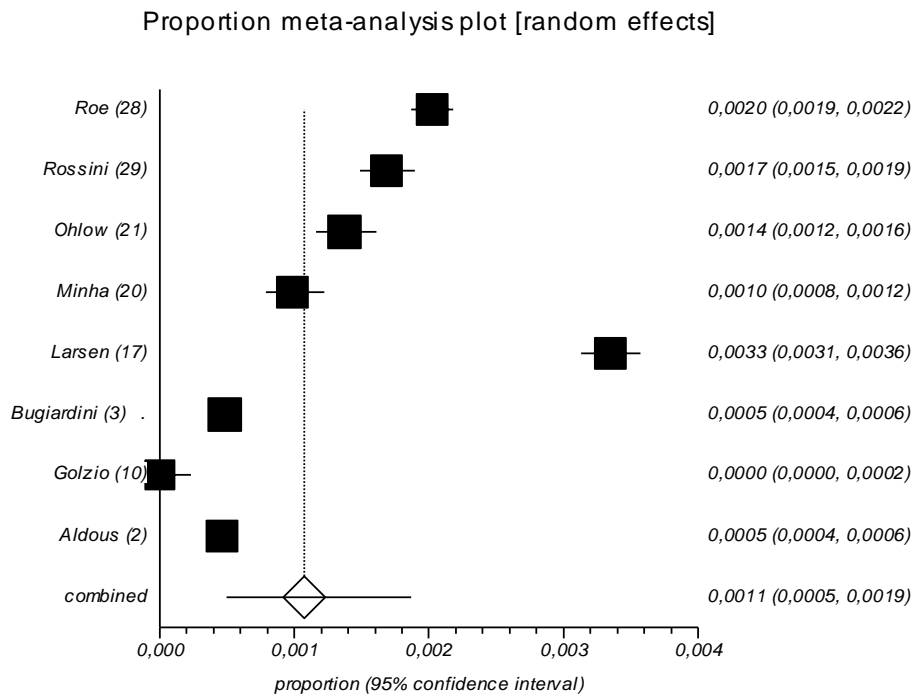
**Figure S50.** Meta-analysis estimating the monthly rates of re-infarction among mildly-obstructive CAD patients (1%-50% stenosis).



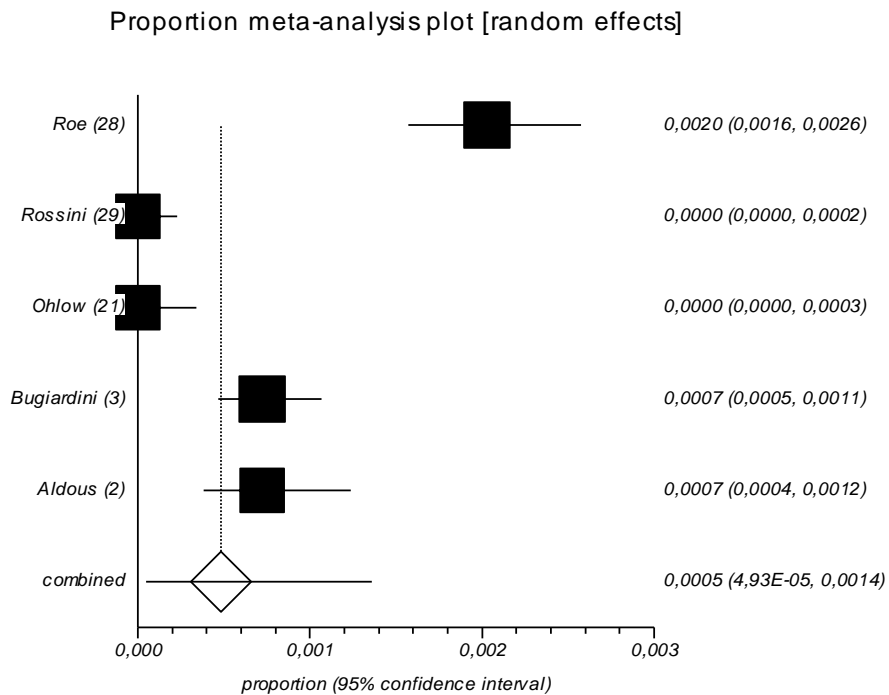
**Figure S51.** Meta-analysis estimating the monthly rates of all-cause death + re-infarction among mildly-obstructive CAD patients (1%-50% stenosis).



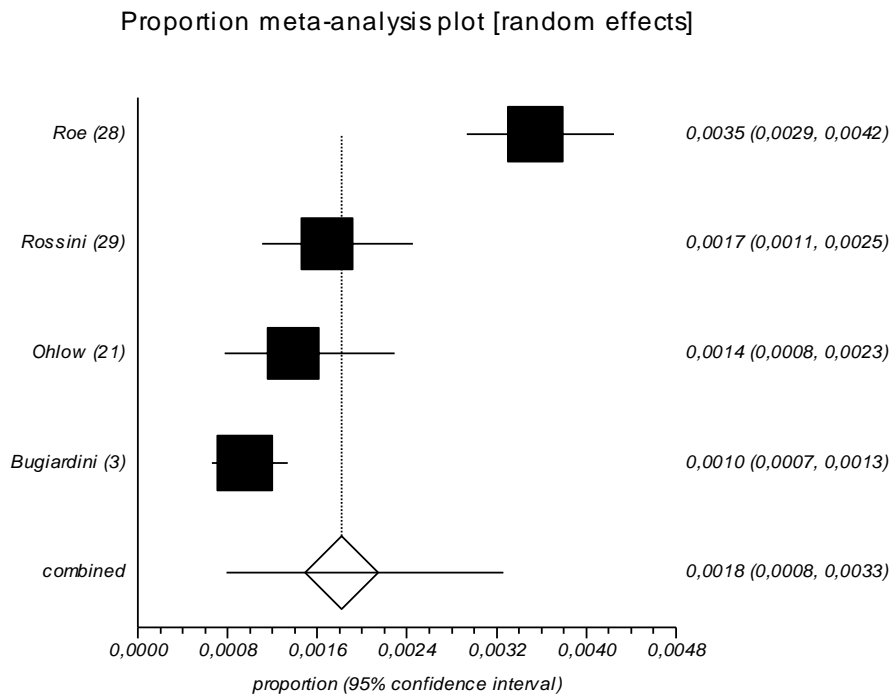
**Figure S52.** Meta-analysis estimating the monthly rates of all-cause death among normal artery CAD patients (0% stenosis).



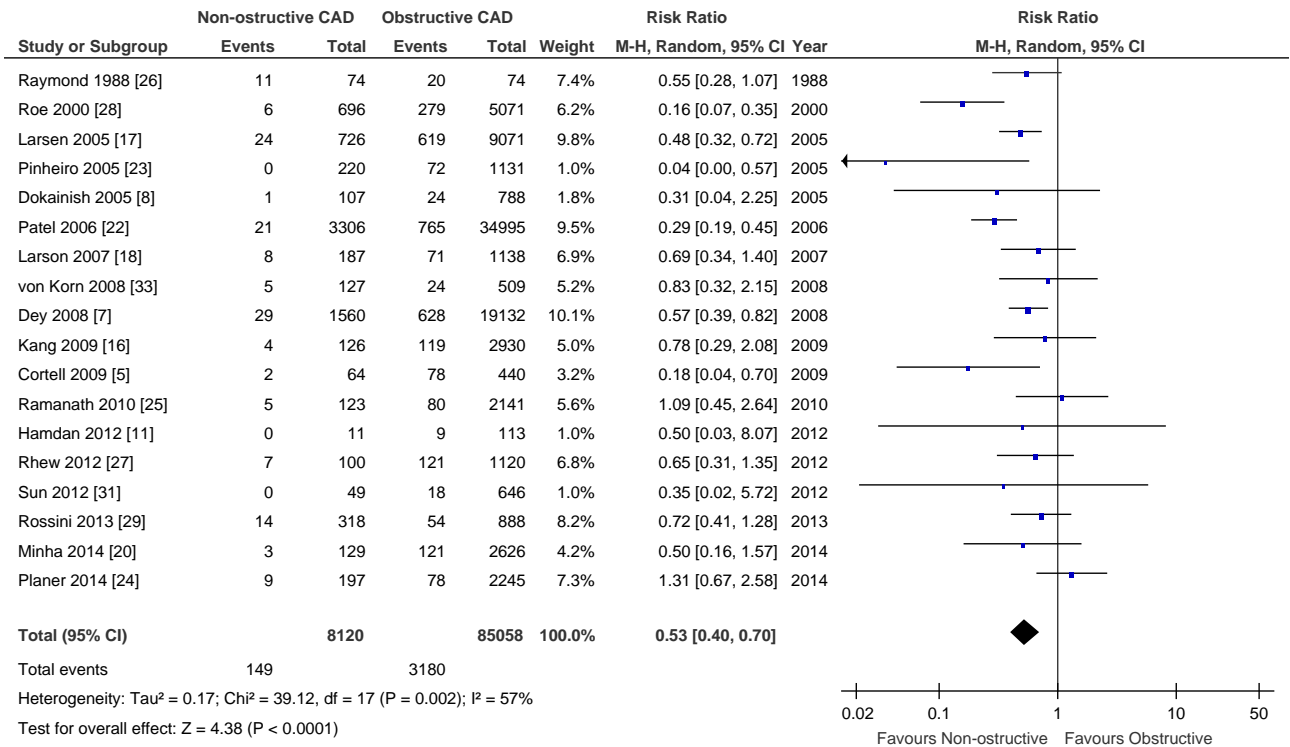
**Figure S53.** Meta-analysis estimating the monthly rates of re-infarction among normal artery CAD patients (0% stenosis).



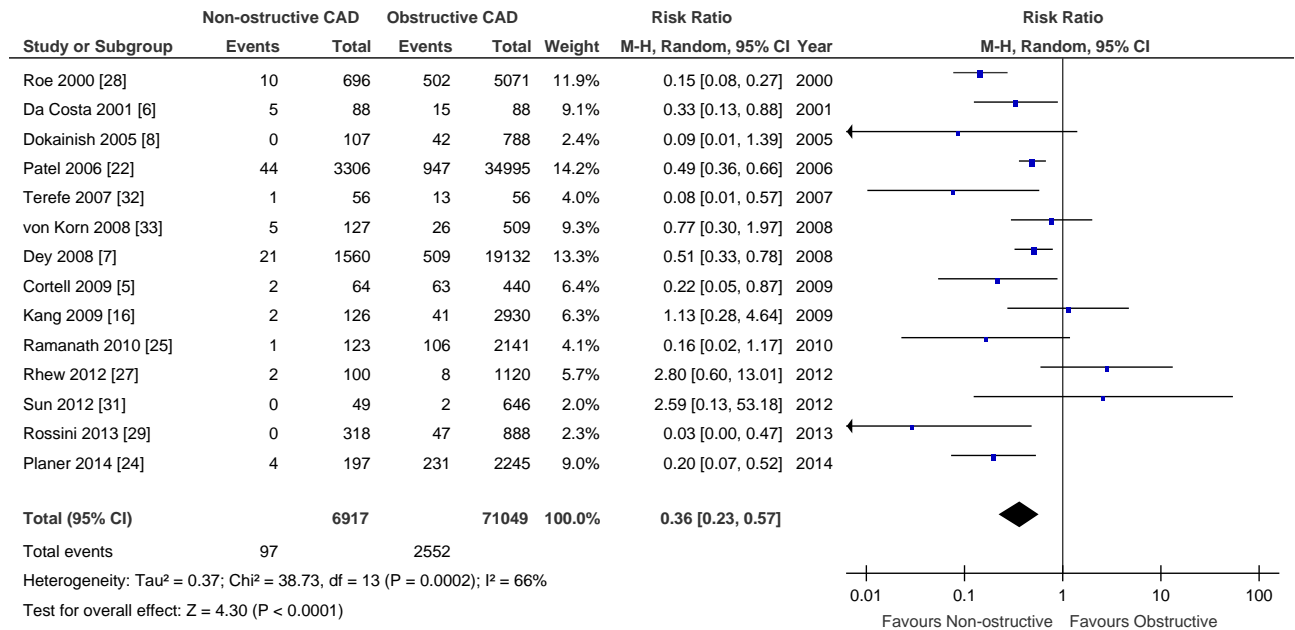
**Figure S54.** Meta-analysis estimating the monthly rates of all-cause death + re-infarction among normal artery CAD patients (0% stenosis).



**Figure S55.** Meta-analysis comparing all-cause mortality among non-obstructive vs obstructive CAD patients.

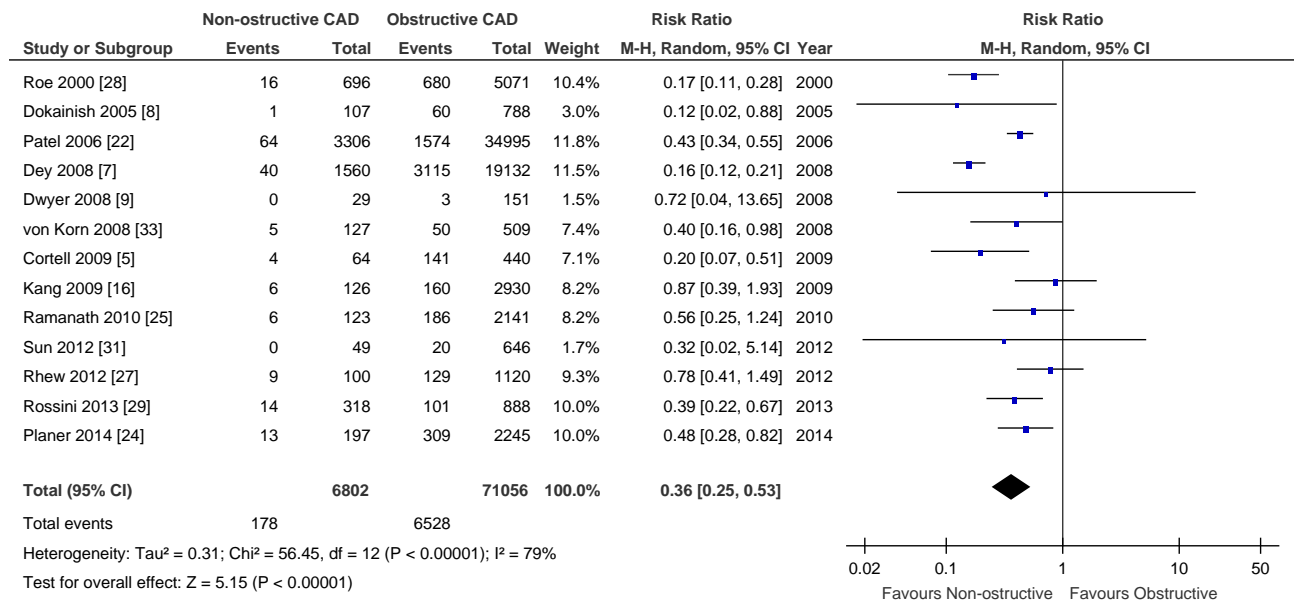


**Figure S56.** Meta-analysis comparing the re-occurrence of myocardial infarction among non-obstructive vs obstructive CAD patients.

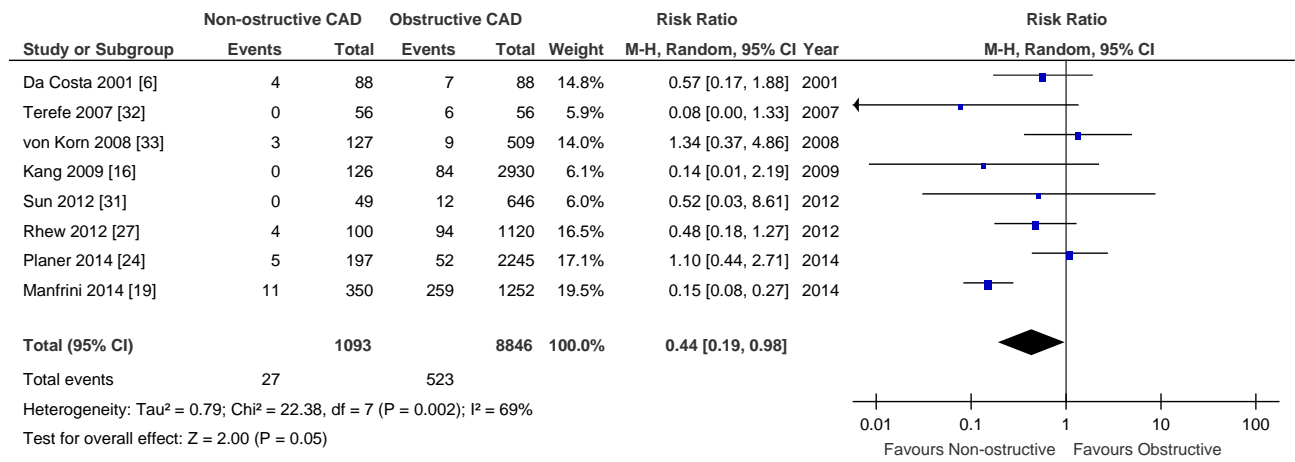




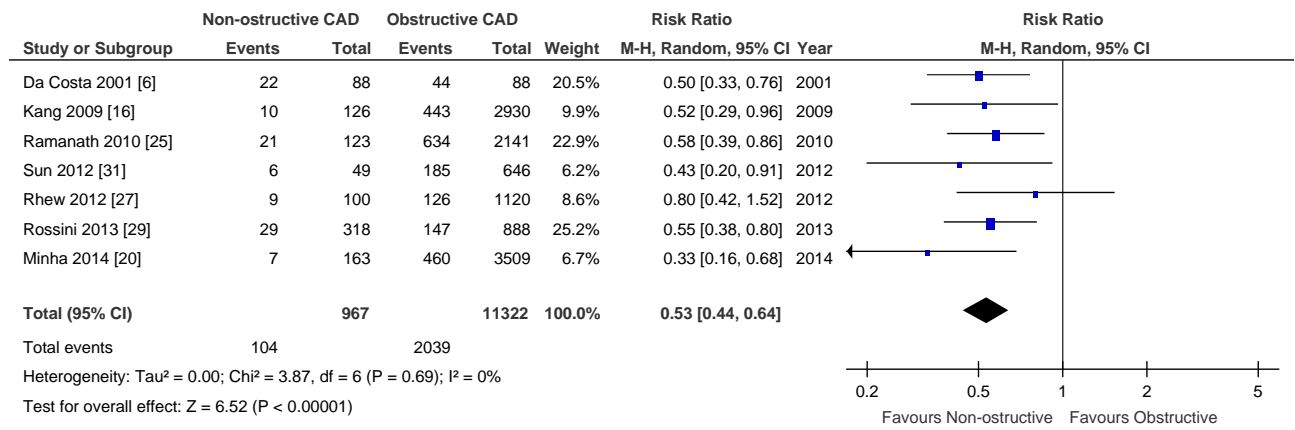
**Figure S57.** Meta-analysis comparing all-cause mortality + myocardial re-infarction among non-obstructive vs obstructive CAD patients.



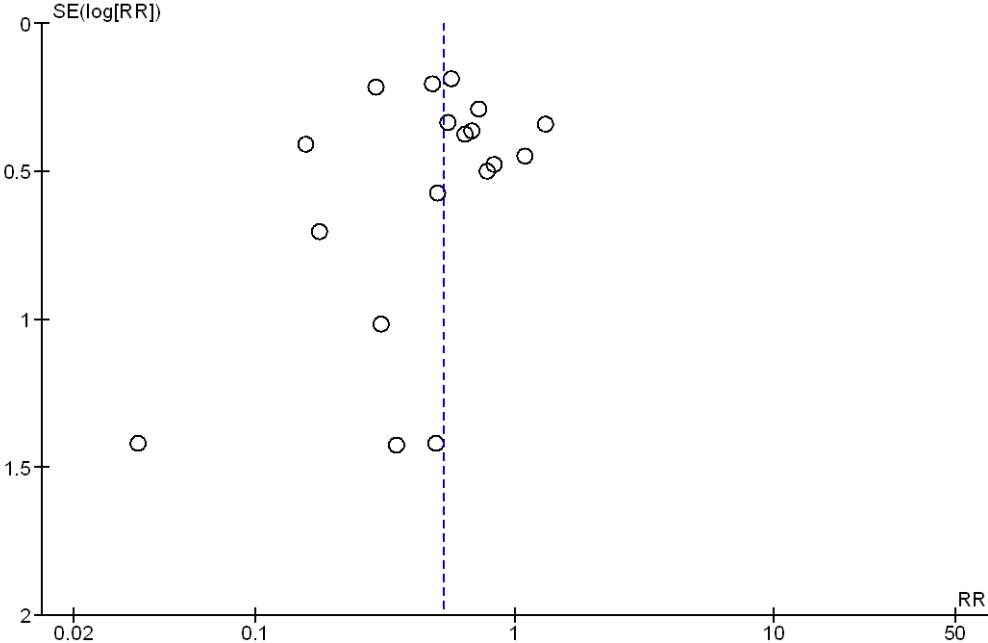
**Figure S58.** Meta-analysis comparing cardiovascular mortality among non-obstructive vs obstructive CAD patients.



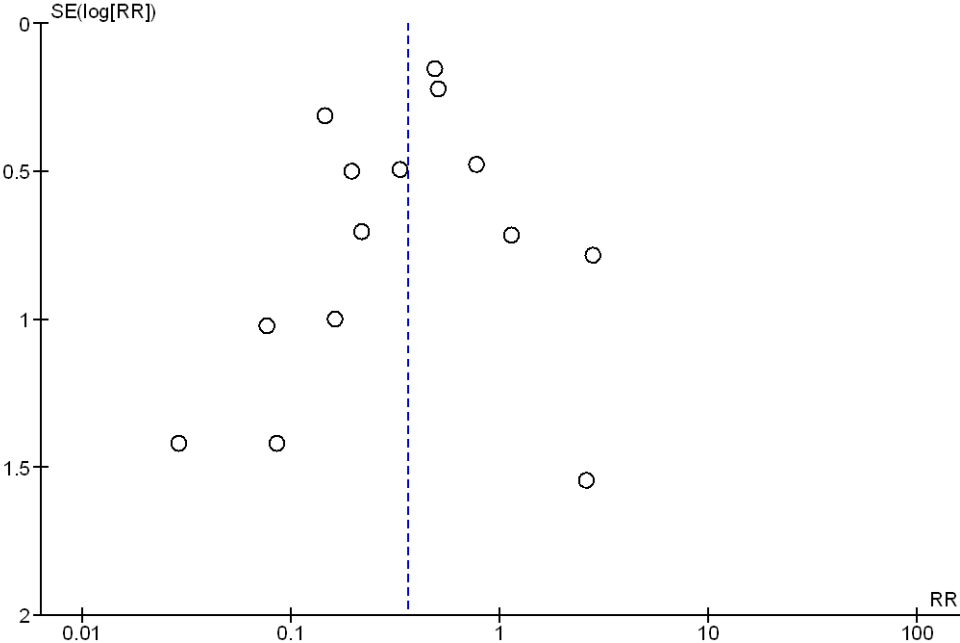
**Figure S59.** Meta-analysis comparing the occurrence of MACE among non-obstructive vs obstructive CAD patients.



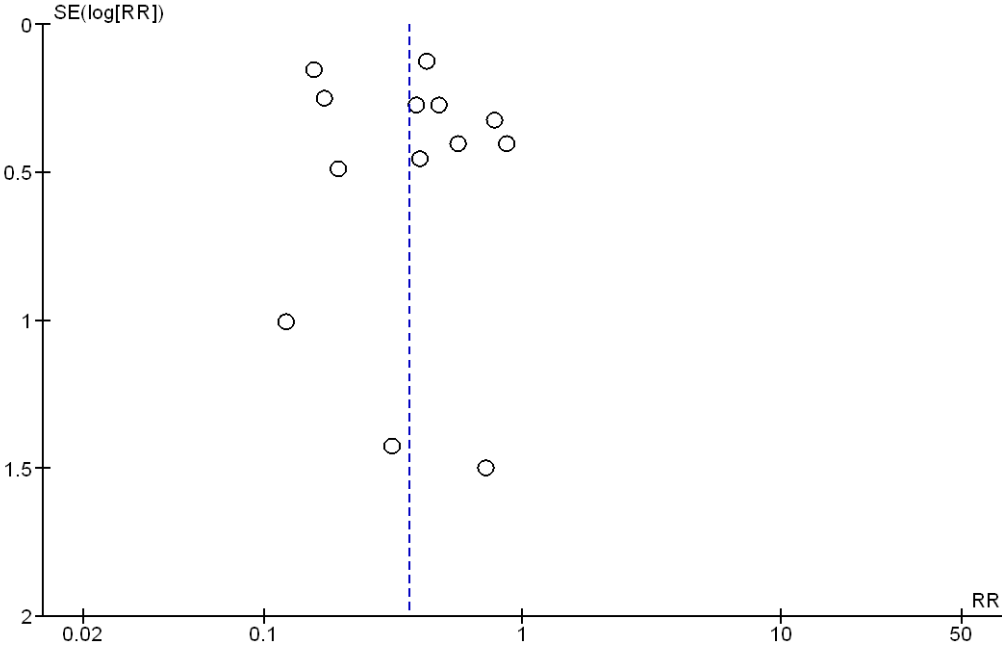
**Figure S60.** Funnel plot of relative risks vs the logarithms of their standard errors (all-cause mortality).



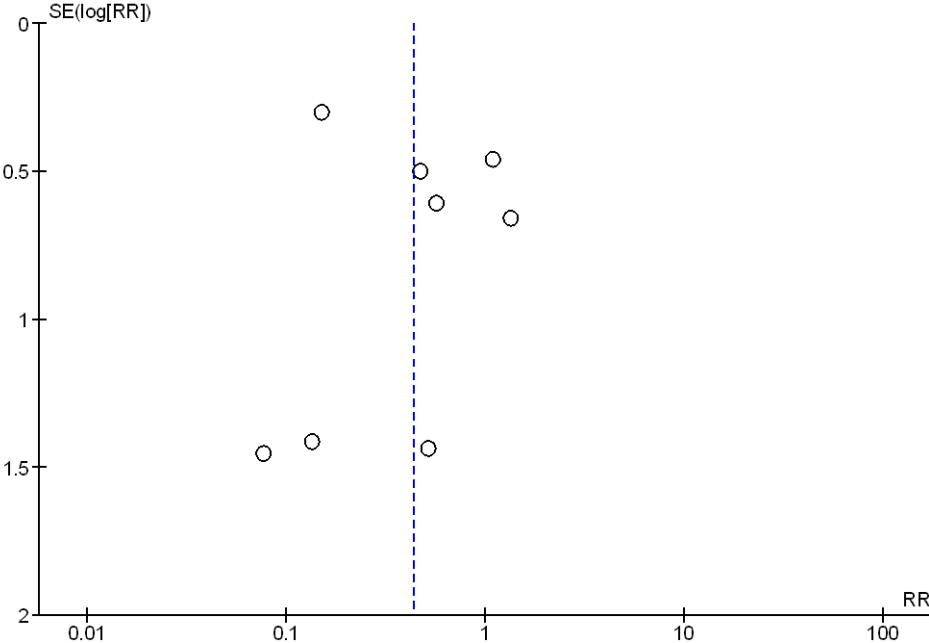
**Figure S61.** Funnel plot of relative risks vs the logarithms of their standard errors (myocardial infarction).



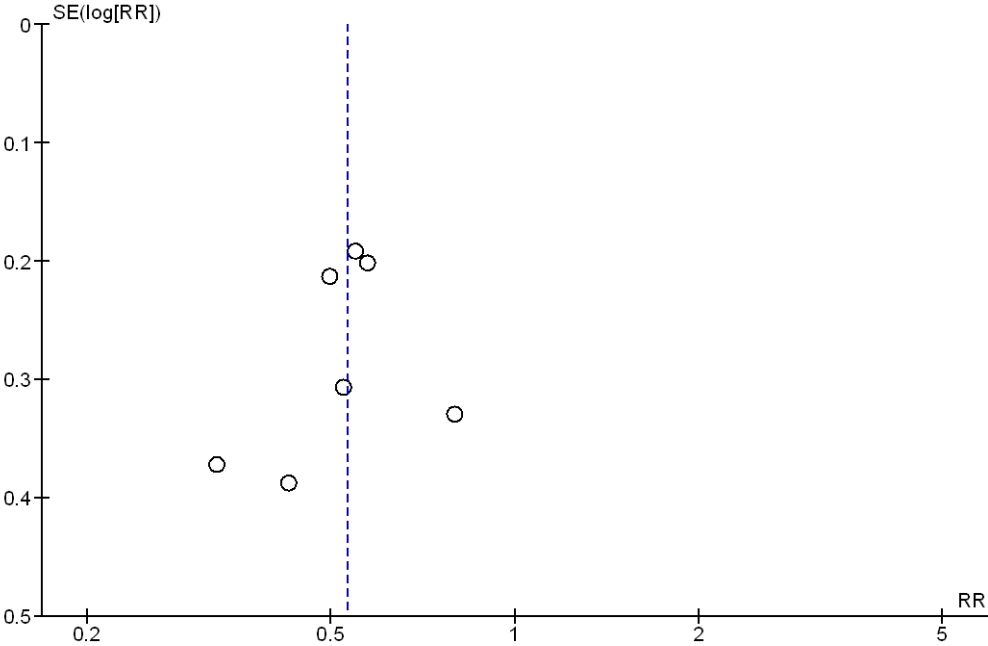
**Figure S62.** Funnel plot of relative risks vs the logarithms of their standard errors (all deaths + myocardial infarction).



**Figure S63.** Funnel plot of relative risks vs the logarithms of their standard errors (cardiac death).

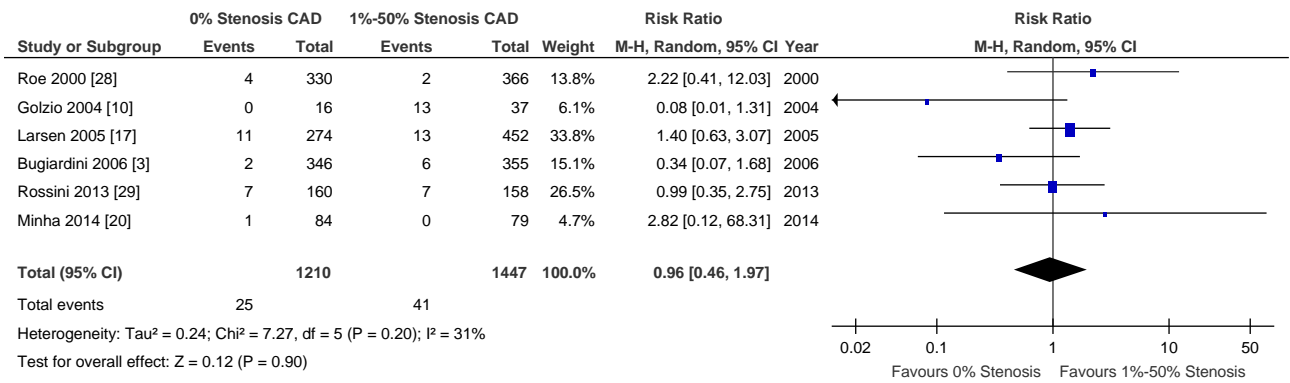


**Figure S64.** Funnel plot of relative risks vs the logarithms of their standard errors (Major adverse cardiovascular events).

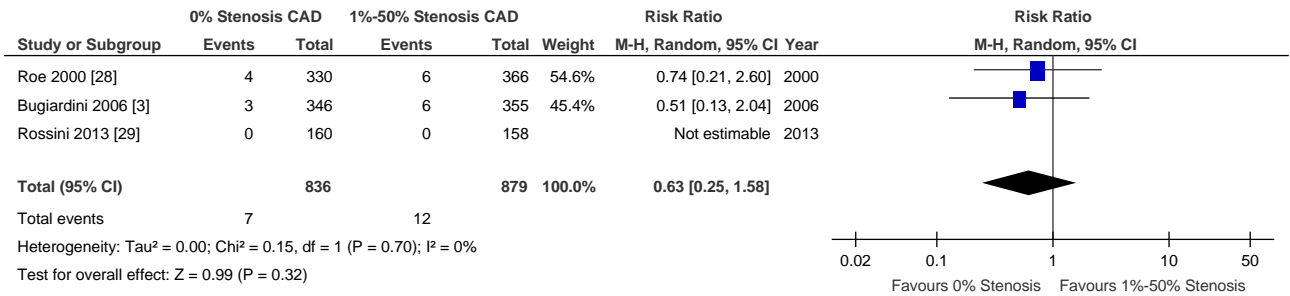




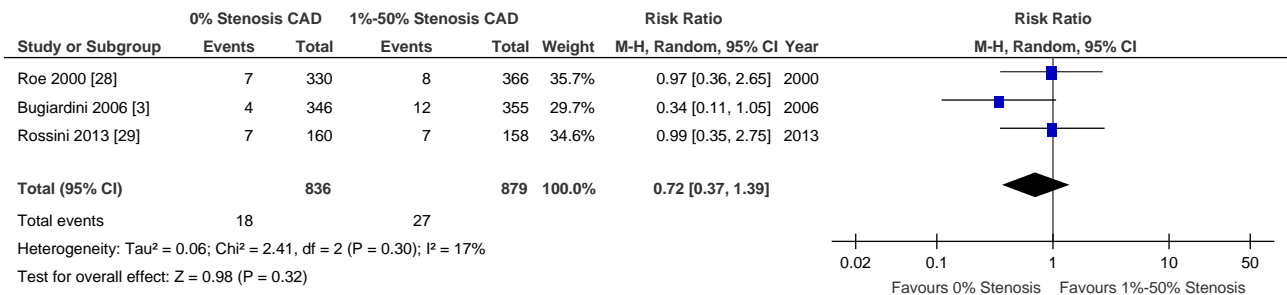
**Figure S65.** Meta-analysis comparing all-cause mortality among mildly obstructive CAD (1%-50% stenosis) versus normal artery CAD (0% stenosis).



**Figure S66.** Meta-analysis comparing re-infarction among mildly obstructive CAD (1%-50% stenosis) versus normal artery CAD (0% stenosis).



**Figure S67.** Meta-analysis comparing all-cause mortality plus re-infarction among mildly obstructive CAD (1%-50% stenosis) versus normal artery CAD (0% stenosis)



## Supplemental References:

1. Abid L, Bahloul A, Frikha Z, Mallek S, Abid D, Akrouf M, Hentati M and Kammoun S. Myocardial infarction and normal coronary arteries: the experience of the cardiology department of Sfax, Tunisia. *Intern Med.* 2012;51:1959-67.
2. Aldous S, Elliott J, McClean D, Puri A and Richards AM. Outcomes in Patients Presenting with Symptoms Suggestive of Acute Coronary Syndrome with Elevated Cardiac Troponin but Non-obstructive Coronary Disease on Angiography. *Heart Lung Circ.* 2015;24:869-78.
3. Bugiardini R, Manfrini O and De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. *Arch Intern Med.* 2006;166:1391-5.
4. Chan MY, Mahaffey KW, Sun LJ, Pieper KS, White HD, Aylward PE, Ferguson JJ, Califf RM and Roe MT. Prevalence, predictors, and impact of conservative medical management for patients with non-ST-segment elevation acute coronary syndromes who have angiographically documented significant coronary disease. *JACC Cardiovasc Interv.* 2008;1:369-78.
5. Cortell A, Sanchis J, Bodi V, Nunez J, Mainar L, Pellicer M, Minana G, Santas E, Dominguez E, Palau P and Llacer A. Non-ST-elevation acute myocardial infarction with normal coronary arteries: predictors and prognosis. *Rev Esp Cardiol.* 2009;62:1260-6.
6. Da Costa A, Isaaz K, Faure E, Mourouf S, Cerisier A and Lamaud M. Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram; a 3-year follow-up study of 91 patients. *Eur Heart J.* 2001;22:1459-65.
7. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA and Eagle KA. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart.* 2009;95:20-6.
8. Dokainish H, Pillai M, Murphy SA, DiBattiste PM, Schweiger MJ, Lotfi A, Morrow DA, Cannon CP, Braunwald E and Lakkis N. Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J Am Coll Cardiol.* 2005;45:19-24.
9. Dwyer JP, Redfern J and Freedman SB. Low utilisation of cardiovascular risk reducing therapy in patients with acute coronary syndromes and non-obstructive coronary artery disease. *Int J Cardiol.* 2008;129:394-8.
10. Golzio PG, Orzan F, Ferrero P, Bobbio M, Bergerone S, Di Leo M and Trevi GP. Myocardial infarction with normal coronary arteries: ten-year follow-up. *Ital Heart J.* 2004;5:732-8.
11. Hamdan R, Frangieh A, Zadri Z, Hajje F, Hazar R, Salame E, Jaoude SA, Kassab R and Badaoui G. What do we know about myocardial infarction with normal coronary arteries? *Gazzetta Medica Italiana Archivio per le Scienze Mediche.* 2012;171:7-12.
12. Hansen KW, Hvelplund A, Abildstrom SZ, Prescott E, Madsen M, Madsen JK, Jensen JS, Thuesen L, Thyssen P, Tilsted HH, Jorgensen E and Galatius S. No gender differences in prognosis and preventive treatment in patients with AMI without significant stenoses. *Eur J Prev Cardiol.* 2012;19:746-54.
13. Harris PJ, Behar VS, Conley MJ, Harrell FE, Jr., Lee KL, Peter RH, Kong Y and Rosati RA. The prognostic significance of 50% coronary stenosis in medically treated patients with coronary artery disease. *Circulation.* 1980;62:240-8.
14. Hung MJ, Cherng WJ, Kuo LT and Wang CH. Acute myocardial infarction in Taiwanese with angiographically normal coronary arteries: Role of coronary artery spasm. *Acta Cardiologica Sinica.* 2003;19:31-38.
15. Johnston N, Jonelid B, Christersson C, Kero T, Renlund H, Schenck-Gustafsson K and Lagerqvist B. Effect of Gender on Patients With ST-Elevation and Non-ST-Elevation Myocardial Infarction Without Obstructive Coronary Artery Disease. *Am J Cardiol.* 2015;115:1661-6.
16. Kang WY, Jeong MH, Ahn YK, Kim JH, Chae SC, Kim YJ, Hur SH, Seong IW, Hong TJ, Choi DH, Cho MC, Kim CJ, Seung KB, Chung WS, Jang YS, Rha SW, Bae JH, Cho JG and Park SJ. Are patients with angiographically near-normal coronary arteries who present as acute myocardial infarction actually safe? *Int J Cardiol.* 2011;146:207-12.
17. Larsen AI, Galbraith PD, Ghali WA, Norris CM, Graham MM and Knudtson ML. Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries. *Am J Cardiol.* 2005;95:261-3.

18. Larson DM, Menssen KM, Sharkey SW, Duval S, Schwartz RS, Harris J, Meland JT, Unger BT and Henry TD. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. *JAMA*. 2007;298:2754-60.
19. Manfrini O, Morrell C, Das R, Barth JH, Hall AS, Gale CP, Cenko E and Bugiardini R. Effects of angiotensin-converting enzyme inhibitors and beta blockers on clinical outcomes in patients with and without coronary artery obstructions at angiography (from a Register-Based Cohort Study on Acute Coronary Syndromes). *Am J Cardiol*. 2014;113:1628-33.
20. Minha S, Gottlieb S, Magalhaes MA, Gavriellov-Yusim N, Krakover R, Goldenberg I, Vered Z and Blatt A. Characteristics and management of patients with acute coronary syndrome and normal or nonsignificant coronary artery disease: results from Acute Coronary Syndrome Israeli Survey (ACSIS) 2004-2010. *J Invasive Cardiol*. 2014;26:389-93.
21. Ohlow MA, Wong V, Brunelli M, von Korn H, Farah A, Memisevic N, Richter S, Tukhiashvili K and Lauer B. Acute coronary syndrome without critical epicardial coronary disease: prevalence, characteristics, and outcome. *Am J Emerg Med*. 2015;33:150-4.
22. Patel MR, Chen AY, Peterson ED, Newby LK, Pollack CV, Jr., Brindis RG, Gibson CM, Kleiman NS, Saucedo JF, Bhatt DL, Gibler WB, Ohman EM, Harrington RA and Roe MT. Prevalence, predictors, and outcomes of patients with non-ST-segment elevation myocardial infarction and insignificant coronary artery disease: results from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE) initiative. *Am Heart J*. 2006;152:641-7.
23. Pinheiro M, Rabelo Junior A, de Jesus RS, Nascimento LC and Costa UM. [Acute coronary syndromes in the absence of significant coronary artery disease]. *Arq Bras Cardiol*. 2005;84:24-8.
24. Planer D, Mehran R, Ohman EM, White HD, Newman JD, Xu K and Stone GW. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the acute catheterization and urgent intervention triage strategy trial. *Circ Cardiovasc Interv*. 2014;7:285-93.
25. Ramanath VS, Armstrong DF, Grzybowski M, Rahnama-Mohagdam S, Tamhane UU, Gordon K, Froehlich JB, Eagle KA and Jackson EA. Receipt of cardiac medications upon discharge among men and women with acute coronary syndrome and nonobstructive coronary artery disease. *Clin Cardiol*. 2010;33:36-41.
26. Raymond R, Lynch J, Underwood D, Leatherman J and Razavi M. Myocardial infarction and normal coronary arteriography: a 10 year clinical and risk analysis of 74 patients. *J Am Coll Cardiol*. 1988;11:471-7.
27. Rhew SH, Ahn Y, Kim MC, Jang SY, Cho KH, Hwang SH, Lee MG, Ko JS, Park KH, Sim DS, Yoon NS, Yoon HJ, Kim KH, Hong YJ, Park HW, Kim JH, Jeong MH, Cho JG, Park JC and Kang JC. Is Myocardial Infarction in Patients without Significant Stenosis on a Coronary Angiogram as Benign as Believed? *Chonnam Med J*. 2012;48:39-46.
28. Roe MT, Harrington RA, Prosper DM, Pieper KS, Bhatt DL, Lincoff AM, Simoons ML, Akkerhuis M, Ohman EM, Kitt MM, Vahanian A, Ruzyllo W, Karsch K, Califf RM and Topol EJ. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. *Circulation*. 2000;102:1101-6.
29. Rossini R, Capodanno D, Lettieri C, Musumeci G, Limbruno U, Molfese M, Spataro V, Calabria P, Romano M, Tarantini G, Gavazzi A and Angiolillo DJ. Long-term outcomes of patients with acute coronary syndrome and nonobstructive coronary artery disease. *Am J Cardiol*. 2013;112:150-5.
30. Shishehbor MH, Lauer MS, Singh IM, Chew DP, Karha J, Brener SJ, Moliterno DJ, Ellis SG, Topol EJ and Bhatt DL. In unstable angina or non-ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culprit-only stenting? *J Am Coll Cardiol*. 2007;49:849-54.
31. Sun J, Zhang W, Zeng Q, Dong S and Sun X. Three-year follow-up in patients with acute coronary syndrome and normal coronary angiography. *Coron Artery Dis*. 2012;23:162-6.
32. Terefe YG, Niraj A, Pradhan J, Kondur A and Afonso L. Myocardial infarction with angiographically normal coronary arteries in the contemporary era. *Coron Artery Dis*. 2007;18:621-6.
33. von Korn H, Graefe V, Ohlow MA, Yu J, Huegl B, Wagner A, Gruene S and Lauer B. Acute coronary syndrome without significant stenosis on angiography: characteristics and prognosis. *Tex Heart Inst J*. 2008;35:406-12.

34. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ and Califf RM. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIB Investigators. *N Engl J Med.* 1999;341:226-32.
35. Germing A, Lindstaedt M, Ulrich S, Grewe P, Bojara W, Lawo T, von Dryander S, Jager D, Machraoui A, Mugge A and Lemke B. Normal angiogram in acute coronary syndrome-preangiographic risk stratification, angiographic findings and follow-up. *Int J Cardiol.* 2005;99:19-23.
36. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M and Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) Study. *J Am Coll Cardiol.* 2008;52:523-7.
37. Chokshi NP, Iqbal SN, Berger RL, Hochman JS, Feit F, Slater JN, Pena-Sing I, Yatskar L, Keller NM, Babaev A, Attubato MJ and Reynolds HR. Sex and race are associated with the absence of epicardial coronary artery obstructive disease at angiography in patients with acute coronary syndromes. *Clin Cardiol.* 2010;33:495-501.