

## SUPPLEMENTARY MATERIAL

### Appendix 1. Search Terms

Key: mh = exploded MeSH: Medical subject heading (Medline medical index term); tw = text word; pt = publication type; the asterisk (\*) stands for any character(s)

#### DM

- 1 exp Diabetes Mellitus/
- 2 diabet\$.tw, ot.
- 3 (IDDM or NIDDM or MODY or T1DM or T2DM or T1D or T2D).tw,ot.
- 4 (non insulin\$ depend\$ or noninsulin\$ depend\$ or non insulin?depend\$ or noninsulin?depend\$).tw,ot.
- 5 (insulin\$ depend\$ or insulin?depend\$).tw,ot.
- 6 or/1-5

#### CVD

- 7 exp Cardiovascular Diseases/
- 8 cardio\*.tw.
- 9 cardia\*.tw.
- 10 heart\*.tw.
- 11 coronary\*.tw.
- 12 angina\*.tw.
- 13 ventric\*.tw.
- 14 myocard\*.tw.
- 15 pericard\*.tw.
- 16 isch?em\*.tw.
- 17 exp Stroke/
- 18 (stroke or stokes).tw.
- 19 cerebrovasc\*.tw.
- 20 (brain adj2 accident\*).tw.
- 21 ((brain\* or cerebral or lacunar) adj2 infarct\*).tw.
- 22 or/7-21

### **Familial hypercholesterolaemia**

- 23 familial hypercholesterolemia.tw,ot.
- 24 familial hypercholesterolaemia.tw,ot.
- 25 FH
- 26 heterozygous familial hypercholesterolemia.tw,ot.
- 27 heterozygous familial hypercholesterolaemia.tw,ot.
- 28 heterozygous FH.tw,ot.
- 29 familial combined hyperlipidaemia
- 30 familial combined hyperlipidemia
- 31 FCH
- 32 FCHL
- 33 Mixed hyperlipidaemia
- 34 mixed hyperlipidemia
- 35 Genetic hypercholesterolemia
- 36 Genetic hypercholesterolaemia
- 37 or/23-36

### **SCORE**

- 38 Score.tw,ot.
- 39 systematic coronary risk evaluation.tw,ot.
- 40 or/38-39

### **LDL**

- 41 Cholesterol.tw,ot.
- 42 lipid.tw,ot.
- 43 LDL-cholesterol.tw,ot.

- 44 non-HDL cholesterol.tw,ot.
- 45 non HDL cholesterol
- 46 LDL Cholesterol.tw,ot.
- 47 Low Density Lipoprotein Cholesterol.tw,ot.
- 48 beta-Lipoprotein Cholesterol.tw,ot.
- 49 beta Lipoprotein Cholesterol.tw,ot.
- 50 LDL Cholesteryl Linoleate.tw,ot.
- 51 or/41-50

**Observational studies**

- 52 Epidemiologic Studies/
- 53 exp Case-Control Studies/
- 54 exp Cohort Studies/
- 55 Cross-Sectional Studies/
- 56 (epidemiologic adj (study or studies)).ab,ti.
- 57 case control.ab,ti.
- 58 (cohort adj (study or studies)).ab,ti.
- 59 cross sectional.ab,ti.
- 60 cohort analy\$.ab,ti.
- 61 (follow up adj (study or studies)).ab,ti.
- 62 longitudinal.ab,ti.
- 63 retrospective\$.ab,ti.
- 64 prospective\$.ab,ti.
- 65 (observ\$ adj3 (study or studies)).ab,ti.
- 66 adverse effect?.ab,ti.
- 67 or/52-66

**Overall search**

68 6, 22, 37, 40

69 68 AND 51 AND 67

## Appendix 2. Evidence table

Study by risk group	n	Age, years	Men, %	LDL-C, mmol/L (mg/dL)	LDL-C goal achievement (%)	Statin treatment (%)	Any lipid lowering treatment (%)	Active smoking (%)	Hypertension (%)	Diabetes (%)	BMI (kg/m <sup>2</sup> )
<b>Clinical CVD</b>											
2L cardio registry <sup>51</sup>	6711	65.6 (10.1)	70.6	100.5 (85.0-123.0)	<2.6: 48.7	100	100	15.6	75.8	36.5	28.5 (4.3)
ADRIE study <sup>52</sup>	771	62.9 (12.1)	81	NA	<2.6: 64	89	NA	75	57	22	26.4 (4.2)
ARTEMIS <sup>53</sup>	1490	66.0 (9.0)	69.5	2.3 (0.8)	NA	90.9	NA	9	81	55.7	26.6 (3.6)
ASPIRE-S <sup>54</sup>	302	69.1 (12.8)	57.3	2.1 (0.88)	<2.5: 77; <1.8: 56		94.5	28.1	57	19.9	26.8 (4.5)
ATHEROREMO-IVUS <sup>55</sup>	581	61.5 (11.3)	75.5	2.72 (2.12-3.54)	NA	62.3	NA	29.0	52.1	17.2	NA
Back et al <sup>56</sup>	332	65 (9.1)	77.5	2.3 (1.9-2.7)	NA	NA	94.9	18.8	47.9	17.6	
Brath et al <sup>57</sup>	921	NA	NA	NA	<1.8: 38.5; <2.6: 76.3	96.4	99.9	NA	NA	100	NA
CEPHEUS CVD <sup>58</sup>	NA	NA	NA	NA	<2.5: 55.9	NA	NA	NA	NA	NA	NA
CEPHEUS FH <sup>58</sup>	NA	NA	NA	NA	<2.5: 44.2	NA	NA	NA	NA	NA	NA
CIBAR study <sup>59</sup>	1848	69.2 (11.1)	72	NA	<100: 41	87.3	88.1	9.9	65.5	28.7	39.40%

Citarella et al <sup>60</sup>	10417		60.6	NA	<2.6: 10.9	100	100		85.0	18.6	NA
CLARIFY <sup>61</sup>	12294	66.1 (10.0)	78.8	2.4 (1.9- 2.9)	<1.8: 20.1; <2.6: 61.5		92.5	11.6	69.8	3272 (26.6)	27.7 (25.4- 30.5)
Co-Laue study <sup>62</sup>	303	NA	NA	NA	<1.8: 54.7	NA	53.2	NA	NA	NA	NA
Copenhagen General Population Study <sup>63</sup>	1521	NA	NA	NA	<2.5: 55.3	NA	70	NA	NA	NA	NA
Cordero et al <sup>64</sup>	1583 (2006)	66.8 (11.4)	73	112.3 (36.2)	<1.8: 9.5	69	NA	12.3	67	38	28.2±3.9
Cordero et al <sup>64</sup>	1110 (2014)	66.7 (10.4)	80.8	98.0 (43.7)	<1.8: 27.3	96	NA	15.4	62.6	34.5	28.6±4.5
Do Rego et al <sup>65</sup>	1240 (with MS)	64.6 (11.0)	NA	112 (89- 140)	<1.8: 10.9	93.5	NA	NA	NA	NA	NA
Do Rego et al <sup>65</sup>	361 (without MS)	64.6 (11.0)	NA	105.0 (86.2- 130.0)	<1.8: 12.2	89.3	NA	NA	NA	NA	NA
EDICONDIS- ULISEA	329	NA	NA	NA	<1.8: 65.3		NA	NA	NA	NA	NA
ELDERCIC study, >65 <sup>66</sup>	524	73.3 (5.3)	66.9	NA	<1.8: 42.4	82.8	NA	14.3	75.9	32	29.1 (4.3)
ELDERCIC study, ≤ 65 <sup>66</sup>	514	55.6 (6.8)	75.7	NA	<1.8: 46.5	83.1	NA	25.6	60.4	28.7	28.3 (4.1)
EUROASPIRE III <sup>67</sup>	13935	61.9 (10.0)	72.6	2.77 (0.99)	NA	78	NA	17.2	NA	NA	28.9 (4.5)
EUROASPIRE IV <sup>16</sup>	6648	68.4% ≥60 years	75.6	NA	<1.8: 19.3; <2.5: 57.8	86	NA	15.6	NA	25.7	37.10%

Ferreras Amez <sup>68</sup>	4087	67.7 (0.5)	73.8	118.3 (36.2)	<2.6: 30.4	NA	NA	35.5	89.5	50.5	28.8 (4.36)
Frigola-Capell et al <sup>69</sup>	722	72 (12)	63%	104.04 (28.64)	<2.6: 23.5	69.5	NA	7.5	61.2	NA	NA
Garzon et al <sup>70</sup>	9647	73.2	64.8	NA	<2.6: 75.3	NA	NA	16.8		100	
Gencer et al <sup>71</sup>	1602	61.8 (11.9)	81	NA	<1.8: 35; <2.6: 72	94	NA	52	53	16	339 (21%)
Git et al <sup>72</sup>	3273	66.1 (10.2)	70.4	2.7	<1.8: 9.0; <2.6: 52.4	82.0	NA	16.5	88.5	15.1	28.0 (4.0)
Homburg Cream and Sugar Study <sup>73</sup>	502	68 (59- 74)	83.3	100 (80- 129)	NA	NA	NA	18.8	92.7	32.7	28 (26- 31)
ICP-Bypass study <sup>74</sup>	771	67.7 (9.6)	71.4	93.5 (35.1)	<1.8: 26.6; <2.6: 64.4	93.6	771	8.0	78.1	100	29.1 (4.5)
Jameson et al <sup>75</sup>	1773 (CHD or ASCVD)	69.1 (10.2)	65.5	2.30 (0.83)	<2.5: 74.5	100	100	NA	NA	0	NA
Jameson et al <sup>75</sup>	468 (CHD or ASCVD + DM)	69.2 (9.7)	63.5	2.15 (0.78)	<2.5: 81.4	100	100	NA	NA	100	NA
Jankowski et al <sup>76</sup>	640	61.1 (8.9)	71.1	NA	<2.5: 61.5; <2.0: 32.1; <1.8: 21.6	94.5	95.6	19.7	48.2	13	33
Jankowski et al <sup>76</sup>	466	65.9 (9.9)	60.7	NA	<2.5: 63.4; <2.0: 38.1; <1.8: 29.7	94.0	94.4	17	35.4	12.4	26.8
Laforest et al <sup>77</sup>	1201	68.4 (9.8)	73.7	NA	<2.6: 51	100	100	11.5	80	42.8	30.70%
Libungan et al <sup>78</sup>	402	65.0 (9.4)	77	NA	<2.5: 60		94	23	48	18	
LifeLines Cohort study <sup>79</sup>	1302	63 (12)	68.4	2.8 (0.9)	NA	NA	69	19.1	33.6	11.7	28 (4.1)

LIMA registry <sup>80</sup>	4884 (CHD)	65.2 (10.5)	66.1	2.7	<1.8: 7.5; <2.6: 48.9	100	100	NA	NA	0	27.8 (3.9)
LIMA registry <sup>80</sup>	3579 (CHD + DM)	67.6 (9.4)	63.5	2.6	<1.8: 11.5; <2.5: 54.3	100	100	NA	NA	100	30.0 (4.7)
Margalhaes et al <sup>81</sup>	256	61.1 (10.6)	76.2	NA	<2.6: 68	NA	NA	28.5	62.5	34.4	84.8% >30
Palomaki et al <sup>82</sup>	219	66.5 (8.3)	79	2.07 (0.64)	NA	96.8	NA	NA	NA	27	27.0 ± 4.1
Pello et al <sup>83</sup>	684	61.4 (12.3)	75.7	83.3 (25.8)	NA	87.4	NA	NA	NA		28.7 (5.4)
Perez de Isla <sup>84</sup>	2586 (CAD)	64.2 (11.1)	62.7	112.7 (36.0)	<1.8: 11.6; <2.6: 32.9	91.3	NA	13.2	66.7	0	28.1 (4.0)
Perez de Isla <sup>84</sup>	1748 (CAD + DM)	66.7 (10.1)	62.7	107.2 (38.0)	<1.8: 18.9, <2.6: 40.9	90	NA	9.3	81.9	100	30.0 (4.8)
PERIFERICA <sup>85</sup>	4087	68	74	119 (36)	<2.6: 30.4	76.2	79.1	25.5	89.5	50.5	28.8 (4.4)
Perrone-Filardi et al <sup>86</sup>	913	65	78		<2.6: 57; <1.8: 20	91	NA	13	21	26	20% >30
Pillois et al <sup>87</sup>	240	53.1 (10.8)	87	2.59 (0.85)	<2.6: 73.8	100	100	65	30	NA	27.4 (4.4)
PRIMULA <sup>88</sup>	3392	NA	NA	NA	<2.0: 41.9	NA	100	NA	NA	NA	NA
Rallidis et al <sup>89</sup>	1337	61.2 (9.5)	85.7	NA	<2.6: 50.6	82.6	86.5	30.6	65.2	33.3	28.8 (4.5)
Reiner et al <sup>90</sup>	1811	63.1	55.4	NA	<2.5: 35.5	100	100	NA	NA	42.1	NA
REPAR study <sup>91</sup>	1055	67 (10)	81.4	94 (44)	<1.8: 26	91.0	95.3	15.5	NA	34.7	NA
Rizza et al <sup>92</sup>	421	66 (9)	79	116 (34)	NA	NA	NA	74	NA	19.5	27 (4)



Schnoell et al <sup>93</sup>	1195	64.6 (9.8)	74	85 (69-101)	NA	NA	NA	3.6	NA	18.3	NA
SMART <sup>94</sup>	7216	60.1 (10.3)	74	2.87 (1.04)	NA	66		32	86	17	26.8 (4.0)
SWEDEHEART <sup>95</sup>	17236	61.9 (8.5)	73.9	2.3 (0.8)	<2.5: 72.3	NA	92.9	31.6	40.4	19.7	27.4 (4.3)
Target study <sup>96</sup>	366	63.9 (12.9)	78	97.8 (33.8)	<2.6: 57.4; <1.8: 18.2	87.7	NA	NA	NA	NA	NA
Toste et al <sup>97</sup>	253	61.6 (9.1)	75.5	109.4 (34.6)	NA	NA	NA	21.7	70.4	100	204 (80.6)
Toste et al <sup>97</sup>	429	58.6 (11.0)	78.8	110.5 (32.8)	NA	NA	NA	37.1	52.4	0	258 (60.1)
TROL registry (2003-2010)	92071	63.4 (11.6)	72.4	116.2 (37.7)	<2.6: 71.9	90.1	NA	16.3	83.9	32.2	28.1 (4.6)
TROL registry (2010)	7950	62.1 (12.0)	75.6	86 (26)	<2.6: 75.7	90.6	NA	19.8	84.3	30.3	28.4 (4.9)
Tunon et al <sup>98</sup>	628	59.0 (51-71)	77	82.7 (24.2)	NA	89	NA	6.7	62	22	28.4 (25.8-30.8)
Van Lieshout et al <sup>99</sup>	2960	68.7	67	NA	<2.5: 47.5	82.7	NA	NA	NA	NA	NA
Vonbank et al <sup>100</sup>	850	66.5 (10.5)	66.5	123 (40)	<1.8: 9.5; <2.6: 48.5	39.1	NA	57.2	73.9	26.9	27.8 (4.6)
<b>DM &amp; target organ damage</b>											
ADAN study <sup>101</sup>	1462	78.1 (5.6)	59.1	112.0 (39.9)	<2.6: 35.8	96.4	NA	14.4	80.4	100	NA
Ciardullo et al <sup>102</sup>	4781	73.4 (11.5)	51	126.5 (35.6)	<2.6: 5.8	15.1	NA	12.1	NA	100	28.9 (5.2)

GERODIAB <sup>103</sup>	987	77.1 (5.0)	47.9	97 (36)	<4.1: 95.2	62.9	NA	NA	89.8	100	29.7 (5.2)
MADIABETES cohort study <sup>104</sup>	965	75.7 (8.2)	38.7	112.3 (30.3)	NA	72.7	NA	9	86.6	100	30.1 (0.5)
PRESCAP – diabetes <sup>105</sup>	1742 (bad BP control)	68.6 (10.0)	48.6	121.8 (36)	NA	NA	NA	16.9	100	100	53%
PRESCAP – diabetes <sup>105</sup>	2251 (good BP control)	68 (10)	50.9	112 (32)	NA	NA	NA	12.5	100	100	47.60%
PRESDIAB <sup>106</sup>	526	66.2 (10.6)	61.3	110.1 (37.7)	NA	60	NA	12.8	100	100	29.7 (5.0)
STONE study <sup>107</sup>	625	66.6 (65.7- 67.4)	53.4	2.28 (2.22- 2.35)	NA	NA	NA	10.6	82.7	100	32.8 (95 CI 32-33)
<b>FH</b>											
Beliard et al <sup>108</sup>	733	NA	NA	165 (60)	<2.6: 9	79.3	84	NA	NA	NA	NA
Besseling et al <sup>109</sup>	25137	38 (20.6)	47.4	204 (76)	NA	28.9	NA	19.8	NA	1.8	23.5 (5.4)
Clarke et al <sup>110</sup>	204	55 (14)	47	6.20 (2.24)	NA	NA	NA	13	21	1	NA
EDICONDIS- ULISEA <sup>111</sup>	Spain	46.0 (13.1)	46.9	133 (40)	<2.6: 15.8	94.6	NA	28.3	18.3	7.1	NA
Galema-Boers <sup>112</sup>	321	45.6 (13.9)	47.4	3.4 (1.1)	<2.5: 18.7	97.8	NA	15.6	15.6	3.1	26.1 (4.4)
Huijgen et al <sup>113</sup>	781	42 (12)	46	3.2 (1.1)	<2.5: 22	NA	81	42.1	9.8	2.5	NA
Huijgen et al <sup>114</sup>	9169	39 (22- 55)	48	4.46 (4.44- 4.50)	NA	NA	NA	NA	NA	NA	NA
Jaruata et al <sup>115</sup>	279	47.6 (12.1)	42.7	216	NA	65	NA	19.1	22.6	2.2	25.4 (4.2)

Pijlman et al <sup>116</sup>	1249	49	47	3.2 (1.1)	<2.5: 21	96	NA	NA	20	2	NA
SAFEHEART <sup>117</sup>	2752	44 (34.0- 57.0)	45.9	165.0 (138.6- 207.8)	<2.6: 11.2	NA	80.5	26.4	14.4	3.2	25.9 (23.0- 29.1)
Talmud et al <sup>118</sup>	321 (no known mutation)	54.9 (13.9)	46.8	4.22 (1.58)	NA	NA	NA	NA	NA	NA	NA
Talmud et al <sup>118</sup>	319 (known mutation)	49.5 (14.0)	53.2	5.49 (1.34)	NA	NA	NA	NA	NA	NA	NA
<b>SCORE ≥5%</b>											
ACT II <sup>47</sup>	1682	64 (10)	NA	95 (26)	<1.8:13.5; <2.6: 60.8	96	NA	NA	NA	NA	NA
Barkas et al <sup>48</sup>	408 high risk	63 (13)	45	109 (33)	<2.6: 42	88	NA	15	73	21	28.6 (4.3)
Barkas et al <sup>48</sup>	477 v high risk	63 (13)	45	90 (30)	<1.8: 25	94	NA	15	73	21	28.6 (4.3)
Brotans et al <sup>119</sup>	3409 high risk	NA	NA	NA	<2.6: 18.7	NA	23.6	NA	NA	NA	NA
Brotans et al <sup>119</sup>	747 v high risk	NA	NA	NA	<1.8: 3.1	NA	31.8	NA	NA	NA	NA
CHALLENGE <sup>50</sup>	500	62 (11.7)	55	140.9 (44.1)	<2.6: 23.3	NA	92.0	25.6	NA	35.6	28.6 (4.41)
DYSIS <sup>120</sup>	22063	65.7 (9.9)	58.2	2.7 (1.0)	<2.5: 48.5	100	100	15.1	74.8	39.1	28.8 (5.2)
FOCUS <sup>121</sup>	506	66.3 (9.4)	57.9	2.45 (0.9)	<2.6: 63.1	100	100	14.8	75.5	54.3	28.5 (4.96)

Garcia Gil et al <sup>121</sup>	21636	63.3 (6.3)	81.6	3.06 (1.11)	<3.4: 63.7; <2.6: 5.1	100	NA	52.2	68.3	56.0	29.92 (4.85)
Gibson et al <sup>122</sup>	375	57.5	49.4	2.53 (0.74)	<2.5: 49	65.1	NA	NA	NA	18.9	32.0 (6.2)
Haberka et al <sup>123</sup>	420	61.2 (7.0)	66	101.2 (41.3)	38% of obese met targets (depend on HR/VHR), 30% non obese	100	NA	NA	81	32	30.8 (5.9)

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; DM, diabetes mellitus; FH, familial hypercholesterolaemia; NA, not applicable; SCORE, systematic coronary risk evaluation

### Appendix 3. Study characteristics

Study name	Country	Type of study	EAS/ESC risk group reported	Sample size	Year(s) of LDL-C measurement
<b>Clinical CVD</b>					
2L cardio registry <sup>51</sup>	Germany	Registry	Clinical CVD (CAD)	6711	May – December 2006
ADRIE study <sup>52</sup>	Switzerland	Cohort	Clinical CVD (ASCVD)	771	June 2006-December 2008
ARTEMIS <sup>53</sup>	Finland	Cohort	Clinical CVD (CAD)	1490	2011-2013
ASPIRE-S <sup>54</sup>	Ireland	Cohort	Clinical CVD (ischaemic stroke)	302	October 2011-October 2012
ATHEROREMO-IVUS <sup>55</sup>	Netherlands	Cross-sectional	Clinical CVD (CAD)	581	2008-2011
Back et al <sup>56</sup>	Sweden	Cohort	Clinical CVD (CAD)	332	2007-2010
Brath et al <sup>57</sup>	Austria	Cohort	Clinical CVD (DM + CAD / PAD/ cerebrovascular disease)	921	2007
CEPHEUS study <sup>58</sup>	8 EU countries	Cross-sectional	Clinical CVD or FH	4167 & 355	April 2006-January 2007
CIBAR study <sup>59</sup>	Spain	Cohort	Clinical CVD (CAD)	1848	Feb-07
Citarella et al <sup>60</sup>	Sweden	Cohort	Clinical CVD (previous CV event)	10417	July 2006-June 2007
CLARIFY <sup>61</sup>	21 EU countries	Registry	Clinical CVD (CAD)	12294	November 2009-July 2010
Co-Laus study <sup>62</sup>	Switzerland	Cohort study	Clinical CVD	303	2009-2012
Copenhagen General Population Study <sup>63</sup>	Denmark	Cross-sectional	Clinical CVD (MI)	1521	2004-2010
Cordero et al <sup>64</sup>	Spain	Registry	Clinical CVD (stable IHD)	1583 & 1110	2006 & 2014
Do Rego et al <sup>65</sup>	Spain	Cross-sectional	Clinical CVD (CAD)	2586	June-November 2006

EDICONDIS-ULISEA	Spain	Cohort	Clinical CVD (ASCVD)	329	December 2011-February 2012
ELDERCIC study <sup>66</sup>	Spain	Cross-sectional	Clinical CVD (CHD)	1038	Nov-08
EUROASPIRE III <sup>67</sup>	22 EU countries	Cross-sectional	Clinical CVD (CHD)	13935	2006-2007
EUROASPIRE IV <sup>16</sup>	24 EU countries	Cross-sectional	Clinical CVD (CHD)	6648	May 2012- April 2013
Ferreras Amez et al <sup>68</sup>	Spain	Cross-sectional	Clinical CVD (PAD)	4087	May-December 2009
Frigola-Capell et al <sup>69</sup>	Spain	Cohort study	Clinical CVD (CHD)	722	2008-2009
Garzon et al <sup>70</sup>	Spain	Cross-sectional	Clinical CVD (T2DM and CVD)	9647	2013
Gencer et al <sup>71</sup>	Switzerland	Cohort study	Clinical CVD (ACS)	1602	2009-2012
Gitt et al <sup>72</sup>	Germany	Cohort	Clinical CVD	3273	September 2007- March 2009
Homburg Cream and Sugar Study <sup>73</sup>	Germany	Cohort	Clinical CVD (CAD + DM)	504	February 2008- March 2009
ICP Bypass Study <sup>74</sup>	Spain	Cross-sectional	Clinical CVD (DM + coronary revascularisation)	771	2009
Jameson et al <sup>75</sup>	UK	Cohort	Clinical CVD (CHD or ASCVD)	2241	November 2008-November 2011
Jankowski et al <sup>76</sup>	Poland	Cohort	Clinical CVD (CAD)	640 & 466	2005-2006 & 2010-2011
Laforest et al <sup>77</sup>	France	Cross-sectional	Clinical CVD (ASCVD or DM + target organ damage)	1201	December 2007-May 2008
Libungan et al <sup>78</sup>	Sweden	Cross-sectional	Clinical CVD (CAD)	402	October 2007- October 2009
LifeLines Cohort study <sup>79</sup>	Netherlands	Cohort	Clinical CVD (CAD, stroke, PAD)	1302	2006-2012
LIMA registry <sup>80</sup>	Germany	Registry	Clinical CVD (CHD or PAD ± DM)	4884 & 3579	September 2007- March 2009
Magalhaes et al <sup>81</sup>	Portugal	Cohort	Clinical CVD (CAD)	256	January 2008- December 2009

Palomaki et al <sup>82</sup>	Finland	Cohort study	Clinical CVD (post op CABG)	219	2005-2009
Pello et al <sup>83</sup>	Spain	Cross-sectional	Clinical CVD (CHD)	684	January 2007-February 2011
Perez de Isla et al <sup>84</sup>	Spain	Cohort	Clinical CVD (CAD with and without DM)	2686 & 1748	July-November 2006
PERIFERICA <sup>85</sup>	Spain	Cross-sectional	Clinical CVD (PAD)	4087	May-December 2009
Perrone-Filardi et al <sup>86</sup>	Italy	Cross-sectional	Clinical CVD (CAD)	913	November 2006-February 2008
Pillois et al <sup>87</sup>	France	Cohort	Clinical CVD (CAD)	240	September 2006- January 2008
PRIMULA <sup>88</sup>	UK	Cross-sectional	Clinical CVD (CHD, cerebrovascular disease or PAD)	3392	April 2006-December 2008
Rallidis et al <sup>89</sup>	Greece	Cohort	Clinical CVD (CHD)	1337	2006-2010
Reiner et al <sup>90</sup>	Croatia	Cross-sectional	Clinical CVD (ASCVD, DM + target organ damage or SCORE >5%)	1811	January – September 2011
REPAR study <sup>91</sup>	Spain	Cohort study	Clinical CVD (stable CHD)	1055	November 2013-July 2014
Rizza et al <sup>92</sup>	Italy	Cohort	Clinical CVD (prior MACE)	411	2005-2012
Schnoell et al <sup>93</sup>	Germany	Cohort	Clinical CVD (CAD)	1195	September 2008- August 2009
SMART <sup>94</sup>	Netherlands	Cohort study	Clinical CVD (ASCVD)	7216	September 1996-March 2014
SWEDEHEART <sup>95</sup>	Sweden	Registry	Clinical CVD (MI)	17236	January 2006-June 2009
TARGET study <sup>96</sup>	Greece	Cohort	Clinical CVD (ACS)	366	January-June 2010
Toste et al <sup>97</sup>	Portugal	Cohort study	Clinical CVD	253 & 429	January 2009-June 2013
TROL registry <sup>124</sup>	Germany	Registry	Clinical CVD (ACS)	7950	2010
TROL registry <sup>125</sup>	Germany	Registry	Clinical CVD (ACS)	92071	2003-2010

Tunon et al <sup>98</sup>	Spain	Cohort	Clinical CVD (CAD)	628	January 2007-February 2011
Van Lieshout et al <sup>99</sup>	8 EU countries	Cohort	Clinical CVD (CHD)	2960	2008-2009
Vonbank et al <sup>100</sup>	Austria	Cohort	Clinical CVD (CAD)	850	August 2005-February 2007
<b>DM &amp; target organ damage</b>					
ADAN study <sup>101</sup>	Spain	Cross-sectional	DM + target organ damage (DM + hypertension)	1462	June-October 2009
Ciardullo et al <sup>102</sup>	Italy	Cross-sectional	DM +target organ damage (microvascular disease)	4781	2006-2007
GERODIAB <sup>103</sup>	France	Cohort	DM + target organ damage (DM + hypertension)	987	June 2009-July 2010
MADIABETES cohort study <sup>104</sup>	Spain	Cohort	DM + target organ damage (DM + CKD)	965	2007-2012
PRESCAP-Diabetes <sup>105</sup>	Spain	Cohort	DM + target organ damage (DM + hypertension- poor and good control)	1742 & 2251	Jun-10
PRESDIAB <sup>106</sup>	Spain	Cross-sectional	DM + target organ damage (DM + hypertension)	526	April-July 2008
STONE study <sup>107</sup>	Finland	Cohort	DM + target organ damage (DM + hypertension)	629	March 2011- August 2012
<b>FH</b>					
Beliard et al <sup>108</sup>	France	Cross-sectional	Heterozygous FH	733	2005-2014
Besseling et al <sup>109</sup>	Netherlands	Cohort study	FH (genetic diagnosis)	25137	1994-2014
Clarke et al <sup>110</sup>	UK	Cohort	FH	204	2005-2011
EDICONDIS-ULISEA <sup>111</sup>	Spain	Cohort	Heterozygous FH	241	June-October 2010
Galema-Boers et al <sup>112</sup>	Netherlands	Cross-sectional	Heterozygous FH	321	January 2008-December 2009
Huijgen et al <sup>113</sup>	Netherlands	Cross-sectional	FH (with known mutation)	9169	2003-2010
Huijgen et al <sup>114</sup>	Netherlands	Cross-sectional	FH (molecular diagnosis)	781	2008
Jarauta et al <sup>115</sup>	Netherlands	Cohort	FH	279	January 2007-September 2012



Pijlman <sup>116</sup>	Netherlands	Cross-sectional	FH	1249	February 2006-2008
SAFEHEART <sup>117</sup>	Spain	Registry	Heterozygous FH	2752	January 2004-November 2013
Talmud et al <sup>118</sup>	UK	Cross-sectional	FH (with and without known mutation)	319 & 321	Nov-11
<b>SCORE <math>\geq 5\%</math></b>					
ACT II study <sup>47</sup>	Austria	Cohort	SCORE $\geq 5\%$	1682	2009-2010
Barkas et al <sup>48</sup>	Greece	Cohort	SCORE $\geq 5\%$	408 & 477	1999-2013
Brotons et al <sup>119</sup>	Spain	Cross-sectional	SCORE $\geq 5\%$	4156	January-December 2011
DYSIS study <sup>50</sup>	11 European countries	Cross-sectional	SCORE $\geq 5\%$	22063	April 2008-February 2009
FOCUS study <sup>120</sup>	Switzerland	Cross-sectional	SCORE $\geq 5\%$	506	July 2008-June 2009
Garcia-Gil et al <sup>121</sup>	Spain	Cohort	SCORE $\geq 5\%$	21636	July 2006-December 2010
Gibson et al <sup>122</sup>	Ireland	Cohort	SCORE $\geq 5\%$	375	2009-2012
Haberka et al <sup>123</sup>	Poland	Cohort	SCORE $\geq 5\%$	420	2011-NS
CHALLENGE <sup>49</sup>	Greece	Cross-sectional	SCORE $\geq 5\%$	500	December 2012-April 2013

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; DM, diabetes mellitus; EAS, European Atherosclerosis Society; EU, Europe; ESC, European Society of Cardiology; FH, familial hypercholesterolaemia; IHD, ischaemic heart disease; LDL-C, low density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; NS, not stated; PAD, peripheral artery disease; SCORE, systematic coronary risk evaluation; T2DM, type 2 diabetes.

#### Appendix 4. Method of FH diagnosis among included studies

FH	Country	Type of study	Method of FH diagnosis
Beliard et al	France	Cross-sectional	Heterozygous FH: known mutation in LDL-R, ApoB or the PCSK9 gene. If no mutation then clinically diagnosed using Simon Broome or Dutch lipid criteria.
Besseling et al	Netherlands	Cohort study	Heterozygous FH: genetic diagnosis with deleterious mutations only.
Clarke et al	UK	Cohort	FH: Simon Broome criteria
EDICONDIS-ULISEA	Spain	Cohort	Heterozygous FH: genetic diagnosis only
Galema-Boers et al	Netherlands	Cross-sectional	Heterozygous FH: mutation in LDL-R/ ApoB or Aalst Cohen criteria.
Huijgen et al	Netherlands	Cross-sectional	Heterozygous FH: mutation in LDL-R/ ApoB
Huijgen et al	Netherlands	Cross-sectional	Heterozygous FH: mutation in LDL-R/ ApoB
Jarauta et al	Netherlands	Cohort	Heterozygous FH: off-treatment LDL cholesterol higher than the age- and sex-specific 95th percentile of a Spanish reference population, triglycerides <200 mg/dL, and familial vertical transmission with at least 1 first-degree relative with LDL cholesterol higher than age- and sex specific 95th percentiles.
Pijlman	Netherlands	Cross-sectional	Heterozygous FH: mutation in LDL-R/ ApoB or WHO criteria.
SAFEHEART	Spain	Registry	Heterozygous FH: mutation in LDL-R
Talmud et al	UK	Cross-sectional	FH: mutation in LDL-R, ApoB or the PCSK9 gene.

Apo-B, apolipoprotein B; FH, familial hypercholesterolaemia; LDL-R, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kelvin type 9; UK, United Kingdom;

## Appendix 5. Risk of bias assessment

Study name	Confounding	Selection	Measurement of intervention	Missing data	Measurement of outcomes	Reported result
<b>Clinical CVD</b>						
2L cardio registry	Moderate	Low	Low	Low	Low	Moderate
ADRIE study	Moderate	Low	Low	Low	Low	Moderate
ARTEMIS	Moderate	Low	Low	Low	Low	Moderate
ASPIRE-S	Moderate	Low	Low	Low	Low	Moderate
ATHEROREMO-IVUS	Moderate	Low	Low	Low	Low	Moderate
Back et al	Moderate	Low	Low	Low	Low	Moderate
Brath et al	Moderate	Low	Low	Moderate	Low	Moderate
CEPHEUS study	Moderate	Low	Low	Moderate	Low	Moderate
CIBAR study	Moderate	Low	Low	Low	Low	Moderate
Citarella et al	Moderate	Low	Low	Low	Low	Moderate
CLARIFY	Moderate	Low	Low	Low	Low	Moderate
Co-Laus study	Moderate	Low	Low	Low	Low	Moderate
Copenhagen General Population Study	Moderate	Low	Low	Low	Low	Moderate
Cordero et al	Moderate	Low	Low	Low	Low	Moderate
Do Rego et al	Moderate	Low	Low	Low	Low	Moderate
EDICONDIS-ULISEA	Moderate	Low	Low	Moderate	Low	Moderate
ELDERCIC study	Moderate	Low	Low	Low	Low	Moderate
EUROASPIRE III	Moderate	Low	Low	Low	Low	Moderate
EUROASPIRE IV	Moderate	Low	Low	Low	Low	Moderate
Ferreras Amez et al	Moderate	Low	Low	Low	Low	Moderate
Frigola-Capell et al	Moderate	Low	Low	Low	Low	Moderate
Garzon et al	Moderate	Low	Low	Low	Low	Moderate
Gencer et al	Moderate	Low	Low	Low	Low	Moderate
Git et al	Moderate	Low	Low	Low	Low	Moderate
Homburg Cream and Sugar Study	Moderate	Low	Low	Low	Low	Moderate
ICP Bypass Study	Moderate	Low	Low	Low	Low	Moderate
Jameson et al	Moderate	Low	Low	Low	Low	Moderate
Jankowski et al	Moderate	Low	Low	Low	Low	Moderate
Laforest et al	Moderate	Low	Low	Low	Low	Moderate
Libungan et al	Moderate	Low	Low	Low	Low	Moderate

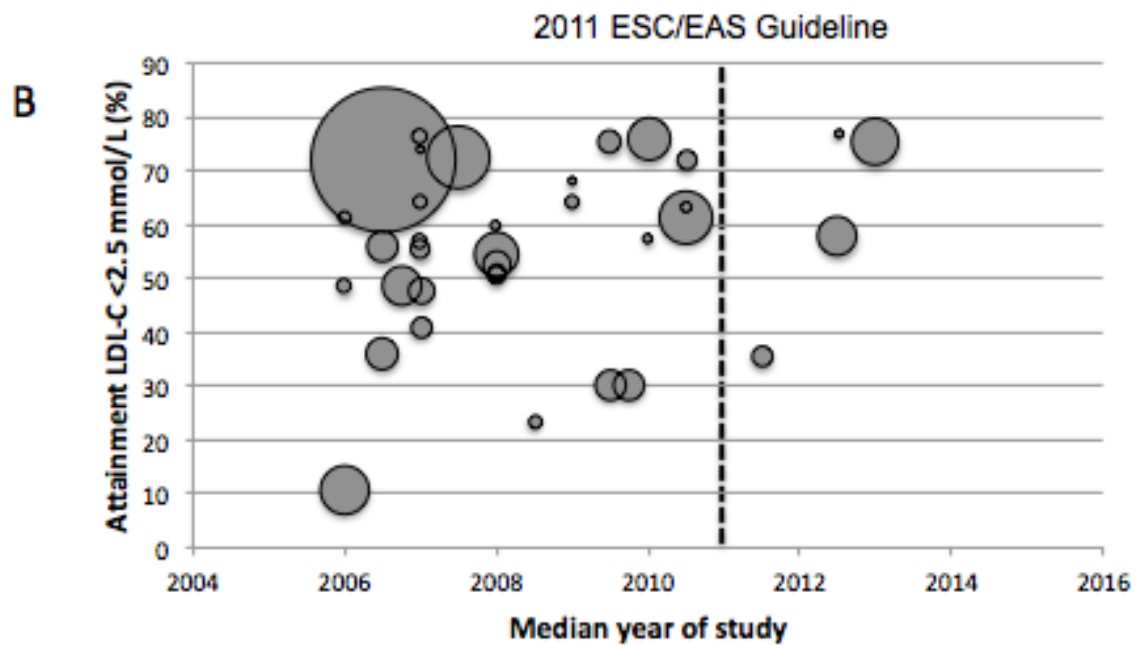
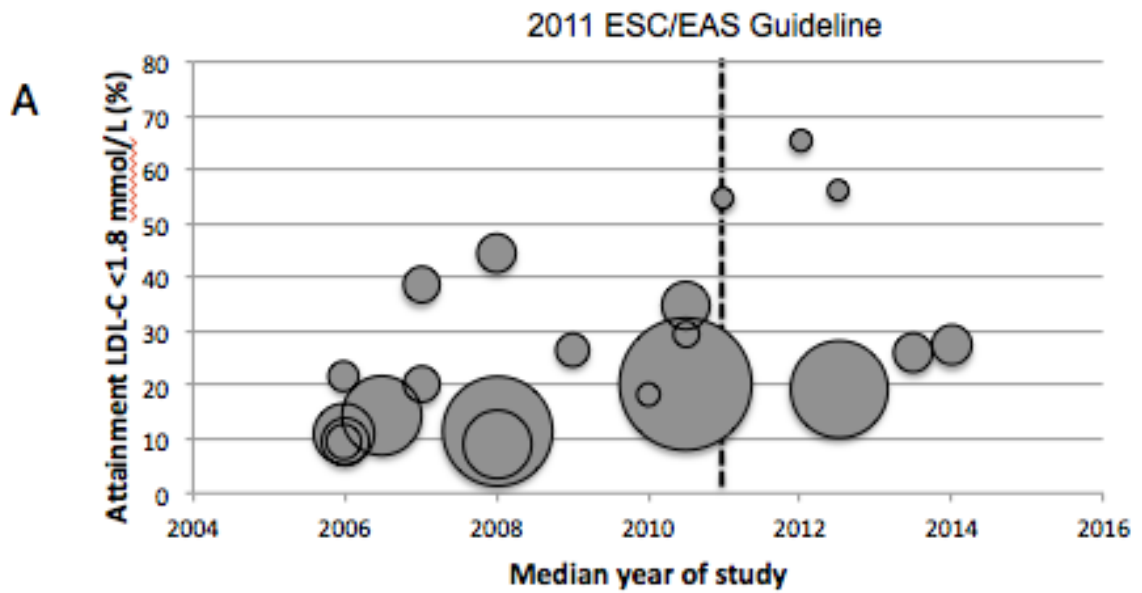
LifeLines Cohort study	Moderate	Low	Low	Low	Low	Moderate
LIMA registry	Moderate	Low	Low	Low	Low	Moderate
Margalhaes et al	Moderate	Low	Low	Low	Low	Moderate
Palomaki et al	Moderate	Low	Low	Low	Low	Moderate
Pello et al	Moderate	Low	Low	Low	Low	Moderate
Perez de Isla et al	Moderate	Low	Low	Low	Low	Moderate
PERIFERICA	Moderate	Low	Low	Low	Low	Moderate
Perrone-Filardi et al	Moderate	Low	Low	Low	Low	Moderate
Pillois et al	Moderate	Low	Low	Low	Low	Moderate
PRIMULA	Moderate	Low	Low	Moderate	Low	Moderate
Rallidis et al	Moderate	Low	Low	Low	Low	Moderate
Reiner et al	Moderate	Low	Low	Low	Low	Moderate
REPAR study	Moderate	Low	Low	Low	Low	Moderate
Rizza et al	Moderate	Low	Low	Low	Low	Moderate
Schnoell et al	Moderate	Low	Low	Low	Low	Moderate
SMART	Moderate	Low	Low	Low	Low	Moderate
SWEDEHEART	Moderate	Low	Low	Low	Low	Moderate
TARGET study	Moderate	Low	Low	Low	Low	Moderate
Toste et al	Moderate	Low	Low	Low	Low	Moderate
TROL registry	Moderate	Low	Low	Low	Low	Moderate
TROL registry	Moderate	Low	Low	Low	Low	Moderate
Tunon et al	Moderate	Low	Low	Low	Low	Moderate
Van Lieshout et al	Moderate	Low	Low	Low	Low	Moderate
Vonbank et al	Moderate	Low	Low	Low	Low	Moderate
<b>DM &amp; target organ damage</b>						
ADAN study	Moderate	Low	Low	Low	Low	Moderate
Ciardullo et al	Moderate	Low	Low	Low	Low	Moderate
GERODIAB	Moderate	Low	Low	Low	Low	Moderate
MADIABETES cohort study	Moderate	Low	Low	Low	Low	Moderate
PRESCAP-Diabetes	Moderate	Low	Low	Low	Low	Moderate
PRESIDIAB	Moderate	Low	Low	Low	Low	Moderate
STONE study	Moderate	Low	Low	Low	Low	Moderate
<b>FH</b>						
Beliard et al	Moderate	Low	Low	Moderate	Low	Moderate

Besseling et al	Moderate	Low	Low	Low	Low	Moderate
Clarke et al	Moderate	Low	Low	Low	Low	Moderate
EDICONDIS-ULISEA	Moderate	Low	Low	Low	Low	Moderate
Galema-Boers et al	Moderate	Low	Low	Low	Low	Moderate
Huijgen et al	Moderate	Low	Low	Low	Low	Moderate
Huijgen et al	Moderate	Low	Low	Low	Low	Moderate
Jaruata et al	Moderate	Low	Low	Low	Low	Moderate
Pijlman	Moderate	Low	Low	Low	Low	Moderate
SAFEHEART	Moderate	Low	Low	Low	Low	Moderate
Talmud et al	Moderate	Low	Low	Low	Low	Moderate
<b>SCORE <math>\geq</math>5%</b>						
ACT II study		Low	Low	Low	Low	Moderate
Barkas et al	Moderate	Low	Low	Low	Low	Moderate
Brotons et al	Moderate	Low	Low	Moderate	Low	Moderate
DYSIS study	Moderate	Low	Low	Low	Low	Moderate
FOCUS study	Moderate	Low	Low	Low	Low	Moderate
Garcia-Gil et al	Moderate	Low	Low	Low	Low	Moderate
Gibson et al	Moderate	Low	Low	Low	Low	Moderate
Haberka et al	Moderate	Moderate	Low	Low	Low	Moderate
CHALLENGE	Moderate	Low	Low	Low	Low	Moderate

## Appendix 6. LDL-C goal attainment among patients with established CVD

A corresponds to achievement of LDL-C <1.8 mmol/L; B corresponds to achievement of LDL-C <2.5 mmol/L. The size of the bubble corresponds to the number of patients in each of the included studies

LDL-C, low-density lipoprotein cholesterol.



### Appendix 7. Event rates per 1000 person years

Study name	Sample size, n	LDL-C, mmol/L	ACM, per 1000 PY	Stroke, per 1000 PY	MI, per 1000 PY	MACE, per 1000 PY
<b>Clinical CVD</b>						
ADRIE study	771			9.5	13.8	51.9
CIBAR	1848		13.5			
Homburg Cream and Sugar Study	502	2.6 (2.1-3.3)				108.1
LIMA registry (CHD + DM)	4884	2.7	7	5.9	13	
LIMA registry (CHD alone)	3579	2.6	3.1	3.1	11	
Pello et al	684	2.2 (0.7)	15.3	4.9	29.2	
Rallidis et al	1337			1.2	32.4	76.6
Rizza et al	421	3.0 (0.9)				10.7
SMART	7216	2.9 (1.04)	28.2	7	9.3	25.3
Target study	366	2.5 (0.9)	58.5			167.5
<b>FH</b>						
SAFEHEART	2752	4.3 (3.6-5.4)				9.4
<b>DM</b>						
MADIABETES	965	2.9 (0.8)	51.5			

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; ACM, all-cause mortality; DM, diabetes mellitus; FH, familial hypercholesterolaemia; MI, myocardial infarction; MACE, major adverse cardiovascular event

## Appendix 8. List of included studies

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established coronary heart disease: baseline results from the STABILITY study. *European journal of preventive cardiology*. 2013;20:678-685.

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