SUPPLEMENTAL MATERIAL

Table S1. Search terms for the PubMed database

Search Element	Search Terms		
Initial Search Filters	*English language, abstract available, 2000-2013*		
Disease condition	1	("Familial Hypercholesterolemia" [All Fields] OR "Hyperlipidemia, Familial Combined"[Mesh])	
Intervention	2	("blood component removal"[MeSH Terms] OR apheresis [All fields])	
Practice patterns	3	("guidelines"[All fields] OR "practice pattern"[All fields] OR "Guideline" [Publication Type])	
Healthcare utilization / economics	4	("Physician Visits" [All fields] or "Ambulatory Visit" [All fields] or "Hospital Admission" [All fields] or " Length of Stay" [All fields] or "Health Economics" [All fields] or "Economic Model" [All fields] or "Medical Resource Use" [All fields] or "Medical Resource Utilization" [All fields] or "Health Economic Resource Utilization" [All fields] or "Healthcare Resource Utilization" [All fields] or "Cost Effectiveness" [All fields] or "Budget Impact" [All fields] or "Cost Utility" [All fields] or "Healthcare Utilization" [All fields] or "Healthcare Cost" [All fields] or "Direct Cost" [All fields] or "Pharmaceutical Cost" [All fields] or "Hospital Cost" [All fields] or "Inpatient Cost" [All fields] or "Laboratory Cost" [All fields] or "ER Cost" [All fields] or "Ambulatory Cost" [All fields] or "Outpatient Cost" [All fields] or "Total Cost of Care" [All fields] or "Cost-Benefit Analysis"[Mesh] or "Costs and Cost Analysis"[Mesh] or "Health Services/utilization"[Mesh] or "Health Services/economics"[Mesh] or "cost"[All fields] or "Health Care Costs" [MeSH])	
Utilities	5	("Cost-effectiveness"[All Fields] OR "Cost-value"[All Fields] OR "Cost-benefit"[All Fields] OR "Cost-Benefit Analysis"[Mesh] OR "Cost-utility" [All Fields] OR "Utility Score" [All Fields] OR "Utility value" [All Fields])	
CV events	6	"Myocardial Infarction" [MeSH] OR "Myocardial Infarction" [All [Fields] OR "Heart attack" [All Fields] OR Angina [All fields] OR "Heart Failure" [MeSH] OR "Heart Failure" [All Fields] OR "Ischemic Attack, Transient" [MeSH] OR Stroke [MeSH] OR Stroke [All Fields] OR "Cerebral Revascularization" [MeSH] OR "Cerebral Revascularization" [All Fields] OR	

		“Myocardial Revascularization” [MeSH] OR “Myocardial Revascularization” [All Fields] OR "Peripheral Arterial Disease"[MeSH] OR “Cerebrovascular Disorders” [MeSH] OR “Coronary Artery Disease” [MeSH] OR “Coronary Artery Disease” [All Fields] OR “Cardiovascular Diseases” [MeSH] OR “Cardiovascular Diseases” [All Fields] OR “Cardiovascular” [All Fields] OR "Cardiovascular Diseases/economics"[MAJR]	
Summation			
FH + Apheresis	**7**	**1 AND 2**	**156**
FH + Apheresis + Practice patterns	**8**	**1 AND 2 AND 3**	**7**
FH + Apheresis + HRU	**9**	**1 AND 2 AND 4**	**6**
FH + Utilities	**10**	**1 AND 5**	**3**
FH + Apheresis + CV event	**11**	**1 AND 2 AND 6**	**108**
FH + Apheresis + Practice patterns+ HRU + Utilities + CV events	**12**	**8-11 (OR)**	**111**

Table S2. Familial hypercholesterolemia treatment guideline recommendations

Familial Hypercholesterolaemia Australasia Network Consensus Group (Australian Atherosclerosis Society) 2011 (Australia)[1]	
Guideline type	FH treatment
Patients	(1) HoFH (2) Compound HeFH (HeFH with other lipid disorders) (3) Treatment-refractory HeFH with CHD (4) Children with HoFH (5) Women with HoFH/HeFH, stable CHD, and who have discontinued lipid-lowering therapy
Thresholds for apheresis treatment	HoFH: LDL-C > 271 mg/dL Compound HeFH: LDL-C > 271 mg/dL HeFH with CHD and are treatment-refractory: LDL-C > 193 mg/dL Alternative criterion for HoFH and HeFH: < 50% reduction with pharmacotherapy
Frequency	Adjusted according to treatment targets
Targets	HoFH: time-average interval plasma LDL-C: 251 mg/dL HeFH: time-average interval plasma LDL-C: 97 mg/dL Mean plasma reduction between treatments: > 65% Targets typically require an acute LDL-C reduction ≥ 70% (immediately after apheresis)
Japanese National Guidelines 2012 (Japan)[2]	
Guideline type	FH treatment
Patients	(1) HoFH (2) HoFH children age 4-6 years old (3) Treatment-refractory HeFH with CAD
Thresholds for apheresis treatment	HoFH: LDL-C apheresis and statin or ezetimibe therapy is first-line HeFH: Treatment-refractory with coronary lesion and where LDL-C > 250 mg/dL despite drug therapy or with severe CAD
Frequency	HoFH: every 1-2 weeks HeFH: not specified
Targets	not specified
NICE 2008 (UK)[3]	
Guideline type	FH treatment
Patients	(1) HoFH after lipid-lowering drug therapy (2) Treatment-refractory HeFH with progressive CHD symptoms
Thresholds for apheresis treatment	not specified
Frequency	not specified
Targets	not specified
American Heart Association 2006 (USA)[4]	

Guideline type	FH treatment
Patients	(1) Children with HoFH who are at high risk for early cardiovascular disease
Thresholds for apheresis treatment	not specified
Frequency	Every 1 – 2 weeks
Targets	not specified
National Lipid Association 2011 (USA)[5]	
Guideline type	FH treatment
Patients	(1) HoFH and treatment refractory (2) HeFH with CVD risk factors and treatment refractory • CVD risk factors include hypertension, diabetes, and smoking
Thresholds for apheresis treatment	•HoFH with LDL-C >=300 mg/dL •HeFH with LDL-C >= 300 mg/dL and 0-1 risk factors •HeFH with LDL-C >= 200 and 2 or more risk factors or high Lp(a) >= 50 mg/dL •HeFH with LDL-C >= 160 mg/dL and very high risk characteristics i.e., CHD, CVD, diabetes
Frequency	Every 1-2 weeks
Targets	not specified
International Panel on Management of Familial Hypercholesterolemia 2004 (Spain)[6]	
Guideline type	FH treatment
Patients	HeFH with ineffective drug therapy and CVD
Thresholds for apheresis treatment	HeFH patients unresponsive to drug therapy, with LDL-C >300 mg/dL, without CVD or LDL-C >200 mg/dL with 200 mg/dL (FDA) HeFH patients with symptomatic CHD with LDL-C >160 mg/dL or <40% LDL-C reduction on maximal drug therapy
Frequency	not specified
Targets	LDL-C <100 mg/dL or 50-75% LDL-C reduction Interval LDL-C <150 mg/dL level

Treatment refractory: high LDL-C levels despite lipid-lowering therapy, FDA= Food and Drug Administration, FH= Familial hypercholesterolemia, HoFH= Homozygous familial hypercholesterolemia, HeFH= Heterozygous familial hypercholesterolemia, CHD= Coronary heart disease, LDL-C= Low-density lipoprotein cholesterol, mg= milligram, dl= deciliter

Table S3. Apheresis treatment guidelines recommendations

The German Apheresis Working Group 2012 (Germany)[7]	
Guideline type	Apheresis treatment
Patients	(1) FH patients, genotype unspecified (2) Hyperlipidemia with ineffective drug therapy and CVD
Thresholds for apheresis treatment	FH patients with LDL-C > 160 mg/dL, ineffective drug therapy, and CVE in close relatives (primary prevention) Hyperlipidemia: LDL-C > 120-130 mg/dL, ineffective drug therapy, and CVE Severe hyperlipidemia: Lp(a) > 60 mg/dL, ineffective drug therapy, with progressive CVD
Frequency	not specified
Targets	not specified
Recommended Updates to German Guidelines 2013 (Germany)[8]	
Guideline type	Apheresis treatment
Patients	(1) HoFH (2) HeFH as soon as medical incompatibilities or rapid progression of atherosclerosis is identified
Thresholds for apheresis treatment	not specified
Frequency	not specified
Targets	High risk patients with CAD: LDL-C < 100 mg/dL Very high risk patients with CAD and diabetes or unstable angina: LDL-C < 70 mg/dL
Medical Scientific and Research Committee of the Hyperlipidemia Education And Research Trust (HEART-UK) LDL-C apheresis Working Group 2008 (UK)[9]	
Guideline type	Apheresis treatment
Patients	(1) HoFH (2) Compound HeFH (HeFH with other lipid disorders) (3) HeFH with coronary disease and intolerant or refractory to lipid-lowering therapy
Thresholds for apheresis treatment	HoFH/compound HeFH: LDL-C reduction < 50% or LDL-C > 350 mg/dL HeFH: LDL-C reduction < 40% or LDL-C > 190 mg/dL with ineffective drug therapy, coronary disease
Frequency	Every 1-2 weeks
Targets	Acute LDL-C reduction of ≥ 60% (immediately following apheresis)
The Division of Endocrinology, Metabolism, Nutrition and Internal Medicine and Division of Transfusion Medicine at the Mayo Clinic 2001 (USA)[10]	
Guideline type	Apheresis Treatment
Patients	(1) HoFH (2) HeFH with ineffective drug therapy and CVD
Thresholds for apheresis treatment	(1) HoFH: LDLC levels of 500mg/dL or higher (2) HeFH: documented ischemic heart disease, failure of drug therapy and LDL-C ≥ 200mg/dL or failure of drug therapy and LDL-C ≥ 300 mg/dL

Frequency	Every 2 weeks
Targets	not specified
Apheresis Applications committee of the American Society for Apheresis 2010 (USA)[11]	
Guideline type	Apheresis Treatment
Patients	(1)HoFH (2)HeFH with ineffective drug therapy and CVD
Thresholds for apheresis treatment	HoFH: unresponsive to drug therapy with LDL-C >500 mg/dL HeFH: unresponsive to drug therapy with LDL-C >300 mg/dL without CVD or LDL-C >200 mg/dL with CVD (FDA)
Frequency	Every 2-3 weeks
Targets	Time-average LDL-C reduction of 40-60%
National Lipid Association Expert Panel on Familial Hypercholesterolemia 2011 (USA)[5]	
Guideline type	Apheresis Treatment
Patients	(1)HoFH (2)HeFH with ineffective drug therapy and ≥1 risk factor
Thresholds for apheresis treatment	HoFH: unresponsive to drug therapy with LDL-C ≥300 mg/dL HeFH: unresponsive to drug therapy with LDL-C ≥300 mg/dL and 0-1 risk factors or LDL-C ≥200 mg/dL with ≥2 risk factors or Lp(a) ≥50 mg/dL or LDL-C ≥160 mg/dL with established CHD, CVD, or diabetes.
Frequency	not specified
Targets	not specified

FH= Familial hypercholesterolemia, CAD= Coronary artery disease, CHD= Coronary heart disease, CVE= Cardiovascular events, HoFH= Homozygous familial hypercholesterolemia, HeFH= Heterozygous familial hypercholesterolemia, LDL-C= Low-density lipoprotein cholesterol, Lp(a)= Lipoprotein(a), mg= milligram, dl= deciliter,

SUPPLEMENTAL MATERIAL REFERENCE LIST

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