COST-EFFECTIVENESS ANALYSIS OF HIGHLY CONCENTRATED n-3 POLYUNSATURATED FATTY ACIDS IN SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION

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A Dissertation Submitted in Partial Fulfillment of the Requirements
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การวิเคราะห์ต้นทุนประสิทธิผลของการใช้ยา n-3 polyunsaturated fatty acids ในการป้องกันชนิดทุติยภูมิของโรคกล้ามเนื้อหัวใจตาย

นางอดาวัลย์ เพิ่มพานิช

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเภสัชศาสตร์สังคมและบริหาร ภาควิชาเภสัชศาสตร์สังคมและบริหาร
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Thesis Title	COST-EFFECTIVENESS ANALYSIS OF HIGHLY CONCENTRATED n-3 POLYUNSATURATED FATTY ACIDS IN SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION
By	Mrs. Adawan Permpanich
Field of Study	Social and Administrative Pharmacy
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อดาวัลย์ เพิ่มพานิช : การวิเคราะห์ต้นทุนประสิทธิผลของการใช้ยา n-3 polyunsaturated fatty acids ในการป้องกันชนิดทุติยภูมิของโรคกล้ามเนื้อหัวใจตาย. (COST-EFFECTIVENESS ANALYSIS OF HIGHLY CONCENTRATED n-3 POLYUNSATURATED FATTY ACIDS IN SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ภก. ดร. วิทยา กุลสมบูรณ์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ผศ. นพ. กมล อุดล, 136 หน้า.

โรคกล้ามเนื้อหัวใจตายเฉียบพลันเป็นสาเหตุหลักของการเสียชีวิตและการเข้ารับการรักษาในโรงพยาบาลด้วยโรคทางหัวใจและหลอดเลือด ผู้ที่รอดชีวิตจากโรคกล้ามเนื้อหัวใจตายเฉียบพลันมีความเสี่ยงเพิ่มขึ้นต่อการเสียชีวิตและการเกิดโรคทางหัวใจและหลอดเลือดตามมาเมื่อเปรียบเทียบกับผู้ที่ไม่เป็นโรคนี้ จากการศึกษาพบว่า n-3 polyunsaturated fatty acids (PUFAs) มีประโยชน์ต่อหัวใจและหลอดเลือดในผู้ป่วยที่มีประวัติโรคกล้ามเนื้อหัวใจตายเฉียบพลัน การศึกษานี้มีวัตถุประสงค์ที่จะศึกษาความคุ้มค่าทางเศรษฐศาสตร์ของการใช้ n-3 PUFAs ความเข้มข้นสูงเพิ่มเติมจากการรักษาแบบปกติเทียบกับการไม่ใช้ n-3 PUFAs ในผู้ป่วยโรคกล้ามเนื้อหัวใจตายในประเทศไทย แบบจำลองมาร์คอฟใช้ในการประเมินต้นทุน จำนวนปีชีวิตที่เพิ่มขึ้นและจำนวนปีสุขภาวะที่เพิ่มขึ้นตลอดช่วงอายุขัยของผู้ป่วยโรคกล้ามเนื้อหัวใจตายในมุมมองของโรงพยาบาล โดยข้อมูลได้มาจาก Thai Acute Coronary Syndrome Registry การวิเคราะห์อภิมานและบทความทางวิชาการ ผลลัพธ์นำเสนอในรูปของอัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่มของปีชีวิตที่ยืนยาวขึ้นและปีสุขภาวะที่เพิ่มขึ้น การวิเคราะห์ความไวของผลลัพธ์ที่เกิดจากความไม่แน่นอนของตัวแปรในแบบจำลองแบบไม่อาศัยความน่าจะเป็น (deterministic) และแบบอาศัยความน่าจะเป็น (probabilistic) เพื่อดูผลของตัวแปรสำคัญในแบบจำลอง ผลการศึกษาพบว่า n-3 PUFAs เพิ่มปีชีวิตได้ 2.34 ปีโดยมีอัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่ม 256,199 บาทต่อปีชีวิตที่เพิ่มขึ้น เมื่อเทียบกับการรักษาแบบปกติสำหรับกรณีฐาน (base case analysis) ปีสุขภาวะเพิ่มขึ้น 2.01 ปีโดยมีอัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่ม 297,193 บาทต่อปีสุขภาวะเมื่อใช้ n-3 PUFAs ทั้งอัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่มต่อปีชีวิตและต่อปีสุขภาวะมีค่าลดลงเมื่อผู้ป่วยมีอายุมากขึ้น อัตราส่วนต้นทุนประสิทธิผลส่วนเพิ่มต่อปีสุขภาวะในผู้ป่วยโรคกล้ามเนื้อหัวใจตายอายุ 45-85 ปีมีค่า 216,200 - 414,049 บาท เมื่อพิจารณาค่าความเต็มใจที่จะจ่ายในปัจจุบันที่ 160,000 บาทต่อปีสุขภาวะ การใช้ n-3 PUFAs ความเข้มข้นสูงในการป้องกันชนิดทุติยภูมิของโรคกล้ามเนื้อหัวใจตายจึงยังไม่คุ้มค่าทางเศรษฐศาสตร์เมื่อเปรียบเทียบกับการรักษาแบบปกติในประเทศไทย

ภาควิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต .....
สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก .....
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ADAWAN PERMPANICH: COST-EFFECTIVENESS ANALYSIS OF HIGHLY CONCENTRATED N-3 POLYUNSATURATED FATTY ACIDS IN SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION. ADVISOR: ASSOC. PROF. VITHAYA KULSOMBOON, Ph.D., CO-ADVISOR: ASST. PROF. KAMOL UDOL, M.D., 136 pp.

Acute myocardial infarction (MI) is a leading cause of cardiovascular (CV) mortality and hospitalization. Survivors of acute MI have higher risk of subsequent CV events and death, compared to individuals without MI. Evidences have demonstrated the CV benefits of n-3 polyunsaturated fatty acids (PUFAs) in patients who experienced MI. This study aimed to assess the cost-effectiveness of highly concentrated n-3 polyunsaturated fatty acids (PUFAs) in addition to standard therapy compared with standard therapy alone in post-MI patients in Thailand. A Markov model was constructed to assess costs, life years, and quality-adjusted life years (QALYs) with lifetime horizon in post-MI patients, on the basis of provider perspective. Input data were based on information from the Thai Acute Coronary Syndrome (ACS) Registry, a meta-analysis of mortality data and published articles. Outcomes have been presented as incremental cost-effectiveness ratios of life expectancy and quality-adjusted life expectancy. Deterministic and probabilistic sensitivity analyses were performed for key variables in the model. n-3 PUFAs increased life expectancy by 2.34 life-years at an incremental cost-effectiveness ratio (ICER) of 256,199 Thai baht (THB) per life-year gained (LYG), compared to the standard therapy alone in the base case analysis. The quality-adjusted life years (QALY) increased by 2.01 with ICER of 297,193 THB per QALY from n-3 PUFAs supplementation. Both ICER/QALY and ICER/LYG decreased as the age of patients increased. The incremental cost per QALY gained in post-MI patients aged 45 to 85 years old ranged from 216,200 THB to 414,049 THB. Considering the current willingness-to-pay threshold of 160,000 THB/QALY, highly concentrated n-3 PUFAs as secondary prevention of MI appears not to be cost-effective compared to standard treatment alone in Thailand.

Department:	Social and Administrative Pharmacy	Student's Signature	.....
		Advisor's Signature	.....
Field of Study:	Social and Administrative Pharmacy	Co-Advisor's Signature	.....
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LIST OF ABBREVIATION

AA	arachidonic acid
ACCF	American College of Cardiology Foundation
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AF	atrial fibrillation
AHA	American Heart Association
ALA	α-linolenic acid
AMDR	acceptable macronutrient distribution range
AMI	acute myocardial infarction
ARIC	the Atherosclerosis Risk in Community
BMI	body mass index
Ca	calcium
CAD	coronary artery disease
CE	cost-effectiveness
CHD	coronary heart disease
CHF	chronic heart failure
CI	confidence interval
CV	cardiovascular
CVD	cardiovascular disease
d	day
DART	the Diet and Reinfarction Trial
DHA	docosahexaenoic acid

DM	diabetes
EACTS	European Association for Cardio-Thoracic Surgery
EET	epoxyeicosatrienoic acids
EPA	eicosapentaenoic acid
ESC	European Society of Cardiology
FA	fatty acid
g	gram
GSH	glutathione
GISSI-HF	the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – Heart Failure
GISSI-P	the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – Prevenzione
HD	hemodialysis
HDL	high-density lipoprotein
HF	heart failure
HF*r*EF	heart failure with reduced ejection fraction
HF*p*EF	heart failure with preserved ejection fraction
HPETE	hydroperoxy eicosatetraenoic acids
HR	hazard ratio
ICD	implantable cardioverter-defibrillators
ICER	incremental cost-effectiveness ratio
JACC	the Japan Collaborative Cohort Study for Evaluation of Cancer Risk
JELIS	the Japan EPA Lipid Intervention Study
LDL	low-density lipoprotein
LE	life expectancy
LT	leukotrienes

LV	left ventricular
LVEF	left ventricular ejection fraction
LYG	life year gained
mg	milligram
MI	myocardial infarction
Na	sodium
NICE	National Institute of Health and Clinical Excellence
NNT	number needed to treat
NSTEMI	non ST-elevated myocardial infarction
NYHA	The New York Heart Association
OMEGA	The Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death after Myocardial Infarction
PG	prostaglandin
PGI2	prostacyclin
PLA2	phospholipase A2
PPAR	peroxisome proliferator-activator receptor
PUFA	polyunsaturated fatty acid
QALY	quality-adjusted life years
QALYG	quality-adjusted life years gained
RCT	randomized controlled trial
RR	relative risk
SCD	sudden cardiac death
SCIMO	The Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 fatty acids
SE	standard error
SOFA	The Study on Omega-3 Fatty acids and ventricular Arrhythmia

STEMI	ST-elevated myocardial infarction
TG	triglyceride
TNF	tumor necrosis factor
TX	thromboxane
U.S.	The United States of America
VF	ventricular fibrillation
VLDL	very low density lipoprotein
VT	ventricular tachycardia
WTP	willingness-to-pay

CHAPTER I
INTRODUCTION

1. Background and significance of the problem

Despite several new treatments having been developed for the treatment of acute myocardial infarction (MI), survivors from acute MI have higher risk to subsequent cardiovascular (CV) events and mortality. Data from the Thai Acute Coronary Syndrome (ACS) Registry showed approximately 20% of post-MI patients died, 4% had recurrent MI and 10% experienced non-fatal stroke within 1 year after their first MI. In the Asia-Pacific region, cardiovascular death accounts for nearly one third of all deaths, whereas ischemic heart disease and stroke comprise approximately 80% of all cardiovascular deaths in Thailand (1).

There are numerous epidemiologic, observational and clinical studies on the benefits of n-3 polyunsaturated fatty acids (n-3 PUFAs), commonly known as "omega-3 fatty acids", during the past 3 decades (2-9). In 1944, Sinclair found low prevalence of cardiovascular diseases (CVD) in the Eskimos in Greenland (Inuits) resulting from their high consumption of whale, seal, and fish (10). In late 1960s, Bang and Dyerberg reported that the risk of MI in Greenland inuits was significantly lower compared with age-matched residents of Denmark, although the inuits consumed high amount of saturated fat and cholesterol but low in vegetables and fruit (11-15). It was estimated that the Eskimos consumed fish in an average of approximately 400 grams (g) per day (d) (13). Japanese fishermen who had high consumption of fish and fish products were also reported of low mortality rate from CVD (16). The average per capita fish consumption in Japan is estimated to be about 100 g daily (17). The dietary study from Holland showed 50% lower coronary heart disease (CHD) mortality in subjects with a low fish consumption e.g. 30 g of fish per day over many years, compared with subjects who ate no fish at all (3). This risk reduction on CVD mortality was also found in the observations from the multiple risk factor intervention trial (MRFIT) reported in 1990 (18) and the cohort study by Daviglus et al in 1997 (19). Various animal studies (20-22), metabolic and epidemiological studies (23, 24) as well as clinical trials (5, 7), demonstrated that PUFAs exert some form of basic control over cardiac and neural

function. n-3 PUFAs have shown benefits on cardiovascular diseases (9, 25), as well as on reducing sudden death (4).

N-3 polyunsaturated fatty acids (PUFAs) contain 18-24-carbons with at least three methylene-interrupted double bonds where the last double bond (from carboxyl group) is three carbons from the methyl end of the molecule. Mammalians cannot produce enzymes capable of adding double bonds (desaturate) to fatty acids after the ninth carbon from the carboxyl end of the molecule. Therefore, n-3 PUFAs cannot be synthesized and must be taken from diet (26). The key n-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which were obtained mainly from fatty fish (27).

Dietary guidelines recommended fish consumption twice weekly for prevention of CHD (28). American Heart Association (AHA) also has recommendation for the patients with coronary and other atherosclerotic vascular disease to consume fish or fish oil capsule to get n-3 PUFAs 1 g daily (29). The same dosage is recommended by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) in patients after myocardial revascularization (30). The Joint British Societies' Guideline on Prevention of Cardiovascular Disease in Clinical Practice (JBS 2) recommended fish oil for severe hyperlipidaemia (2-4 g daily) and CHD prevention (1-2 g daily) (31).

The significant cardiovascular benefits of n-3 polyunsaturated fatty acids (PUFAs) were demonstrated in people who consumed fish or n-3 PUFAs supplementation (3, 4, 6, 7, 9), while non-significant results compared to placebo were also shown in some studies (32-35). Several meta-analyses of n-3 PUFAs studies in patients at high risk of CV diseases demonstrated inconsistency of cardiovascular benefits which may be due to differences in study populations, baseline consumption of fish, doses and duration of n-3 PUFAs used and so on (36-41). The high concentration and long-term usage of n-3 PUFAs was found associated with lower risk of CV events (42). As such, the meta-analysis of studies using high concentration of n-3 PUFAs for at least 1-year, which would be long enough for n-3 PUFAs to demonstrate efficacy, would be a suitable evidence of the effectiveness of n-3 PUFAs in specific groups of patients.

Due to the development of medications and technologies, people tend to live longer. As a result, CV events increase over time, together with the costs of treatment of these diseases. Despite the proven efficacy, the limited resources are of concern. As the use of n-3 PUFAs is approved as supplemental treatment in secondary prevention after MI in addition to other standard therapies, this study aimed to assess the cost-effectiveness (CE) of adding highly concentrated n-3 PUFAs to the standard treatment in patients experienced MI in Thailand. The model in this study included cardiovascular mortalities and major cardiovascular (CV) events, i.e. myocardial infarction, stroke, and heart failure. Thus this model is more complete than other models which were formerly performed.

2. Objectives of the study

2.1 To assess the CE of n-3 polyunsaturated fatty acids supplementation for post-MI patients

2.2 To evaluate the CE of n-3 PUFAs supplementation in different age groups of post-MI patients

3. Expected benefits

3.1 Demonstration of cost-effectiveness associated with the use of n-3 PUFAs in post-MI patients

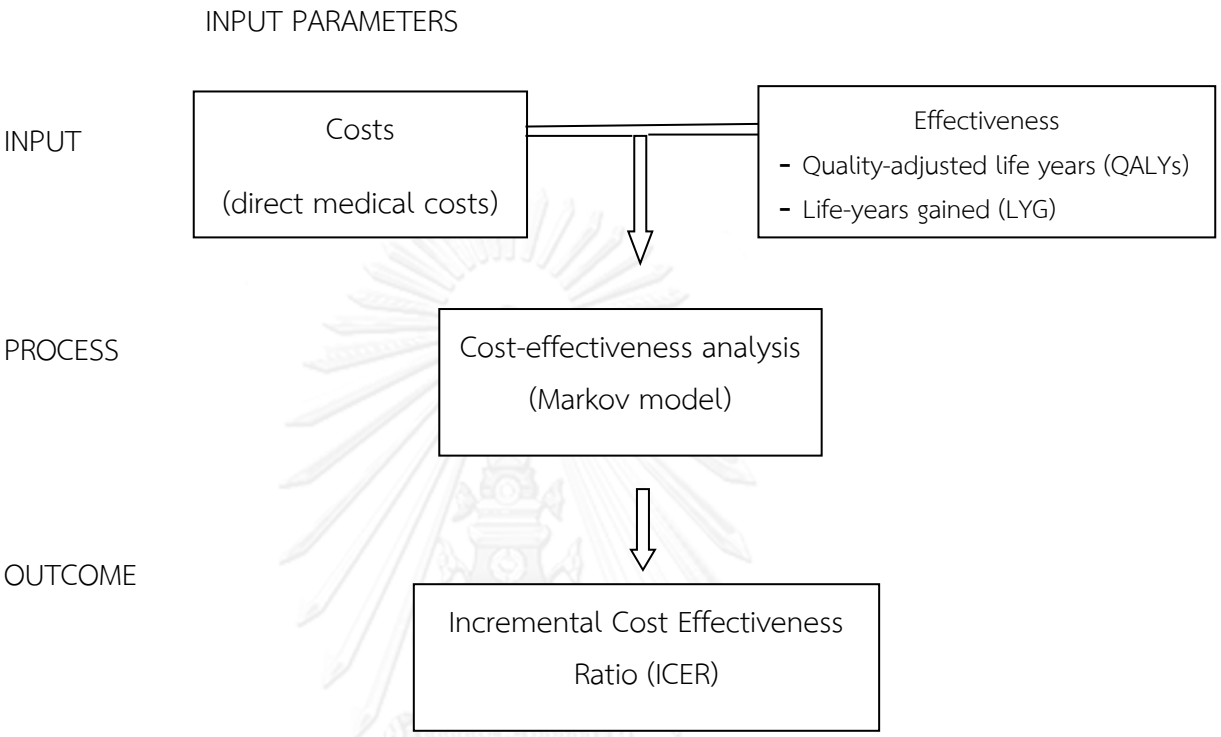
3.2 Suggestion for the healthcare professionals the economic value of n-3 PUFAs provided to patients after MI.

3.3 Pharmacoeconomic evidence for the health care payers to support the decision whether the health insurance scheme will reimburse n-3 PUFAs for post-MI patients.

4. Scope of the study

This is a CE study, so input parameters consist of effectiveness, costs and utilities as shown below in the Conceptual Framework. The input parameters are entered into the Markov model for processing and the outcome of the analysis is Incremental Cost Effectiveness Ratio (ICER).

Conceptual Framework of the Study



CHAPTER II
LITERATURE REVIEW

This chapter consists of 6 major parts. The first part describes the information of n-3 PUFAs and their mechanism of actions. The second part shows the effects on cardiovascular diseases. The third part demonstrates clinical evidences in CVD. The fourth part shows data of CE analyses. The fifth part describes relevant guidelines and the last part mentions the concept of CE analysis.

1. General information

As human cannot synthesize n-3 and n-6 PUFAs due to the lack of enzymes to introduce double bonds at carbon atoms beyond the C-9 in the fatty acid chain, we must receive them from the food. N-6 PUFAs, such as linoleic acid (LA or 18:2n-6), can be obtained from vegetable oils e.g. corn oil, safflower oil, sunflower oil. The key n-3 PUFAs consist of eicosapentaenoic acids (EPA), docosahexaenoic acids (DHA) and α-linolenic acid (ALA). ALA is available from certain plants such as flaxseed, soybean, walnut, while EPA and DHA are received from fish and fish oils. Figure 1 showed types and components of fatty acids (43). Humans can convert ALA to EPA in the small amount and even less to DHA (44). Figure 2 showed the structure and pathway of n-3 and n-6 PUFAs (43). Data from the experimental study indicated that the consumption of 3-4 g/d of ALA and 0.3 g/d of EPA has equivalent effect on the EPA content of plasma phospholipids (45). Though from meta-analysis and randomized controlled trials, dietary ALA was found associated with the risk reduction of fatal coronary heart disease (7, 46, 47), lack of convincing clinical studies makes the cardioprotective role of ALA still unclear.

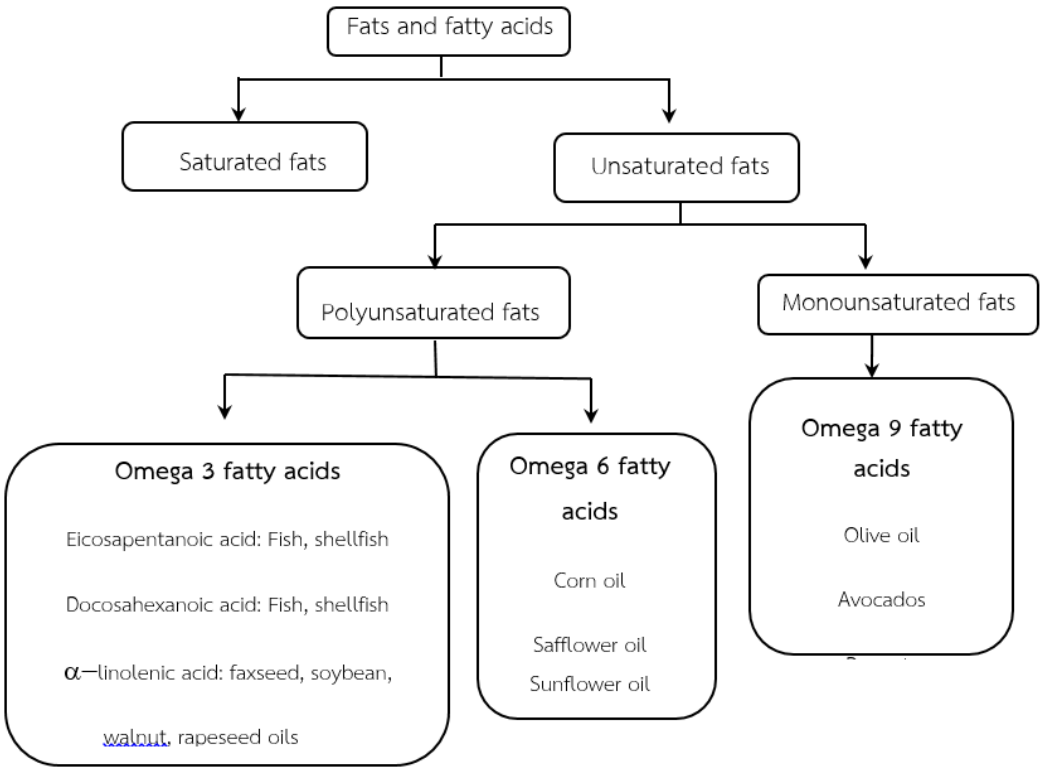


Figure 1 Components of fatty acids

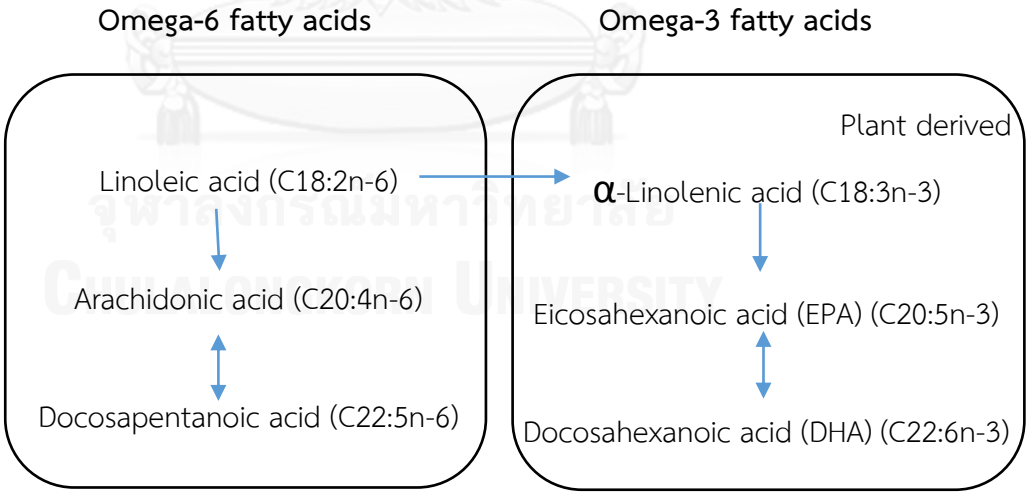


Figure 2 Structures and pathway of n-6 and n-3 polyunsaturated fatty acids

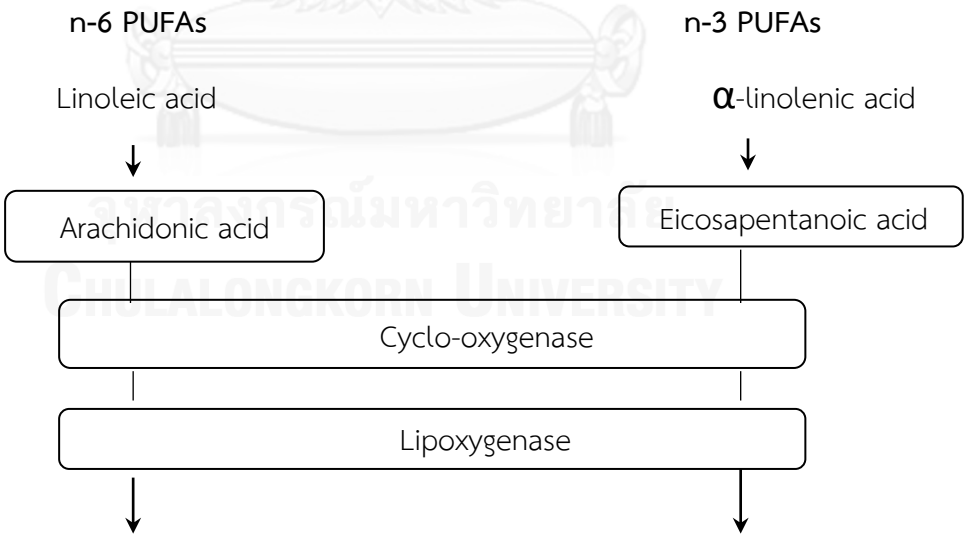
After ingestion, ALA is converted to EPA and DHA. LA is converted into arachidonic acid (AA or 20:4n-6) using the same enzymes as ALA in competitive manner.

The prostaglandins, thromboxanes and leukotrienes derived from EPA have different biological properties from those derived from AA, with in less vasoconstriction, platelet aggregation and leukocyte toxicity. Thus, when the EPA level increases from food intake, EPA competes with AA in using cyclooxygenase and lipoxygenase enzymes in eicosanoid metabolism, resulting in metabolites with antithrombotic, anti-inflammatory and vasodilative properties (48).

2. Effect on cardiovascular diseases

Numerous evidences indicate that n-3 PUFAs have effects which affect the risk reduction of CVD, i.e. anti-inflammatory, antiatherogenic, and antiarrhythmic effects (49-51). The experimental animal models showed that intravenous administration of free n-3 PUFAs can prevent ventricular fibrillation, a life-threatening cardiac arrhythmia and a major cause of ischemic heart disease mortality (52). In men who had no history of CVD, n-3 PUFAs were found associated with a decreased risk of sudden death (53).

The metabolism of n-3 and n-6 PUFAs describes various effects on platelet and vasculature which may support protective effect of n-3 PUFAs on coronary heart disease as shown in Figure 3 (43, 54).



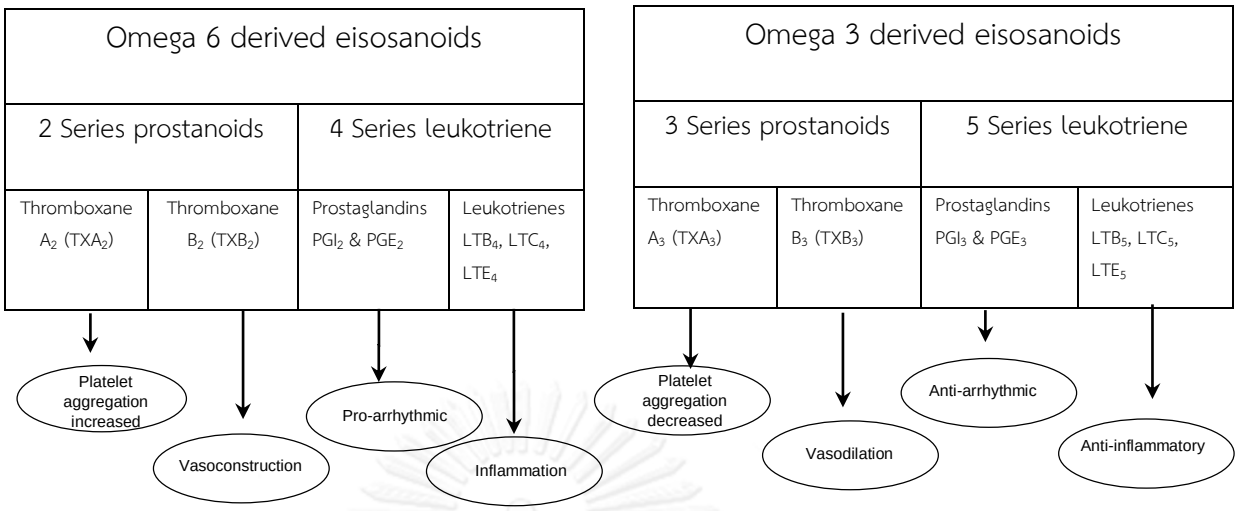


Figure 3 Effects of n-3 and n-6 polyunsaturated fatty acids on the arachidonic cascade

2.1 **Anti-arrhythmic effect**

The experiments in animals demonstrated that n-3 PUFAs can change the function of membrane ion channels (e.g. L-type Ca2+ channels, Na+/Ca2+ exchanger) or 'cell–cell conexins', which may reduce myocyte excitability, potentially reducing arrhythmia triggering (55). N-3 PUFAs can inhibit voltage-gated sodium channels so the refractory period is prolonged and increased voltage is needed for membrane depolarization, resulting in heart rate reduction (56, 57). These effects on every monocyte in the heart would account for the increased electrical stability and resistance of the heart to lethal arrhythmias. The study by Mozaffarian et al demonstrated that patients who had high non-fried fish intake reduced the risk of atrial fibrillation (AF) by 30% over a 12-year follow-up (58). But this correlation was not found in the Rotterdam study (59). A 54% risk reduction of postoperative AF was found in patients undergoing coronary artery bypass surgery treated with 1700 mg/d of EPA/DHA (60). The number needed to treat in this study was only 5.5 and the number of days hospitalized was also significantly reduced. Macchia et al assessed the relationship between n-3 PUFAs and AF occurrence in 3,242 post-MI patients. The results showed that n-3 PUFAs reduced the relative risk of hospitalization for AF (HR 0.19, 95% CI 0.07-0.51); and the association of n-3

PUFAs with risk reduction of total mortality (HR 0.15, 95% CI 0.05-0.46) (61). A recent study in patients with prior AF using 1 g daily of n-3 PUFAs did not show conclusive results of the antiarrhythmic effects (62). Due to the low event rate of AF, the study was stop prematurely since the study would not be powered adequately to detect a difference in AF reduction. A randomized, double-blind, multinational study using pre-operative loading dose of 10 grams n-3 PUFAs over 3 - 5 days followed by post-operative n-3 PUFAs dosing of 2 grams/day until discharge or post-op day 10 did not show the reduction of the incidence of Post-operative atrial fibrillation/flutter (PoAF) among patients undergoing cardiac surgery (63). Thus, the pre-operative treatment duration in this OPERA trial (3 – 5 days) may have been too short to build up a sufficient level of n-3 PUFAs to demonstrate anti-arrhythmic effect. In a meta-analysis of 7 cohort studies and 11 randomized trials of new onset incident/recurrent AF following exposure to fish/fish oil or long-chain PUFAs, the pooled odds ratio (OR) was 0.79 (95% CI, 0.56-1.12) for RCTs and 0.83 (95% CI, 0.59-1.16) for cohort studies. In the sensitivity analysis, no statistically significant difference was noted when stratified by study design or quality of the studies, concluded that no major effect of fish/fish oil or n-3 PUFAs on the risk of AF is suggested (64).

2.2 Reduce resting heart rate

In a large study of 5,096 people who had high fish consumption, the heart rate tended to be lowered, together with slower atrial ventricular conduction and prolonged QT interval (42). In patients with complex ventricular arrhythmias, the average heart rate decreased when EPA/DHA 1260 mg/d was taken for 14 weeks (65). From using moderate dose of n-3 PUFAs (810 mg/d EPA/DHA) for 4 months, the resting heart rate reduced and heart rate variability improved significantly (66).

2.3 Antithrombotic effect

EPA/DHA can inhibit the synthesis of arachidonic acid (AA) and take its place in membrane phospholipids, leading to the reduction of tissue levels of

AA. 3-series eicosanoid derivatives of EPA cause less platelet aggregation than AA-derived 2-series eicosanoids. However, the effect of n-3 PUFAs on platelet aggregation and thrombosis are still unclear (67, 68). Platelet aggregation occurred from large doses of n-3 PUFAs, but smaller amounts have modest platelet inhibitory effect (69).

2.4 Anti-inflammatory effect

Inflammation is one of the key risk factors for coronary artery disease. N-3 PUFAs compete with AA for enzymatic conversion into omega-3 derived eicosanoids, resulting in antagonizing the pro-inflammatory action of omega-6 eicosanoids. Additional effects of n-3 PUFAs are suppression of pro-inflammatory cytokines and reduction of expression of cell adhesion molecules (70). The actual action and anti-inflammatory effect of n-3 PUFAs on CVD remains to be established.

2.5 Reduce blood pressure

A meta-analysis of 36 randomized studies demonstrated a reductions of 2.1 mmHg in systolic blood pressure and 1.6 mmHg in diastolic blood pressures using a median dose of 3.7 g/d of n-3 PUFAs (71). Hypertensive patients or patients older than 45 years had higher blood pressure reduction from n-3 PUFAs consumption. It was shown that CAD mortality could reduce by 4% from the reduction of systolic blood pressure by as little as 2 mmHg (72).

2.6 Triglyceride lowering effect

EPA/DHA can increase intracellular degradation of lipoproteins which contains apolipoprotein B-100, leading to inhibition of very-low-density lipoprotein (VLDL) secretion, thus plasma triglyceride (TG) levels decrease (54). N-3 PUFAs also exert the following effects: 1) acceleration of chylomicron TG clearance through improvement of lipoprotein lipase activity (73); 2) increasing conversion of VLDL to low-density lipoprotein (LDL) (74); 3) inhibition of LDL

synthesis, and 4) postprandial lipemia reduction (75). Various trials confirmed that n-3 PUFAs reduced plasma TG (25, 76). In CVD patients and TG levels <150 mg/dL, the study results showed 10%-30% TG reduction. In patients with higher TG levels (>500 mg/dL), EPA/DHA in the dose of >3 grams/day can reduce TG levels by 40% to 79% (77-79). In diabetic patients, 25%-45% reduction in TG levels were reported (80).

2.7 Possible increased incidence of type 2 diabetes

N-3 PUFAs in high doses (≥10 g/d) have effect on blood glucose level while lower doses showed no effect on glucose tolerance (80). Seventeen randomized trials showed no consistent effect of n-3 PUFAs on fasting plasma glucose levels (54). The level of glycosylated hemoglobin and fasting glucose levels were not changed in diabetic patients from a meta-analysis of 26 studies (81).

2.8 Heart failure

The mechanism of n-3 PUFAs on heart failure (HF) is still unclear. EPA/DHA are potent activators of peroxisome proliferator-activator receptor (PPAR) (82), thus they regulate the expression of genes encoding key proteins controlling myocardial fatty acid uptake and metabolism (83). The experiment in rat showed that 1.6 grams of EPA/DHA increased serum levels of the cardioprotective adipokine adiponectin subjected to either sham treatment or hypertension induced by abdominal aortic banding (84). It is found that adiponectin increasing corresponded to significant attenuation of left ventricular (LV) hypertrophy and correlated with decreased LV end-systolic volume. Recent studies demonstrated that the ligand activation of PPAR-γ by EPA/DHA up-regulates adiponectin and suppresses inflammatory cytokines (85-87), leading to the improvement of cardiac structure and function in HF (88, 89). From a pilot study using EPA/DHA 5.1 g daily in 14 patients with class III to IV HF, the inflammatory cytokines, such as tumor necrosis factor (TNF)-alpha

and interleukin-1, and percent body fat improved (90). This study suggests potential benefits of n-3 PUFAs in patients with advanced HF.

3. Clinical evidences

3.1 Evidences in cardiovascular diseases

Several evidences have demonstrated that consumption of fish decreased the risk of CV death in patients with history of MI (6) and without history of MI (19, 53, 91-93). The association between frequency of fish intake and the risk reduction of CHD was shown in a meta-analysis of cohort study (94). People who had fish intake at least once a week had lower risk of CHD mortality than those consuming less than once per month (94). The higher level of n-3 PUFAs in the blood associated with lower risk of sudden cardiac death (SCD) incidence (53). Different forms of eicosanoid such as ALA also demonstrated benefits in CHD (7, 48). Fish oil supplementation reduced CV mortality in many studies (7, 9, 95).

In the largest secondary prevention clinical study of n-3 PUFAs, GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico-Prevenzione) study, 11,323 patients with recent MI (≤ 3 months) were randomized to receive either of the following treatments: 1) 850 mg daily of n-3 PUFAs as ethyl esters, 2) 300 mg daily of vitamin E, 3) n-3 PUFAs and vitamin E, and 4) placebo, in addition to healthy dietary habits and recommended pharmacological treatments for secondary prevention at that time. Impaired LV function (ejection fraction < 40%) was presented in about 14% of the enrolled patients, and fish consumption of at least once a week was reported in more than 70% of patients at the beginning of the trial, similarly in both the treatment and control groups. N-3 PUFAs were found significantly associated with the risk reduction of two primary endpoints; the combination of death, non-fatal MI, or non-fatal stroke and the combination of cardiovascular death, non-fatal MI, or non-fatal stroke. The risks of the following secondary endpoints were also significantly reduced: all fatal events by 20%, cardiovascular deaths by 30%, cardiac deaths by 35%, coronary death by 35% and sudden death by

45% (9). The reduction of sudden death was evident after only 4 months. Subgroup analysis showed that the risk reduction of all-cause mortality and sudden cardiac death increased when left ventricular (LV) systolic function decreased (96). In every 1000 post-MI patients treated with 1g daily of n-3 PUFA, up to 5.7 lives could be saved per year. This can be comparable to the result of LIPID trial (97), of which 5.2 lives could be saved from using pravastatin in 1000 hypercholesterolemic and CHD patients for one year (98).

However, there was low usage of statins in all groups of the patients in GISSI-P study because statins were not recommended for secondary prevention of post-MI during the study period. Only 4.7% of subjects used statins at baseline and increased to 45.5% at the end of study in the same proportion in all groups. Therefore, it is questionable that the risk reductions from GISSI-P study will represent the protective benefits of n-3 PUFAs under the current guideline practice due to underuse of statins. The evidence which supported the benefits of n-3 PUFAs regardless of statin usage was done by Poole et al (99). Recent retrospective, matched-cohort study used data from the General Practice Research Database of 2,466 patients who used 1 g of n-3 PUFAs within 90 days of first MI. Lipid-lowering drugs, antihypertensives and antiplatelets were used in more than 90% of the exposed patients. The 22% risk reduction of all-cause mortality was found to be in concordant with the result of GISSI-P (P = 0.0159). In patients initiating n-3 PUFAs within 14 days, 32% risk reduction was demonstrated (P = 0.0288). This data supports that statins may not override the risk reduction of n-3 PUFAs on mortality in post-MI patients.

The n-3 PUFAs benefits were also shown even in population who had high fish consumption like Japanese. The Japan EPA Lipid Intervention study (JELIS) was an open-label, blinded analysis (PROBE design) in 18,645 Japanese patients with high total cholesterol levels at baseline. The patients were randomized to receive EPA (1.8 g/day) and a statin versus statin alone for 5 years. The relative risk of major CV events was reduced by 19% in EPA group compared with statins alone (P=0.011) (95, 100). The significant reduction of unstable angina and non-fatal coronary events were 24% and 19%,

respectively, but there were no differences on sudden cardiac death and coronary death between 2 groups. Despite aggressive therapy with standard treatment, including statins, ACEIs, β-blockers, aspirin, EPA has been proven to lower CV risk. This study also revealed that the 19% reduction in major coronary events in the EPA group was not related to EPA levels in serum and EPA did not affect LDL-C concentration, suggesting that the mechanisms of EPA are independent of LDL-C reduction.

However, no difference in sudden cardiac death (SCD) between treatment and placebo group was found in JELIS. This different result from GISSI-P study, in which DHA and EPA reduced SCD, might indicate that EPA has less impact than DHA on the myocardial cell membranes stabilization and rhythm abnormalities prevention. The other possible reason of the difference may be due to the non-linearity of the benefit of n-3 PUFAs on cardiac death and high baseline consumption of fish among the Japanese participants in JELIS study. Data from a pooled analysis of observational and clinical studies showed that risk reduction of cardiac death mostly occurred at modest fish intake, which is 250 mg/day of EPA/DHA (42). Little additional benefit can be seen above this threshold (42). The average fish intake in Japan is approximately 900 mg EPA/DHA so most Japanese people are already above the threshold for preventing cardiac death (101).

The strong protective effect of n-3 PUFAs on cardiac death and, more specifically, on sudden cardiac death was confirmed by the results of several epidemiological and clinical studies (4, 6, 8, 9, 53, 102). As sudden cardiac deaths are mostly caused by ventricular arrhythmia, there are high tendency that n-3 PUFAs would have strong anti-arrhythmic effect. However, 3 studies conducted in patients with implantable cardioverter-defibrillators (ICD) did not indicate evidence of n-3 PUFAs benefits on ventricular arrhythmia in such patients (59, 103, 104). The sample size in each study was 200-500 patients with ICD. The inadequate power of these studies was found, leading to non-statistically significant anti-arrhythmic effect of n-3 PUFAs. However, data from multivariate analysis of the study conducted by Leaf et al showed the

significant reduction of time to first ICD event for VT or VF by 33% (P=0.024). Protective benefits of n-3 PUFAs were also found when therapies for probable episodes of VT or VF were included (RR, 0.69; 95% CI, 0.49-0.97), in subgroup of patients who took n-3 PUFAs for at least 11 months (RR, 0.62; 95% CI, 0.39-0.97), and in subgroup of patients with LVEF 30% (HR, 0.597; 95% CI, 0.375-0.950) (103).

In patients with chronic hemodialysis (HD), n-3 PUFAs showed no significant effect on the primary composite endpoint of cardiovascular events and death (RR, 1.04; 95% CI, 0.72-1.48). But 70% risk reduction on MI (95% CI, 0.10-0.92) and 60% risk reduction on major coronary events (95% CI, 0.17-0.97) was demonstrated as secondary outcomes. However, this study had small sample size and a large number of withdrawal (25%) (105).

Some studies did not show favorable result of n-3 PUFAs (32, 105-109). DART2 study conducted in 3114 patients reported that angina patients who were advised to take oily fish or n-3 PUFAs increased the risk of SCD by 54% compare with those not so advised (P=0.025), and increased the risk of cardiac death by 26% (P=0.047). The reduction of total mortality was not found in both groups. The author could not explain the result and concluded that it might be due to risk compensation, contamination in fish, interaction of fish oil with angina drugs, or some other effects on the behavior of patients or physicians (109). As 50% of angina patients in this study had a prior MI, this may suggest that n-3 PUFAs benefits were demonstrated when initiating therapy within the first 3 months after acute MI (110). However, the study was criticized as being suboptimally conducted or reported and the results were questionable (76).

In patients with angiographically proven coronary artery disease (CAD), high dose of n-3 PUFAs (6 g/day) for 28 months did not alter the diameter of atherosclerotic coronary arteries (106). However, the Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 fatty acids (SCIMO), done in larger sample size of 223 patients, revealed that coronary arteries in n-3 PUFAs group progressed less and regressed more than in the

placebo group (76). The daily dose of n-3 PUFAs in SCIMO was in the same range as in DART study.

The study done in Norway also did not show CV benefits of n-3 PUFAs. Post-MI patients were randomized to receive either 3.5 g daily of EPA/DHA or placebo (corn oil) with the follow-up period of 1.5 years. Norwegian population normally has high consumption of n-3 PUFAs, similar to Japanese people. Unlike the CV benefits of n-3 PUFAs in JELIS, no association was found between use of n-3 PUFAs and mortality and CV events in this study. Small sample size may be the factor for the difference of these 2 studies (107). Moreover, the Norwegian study was powered to assess the effects on serum lipids only. The level of total cholesterol reduced in both groups. HDL-C levels increased in the treatment group compared with control group. It is also noted that most of studies with small sample size in the range of 100-600 patients demonstrated no benefits of n-3 PUFAs on mortality and CVD (59, 103, 104, 111, 112).

The German OMEGA (Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death after Myocardial Infarction) study randomized 3,851 patients within 3-14 days after acute MI to receive 1 g of n-3 PUFAs (460 mg of EPA and 380 mg of DHA) or placebo to examine the impact on SCD within the first year. Due to the current guideline for prevention of CV events, 85% -95% of patients in the study received aspirin, clopidogrel, statins, β-blockers and angiotensin-converting enzyme inhibitors (ACEI) leading to low incidence of arrhythmia (0.7%) and total mortality (3.7%). The result of no benefit of n-3 PUFAs in this study may be due to the underpower to adequately determine the effect of this medication for secondary prevention of CVD (32).

Similarly, Alpha Omega (Study of Omega-3 Fatty Acids and Coronary Mortality), was also underpowered and showed neutral result of n-3 PUFAs versus placebo in post-MI patients. This study used margarine supplemented with low-dose of EPA+DHA (400 mg/day) or ALA (2 g/day), EPA+DHA+ALA or a control margarine in 4,837 patients who had suffered an MI an average of 2.5 years previously. The study was initially planned to have 25% reduction in

death from CHD but the final study power to address this end point was approximately 35% (113).

Apart from clinical studies on efficacy, the blood levels of EPA/DHA were determined to find out the association with risk of total death in patients with stable coronary heart disease (114). A cohort study of 956 patients with a 5.9-year follow-up showed that 27% decreased risk of death (HR, 0.73; 95% CI, 0.56-0.94) was found in patients having baseline EPA/DHA levels at or above the median (≥3.6%) compared with those below the median. After adjusted for possible confounders (age, sex, ethnicity, medical center, socioeconomic status, traditional cardiovascular risk factors, statin use, lipids, aspirin use, and inflammatory markers), the association between EPA/DHA blood level and risk reduction of all-cause mortality was still significant with the hazard ratio of 0.74 ($P<0.05$). The adjusted hazard ratios between key baseline variables and all-cause mortality for the following variables: statin use, aspirin use, sex (male) and diabetes mellitus (DM) were 0.59 (95% CI, 0.44-0.80), 1.04 (95% CI, 0.74-1.45), 1.47 (95% CI, 0.91-2.28), 1.48 (95% CI, 1.09-2.03), respectively (114).

The review of 25 trials by Harris et al found the association between the risk of coronary heart disease (CHD) events and serum levels of n-3 PUFAs and showed the inverse correlation of CV events reduction with the tissue levels of EPA, and even more so, with DHA (115).

The details of key studies of n-3 PUFAs were shown in Appendix B.

3.2 Evidences in heart failure

The Cardiovascular Health Study in 4,738 patients aged 65 years or older demonstrated that baked or broiled fish consumption associated with lower CHF incidence (116). The Atherosclerosis Risk in Community (ARIC) study in women also demonstrated the same result that n-3 PUFAs intake was associated with lower HF incidence (117). The JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) study conducted in 57,972 Japanese patients demonstrated that fish and n-3 PUFAs consumption reduced the

mortality risk from heart failure [24% (95% CI,0.53-1.09) for fish and 42% (95% CI, 0.36-0.93) for n-3 PUFAs] (118).

Further analysis from the Physicians' Health Study confirmed the inverse and nonlinear relationship of plasma phospholipid ALA and DHA with HF risk, but plasma EPA and DHA were not associated with HF (119).

GISSI-HF included 6,975 patients with class II to IV HF, supported the benefit of n-3 PUFAs in reducing total mortality (-9%; $P<0.05$) and total mortality or hospitalization (-8%; $P<0.01$). This means that 56 patients are needed to be treated for 4 years to avoid 1 death and 44 to avoid one event like death or hospitalization from CV events (120). From subgroup analysis, the CV protection of n-3 PUFAs was significantly found in patients with LVEF ≤ 40%, DM, and median total cholesterol ≤ 4.87 mmol/L. Unlike GISSI-P study(9), which used the same dose of n-3 PUFAs, no association between the medication and reduction of SCD was found in this study (adjusted HR, 0.93; 95% CI, 0.79-1.08).

3.3 Meta-analyses

There were a number of meta-analyses evaluating the cardiovascular effects of n-3 PUFAs over the last 10 years (Appendix C). Bucher et al demonstrated in a meta-analysis of 11 trials that n-3 PUFAs supplements significantly reduced the risk of all-cause mortality by 20%, fatal MI by 30% and sudden cardiac death by 30% in patients with CHD (39). This analysis included various kinds of omega-3 such as fish intake and nutritional supplement products, and the control groups included control diet and placebo.

A meta-analysis of observational studies (14 cohorts and 5 case-control) published before May 2003 found the significant association of fish intake with fatal CHD (RR 0.83) and total CHD (RR 0.86), when compared with little to no fish consumption. The benefit of n-3 PUFAs on fatal CHD was more striking in those consuming 2 to ≤4 servings of fish per week than those consuming <2 portion of fish per week. The group who take ≥4 serving of fish per week had higher RR of fatal CHD, which may have resulted from mercury contamination in the consumed fish (121).

Another meta-analysis of Cochrane review done by Hooper et al was published in 2009 (36). Randomized controlled trials (RCT) and cohort studies, where n-3 PUFAs consumption (from plants sources, fish oil supplements or fish consumption) or advice was allocated and study duration of at least six months, were included until February 2002. The relative risk of total mortality in participants received n-3 PUFAs or advice was 0.87 (95% CI, 0.73-1.03), compared with those on placebo or no dietary advice, with significant heterogeneity ($P_{heterogeneity}$ 0.04). After all studies with medium and high risk of bias were removed, the effect on mortality was still not significant; the relative risk was 0.98 (95% CI, 0.70-1.36, $P_{heterogeneity}$ 0.57). However, after removal of DART 2 study (109), the large study including 3114 angina male patients which had the relative risk of 1.15 (95% CI 0.98-1.34), the relative risk of death became 0.83 (95% CI, 0.75-0.91, $P_{heterogeneity}$ 0.52). The funnel plot of RCTs was asymmetrical, suggesting that smaller studies were more likely to show a reduction in mortality in the n-3 PUFAs arm. The funnel plot showed less bias when the studies with fewer than 50 deaths were removed. However, there was still very strong heterogeneity; the relative risk was 0.88 (95% CI, 0.71-1.10, $P_{heterogeneity}$ 0.002). Meta-analysis of cohort studies demonstrated the relative risk of 0.65 (95% CI, 0.48-0.88) on total mortality of n-3 PUFAs with no significant heterogeneity ($P_{heterogeneity}$ 0.21). The effect of n-3 PUFAs on cardiovascular events was not statistically significant with relative risk of 0.95 (95% CI, 0.82-1.12, $P_{heterogeneity} < 0.001$). Sensitivity analysis, which removed the studies with a medium or high risk of bias, and cohort studies showed no significant effect on CV events. Only subgroup of 24-47-month usage had a significant protective effect with the relative risk of 0.90 (95% CI, 0.82-0.98, $P_{heterogeneity}$ 0.54). The funnel plot also showed asymmetry, suggesting bias. Though small studies were removed and the funnel plot appeared less biased, the heterogeneity was still high ($P_{heterogeneity}$ 0.0004). No significant effect on CV deaths was found from the meta-analysis of RCTs, but a significant effect was found from that of cohort studies with the relative risk of 0.79 (95% CI 0.63-0.99, $P_{heterogeneity}$ 0.001). Effect on fatal MI was significant when DART 2 study was removed (RR, 0.70; 95% CI,

0.54-0.91) and from cohort study (RR, 0.42; 95% CI, 0.21-0.82) which included only 1 available study. The meta-analysis of cohort studies also showed a significant effect on sudden death with the relative risk of 0.44 (95% CI, 0.21-0.91). The result from this meta-analysis demonstrated a significant effect of n-3 PUFAs on heart failure with the relative risk of 0.51 (95% CI, 0.31-0.85) with no significant heterogeneity ($P_{heterogeneity}$ 0.91). There were no significant effect on stroke, angina, peripheral vascular events and revascularization demonstrated in this meta-analysis.

The reduction of sudden cardiac death by n-3 PUFAs in GISSI-P study raised the interest in their potential antiarrhythmic properties. A meta-analysis of which the primary outcomes were the arrhythmic end points of appropriate ICD intervention and SCD was done by Leon et al (40). Twelve randomized controlled trials of n-3 PUFAs as dietary supplements in 32,779 patients were analyzed and demonstrated 20% reduction in cardiac death (95% CI, 0.69-0.92). No association between n-3 PUFAs and sudden cardiac death and overall death was found, with relative risk of 0.81 (95% CI, 0.52-1.25) and 0.92 (95% CI, 0.82-1.03), respectively. The limitations of this analysis are 1) the two studies, GISSI-P and JELIS, accounted for 92% of total patients, thus dominating the results of this meta-analysis; 2) wide range of EPA and DHA amount (0-2000 mg/day) in the formulations was used in the reviewed studies, 3) the statistically significant heterogeneity (I^2=70.6%) among the outcomes measured in the implantable cardiac defibrillator studies. These limitations may limit the validity of this analysis.

Dietary supplementation with n-3 PUFAs was recommended to be considered for secondary prevention in patients who experienced cardiovascular events according to the results of a meta-analysis (38). There was 11 trials included in this meta-analysis, as well as the 2 large open-label trials, GISSI-P and JELIS. However, Kwak et al found that when excluded these 2 studies, the meta-analysis of the remaining 9 trials showed no benefits on cardiovascular risk reduction with relative risk of 0.94 on sudden cardiac death (95% CI, 0.81-1.09); 0.93 on total mortality (95% CI, 0.86-1.00); 0.96 on non-fatal

cardiovascular events (95% CI, 0.92-1.01), but only little benefit on cardiovascular death with relative risk of 0.91 (95% CI, 0.83-0.99) (41). This finding was consistent with the meta-analysis of 14 double-blind, randomized controlled trials only, which also showed no preventive benefits of n-3 PUFAs supplements in patients with a history of cardiovascular disease on overall CV events with relative risk of 0.99 (95% CI, 0.89-1.09; I^2 = 27.1%) and on total mortality with relative risk of 0.96 (95% CI, 0.90-1.02) (41). However, the 9% risk reduction of CV death was presented in this meta-analysis.

A meta-analysis included 20 randomized controlled trials also showed that n-3 PUFAs were not significantly associated with the risk reduction of CV events. Fourteen studies in this analysis are the same studies as in the meta-analysis by Kwak et al. The relative risk of overall mortality was 0.96 (95% CI, 0.91-1.02), sudden death 0.87 (95% CI, 0.75-1.01), MI 0.89 (95% CI, 0.76-1.04), stroke 1.05 (95% CI, 0.93-1.18). N-3 PUFAs significantly reduced only the cardiac mortality risk with relative risk of 0.91 (95% CI, 0.85-0.98). Though most of the studies in this analysis used n-3 PUFAs as secondary prevention of CVD, 4 studies used for primary and secondary prevention, 3 used in ICD and 1 used in patients on hemodialysis (37). The sources of n-3 PUFAs used in the studies were dietary (2 studies) and supplements (18 studies) and the dose ranged from 0.24 g to 6 g daily of n-3 PUFAs.

A meta-analysis including 3 analyses published in 2012 have demonstrated inconsistency due to a number of factors (37). First, RCTs which did not use placebo or control arm were included in some meta-analyses. Second, different doses and sources of n-3 PUFAs were included, thus heterogeneity likely generated. Third, studies with follow-up period less than 1 year may not be able to detect clinical benefit because the change in tissue lipid composition, together with anti-atherogenic and anti-inflammatory properties of n-3 PUFAs may take time to manifest (36, 39, 122). Finally, inconsistency may also derive from differences in the patients' inclusion criteria of the studies. Some studies included patients with high risk (9, 32, 35, 105-107), while others mainly investigated primary prevention (4, 93, 95).

The recent meta-analysis included 11 RCTs of 15,348 patients with existing CVD (i.e. in the setting of secondary prevention of CV outcomes) taking at least 1 g/day of n-3 PUFAs for at least 1 year in order to have time window long enough to manifest the preventive action of n-3 PUFAs (123). The significant risk reductions were found in cardiac death with relative risk of 0.68 (95% CI, 0.56 to 0.83), sudden death with relative risk of 0.67 (95% CI, 0.52 to 0.87), and myocardial infarction with relative risk of 0.75 (95% CI, 0.63 to 0.88), but not in total mortality (RR, 0.89; 95% CI, 0.78 to 1.02) and stroke (RR, 1.31; 95% CI, 0.90 to 1.90).

4. Clinical guidelines

Various guidelines have recommended consumption of n-3 PUFAs for prevention of CHD mortality with the dose of at least 250 mg/d or 2 servings/week of fish. There is no difference by race/ethnicity or sex for n-3 PUFAs consumption, except specific recommendations for young children and women who are or might become pregnant and nursing mothers to avoid selected higher-mercury fish species (124) and to consume appropriate DHA level for brain development of their children (125). Table 1 summarized the guidelines recommended for patients with CVD. The dose of 1 g/day of n-3 PUFAs is recommended for patient with history of myocardial infarction.

Table 1 International guideline for n-3 PUFAs consumption in patients with CVD

Year	Source	Patient type	n-3 PUFAs type	Dose and duration
2010	The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for	Patients after myocardial revascularization	Omega-3 fatty acids	1 g/day

Year	Source	Patient type	n-3 PUFAs type	Dose and duration
	Cardio-Thoracic Surgery (EACTS) (126)			
2011	American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) (127)	Patients with coronary and other atherosclerotic vascular disease	Omega-3 fatty acid from fish or fish oil capsules	1 g/day
2013	American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) (128)	Patients with NYHA class II-IV symptoms and HF*r*EF or HF*p*EF	Omega-3 fatty acid	N/A

5. Published literature on cost-effectiveness analysis

As GISSI-P is the largest study of n-3 PUFAs regarding CV outcomes, several CE analyses based on morbidity and mortality data from this study were performed in different countries in the third-party payer perspective. The study in Italy found that the incremental cost-effectiveness ratio (ICER) for n-3 PUFAs in the base case scenario was €24,603 (1999 values) per life-year gained (LYG). One hundred and seventy-two patients would need to be treated per year with n-3 PUFAs, at €68,000 per year, in order to save 1 patient. It was considered comparable with the number needed to treat (NNT) for and annual cost for simvastatin for secondary prevention after MI (129). The NNT of n-3 PUFAs is similar to other NNTs reported for prophylactic treatment. For example, aspirin in primary prevention for MI had an NNT of 220 per year (130), and lipid-lowering treatments had an NNT of 181 per year (131).

The second CE analysis based on GISSI-P study was done by Quilici and colleagues for UK setting (132). Cost per QALY gained at 4 years and over a life time were £3,717 and £15,189 respectively. Cost per life years gained was £2,812 at 4 years and £12,011 for life-long. The cost per death avoided at 4 years was £31,786, which was much lower than the cost from Franzosi's study. Survival curve was extrapolated from the trial duration of 42 months for both n-3 PUFAs and control groups. The mortality rates obtained from these survival curves were used in the Markov model. The model used a cohort of 1000 patients and included nine different health states to reflect the outcomes used in GISSI-P. Each patient transited to the health states during the 41 cycles (starting from the mean age of 59 years from GISSI-P), 1 year per cycle, until the patient had reached the age of 100 years or had died.

Lamotte et al assessed the cost effectiveness of n-3 PUFAs in 5 countries, i.e. Australia, Belgium, Canada, Germany and Poland. The life year gained yielded between 0.261 (Poland) and 0.284 (Australia), at an additional cost of €787 (Canada) to €1439 (Belgium). The ICER ranged between €2788 (Canada) and €5097 (Belgium) per LYG. The second-order Monte Carlo simulation demonstrated that n-3 PUFAs are cost effective in 93% of simulation in Poland and in > 98% of simulation in the other countries, assuming the country-specific societal willingness-to-pay threshold (133).

A recent study evaluated the CE of adding n-3 PUFAs 1 g/day to current secondary prevention therapies following acute MI in patients in the Irish and Estonian public healthcare systems (134). Based on the outcomes from the GISSI-P study, separate models were developed for Ireland and Estonia using lifetime and 3-year time horizons. The study demonstrated that lifelong treatment with n-3 PUFAs was associated with 0.26 life years gained (LYG) and 0.19 quality-adjusted life years gained (QALYG) for Irish patients and 0.24 LYG for Estonian patients. Data equated to an incremental cost-effectiveness ratio (ICER) of €6223/LYG and €8210/QALYG for patients in the Irish healthcare system and €5079/LYG for Estonian patients. Findings from the analysis suggested that the addition of n-3 PUFAs to standard secondary prevention therapies is likely to be cost-effective in Ireland and Estonia (134).

Summary of CE analysis was shown in Appendix D.

6. Economic modeling

A Markov model is an approach to represent a changing set of health states over time, where there is a known probability or rate of transition from one health state to another. It is useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once. The assumption In Markov model is that a patient is always in one of a finite number of discrete health states, called Markov states, and can move from one state to another at the rate defined by transition probabilities. Total probabilities of moving from one state to all possible states in each cycle always equal to 1 for a patient. The previous CE analyses of n-3 PUFAs used Markov model (132, 135) and decision tree (133). Since the structure of the decision tree does not allow the events to move back and forth between states and can only move forward (left to right), this approach is not suitable for the chronic diseases in which the events can recur, such as MI, stroke and heart failure. It is more complicated and may require unrealistic simplifying assumptions if decision tree is used in such clinical settings. Therefore, Markov model is more appropriate for the CE analysis of these cardiovascular diseases.

CHAPTER III
METHODOLOGY

This chapter provides the description of the methodology including the perspective of the study, comparator, outcome, model structure and assumption. The 4 components of data required comprised of effectiveness, cost, utility and transition probability, as well as uncertainty analysis were also described.

1. Perspective of the study

The perspective concerned in this study is provider perspective. Thus, only the direct health care costs were included.

2. Comparator

This analysis compared the supplementation of n-3 PUFAs on standard treatment versus no supplementation in patients experienced MI.

3. Outcome

The health outcome measures were QALY and LYG. QALY was used to measure overall health-related quality of life, which was the preferred approach in economic evaluation of health intervention. LYG was a modified mortality measure when remaining life expectancy was taken into account. Life years were calculated as the remaining life expectancy at the point of each averted death.

The results of CE analysis were presented as (1) incremental cost effectiveness ratio (ICER) per QALY, which estimated the additional cost per additional QALY gained using n-3 PUFAs supplements compared with no supplements in secondary prevention of post-MI patients; (2) ICER per life-year gained, which estimated the additional cost per additional life-year gained from using n-3 PUFAs.

4. Model structure and assumption

Markov model is useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when events can occur more than once. So Markov model was used to evaluate the incremental costs

and effects of lifetime treatment with n-3 PUFAs in post-MI patients. The model was developed in Excel version 2013.

In Markov model, there are different health states. It is assumed that at any point of time, all patients must be in one and only one of the states. All patients start in the event-free MI ("Post-MI" health state in the model). During each 1-year cycle of the model, some patients enter one of the four health states (cardiovascular mortality, non-fatal MI, non-fatal stroke, and heart failure (HF)), while others remains in the event-free state (Figure 4). Other outcomes such as peripheral artery disease will not be considered due to limited events recorded in the trials. Revascularization is done in nearly all post-MI patients so it is not considered a health state, as in the model of other studies. The patients can enter into more than one non-fatal event in subsequent periods of the model.

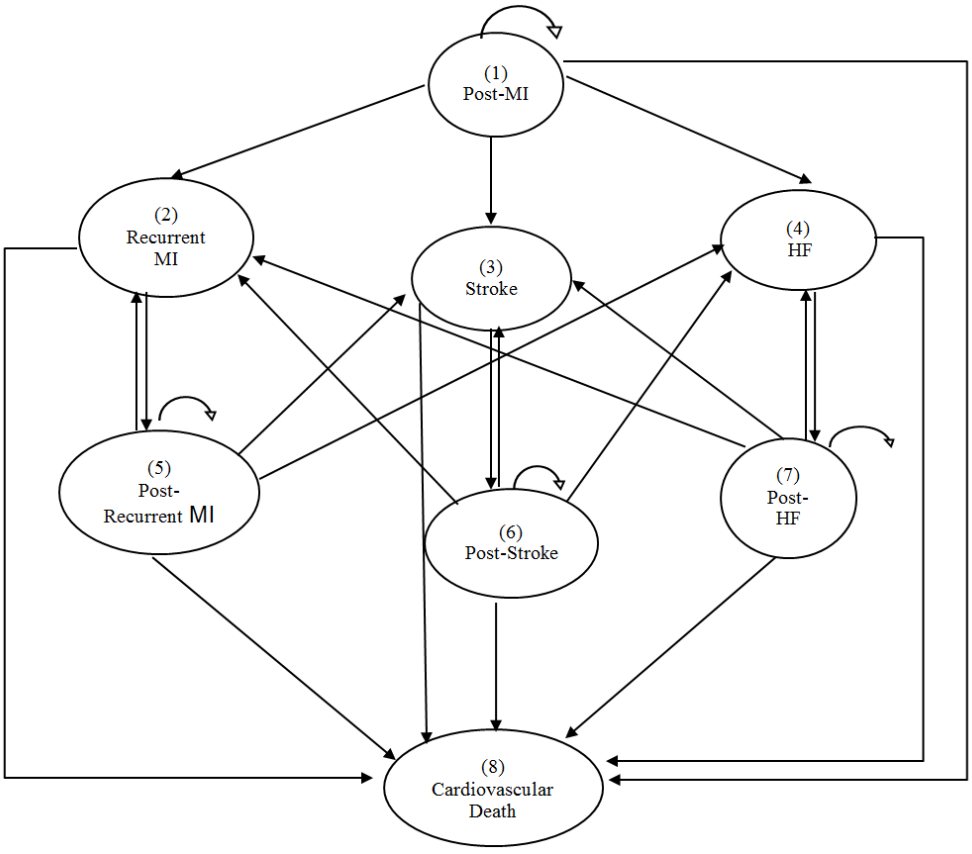


Figure 4 Schematic representation of the Markov model

The rate that the patients move through the model is defined by transition probabilities, which describe the probabilities of moving from one state to another in each model cycle. The transition between each state and event is determined by probabilities and adjusted factors obtaining from randomized control trials and local registry database. The model will run until the patients reach 100 years old or die.

The main assumptions made in this model were as follows: 1) patients in the acute health state (MI, stroke, HF) would not move to other acute health state; 2) the effectiveness of n-3 PUFAs would be maintained over life-time horizon; 3) the period in each cycle was 1 year.

The discount rate of 3% was applied for both costs and outcomes. The time horizon of the model and the effects in life expectancy were life-long calculation. The provider perspective was chosen for this study; thus only direct health care costs were used in the analysis.

5. Data required

The following 4 components are required for conducting this CE analysis.

a. Effectiveness data

The treatment effectiveness of the intervention concerned, n-3 PUFAs, was used in the analysis. The relative risk (RR) and standard error (SE) were collected from published studies. A meta-analysis was conducted to gain the pooled data in post-MI patients.

b. Cost data

As the perspective in this evaluation is provider perspective, only the direct health care costs of MI, stroke and HF, paid by the provider, were used.

c. Utility data

The utility weights for patients with MI, stroke or HF were derived from published articles. The utility score is between 0 and 1, where 0 represents death and 1 represents perfect health. The patients in the acute state of any diseases (MI, stroke, HF) have lower utility weights than those in the post state (or stable state) of the diseases.

d. Transition probability

The transition probability is the chance that each clinical event will occur. In a specified period, the patient can move between health states. The rate of moving from one health state to another is regulated by the transition probabilities. It ranges from 0 to 1.

5.1 Effectiveness

We carried out a meta-analysis to estimate the effectiveness of n-3 PUFAs for the base case analysis. A comprehensive literature search of MEDLINE, EMBASE, and the Cochrane Library (up to September 2013) was conducted using the keywords: fish oil, omega-3 fatty acids, omega fatty acids, n-3 fatty acids, N3 fatty acids, n-3 PUFA, unsaturated fatty acids, polyunsaturated fatty acids, eicosapentaenoic acid, eicosapentanoic acid, icosapentaenoic acid, EPA, docosahexaenoic acid, docosahexanoic acid, DHA, mortality, sudden cardiac death, cardiac sudden death, cardiac death, heart death, overall death, total death, all-cause mortality, cardiovascular disease (CVD), heart disease, coronary disease, coronary artery disease, heart attack, heart arrest, heart infarction, heart failure, myocardial infarction, MI, stroke, trial, study. The search result was limited only in human. In addition, the references of relevant publications were also searched for additional publications. The language of publication was restricted to English.

All trials that met the following criteria were included: 1) the trial enrolled adult patients (aged at least 18 years) with a history of myocardial infarction; 2) n-3 PUFAs were consumed in dose of at least 1 g/day; 3) the follow-up period was at least 1 year, which would be long enough for n-3 PUFAs to demonstrate efficacy ; 4) the outcomes included CVD or events, cardiovascular death, sudden death, all-cause mortality, CHD, HF, stroke, fatal or nonfatal MI. Studies with angiographic primary end points were eligible if data on MI and death was reported.

The exclusion criteria included studies with less than 1-year duration, studies with multiple interventions from which the effects of n-3 PUFAs could not be separated, and studies that did not report CV-related endpoints. We also excluded the reviews and meta-analysis from the analysis. If two or more articles reported results from the same group of patients at different follow-up periods, only the article with longer follow-up period was retained in order to prevent data duplication.

Titles and abstracts obtained from the electronic and bibliographic searches were rejected on initial screening if it could be determined that the article did not meet the eligibility criteria. In case the reviewer was uncertain whether to reject an article based on its title/abstract, the full text of the article was further evaluated.

The information recorded from each study included (1) first investigator's name, (2) journal and year of publication, (3) number of patients in each group, (4) population characteristics, (5) study design, (6) treatment indication, (7) n-3 PUFAs dose, (8) study duration, (9) definition of the end points, (10) effect measure in terms of relative risk and 95% CI. Data extraction was performed by 2 reviewers independently. The reviewers are Adawan Permpanich (B.Sc. in Pharm.) and Nunthida Sookrummi (B.Sc. in Pharm.). In case there were discrepancies, the reviewers discussed or consulted the third reviewer, Vithaya Kulsomboon (Ph.D.) for final decisions. All reviewers have scientific background and are qualified for the article review. If the same studies were presented in more than 1 articles, we included only the larger or the most complete report.

The program used for this meta-analysis was Review Manager 5.2.

5.2 Cost

The discount rate of 3% was applied to all costs according to HITAP guidance (136). All costs were inflated to 2013 values using Consumer Price Index (CPI) of medical care group from the Bureau of Trade and Economic Indices, Ministry of Commerce, as shown in Appendix E (137).

As provider perspective is used for this study, cost data in the study included only direct health care costs, which were defined as the costs of goods and services directly provided by the service provider such as medication cost, hospital cost, intervention cost, etc. The costs in the first year were higher than in the subsequent year because more interventions are usually required.

5.2.1 MI direct health care cost

The data from Ramathibodi Hospital published by Anukoolsawat et al was used (138). This data was collected from the patients in the Thai ACS Registry who were admitted to Ramathibodi Hospital from August 2002 to December 2003. The costs of the first admission, first year, subsequent year and overall costs were recorded from the first hospitalization to the last follow-up.

5.2.2 Stroke direct health care costs

From the prospective observational cohort study done by Khiaocharoen et al (139), the costs of stroke patients from 4-month follow-up were collected in 2 regional hospitals in Thailand, Ratchaburi and Udonthani Hospital. The study was done from July 2008 to May 2009. These provider costs included hospitalization costs and other health care costs after discharge. Total costs of 1 year were extrapolated from the 4-month cost with the assumption that there was one hospitalization in 1 year and 3 follow-up visits for each patient. The details of stroke cost are shown in Appendix G.

5.2.3 Heart failure direct health care costs

There is no database of HF patients in Thailand so the data from the National Health Security Office (NHSO) was used. The costs were derived from 2 sets of data. The first data set was the hospitalization cost of inpatient from government hospitals, collected from October 2009 to September 2012. This cost included all health care costs

incurred during hospitalization. The second data set was the cost of patients visiting the out-patient departments (OPD) of hospitals under Bangkok Metropolitan Administration during October 2011 to September 2012, including drug cost, intervention cost and other medical costs incurred from the OPD visit. The follow-up visit was estimated to be every 3 months from the experts' opinion (cardiologists).

5.2.4 Cost of n-3 PUFAs

Currently, there is only 1 brand of highly concentrated n-3 PUFAs available in Thailand, which is Omacor® (Abbott Laboratories Limited). This product has been registered as a pharmaceutical product and is indicated as a supplemental treatment in secondary prevention after myocardial infarction in dose of 1 gram/day. The n-3 PUFAs cost was obtained from the Drug and Medical Supply Information Center (DMSIC) website, the FDA owned website which provides reference price and/or purchasing price of marketed pharmaceutical products.

5.3 Utility

Quality-of-life utilities were assigned for each health state in the model. The utility weights of acute state of each disease were lower than those of post state (stable state).

5.3.1 Utility of MI

The utility of MI was derived from a study that conducted serial interview of 67 patients who recently had MI (140). The interview was done two to five times with each patient over one and a half years. The mean time-tradeoff scores at the first interview and final interview were recorded and used as the utility of acute state and post state of MI, respectively.

5.3.2 Utility of stroke

QALY measured by the EuroQol 5-dimensional questionnaire was collected from 284 stroke patients visiting outpatient department of Ratchaburi Hospital from August to October 2009 (141). The five dimensions of health are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 3 levels, i.e. no problems, some/moderate problems, and extreme problems. Due to the data unavailability, this data was used as the utility of acute stroke even though it was from the patients with non-acute condition.

The utility of post-stroke was derived using the EQ-5D instrument in the PLATO (Platelet Inhibition and Patient Outcome) trial (142). A total of 8,840 patients were asked to complete the EQ-5D questionnaire at discharge from the hospital, at 6-month follow-up and at the final visit of the study.

5.3.3 Utility of heart failure

The utility score of HF was obtained from the CARE-HF (Cardiac Resynchronisation in Heart Failure) study (143). This international, randomized controlled trial was conducted in 813 patients with heart failure from January 2001 to March 2003. The EuroQoL EQ-5D was used to measure the health status of the patients.

A hundred outpatients at the HF clinic in the Netherlands had answered the EQ-5D questionnaires and the utility of post-HF was recorded (144). This study was conducted between January and July 2012, in patients with HF NYHA functional class I - IV.

5.4 Disease transition probability

The transition probabilities were obtained from literature reviews and survival analysis of Thai patients. As age is the main factor which impacts the

occurrence of CV events, we tried to search the articles that contained data in different age group. In case there is no such data, the relative risk of the event was used to multiply with the incidence rate of normal population. The rates of event occurring in post-MI patients were searched, but in case the data was not available, the event rates occurred in normal population were used.

The event rate (r) must be converted to probability (p) using the following formula:

$p = 1- \exp(-rt)$

where t is the time period of interest

The differences between rates and probabilities are that rates are instantaneous while probabilities are expressed over a time period. The rate can be added or subtracted in a given time period, and can be divided by time and number of patients. We cannot divide or multiply probability to change time period.

The probability can also be converted back to rate to exploit its mathematical features (e.g. changing cycle length), using the following formula:

$r = - [\ln (1-p)]/t$

For example, assume 600 patients are followed up for 2 years after which 45 have had an acute MI.

Rate = - [ln (1- (45/600))] / 2 = 0.0390

To convert to a yearly probability (or transition probability):

Probability = 1- exp ((-0.0390) x 1) = 0.0382

6. Uncertainty analysis

6.1 Deterministic sensitivity analysis

Univariate sensitivity analyses were conducted to identify the variables which have significant impacts on the results. The key individual variables which influence the result of CE were shown in Tornado diagram. The variables tested are as follows:

1. Size of the treatment effects

The robustness of the results to uncertainty over the size of treatment effects was assessed using the upper limit and lower limit of 95% confidence intervals, from the meta-analysis/published literature, of cardiovascular mortality, MI, stroke and HF.

2. Cost of supplements

   The cost of n-3 PUFAs was varied to be 50% less and more than the based price.

3. Costs of cardiovascular disease events

   The costs of all CVD events (MI, stroke, HF) were increased and decreased by 50% to see the change of ICERs.

4. Utility of MI

   The upper limit and lower limit of 95% confidence intervals were used to see the impact of utility of MI on the result.

5. Discount rate

   The discount rates of 0% and 6% of costs and utilities were used.

6.2 Probabilistic sensitivity analysis

To examine the uncertainty of inputs in the model, the probabilistic sensitivity analysis using a second-order Monte-Carlo simulation was performed. Monte Carlo simulation was used by involving random sampling of each variable under the specified probability distribution of each input parameter which was assigned based on their feature to indicate the feasible value range in which each input variable could achieve. Beta distribution was chosen for the probability and utility variables, Gamma distribution was used for all cost parameters and Log normal was used for Relative Risk. The simulation of 1000 times could provide a range of possible values given the specified probability distribution of parameters used in the analysis. The results were presented as costs, effectiveness (QALY, LYG), ICER per QALY and ICER per LYG.

CHAPTER IV
RESEARCH RESULT

The lifetime CE analysis of highly concentrated n-3 PUFAs compared with no supplementation in post-MI patients required the following 4 types of inputs: 1) effectiveness parameters, 2) cost parameters, 3) utilities parameters and 4) transition probabilities from one health state to another. This chapter describes the details of these parameter inputs in sequence, followed by the result of CE analysis and uncertainty analyses.

1. Effectiveness parameters

These parameters were obtained from the meta-analysis. From literature search, 4042 articles were identified. There were 3 studies that met inclusion criteria and did not meet exclusion criteria, i.e. GISSI-P study (9), OMEGA study (32), and GPRD study (99). Details of the selection of eligible studies were shown in Figure 5.

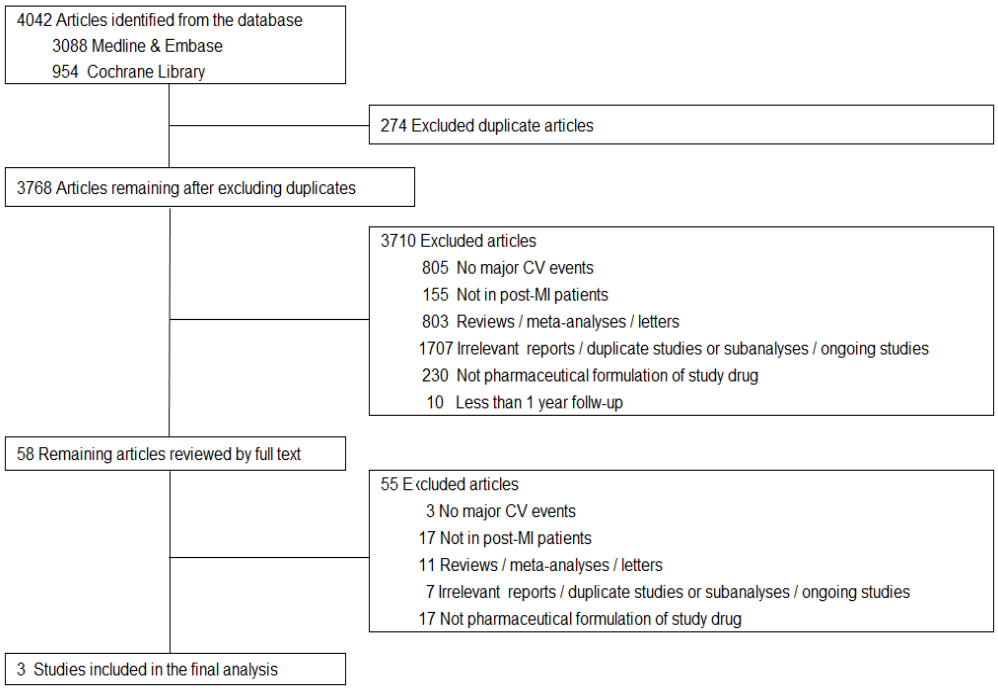


Figure 5 Flow chart for the selection of eligible studies for meta-analysis

The results of meta-analyses on total mortality and sudden death, shown in Figure 6-7, were not statistically significant compared with no supplementation. The heterogeneity of data regarding both outcomes was statistically significant, indicating that the heterogeneity was high. N-3 PUFAs reduced cardiovascular mortality significantly with non-significant heterogeneity from the meta-analysis (Figure 8). Therefore, the outcome of cardiovascular mortality was used in the model. This outcome was reported in 2 studies, i.e. GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico-Prevenzione) study (9, 98), and OMEGA (Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death after Myocardial Infarction) study (32). A total of 15,174 patients after MI were included. The results of included studies were pooled using fixed effect model, weighted by inverse of variance. The Summary of studies used in the meta-analysis for CV mortality outcome was shown in Table 2.

Table 2 Summary of studies included in the meta-analysis for CV mortality outcome

Study	Dose of n-3 PUFAs	Study duration (month)	Total population (treatment/control)	Number of patients with CV mortality (treatment/control)
GISSI-P	1 gram/ day	42	11,324 (5,666/5,658)	680 (310/370)
OMEGA	1 gram/ day	12	3,804 (1,919/1,885)	57 (28/29)

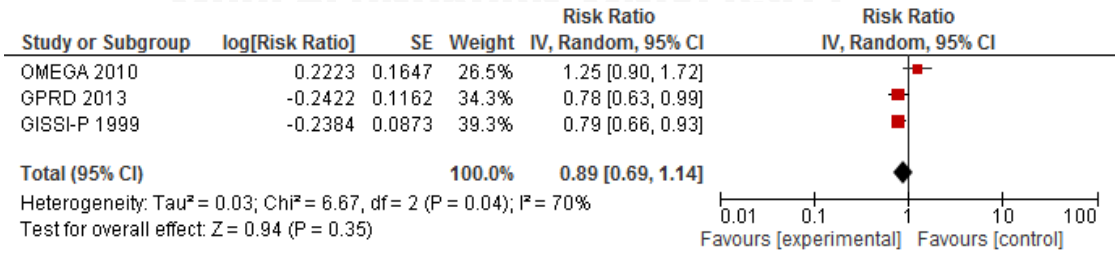


Figure 6 Meta-analysis results on total mortality in post-MI patients using n-3 PUFAs

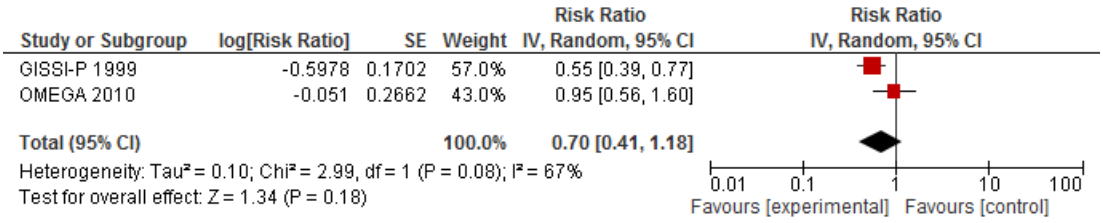


Figure 7 Meta-analysis results on sudden death in post-MI patients using n-3 PUFAs

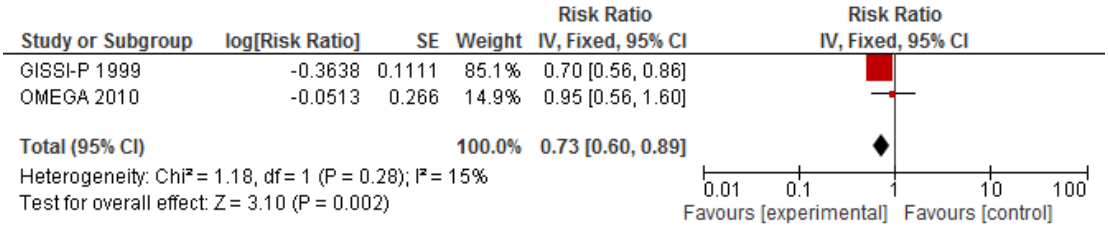


Figure 8 Meta-analysis results on cardiovascular mortality in post-MI patients using n-3 PUFAs

Effectiveness data of n-3 PUFAs on MI and stroke were obtained from the GISSI-P study (9, 98). There was only 1 study on HF using high dose of n-3 PUFAs in 6,975 patients with chronic heart failure, 41% of which had history of MI. The result of this study was used for effectiveness data of HF (120). The effectiveness data were shown in Table 3.

Table 3 Effectiveness parameters for the model

Parameter description	Distribution	RR	SE	Source
Effect of n-3 PUFAs on cardiovascular mortality	Gamma	0.73	0.0740	Meta-analysis
Effect of n-3 PUFAs on nonfatal MI	Gamma	0.91	0.1225	(98)
Effect of n-3 PUFAs on nonfatal stroke	Gamma	1.22	0.3138	(98)
Effect of n-3 PUFAs on nonfatal heart failure	Gamma	0.90	0.0459	(120)

2. Cost parameters

The direct health care costs in this study included costs of MI, stroke, HF and n-3 PUFAs. All costs were summarized in Table 4.

2.1 MI costs

From data of the Thai ACS Registry, 330 medical records of patients admitted to Ramathibodi Hospital from August 2002 to December 2003 were reviewed to calculate the direct healthcare costs from the first hospitalization to the last follow-up. The data consisted of 110 ST-elevation MI (STEMI), 107 non ST-elevation MI (NSTEMI) and 113 unstable angina (UA). The cost of UA patients was excluded and only the average cost of patients with MI (STEMI and NSTEMI) was used for the first year. The calculation of costs in MI patients in the first year was shown in Appendix F. For the cost in the subsequent year, there was no separated data between MI and UA patients, and the follow-up cost in the subsequent year was assumed to be the same, so the median cost of total population in Thai ACS registry was used.

a) MI direct health care costs in the first year

- Average cost directly provided by the hospital in the first year = 175,935 THB (SE 11,358).
- This cost was already adjusted to 2005 value. The consumer price index (CPI) was 96.87 in 2005, and 101.94 in 2013. Therefore, the cost adjusted to 2013 value = 175,935 x 101.94/96.87 = 185,143 THB (SE 11,953).

b) MI direct health care costs in the subsequent year

- Median cost directly provided by the hospital in the subsequent year = 12,912 THB.
- The cost adjusted to 2013 value = 12,912 x 101.94/96.87 = 13,588 THB

2.2 Stroke costs

The cost was derived from the prospective observational study done by Khiaocharoen et al (139). The costs of stroke patients from 4-month follow-up were extrapolated to 1 annual cost, with the assumption that there was one hospitalization in 1 year and 3 follow-up visits for each patient. The details of stroke cost are shown in Appendix G.

a) Stroke direct health care costs in the first year
   - Hospitalization cost = 14,562 THB.
   - Direct health care costs after discharge, including the costs of medicine, alternative medicine, massage and rehabilitation, were 5,096 THB in 4 months, thus extrapolated to be 15,289 THB in 1 year.
   - Total direct heal care costs = 14,562 + 15,289 = 29,851 THB (SE 2109).
   - The consumer price index (CPI) was 99.31 in 2009, and 101.94 in 2013. Therefore, the cost adjusted to 2013 = 29,851 x 101.94/99.31 = 30,642 THB (SE 2165).

b) Stroke direct health care costs in the subsequent year
   - Only the direct health care cost from follow-up is considered, so the costs were 15,289 THB (SE 1727).
   - The cost adjusted to 2013 value = 15,289 x 101.94/99.31 = 15,694 THB (SE 1773).

2.3 HF costs

Two sets of data from the National Health Security Office (NHSO) were obtained. The hospitalization cost of inpatient from government hospitals was collected from October 2009 to September 2012. There were 205,099 admissions, 41% were male. The average days in hospitals

were 5.5 days and the hospitalization cost was 11,372 THB per patient. The other data set was the cost of patients visiting the out-patient departments (OPD) of hospitals under Bangkok Metropolitan Administration during October 2011 to September 2012. This data was obtained from 34,072 HF patients. The average OPD cost per patient was 1,987 THB. The follow-up visit was estimated to be every 3 months.

a) HF direct health care cost in the first year

- Hospitalization cost was 11,373 THB.
- OPD cost was 1,987 x 4 = 7,946 THB.
- Total HF direct health care cost = 11,373 + 7,946 = 19,319 THB.
- The CPI was 100.96 in 2012, and 101.94 in 2013. Therefore, the total direct health care cost adjusted to 2013 value = 19,319 x (101.94/100.96) = 19,507 THB.

b) HF direct health care cost in the subsequent year

- The cost in subsequent year was assumed to be only OPD cost 4 times per year, so the direct health care cost = 1,987 x 4 = 7,946 THB.
- Adjusted to 2013 value = 7,946 x (101.94/100.96) = 8,023 THB.

2.4 Cost of n-3 PUFAs

From the Drug and Medical Supply Information Center (DMSIC) website, the price of n-3 PUFAs is 1168.44 THB/bottle of 28 capsules (value added tax (VAT) inclusive). So the drug cost per year is 15,231.45 THB.

Table 4 Cost parameters for the model

Parameter description	Distribution	Value (THB)	SE	Source
Direct health care cost – adjusted to 2013 values (cost/year)				

Parameter description	Distribution	Value (THB)	SE	Source
Cost of MI in the first year	Gamma	185,143	11,953	(138)
Cost of MI in the subsequent year	Gamma	13,588	679*	(138)
Cost of stroke in the first year	Gamma	30,642	2,165	(139)
Cost of stroke in the subsequent year	Gamma	15,694	1,773	(139)
Cost of heart failure in the first year	Gamma	19,507	975*	NHSO
Cost of heart failure in the subsequent year	Gamma	8,023	401*	NHSO
Cost of n-3 PUFAs per year	Gamma	15,231	762*	DMSIC website

* Assumption (5% of the mean value)

3. Utility parameters

Disease-specific utilities for MI, stroke and HF were obtained from the literatures, as shown in Table 5.

3.1 Utility of MI

From the study using serial interview of 67 post-MI patients, the mean time-tradeoff scores at the first interview was 0.87 (0.82-0.92) and at the final interview was 0.91 (0.86-0.96) (140).

3.2 Utility of stroke

The cross-sectional study conducted in Thai stroke patients in Ratchaburi Hospital demonstrated the mean utility score of stroke

measured by EQ-5D was 0.55±0.29 (141). The utility of post-stroke was derived by using the EQ-5D instrument in the PLATO (Platelet Inhibition and Patient Outcome) trial (142). The utility value of post-stroke was 0.663.

3.3 Utility of heart failure

The utility score of HF using EQ-5D in 813 patients with heart failure in CARE-HF (Cardiac Resynchronization in Heart Failure) trial was 0.60 (0.58-0.62) (143).

A hundred outpatients at a HF clinic in the Netherlands had answered the EQ-5D questionnaires and the utility of post-HF of 0.68±0.26 was obtained (144).

Table 5 Utility parameters in different health states

Parameter description	Distribution	Mean	SE	Source
Utility of acute MI	Beta	0.870	0.0255	(140)
Utility of post-MI	Beta	0.910	0.0255	(140)
Utility of acute stroke	Beta	0.550	0.0172	(141)
Utility of post-stroke	Beta	0.663	0.0106*	(142)
Utility of acute heart failure	Beta	0.600	0.0102	(143)
Utility of post-heart failure	Beta	0.680	0.0260	(144)
Utility of death	Beta	0.000	0.0000	

*Assumption (calculated from the formula SE = SD/√N; N=8840, assumed SD=1)

4. Transition probability parameters

4.1 Probability of post-MI patients developing recurrent MI

[pMItoReMI; p(1,2) (numbers indicate health state according to Figure 4)]

From GISSI-P study, conducted in 11,323 post-MI patients of which 5,658 were in the control group, the recurrent MI occurred in 131 patients in the first year and 102 patients during 2-3.5 years after the first MI (145).

The probability of recurrent MI in the first year after MI = 131/5658 = 0.0232

SE = $\sqrt{(131x(5658-131))/((5658)^2(5658+1)}$ = 0.0020

The probability of recurrent MI in year 2-3.5 after MI = 102/(5658-131) = 0.0185

The rate per year during year 2-3.5 after MI = -[ln (1-0.0185)]/2.5 = 0.0075

The probability per year during year 2-3.5 after MI = $1-e^{-(0.0075x1)}$ = 0.0074

4.2 Probability of post-MI patients developing stroke

[pMItoST; p(1,3)]

From GISSI-P study, stroke occurred in 19 patients in the first year and 38 patients during 2-3.5 years after MI (145).

The probability of stroke in the first year after MI = 19/5658 = 0.0034

SE = $\sqrt{(19x(5658-19))/((5658)^2(5658+1)}$ = 0.0008

The probability of stroke in year 2-3.5 after MI = 38/(5658-19) = 0.0067

The rate per year during year 2-3.5 after MI = -[ln (1-0.0067)]/2.5 = 0.0027

The probability per year during year 2-3.5 after MI = $1-e^{-(0.0027x1)}$ = 0.0027

4.3 Probability of post-MI patients developing HF

[pMItoHF; p(1,4)]

The report from the American Heart Association on 2013 heart disease statistics demonstrated 1.6% incidence rate of HF in post-MI men and 3.6% in women aged 45-64 years old, and 4% and 4.6% in men and women aged over 65 years old, respectively (146). From the National Statistical Office of Thailand in 2012, male accounted for 49% and female 51% of total population. The rate per year in each age group was the sum of the incidence rate in men multiplied by the proportion of male in that age and the incidence rate in women multiplied by the

proportion of female in that age. The probability per year was then calculated from the rate per year, using the formula $p = 1- e^{(-rt)}$, where r = rate/year, t = time period of interest. Table 6 showed the yearly rate and probability of HF in post-MI patients.

Table 6 Probability of HF in post-MI patients

Age	Rate/year			Probability/year
	Male	Female	Total	
45-64	0.016	0.036	0.0262	0.0258
65-100	0.040	0.046	0.0431	0.0421

4.4 Probability of death in post-MI patients

[pMItoD; p(1,8)]

Survival analysis was performed, using STATA 11. The mortality data of post-MI patients was obtained from the Thai ACS Registry, the national database collecting information from Thai patients hospitalized with ACS which comprised of ST-elevation MI (STEMI), non-ST-elevation MI (NSTEMI) and unstable angina (UA). Only data from 1772 STEMI and NSTEMI patients was included in the model, UA was excluded. From 1,525 patients who had completed data, there were 149 cardiovascular death within 1 year. The output from survival analysis was shown in Appendix H. The probability of mortality after MI derived from survival analysis was shown in Table 7.

Table 7 Probability of mortality after MI

Number of year after MI occurrence	Probability
1	0.0852
2	0.0519

Number of year after MI occurrence	Probability
3	0.0439
4	0.0394
5	0.0364
6	0.0341
7	0.0323
8	0.0309
9	0.0297
10	0.0287
11	0.0278
12	0.0270
13	0.0263
14	0.0256
15	0.0250
16	0.0245
17	0.0240
18	0.0236
19 and afterwards	0.0096

4.5 Probability of post-MI patients being stable in post-MI stage [pMItoMI; p(1,1)]

There are 5 probabilities going out from post-MI state and the sum of them should equal to 1. So the probability of p(1,1) can be calculated as shown in the below equation.

$$p(1,1) = 1 - p(1,2) - p(1,3) - p(1,4) - p(1,8)$$

4.6 Probability of death in recurrent MI patients

[pReMItoD; p(2,8)]

Recurrent MI was found to increase the risk of sudden cardiac death by 44% (95%CI, 1.12, 1.86) (147). To get the mortality rate of recurrent MI, the relative risk of 1.44 was multiplied by the mortality rate of normal population of Thailand from WHO website (148). The probability of mortality in patients with recurrent MI was then calculated from the rate, as shown in Table 8.

Table 8 Probability of mortality in patients with recurrent MI

Age	Mortality rate of normal population	Mortality rate of patients with recurrent MI	Probability of mortality in patients with recurrent MI
45-49	0.00471	0.00678	0.00676
50-54	0.00659	0.00949	0.00944
55-59	0.00962	0.01385	0.01376
60-64	0.01475	0.02124	0.02101
65-69	0.02224	0.03203	0.03152
70-74	0.03725	0.05364	0.05223
75-79	0.05264	0.07580	0.07300
80-84	0.07516	0.10823	0.10258
85-89	0.11090	0.15970	0.14760
90-94	0.16898	0.24333	0.21599
95-99	0.26562	0.38249	0.31784
100+	0.42892	0.61764	0.46079

4.7 Probability of recurrent MI being stable in post-recurrent MI state

[pReMItoPReMI; p(2,5)]

The recurrent MI patients may either die or move to post-recurrent MI state. So the probability of p(2,5) can be calculated as per the below equation.

P(2,5) = 1 – p(2,8)

4.8 Probability of death in stroke patients with previous history of MI

[pSTtoD; p(3,8)]

The WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project, which was a registry of stroke patients in Copenhagen during 1982-1991, demonstrated the standardized mortality ratios (SMRs), the quotient of the observed to the expected numbers of death (149). Valid information was collected from 1,887 stroke patients. The SMRs were 5.72 in patients less than 70 years old and 4.46 in patients at least 70 years old. Cardiovascular death was 67.5% of total death reported in this cohort. So the SMRs of CVD in patients of each age group equaled to the SMR of that age multiplied by 0.675 (Table 9). To gain the probability of stroke mortality in each age, the calculated SMRs of CVD was then multiplied by the mortality rate of normal population of Thailand from WHO website (148), as shown in Table 10.

Table 9 Age-specific standardized mortality ratio of cardiovascular diseases

Age	Standardized mortality ratio	Standardized mortality ratio of CVD

45-69	5.72	3.86
70-100	4.46	3.01

Table 10 Probability of stroke mortality in post-MI patients

Age	Mortality rate of normal population	Stroke mortality rate in post-MI patients	Probability of stroke mortality in post-MI patients
45-49	0.00471	0.01819	0.018029
50-54	0.00659	0.025449	0.025129
55-59	0.00962	0.037149	0.036469
60-64	0.01475	0.05695	0.05536
65-69	0.02224	0.08587	0.08229
70-74	0.03725	0.11214	0.10608
75-79	0.05264	0.15847	0.14655
80-84	0.07516	0.22627	0.20250
85-89	0.11090	0.33386	0.28385
90-94	0.16898	0.50871	0.39873
95-99	0.26562	0.79965	0.55051
100+	0.42892	1.00000	0.63212

4.9 Probability of stroke patients with previous history of MI being stable in post-stroke state

[pSTtoPST; p(3,6)]

The stroke patients may either die or move to post-stroke state. So the probability of p(3,6) can be calculated as per the below equation.

$p(3,6) = 1 - p(3,8)$

4.10 Probability of death in HF patients with previous history of MI

[pHFtoD; p(4,8)]

The Atherosclerosis Risk in Communities (ARIC) cohort, a population-based study from 4 United States communities during 1987 to 2002, recorded 1,282 incident HF cases from 198,417 person-years. The age-adjusted 30-day case fatality of 10.4% was used to reflect the acute state of HF (150). The probability of mortality after HF in post-MI patients = $1- e^{-(0.104 \times 1)} = 0.0988$.

4.11 Probability of HF patients with previous history of MI being stable in post-HF state

[pHFtoPHF; p(4,7)]

The HF patients may either die or move to post-HF state. So the probability of p(4,7) can be calculated as shown in the below equation.

$p(4,7) = 1 - p(4,8)$

4.12 Probability of the second recurrent MI in patients suffering the first recurrent MI

[pPReMItoReMI; p(5,2)]

As there is no data on the incidence rate of second recurrent MI available, the transition probability of recurrent MI from post-MI state [p(1,2)] was used.

4.13 **Probability of stroke in post-recurrent MI patients**

[pPReMItoST; p(5,3)]

As there is no data of stroke incidence rate after recurrent MI, the transition probability of stroke from post-MI state [p(1,3)] was used.

4.14 Probability of HF in post-recurrent MI patients

[pPReMItoHF; p(5,4)]

Due to the lack of HF incidence rate after recurrent MI, we used the probability of HF in post-MI patients (146).

4.15 Probability of death in post-recurrent MI patients

[pPReMItoD; p(5,8)]

There is no published data of mortality rate of post-recurrent MI, so the mortality rate of post-MI [p(1,8)] from the survival analysis using data from the Thai ACS Registry was used.

4.16 Probability of post-recurrent MI patients being stable in post-recurrent MI state

[pPReMItoPReMI; p(5,5)]

There are 5 probabilities going out from post-recurrent MI state and the sum of them should equal to 1. So the probability of p(5,5) can be calculated as shown in the below equation.

$p(5,5) = 1 - p(5,2) - p(5,3) - p(5,4) - p(5,8)$

4.17 Probability of recurrent MI in post-stroke patients with history of previous MI

[pPSTtoReMI; p(6,2)]

Data from stroke cohort of 3,149 patients aged ≥60 years were identified from United Healthcare plan during 1995-1998. Recurrent MI occurred in 44 patients with history of stroke within 1 year (151).

The probability of recurrent MI = 44/3149 = 0.01405

$SE = \sqrt{(44x(3149-44))/(3149)^2(3149+1)} = 0.0021$

For patients younger than 60 years old, data from the Thai ACS Registry showed 0.55 times of recurrent MI compared with that in patients above 60 years old. So the probability of patients aged ≥60 years was converted to rate = - (ln(1-0.01405))/1 = 0.01415. The rate of recurrent MI in patients younger than 60 years old = 0.01415 x 0.55 = 0.00776, and the probability = $1-e^{-0.00776}$ = 0.00773.

4.18 Probability of recurrent stroke in post-stroke patients with history of previous MI

[pPSTtoST; p(6,3)]

From the same article as in section 4.17, the recurrent stroke occurred in 181 patients in the same stroke cohort (151).

The probability of recurrent stroke = 181/3149 = 0.0575

SE = $\sqrt{(181x(3149-181))/(3149)^2(3149+1)}$ = 0.0042

The multivariate-adjusted hazard ratio of stroke occurrence in patients younger than 60 years old was approximately half of those 60 years old and above (152). So the probability of stroke in patients aged ≥60 years was converted to rate = - (ln(1-0.0575))/1 = 0.0593. The rate of recurrent MI in patients younger than 60 years old = 0.0593 x 0.5 = 0.0296, and the probability = $1-e^{-0.0296}$ = 0.0292.

4.19 Probability of HF in post-stroke patients with history of previous MI

[pSTtoHF; p(6,4)]

There is no published data of HF in patients with history of stroke, so data of HF in normal population was used, which may underestimate the actual incidence of HF in stroke patients. The Atherosclerosis Risk in Communities (ARIC) cohort, a population-based study from 4 United States communities during 1987 to 2002, recorded 1,282 incident HF cases from 198,417 person-years (150). Thirteen percent of the patients in this cohort had history of MI and 5% had history of stroke. The probabilities of HF in each age group were

calculated using the formula $p = 1-e^{-rt}$. The number of HF occurred, number of patient-year and calculated probability in patients aged 45-64 years old were shown in Table 11.

Table 11 Age-specific probability of heart failure in patients aged 45-64 years old

Age	Incident HF cases	Patient-year	Probability per year
45-49	153	56,558	0.002705
50-54	268	52,935	0.005063
55-59	357	47,555	0.007507
60-64	504	41,374	0.012182

The medical record of patients hospitalized for acute heart failure in 11 area medical centers in Worchester during 2000 also provided the incidence rate of HF (153). However, the patients in this study did not have history of MI, but had history of HF and stroke in 76% and 15% of patients respectively. So only the data in patients aged over 64 were used for the analysis. The probabilities were calculated from the rate and the SE were calculated from the confidence interval, using the formula shown in Appendix A. The age-specific incidence rate, probabilities, CI and SE of HF patients aged over 64 years old were shown in Table 12 (153).

Table 12 Age-specific incidence rate of heart failure in patients aged over 64 years old

Age	Incidence rate	Probability	Confidence interval	SE
65-74	0.00423	0.00422	0.00347-0.00500	0.00020
75-84	0.01100	0.01094	0.00961-0.01238	0.00035
≥85	0.01820	0.01804	0.01529-0.02110	0.00074

4.20 Probability of death in post-stroke patients with previous history of MI

[pPSTtoD; p(6,8)]

The stroke mortality rate from the National Hospital Discharge Register linked with the Cause of Death Register in Sweden was reported (154). Total 38,154 patients with first stroke were identified from 1987 to 2006. The calculated probabilities of stroke mortality in 2005-2006 and SE in each age group were shown in Table 13 (154).

Table 13 Age-specific probability of stroke mortality

Age	Population at risk	No. of death	Probability	SE
45-54	117,715	13	0.00011	0.00003
55-64	108,685	45	0.00041	0.00006
65-74	66,331	101	0.00131	0.00015
75+	78,158	854	0.01028	0.00037

4.21 Probability of post-stroke patients with previous history of MI being stable in post-stroke state

[pPSTtoPST; p(6,6)]

There are 5 probabilities going out from post-stroke state and the sum of them must equal to 1. So the probability of p(6,6) can be calculated as shown in the below equation.

$$p(6,6) = 1 - p(6,2) - p(6,3) - p(6,4) - p(6,8)$$

4.22 Probability of recurrent MI in post-HF patients with history of previous MI

[pPHFtoReMI; p(7,2)]

From 9138 heart failure patients with 28,442 person-years of follow-up, the ischemic heart disease occurred in 3,813 patients within 1 year after initial hospital discharge (155). The patients in this study aged between 63-87 years old.

The probability of recurrent MI after HF = 3813/28442 = 0.1341

SE = $\sqrt{(3813x(28442-3813))/((28442)^2(28442+1)}$ = 0.0020

For patients younger than 63 years old, data from the Thai ACS Registry showed that the incidence of recurrent MI was 0.77 times that of patients aged at least 63 years old. So the probability of recurrent MI in patients aged ≥63 years was converted to rate = - (ln(1-0.1341))/1 = 0.1439. The rate of recurrent MI in patients younger than 60 years old = 0.1439 x 0.77 = 0.1108, and the probability = $1-e^{-0.1108}$ = 0.1049. It was assumed that the probability of recurrent MI in patients older than 83 years old was the same as those aged 63-87 years old in the study done by Lee et al (155).

4.23 Probability of stroke in post-HF patients with history of previous MI

[pPHFtoST; p(7,3)]

A meta-analysis which was performed to find the stroke rate in HF patients, aged < 73 years old, showed that stroke developed in 1.84% of patients during the first year after the diagnosis of HF (156). So the probability equaled $1-e^{-0.0184}$ = 0.0182. The multivariate-adjusted hazard ratio in patients aged over 73 years old compared with those younger than 73 years old was approximately 2.41 (152, 154). So the probability of stroke in patients younger than 73 years was converted to rate = - (ln(1-0.0182))/1 = 0.0184. The rate of stroke in patients aged ≥74 years old = 0.0184 x 2.41 = 0.0444, and the probability = $1-e^{-0.0444}$ = 0.0434.

4.24 **Probability of recurrent HF in post-HF patients with previous history of MI**

[pPHFtoHF; p(7,4)]

The same study as in section 4.22 observed 4,773 recurrent HF in 1 year (155). The patients in this study aged between 63-87 years old. The probability of recurrent HF in this age group = 4773/28442 = 0.1573

SE = $\sqrt{(4773x(28442-4773))/((28442)^2(28442+1)}$ = 0.0022

Gomez-Soto reported that the incidence of HF in patients aged less than 63 years was 0.16 time that of patients aged 63-87 years. The corresponding figure in patients over 87 years old was 1.66 (157). The probability of recurrent HF in patients aged 63-87 years was converted to rate = - (ln(1-0.1573))/1 = 0.1711. Therefore, the rate of HF in patients aged <63 years old = 0.1711 x 0.16 = 0.0272, and the probability = $1-e^{-0.0272}$ = 0.0268. The rate of HF in patients aged ≥87 years old = 0.1711 x 1.66 = 0.2835, and the probability = $1-e^{-0.2835}$ = 0.2469.

4.25 **Probability of death in post-HF patients with history of previous MI**

[pHFtoD; p(7,8)]

A population-based cohort of 7,733 patients, aged over 65 years old, who were hospitalized for a first MI during 1994 to 2000 in Alberta was followed up for 5 years. Cardiovascular disease was the cause of death in 41.2% of the patients (158). So the CV mortality rate was calculated by multiplying the mortality rate per year with 0.412. The yearly probability of mortality was calculated using the formula $p = 1-e^{-rt}$ in each age group of patients aged ≥65 years old, as shown in Table 14. The mortality rates in patients aged 45-54 and 55-64 years old were 0.31 and 0.73 times that of patients aged 65 years old and above, respectively (159). The mortality rates in these age groups were calculated by multiplying the mortality rate in patients aged over 65 years with 0.31 for patients aged 45-54 years, and with 0.73 for patients

aged 55-64 years. Then the probabilities of death in each age group of patients aged < 65 years old were calculated, as shown in Table 15.

Table 14 Age-specific mortality rate after heart failure in post-MI patients aged ≥ 65 years old

Age	Mortality rate in 5 years	Mortality rate in 1 year	CV mortality rate in 1 year	Probability per year
65-69	0.557	0.1114	0.0459	0.0449
70-75	0.617	0.1234	0.0508	0.0496
>75	0.703	0.1406	0.0579	0.0563

Table 15 Age-specific mortality rate after heart failure in post-MI patients aged < 65 years old

Age	Mortality rate ratio compared with patients aged ≥65 years old	Mortality rate per year	Probability per year
45-54	0.31	0.0141	00140
55-64	0.73	0.0336	0.0330

4.26 Probability of post-HF being stable in post-HF state in patients with history of previous MI

[pPHFtoPHF; p(7,7)]

There are 5 probabilities going out from post-HF state and the sum of them should equal to 1. So the probability of p(7,7) can be calculated as shown in the below equation.

$$p(7,7) = 1 - p(7,2) - p(7,3) - p(7,4) - p(7,8)$$

The summary of transition probability used in the model was shown in Table 16.

Table 16 Probability of all transitions in post-MI patients for base case analysis

Data	Probability/year	SE	Source
Probability of recurrent non-fatal MI [p(1,2)] and second recurrent MI [p(5,2)] • Year 1 after MI • Year 2 and afterwards	 0.0232 0.0074	 0.0020 0.0074*	Marchioli 2002 (145)
Probability of non-fatal stroke after first MI [p(1,3)], and non-fatal stroke after post-recurrent MI [p(5,3)] • Year 1 after MI • Year 2 and afterwards	 0.0034 0.0027	 0.0008 0.0027*	Marchioli 2002 (145)
Probability of HF after first MI [p(1,4)], and HF after post-recurrent MI • 45-64 years old • 65-100 years old	 0.0258 0.0421	 0.0258* 0.0421*	Go 2003 (146)
Probability of recurrent MI after post-stroke in post-MI patients [p(6,2)] • 45-59 years old • 60-100 years old	 0.0077 0.0141	 0.0077* 0.0021	Vickrey 2002 (151), Thai ACS Registry
Probability of recurrent stroke after post-stroke in post-MI patients [p(6,3)]			Vickrey 2002 (151), Kaplan 2002 (152)

Data	Probability/year	SE	Source
• 45-59 years old • 60-100 years old	0.0292 0.0575	0.0292* 0.0042	
Probability of HF after post-stroke in post-MI patients [p(6,4)] • 45-49 years old • 50-54 years old • 55-59 years old • 60-64 years old • 65-74 years old • 75-84 years old • 85-100 years old	 0.0027 0.0051 0.0075 0.0122 0.0042 0.0109 0.0180	 0.0002 0.0003 0.0004 0.0005 0.0002 0.0004 0.0007	Goldberg 2005 (153), Loehr 2008 (150)
Probability of recurrent MI after post-HF in post-MI patients [p(7,2)] • 45-62 years old • 63-100 years old	 0.1049 0.1341	 0.1049* 0.0020	Lee 2009 (155), Thai ACS Registry
Probability of non-fatal stroke after post-HF in post-MI patients [p(7,3)] • 40-73 years old • 74-100 years old	 0.0182 0.0434	 0.0182* 0.0434*	Witt 2007 (156), Kaplan 2002 (152)
Probability of recurrent HF after post-HF in post-MI patients [p(7,4)] • 45-62 years old • 63-87 years old • 88-100 years old	 0.0268 0.1573 0.2469	 0.0268* 0.0022 0.2469*	Lee 2009 (155), Gomez-Soto 2011 (157)

Data	Probability/year	SE	Source
Probability of cardiovascular mortality after the first MI and post-recurrent MI [p(1,8), p(5,8)]			Survival analysis using data from the Thai ACS Registry
• Year 1 after MI	0.0938	NA	
• Year 2 after MI	0.0572	NA	
• Year 3 after MI	0.0485	NA	
• Year 4 after MI	0.0435	NA	
• Year 5 after MI	0.0402	NA	
• Year 6 after MI	0.0377	NA	
• Year 7 after MI	0.0357	NA	
• Year 8 after MI	0.0341	NA	
• Year 9 after MI	0.0328	NA	
• Year 10 after MI	0.0316	NA	
• Year 11 after MI	0.0307	NA	
• Year 12 after MI	0.0298	NA	
• Year 13 after MI	0.0290	NA	
• Year 14 after MI	0.0283	NA	
• Year 15 after MI	0.0277	NA	
• Year 16 after MI	0.0271	NA	
• Year 17 after MI	0.0265	NA	
• Year 18 after MI	0.0260	NA	
• Year 19 and afterwards	0.0096	NA	
Probability of cardiovascular mortality after recurrent MI [p(2,8)]			Jokhadar 2004 (147), WHO website 2011 (148)
• 45-49 years old	0.0068	NA	
• 50-54 years old	0.0094	NA	
• 55-59 years old	0.0138	NA	

Data	Probability/year	SE	Source
• 60-64 years old • 65-69 years old • 70-74 years old • 75-79 years old • 80-84 years old • 85-89 years old • 90-94 years old • 95-99 years old • 100 years old	0.0210 0.0315 0.0522 0.0730 0.1026 0.1476 0.2160 0.3178 0.4608	NA NA NA NA NA NA NA NA NA	
Probability of cardiovascular mortality after stroke in post-MI patients [p(3,8)] • 45-49 years old • 50-54 years old • 55-59 years old • 60-64 years old • 65-69 years old • 70-74 years old • 75-79 years old • 80-84 years old • 85-89 years old • 90-94 years old • 95-99 years old • 100 years old	0.0181 0.0251 0.0365 0.0554 0.0823 0.1061 0.1466 0.2025 0.2838 0.3987 0.5505 0.6321	NA NA NA NA NA NA NA NA NA NA NA NA	Brønnum-Hansen 2001 (149), WHO website 2011 (148)
Probability of cardiovascular mortality after HF in post-MI patients [p(4,8)]	0.0988	0.0988*	Loehr 2008 (150)

Data	Probability/year	SE	Source
Probability of cardiovascular mortality after post-stroke in post-MI patients [p(6,8)]			Harmsen 2009 (154)
• 45-54 years old	0.0001	0.0000	
• 55-64 years old	0.0004	0.0001	
• 65-74 years old	0.0015	0.0002	
• 75-100 years old	0.0109	0.0004	
Probability of cardiovascular mortality after post-HF in post-MI patients [p(7,8)]			Ezekowitz 2009 (158), Schocken 1992 (159)
• 45-54 years old	0.0140	0.0140*	
• 55-64 years old	0.0330	0.0330*	
• 65-69 years old	0.0449	0.0449*	
• 70-75 years old	0.0496	0.0496*	
• 76-100 years old	0.0563	0.0563*	

*Assumption (equaled to the probability per year)

5. Cost-effectiveness result

The base case scenario was done in patients aged 63 years old which was the mean age of patients who experienced MI in the Thai ACS Registry. The total life years obtained were 17.82 years for the supplementation of n-3 PUFAs and 15.48 years for no supplementation. The QALYs gained were 15.06 and 13.05 years for n-3 PUFAs supplementation and no supplementation, respectively. Thus incremental effectiveness values for supplementation of n-3 PUFAs were 2.34 life-years gained (LYG) and 2.01 QALYs. The lifetime cost from 1,000 simulations was estimated as 2,600,349 THB in the n-3 PUFAs supplementation cohort, and 2,001,572 THB in the no supplementation group, resulting in the incremental cost of 598,777 THB for the addition of n-3 PUFAs. The incremental cost-effectiveness ratio (ICER) was

297,193 THB per QALY and 256,199 THB per LYG (Table 17). ICER/QALY and ICER/LYG reduced when patients had MI at the older age, thus it is more cost-effective in elderly patients (Figure 9). The probability of CE at different levels of willingness-to-pay in different ages of the patients has been shown in Figure 10.

Table 17 Lifetime costs, quality-adjusted life years, life-year gained, and CE ratio of adding n-3 PUFAs compared to standard therapy in post-MI patients

Strategy	Cost (THB)	QALY	ICER/QALY	LYG	ICER/LYG
No n-3 PUFAs	2,001,572	13.05		15.48	
n-3 PUFAs	2,600,349	15.06	297,193	17.82	256,199

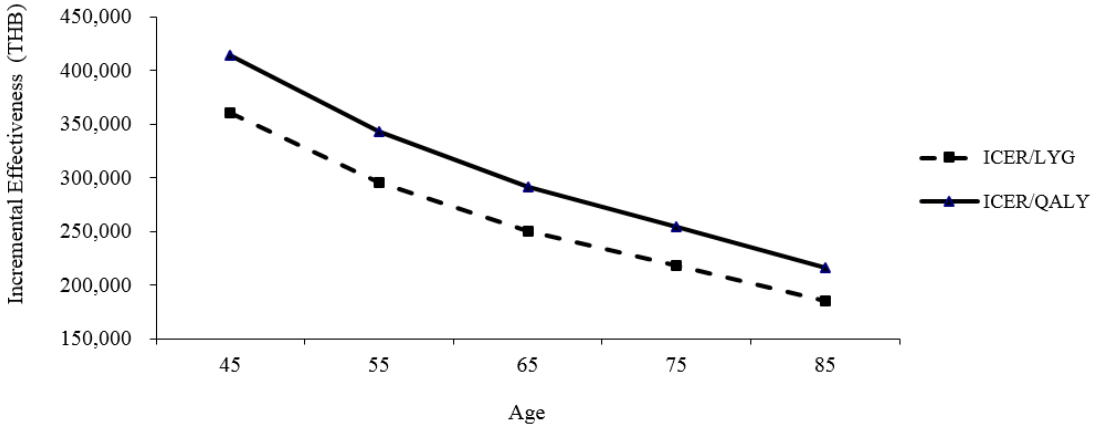
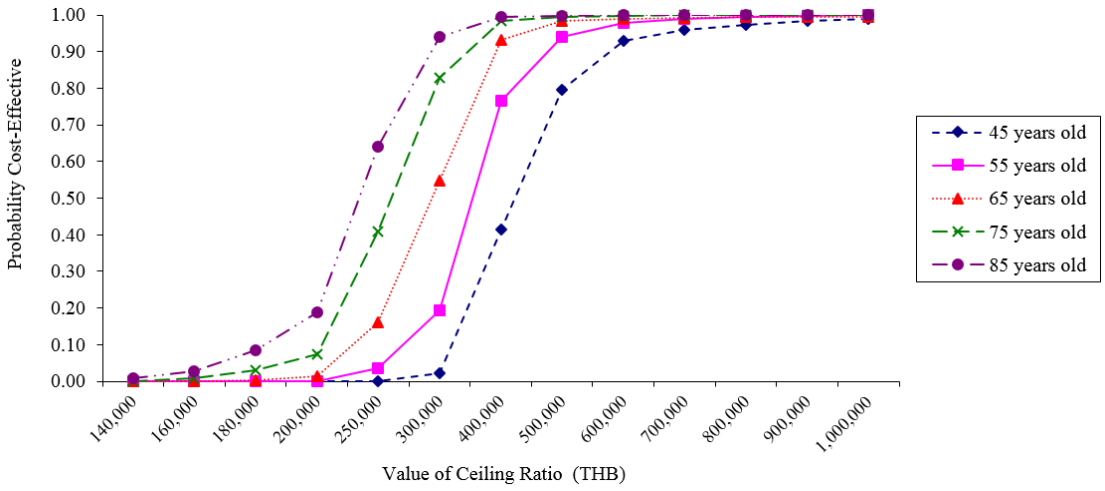


Figure 9 Incremental Effectiveness by Age



**Value of ceiling ratio refers to willingness to pay for 1 QALY*

Figure 10 Cost-Effectiveness Acceptability Curve

6. Uncertainty Analyses

6.1 Deterministic Sensitivity Analysis

The effect of n-3 PUFAs on cardiovascular mortality provided greatest impact to the result as shown in the Tornado Diagram (Figure 11), followed by discount rate, all treatment (excluding n-3 PUFAs) costs, n-3 PUFAs cost, and costs of MI. These 5 parameters had much higher impact on the result than the rest of variables. The CE of n-3 PUFAs is least sensitive to the effect of n-3 PUFAs on stroke and the cost of HF.

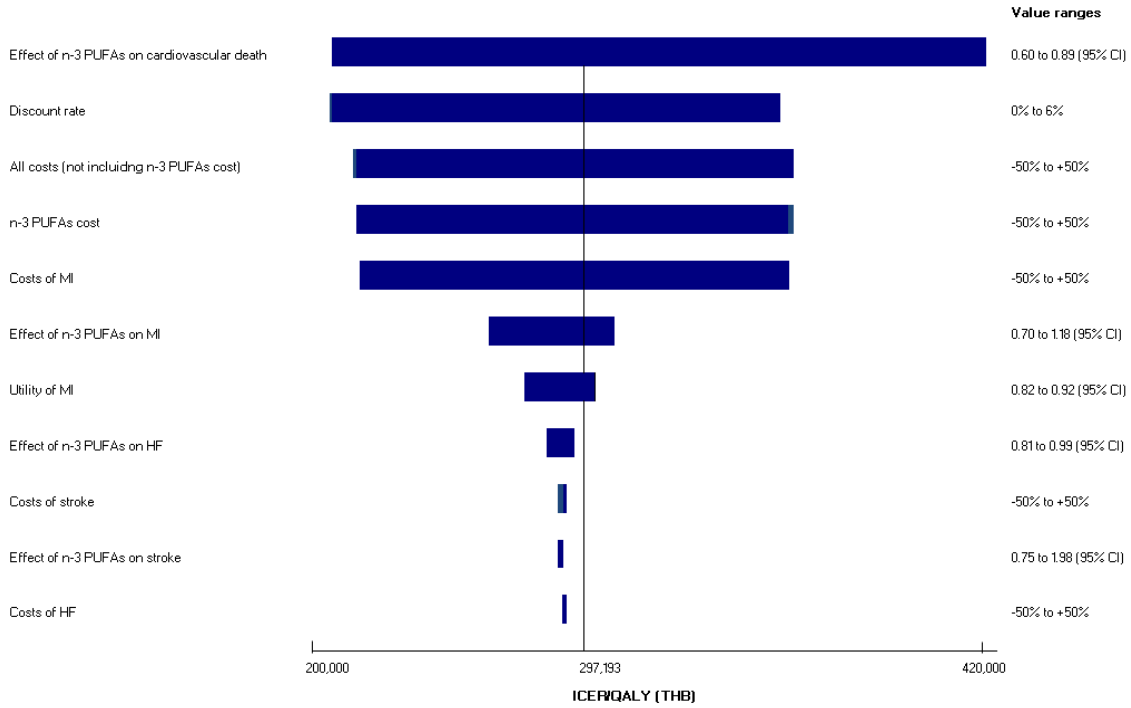


Figure 11 Tornado diagram comparing the relative importance of model parameters on the CE result

6.2 Probabilistic Sensitivity Analysis

The scatter plot of CE plane in Figure 12 shows the result of incremental cost and incremental QALYs from 1000 Monte Carlo simulations. The majority of iterations demonstrated that supplementation of n-3 PUFAs is more effective and more costly than standard therapy. Approximately half of the iterations were above the line with the slope of 160,000 THB/QALY, which is the current willingness-to-pay (WTP) threshold for interventions in Thailand (160).

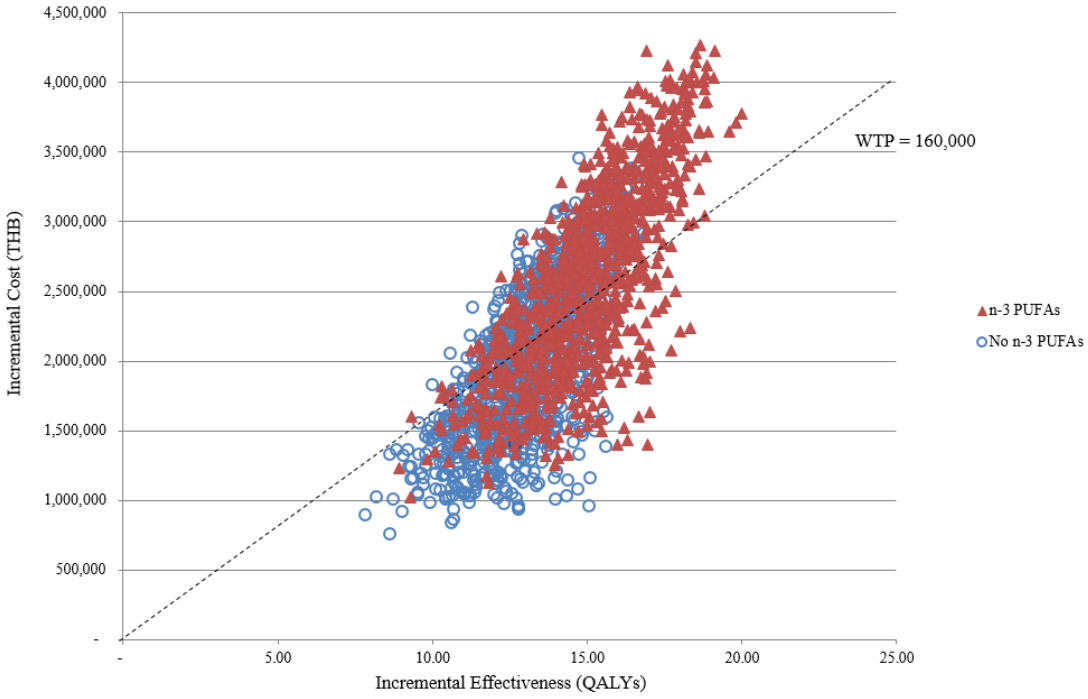


Figure 12 Cost-Effectiveness Plane of n-3 PUFAs supplementation versus standard therapy alone

The cost effectiveness acceptability curve in Figure 13 shows the probability that each strategy is cost effective over a range of potential maximum willingness to pay values that the payer can afford to pay for an additional QALY. At the WTP values less than approximately 297,000 THB, standard treatment without n-3 PUFAs seemed to be more cost-effective than n-3 PUFAs supplementation. But if the WTP is more than 297,000 THB, addition of n-3 PUFAs is more cost-effective.

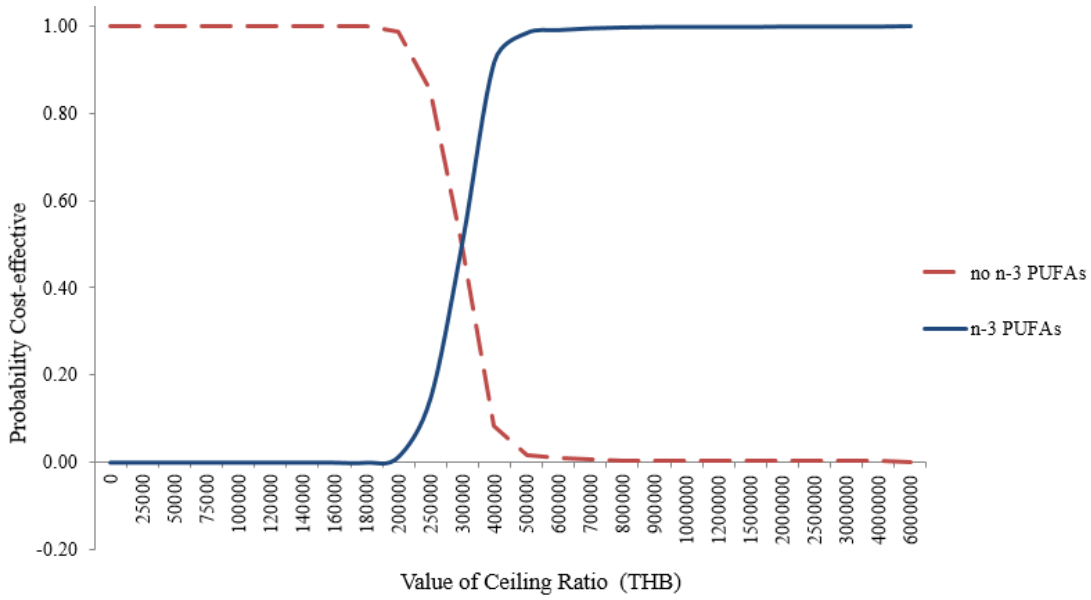


Figure 13 Cost-effectiveness acceptability curve of n-3 PUFAs supplementation versus standard therapy alone

CHAPTER V
CONCLUSION AND RECOMMENDATIONS

This chapter comprises discussion, conclusion, limitation of the study, and recommendation. The discussion part includes the comparison of this analysis with other CE studies conducted earlier based on this indication, and influencing variables that may affect the result. The limitation of the study illustrates the concerned issues due to the availability of data sources, or the nature of model-based study, etc.

1. Discussion

1.1 First meta-analysis on CV mortality in post-MI patients

All published meta-analysis of n-3 PUFAs were conducted to assess the benefit of n-3 PUFAs in patients with or at high risk of CVD. Some meta-analyses had nearly the same inclusion criteria as our study (123), except that we included only the patients who experienced MI. So our meta-analysis is the first one that included only the studies of post-MI patients.

The effectiveness of n-3 PUFAs on mortality used in previous CE analyses was from the GISSI-P study only, while this meta-analysis used the pooled data of GISSI-P and OMEGA study. The pooled relative risk was a little higher than that from the GISSI-P study because OMEGA study did not show the significant difference of the results between treatment and control groups. However, due to the high number of patients in GISSI-P study, the pooled result on cardiovascular mortality showed statistically significance.

1.2 Age-specific CE analysis

As shown in Figure 9 and Figure 10, both ICER/QALY and ICER/LYG were in the same pattern for each age and decreased by age. The lower ICER/QALYs in older patients may be due to the higher incidence rate of cardiovascular events. The increased QALYs from n-3 PUFAs were larger than the increased cost in patients with older age.

1.3 ICER/QALY compared with threshold in other countries

The results of our analysis indicate that the addition of highly concentrated n-3 PUFAs to the standard treatment in patients survived from acute myocardial infarction is not cost-effective according to the willingness-to-pay threshold currently accepted in Thailand.

The ICER/QALY from our evaluation is comparable to the ICER/QALY in Ireland (134), and is a little higher than the ICER/QALY in the U.K. (132). The ICER/LYG in other countries varied from £2,812 in the U.K. (132) to €9,048 in Belgium (133), which ranged approximately from 150,000 THB to 400,000 THB. Our result is consistent with results from those countries, but the willingness-to-pay threshold in Thailand is much lower than that in other countries. The willingness-to-pay threshold, ICER/QALY and ICER/LYG from the studies conducted in other countries, compared with our result, were shown in Table 18.

Table 18 Comparison of ICER/QALY and ICER/LYG from published articles with this analysis

Country	Threshold (THB)	ICER/QALY (THB)	ICER/LYG (THB)	Source
Estonia	1,419,200	-	225,254	(134)
Ireland	887,000	364,114	275,990	(134)
Belgium	887,000	-	401,279	(133)
Germany	887,000	-	368,770	(133)
Poland	471,884	-	258,738	(133)
Canada	1,330,500	-	237,095	(133)
Australia	2,084,450	-	249,203	(133)
U.K.	1,079,800	201,005	151,820	(132)
Thailand	160,000	339,260	292,273	

1 euro = 44.35 THB, 1 pound = 53.99 THB

1.4 Health states in the Markov model

The health states in the model of other CE analysis of n-3 PUFAs in post-MI patients mostly were MI and stroke (132-134), while revascularization was also included in some models (133). We considered not to add revascularization as a health state because nearly all MI cases had revascularization performed as the current practice, so it was considered a part of standard therapy for MI. Our model is the only model that HF was taken into consideration as a separate health state. Since n-3 PUFAs has demonstrated clinical benefits in patients with HF and has been considered cost-effective in this group of patients (135), it is appropriate to include HF in the analysis.

1.5 Good representative database

The mortality rate derived from the Thai ACS Registry database could be a good representative for the probability of cardiovascular mortality of Thai patients who experienced MI. Moreover, all costs used in the study were collected from Thai patients. These data contributed to the robustness of this analysis.

2. Conclusion

The ICER for the base case was 297,193 THB per QALY and 256,199 THB per LYG from adding n-3 PUFAs to the standard treatment in post-MI patients. The incremental QALY yielded 2.01 and LYG yielded 2.34.

The supplementation of n-3 PUFAs to standard treatment for secondary prevention of MI appears not to be cost-effective compared to standard treatment alone in Thailand, given the current willingness-to-pay threshold of 160,000 THB.

3. Limitations of the study

The assumptions were set when data was not available or complete and the data from various sources were used, leading to the following limitations of the study.

1) The parameters from published data of other countries which were used in the Markov model and assumptions on these parameters might not completely reflect the outcome of n-3 PUFAs in post-MI patients in Thailand.

2) The effectiveness data were limited and obtained from only 2 studies which were conducted in European patients. The number of patients in the OMEGA study was only one-third of the GISSI-P study, thus pooled data from meta-analysis may be influenced by the result of GISSI-P study.

3) Though the cost data were collected in Thailand, the costs of MI and stroke were obtained from 1 and 2 sources, respectively. Data from these secondary and tertiary care hospitals might not completely represent the real costs in Thailand. This limitation could be applied to the costs of HF from the NHSO which were collected from voluntary reporting system.

4) Although the actual manifestation of the disease as acute state of each disease might last within a few months and less than 1 year, we have to simplify the discounting process by using 1-year period for the model cycle to make the modeling possible.

5) The incremental cost-effectiveness ratio that was performed based on payer perspective may be more suitable for the results to be used in the Thai national health insurance system. However, the limitation to obtain real cost data reimbursed from the national health system does not allow the evaluation based on payer perspective. To compromise for the possible methodology weakness, cost data which occurred to the provider would be appropriate to be used for calculating cost-effectiveness related to this intervention (n-3 PUFAs supplementation). We assumed that the provider would reimburse such cost from the payer and it could reflect cost based on payer perspective. As such, the result will be useful for the payer's decision making on reimbursement of this intervention.

4. Recommendations

4.1 Recommendation for further study

Though the costs in this study were from Thai patients but they are from various sources. The cost data of each health state in the same settings which can represent Thai population would be beneficial for future analyses.

The effectiveness and utility parameters used in this analysis were derived from European populations. Further studies to collect these data in Thai patients would be useful.

4.2 Recommendation for policy makers

According to the published data and assumptions used in this analysis, supplementation of n-3 PUFAs to the standard therapy is not cost-effective compared to the standard therapy alone in patients experienced MI. However, if key variables which influence the result can be modified, n-3 PUFAs may be considered cost-effective. These variables include the reduction of treatment costs, especially costs of MI, and/or n-3 PUFAs cost, the better effectiveness of n-3 PUFAs, the reduction of discount rate, and the higher level of willingness-to-pay threshold. Providing n-3 PUFAs supplementation to older patients will gain more cost-effectiveness result.

This evaluation was conducted based on economic model, which was based on the effectiveness and cost of pharmaceutically registered n-3 PUFAs (Omacor®). The other equivalent n-3 PUFAs products with lower price can be a good alternative for secondary prevention in post-MI patients.

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APPENDICES

APPENDIX A - Statistical formula used

1. Standard error (SE)
   a. From standard deviation (SD)
      SE = SD/$\sqrt{n}$
      where n = total population in the study
   b. From 95% confidence interval
      SE = (upper limit – lower limit)/3.92

2. Pooled standard deviation (Sp)

$$Sp = \sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2+\cdots+(n_k-1)s_k^2}{n_1+n_2+\cdots+n_k-k}}$$

   where n_i = sample size of the i^{th} sample
   s_i^2 = variance of the i^{th} sample
   k = number of samples being combined

3. Pooled mean (Xp)

$$Xp = \frac{(x_1 \times n_1) + (x_2 \times n_2) + \ldots + (x_k \times n_k)}{n_1 + n_2 + \ldots + n_k}$$

   where n_i = sample size of the i^{th} sample
   k = number of samples being combined

4. Transition probability
   4.1 Probability (p) from rate (r)
      p = 1 – exp (-rt)
      where t = time period of interest
   4.2 Rate (r) from probability (p)
      r = - [ln (1-p)]/t
   1.3 Probability from α and β
      For beta distribution: p = $\alpha/(\alpha+\beta)$
      For gamma distribution: p = $\alpha\beta$
      Where n = sample size
         α = events, β = n- α
   1.4 SE from α and β

For beta distribution: SE = $\sqrt{(\alpha\beta)/[(\alpha+\beta)^2(\alpha+\beta+1)]}$

For gamma distribution: SE = $\sqrt{\alpha\beta^2}$

2. ICER/QALY

$$\text{ICER/QALY} = \frac{\text{(cost of intervention A) – (cost of intervention B)}}{\text{(QALY of intervention A) – (QALY of intervention B)}}$$

3. QALYs

QALY = life year gained (years) x utility

APPENDIX B - Summary of key studies of n-3 PUFAs

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Poole 2013	GPRD	Retrospective	12,178 (2466/ 9712)	Observational	64 (52-78)	Post MI initiating n-3 FA within 90 days of first MI	1	Licensed, highly purified n-3 PUFAs	Secondary	All-cause mortality	For those initiating n-3 fatty acids within 90 days of first MI, the adjusted hazard ratio (HRadj) was 0.782 (0.641–0.995; P=0.0159); for those initiating treatment within 14 days, the HRadj was 0.680 (0.481–0.961; P=0.0288). In patients with T2DM at baseline, the HRadj were 0.714 (0.454–1.124) and 0.597 (95% CI, 0.295–1.211) when initiation was within 90 and 14 days, respectively.

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Bosch 2012	ORIGIN	74 (6.2 years)	12,536 (6281/ 6255)	RCT	64	High risk for CV events and had impaired fasting glucose, impaired glucose tolerance, or diabetes	1	1) n-3 PUFAs ethyl ester (Omacor®) 2) Placebo	Primary/ secondary	All-cause mortality, cardiac death, MI, stroke	The incidence of the primary outcome was not significantly decreased among patients receiving n–3 fatty acids, compared to placebo (HR, 0.98 (0.87-1.10); P = 0.72). No significant effect on the rates of major vascular events (HR, 1.01 (0.93-1.10); P = 0.81), death from any cause HR, 0.98 (0.89-1.07); P = 0.63), or death from arrhythmia (HR, 1.10 (0.93-1.30); P = 0.26) was observed. Triglyceride levels were reduced by 14.5 mg/dL more among patients receiving n–3 fatty acids than among those receiving placebo (P<0.001), without a significant effect on other lipids.

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Eussen 2012 and Kromhout 2010	ALPHA OMEGA	40	4837 (2404/ 2433)	RCT	69 (60-80)	Clinically diagnosed MI up to 10 years	0.4	1) margarine supplemented with 400mg of EPA-DHA 2) margarine supplemented with 2g of ALA 3) margarine supplemented with EPA-DHA and ALA 4) placebo margarine	Secondary	Rate of major cardiovascular events (fatal and nonfatal CV events) and cardiac interventions PCI and CABG (all-cause mortality, cardiac death)	Major CV events 13% in statin users and 15% in statin non-users Statin user receiving EPA-DHA plus ALA vs placebo: HRadj 1.02 (0.80-1.31) non-statin user receiving EPA-DHA plus ALA vs placebo: HRadj 0.46 (0.21-1.01) => borderline stat sig. (p=0.051), 54% lower incidence of major CV events
Einvik 2010		36 (3 years)	563 (282/281)	RCT	70 (64-76)	Healthy elderly men with hypercholesterole	2.4	1) n-3 PUFAs and dietary counseling 2) n-3 PUFAs only	Primary/ secondary	All-cause mortality, sudden death	Adjusted for baseline age, current smoking, hypertension, body mass index and serum glucose, hazard ratios of all-cause mortality and cardiovascular events were

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
						mia (250-320 mg/dL)		3) diet only 4) control			0.53 (0.27–1.04, P= 0.063) and 0.89 (0.55–1.45, P = 0.641), respectively.
Galan 2010	SU.FOL.OM3	56 (4.7 years)	2491 (1253/ 1248)	RCT	61 (54-69)	Patients with a history of MI, UA, and ischemic stroke within 12 months	0.6	1) n-3 PUFAs (0.6 g/d), EPA, and DHA ± vitamin B 2) placebo capsules ± vitamin B	Secondary	Major CV events (non-fatal MI, stroke, or death from CVD)	RR of major CV events (nonfatal MI, stroke, CV death) = 1.08 (0.79-1.47)
Rauch 2010	OMEGA	12	3851 (1925/1893)	RCT	64	AMI	1	1) Omacor® 2) placebo (olive oil)	Secondary	SCD	RR of major CV events (cardiovascular events (total mortality, reinfarction, stroke) = 1.20 (0.98-1.48)
Garbagnati 2009	Nutristroke	12	38 (20/18)	RCT	65	Stroke survivors	0.5	1) N-3 PUFAs (0.5 g/d), ± antioxidants	Secondary	All-cause mortality, CV death	RR of CV death = 0.10 (0.01-1.79)

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								2) placebo capsules ± antioxidant supplements			
Marchioli 2009 and Tavazzi 2008	GISSI-HF	3.9 years	6975 (3494/ 3481)	RCT	67no age limit	CHF with NYHA class II-IV	1	Randomization 1: 1) n-3 PUFAs (Omacor®) 2) placeboRandomization 2: 1) Rosuvastatin 10mg/d 2) placebo	Primary/ secondary	Time to death, and time to death or admission to hospital for CV reasons (all-cause mortality, cardiac death, sudden death, MI, stroke)	CV death (HRadj 0.90; 0.81-0.99); all-cause mortality (HRadj 0.91; 0.833-0.998); admitted for CV reason (HRadj 0.93; 0.87-0.99); died or admitted to hospital for CV reasons (HRadj 0.92; 0.849-0.999); died of a CV cause or admitted for any reasons (HRadj 0.94; 0.89-0.99); NNT = 56 to avoid 1 death; NNT = 44 to avoid 1 death or admission to hospital for CV reasons. Subgroup analysis showed significant reduction only in subgroup with LVEF <= 40% (HR 0.94; 0.88-0.99), diabetes

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
											(HR 0.89; 0.80-0.99), TC ≤ 4.87 mmol/L (HR 0.91; 0.84-0.99). ARR of fatal arrhythmia (FA) was 0.9%, i.e., 50% of the total benefit of PUFAs on mortality. PUFAs decreased significantly major arrhythmia (MA) by 17% (0.83, 0.72-0.95, P=0.009). Survival curves for FA, hospitalization from ventricular arrhythmia (HVA), and MA diverged early and continued to separate during follow-up. As to MA, RRR were 16%, 13%, 13%, and 17% when we right-censored data at 12, 24, 30 months, and study end.
Virtanen 2008	HPFS (Health Profession	216 (18 years)	51,529	Observational	40-75	Male health professionals, free of major	<0.04 to ≥ 0.6	Fish consumption: < 1 serving/m:	Primary	CVD (fatal or nonfatal MI, fatal or nonfatal stroke), cancer, other nontraumatic death	Consumption of fish and EPA/DHA was not associated with the overall incidence of major chronic disease in generally healthy men. Modest fish

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
	als Follow-Up Study)					chronic disease at baseline in 1986		EPA+DHA <0.05 g/d 1-3 servings/m: EPA+DHA 0.05-<0.2 g/d 1 serving/wk: EPA+DHA 0.2-<0.4 g/d 2-4 servings/wk: EPA+DHA 0.4-<0.6 g/d ≥ 5 servings/wk ==> EPA+DHA ≥0.6 g/d			intakes (between 1 and 4 servings/wk) were associated with a lower risk of total CVD. A high n-6 fatty acid intake did not modify these results.

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Yokoyama 2007	JELIS	35 (4.6 years)	18,645 (7503/ 7478) (1823/1841)	RCT	61 (40-75)	Hypercholesterolemia (TC≥260 mg/dL)	1.8	1) EPA 1.8 g/d + statin 2) statin alone	Primary/ secondary	Any major coronary event, including sudden cardiac death, fatal and non-fatal myocardial infarction, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting.	Major CV events reduced by 19% (95% CI 0.69-0.95,P=0.011)
Brouwer 2006	SOFA	12	546 (273/273)	RCT	61	ICD	0.96	1) N-3 PUFAs 0.96 g/d (4 capsules; 2g/d of fish oil) 2) placebo (sunflower oil capsule)	ICD	All-cause death or ICD intervention for VT or VF (All-cause mortality, cardiac death, MI)	RR of total mortality = 0.57 (0.24-1.38) RR of cardiac death = 0.46 (0.18-1.20) RR of primary endpoint = 0.86 (0.64-1.16) RR of prior MI = 0.76 (0.52-1.11)

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Svensson 2006	OPACH	558 days (2 years)	206 (103/103)	RCT	67	Stable HD patients and established CVD	1.7	1) Omacor® (EPA+DHA 1.7 g/d) 2) placebo (olive oil)	Secondary / hemodialysis	Composite of total CV events (AMI, angina pectoris that required coronary investigation or intervention, stroke, TIA, peripheral vascular disease that required surgical intervention) and death	CV events or death 62 vs 59 (HR 1.04; 0.72-1.48) MI 4 vs 13 (HR 0.3; 0.1-0.92; p=0.036) major coronary events 7 vs 17 (HR 0.4; 0.17-0.97; p=0.043) the rest are NS
Leaf 2005		12	402(200/202)	RCT	65	ICD	2.6	1) N-3 PUFAs 2.6 g/d2) placebo (olive oil capsule)	ICD	Time to first episode of ICD, treatments for VT or VF(All-cause mortality, cardiac death)	RR of total mortality = 1.09 (0.49-2.46); RR of cardiac death = 1.01 (0.21-2.50)

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Raitt 2005		24	200 (100/100)	RCT	63	ICD and a recent episode of sustained VT or VF	1.3	1) N-3 PUFAs 1.3 g/d 2) placebo (olive oil capsule)	ICD	Time to first episode of ICD, treatments for VT or VF (All-cause mortality, cardiac death, sudden death, MI)	RR of total mortality = 0.40 (0.12-1.32) RR of cardiac death = 0.40 (0.08-2.01)
Burr 2003	DART 2	60 (5 years)	3114 (1571/1543)	RCT	61	Men with angina	0.34 (D), 0.86 (S)	(1) advised to eat two portions of oily fish each week, or to take three fish oil capsules (Maxepa) daily; (2) advised to eat more fruit, vegetables and oats; (3) given	Secondary	Total mortality, cardiac death, sudden death	Fruit advice had no effects and no reduction of total mortality from any forms of advice. Mortality from cardiac cause increased more in patients taken oily fish than in those not so advised; the adjusted HR was 1.26 (P=0.047), and was 1.54 for sudden cardiac death (P=0.025).

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								both the above types of advice; (4) given no specific dietary advice			
Albert 2002	US Physicians' Health Study	204 (17 years)	20,551	Observational	40-84	Healthy men	NA	Dietary intake of fish was ascertained at 12 months with an abbreviated, semiquantitative food-frequency questionnaire, Information on	Primary	Sudden cardiac death (death within 1 hour of symptom onset)	Base-line blood levels of long-chain n-3 fatty acids were inversely related to the risk of sudden death both before adjustment for potential confounders (P for trend=0.004) and after such adjustment (P for trend=0.007). As compared with men whose blood levels of long-chain n-3 fatty acids were in the lowest quartile, the relative risk of sudden death was significantly lower among men with levels

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								cardiovascular events was updated every six months for the first year and annually thereafter with follow-up questionnaires. Participants were assigned at random: 1) aspirin 2) beta carotene			in the third quartile (adjusted RR, 0.28; 95%CI, 0.09-0.87) and the fourth quartile (adjusted RR, 0.19; 95%CI, 0.05-0.71). As compared with the men with levels of long-chain n-3 fatty acids in the lowest quartile (mean, 3.58 percent of total fatty acids), those with levels in the highest quartile (mean, 6.87 percent) had a relative risk of sudden death of 0.19 (95 percent confidence interval, 0.05 to 0.71) after known confounders were controlled for. The mean time from study enrollment to sudden death was 8.7 years (range, 0.7 to 16.9).

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								3) both 4) placebo			
Hu 2002	Nurses' Health Study	192(16 years)	84,688	Observational	34-59	Women free from CVD and cancer at baseline in 1980	NA	Fish consumption	Primary	Incident nonfatal myocardial infarction and CHD deaths	The risk of CHD was higher in the women who rarely ate fish (1 per month). The more fish consumed, the lower risk of CHD in women. Similarly, the higher n-3 PUFAs consumption, the lower risk of CHD. Fish or n-3 PUFAs consumption was inversely associated with CHD deaths more than with nonfatal myocardial infarction.

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Marchioli 2002	GISSI-P	42 (3.5 years)	11324 (5666/ 5658)	RCT	60	Recent MI (≤3 months)	0.85	1) Omacor® 2) Vit E 3) Omacor® + Vit E 4) placebo	Secondary	Composite endpoints of all-cause mortality, nonfatal MI, nonfatal stroke; and CVD death, nonfatal MI, nonfatal stroke	4.8% in treatment group, 6.8% in control group (p=0.024). ARR 2%, RRR 29.7%, NNT 50. RR of total mortality = 0.86 (0.76-0.97)
Brox 2001		14	120 (40/40/40)	RCT	43-66 median 55	Healthy with high cholesterol	2.6-3.3	1) Seal oil 15 ml/d (EPA 1.1 g, DHA 1.5 g) 2) Cod liver oil 1.5 ml/d (EPA 1.5 g, DHA 1.8 g) 3) dietary supplement	Primary	Cholesterol, platelet activity, blood monocyte activity(tissue factor: TF), inflammatory activity (tumor necrosis factor:TNF)	RR of total mortality = 0.17 (0.01-4.05)
Nilsen 2001		18	300 (150/150)	RCT	64 (29-88)	First week after MI	3.5	1) fish oil (EPA+DHA 3.5 g/d) 2) placebo	Secondary	Cardiac event and serum lipid levels (All-cause mortality, cardiac death, MI)	5.3% in treatment group, 5.3% in control group. RR of total mortality = 1.00 (0.45-2.24)

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								(corn oil capsule)			RR of Fatal or nonfatal cardiac events (cardiac death, resuscitation, recurrent MI, UA) = 1.17 (0.80-1.71)
de Lorgeril 1999	Lyon Diet Heart Study	46 27 (1st study)	605 (302/303)	RCT	53	Post-MI	2	1) ALA 2 g/d (Mediterranean diet) + advice on fish consumption 2) dietary advice by hospital dietician (ALA intake 0.6 g/d) Mediterranean diet was designed to supply 1) <35% of	Secondary	Cardiac death and nonfatal AMI	RR of cardiac death =0.35 (0.15-0.83), RR of primary endpoint = 0.28 (0.15-0.53), RR of all-cause death = 0.44 (0.21-0.94), RR of primary + secondary endpoints = 0.33 (0.21-0.52). RR of major and minor endpoints = 0.53 (0.38-0.74).

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								energy as fat; 2) <10% of energy as saturated fat; 3) <4% of energy as linoleic acid [18:2 (n-6)]; 4) >0.6% of energy as alpha-linolenic acid			
von Schacky 1999	SCIMO	24	223(112/111)	RCT	58(18-75)	Angiographically proven CHD	3.3 (3 months), 1.7 (21 months)	1) N-3 PUFAs (EPA 1.06 g/d; DHA 0.65 g/d); given as 3 capsules2) placebo (fatty acid	Secondary	Change in diameter of atherosclerotic coronary arteries (all-cause mortality, cardiac death, MI, stroke)	RR of total mortality = 0.50 (0.05-5.39); RR of CV events (SCD, fatal or nonfatal MI, CHF, stroke) = 0.28 (0.06-1.33). Fish oil recipient had fewer CV events (P=0.10)

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								mixture) 6 g/d for 3 months and then 3 g/d for 21 months			
Albert 1998	US Physicians' Health Study	132 (11 years)	20,551	Observational	40-84	US male physicians, free of MI, cerebrovascular disease and cancer at baseline	NA	1) Aspirin 2) beta-carotene 3) both 4) placebo fish consumption 35 g/d at 12 months	Primary	Sudden cardiac death (death within 1 hour of symptom onset)	133 sudden deaths for men who consumed fish at least once per week. RR of sudden death was 0.48 (0.24-0.96; p=0.04) compared with men who consumed fish less than monthly. No risk reduction of total MI, nonsudden cardiac death, total CV mortality
Leng 1998		24	120 (60/60)	RCT	66	Stable lower limb atherosclerosis	0.27	1) gamma-linolenic acid 1.68 g/d; EPA 0.27 g/d; given as 6	Secondary	Change in cholesterol, lipoprotein and hemostatic variables (all-cause mortality,	RR of CV death = 1.0 (0.15-6.87)

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								capsules 2) placebo (sunflower oil) 0.5 g/d		cardiac death, MI, stroke)	
Daviglus 1997		360 (30 years) (47,153 person-years)	1,822	Observational (prospective cohort study)	40-55	Men free of CVD at baseline	NA	Fish consumption at least 35 g/d	Primary	Death from MI, death from CHD and death from CVD	Death from CHD (RR 0.62; 0.40-0.94). Death from sudden or nonsudden MI (RR 0.56; 0.33-0.93). Nonsudden death from MI (RR 0.33; 0.12-0.91).
Singh 1997	Indian Experiment of Infarct Survival-4	12	240 (122/120/118)	RCT	49	Suspected AMI	1.8	1) fish oil (EPA+DHA 1.8 g/d); given as 6 capsules 2) mustard seed oil (ALA 2.9 g/d)	Secondary	Total cardiac events (nonfatal MI, cardiac death)	Cardiac death 11.4% in fish oil group, 22% in placebo group ($p<0.05$). No reduction in mustard oil group. ARR 10.6%, RRR 48.2%, NNT 10 RR of total mortality = 0.56 (0.34-0.91). RR of total cardiac events (nonfatal MI, cardiac death) =

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								3) placebo (100 mg aluminum hydroxide) (ALA intake 0.8 g/d)			0.71 (0.48-1.05) Less cardiac events in fish oil and mustard oil (24.5%, 28% vs 34.7% in placebo group; p<0.01) Less non-fatal MI (13%, 15% vs 25.4%; p<0.05)
Eritsland 1996	The Shunt Occlusion Trial	12	610 (317/293) (148/143/ 145/174)	RCT	60	Patients undergoing CABG	3.4	1) ASA 2) ASA + fish oil 4g/d (Omacor® 4 capsules) 3) warfarin 4) warfarin + fish oil	Secondary	Graft occlusion determined by 1-year angiography	RR of total mortality = 1.23 (0.43-3.51) In patients receiving fish oil, the vein graft occlusion rate per distal anastomoses was 27% vs 33% in the control group (OR 0.77, p = 0.034). In the fish oil group, 43% of the patients had 21 vein grafts occluded compared with 51% of the patients in the control group (OR 0.72, p = 0.05).

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
Sacks 1995	HARP	28.8	59 (31/28)	RCT	62 (30-75)	Angiographically documented CHD	6	1) N-3 PUFAs; given as 12 capsules 2) placebo (olive oil)	Secondary	Change in minimal diameter of atherosclerotic coronary arteries (all-cause mortality, cardiac death, MI, stroke)	RR of total mortality = 0.32 (0.01-7.57). RR of CV events (nonfatal MI, PCI, UA, CHF, coronary death, stroke) = 0.90 (0.36-2.25).
Siscovick 1995		72(6 years)	827(334 - case, 493 - control)	Observational (matched case-control study)	25-74	Primary cardiac arrest, free of prior clinical heart disease, major comorbid	0.14 (case)0.18 (control)	Dietary n-3 PUFA intake from seafood	Primary	Primary cardiac arrest	An intake of 5.5 g of n-3 PUFA per month (the mean of the third quartile and the equivalent of one fatty fish meal per week) was associated with a 50% reduction in the risk of primary cardiac arrest [OR 0.5 (0.4-0.8)]. Dose-response relationship between both fish consumption and the concentration of n-3 PUFA in RBC membranes in relation to cardiac arrest. Compared with a red blood cell membrane n-3 polyunsaturated fatty acid

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
											level of 3.3% of total fatty acids (the mean of the lowest quartile), a red blood cell n-3 polyunsaturated fatty acid level of 5.0% of total fatty acids (the mean of the third quartile) was associated with a 70% reduction in the risk of primary cardiac arrest (OR, 0.3; 95% CI, 0.2 to 0.6).
Leaf 1994		6	503 (253/250)	RCT	30-70+	Scheduled for elective PTCA of one or multiple lesions in native coronary arteries that caused	6.9	1) EPA 4.1 g/d, DHA 2.8 g/d; given as 10 capsules 2) placebo (corn oil)	Secondary	Rate of restenosis following percutaneous intraluminal coronary angioplasty (PTCA)	RR of total mortality = 0.20 (0.01-4.18). The restenosis rate among analyzable patients was 46% for corn oil recipients and 52% for fish oil recipients (P=.37).

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
						ischemic symptoms or who had >50% stenosis					
Kaul 1992		6	107 (58/49)	RCT	57	Patients undergoing coronary angioplasty	9	1) EPA 5.4 g/d, DHA 3.6 g/d; given as 10 capsules 2) control: no intervention	Secondary	Rate of restenosis	RR of total mortality = 0.28 (0.01-6.78). The incidence of restenosis was not significantly different between the 2 groups.
Dolecek 1991	MRFIT	72-96 (6-8 years)	12,866	Observational	35-57	High risk of developing CHD	16.8 (total PUFA)	1) Special intervention (SI) group - received intervention to reduce smoking, BP and cholesterol	Primary	CHD death, CVD death, all cause death and cancer death	Marginally significant inverse associations between the total n-3/total n-6 ratio and mortality from CVD and all-cause mortality, but not for CHD. Linoleic acid cannot reduce risk on mortality. ALA (18:3 n-3) has association with CVD

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								2) usual care (UC) group			mortality and all-cause mortality. EPA/DHA has association with CHD mortality, CVD mortality and all-cause mortality. 33% less cancer deaths occurred in the highest intake quintile when compared with the lowest one. 38% cancer death reduction when compared the highest with the lowest intake quintile.
Burr 1989	DART 1	24	2033 (1015/1018)	RCT	<70 median 57	Patients with a diagnosis of acute MI	0.24 (D), 0.86 (S)	1) fat advice, designed to reduce fat intake to 30% of total energy and to increase the polyunsatur	Secondary	Total mortality and IHD events (IHD deaths + non-fatal MI)	Fatty fish reduced mortality in men after MI by about 29% during the first 2 years. RR of total mortality = 0.71 (0.55-0.92). 7.7% in treatment group, 11.4% in control group ($p<0.01$) ARR 3.7%, RRR 32.5%, NNT 27. 29% reduction in all-cause

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								ated/saturated (P/S) ratio to 1:0 2) fish advice, at least two weekly portion (200-400g) of fatty fish 3) fiber advice, increase intake of cereal fiber to 18g/d			mortality, 33% reduction in cardiac mortality
Reis 1989		6	204 (137/67)	RCT	59	Patients after PTCA	9.7	1) EPA 6 g/d, DHA 3.72 g/d; (MaxEPA), given as 12 capsules	Secondary	Rate of restenosis	The incidence of angiographic restenosis was 34% in the fish oil group and 23% in the control group (RR 1.7, 95%CI, 0.9-3.4)

Author	Short title	Treatment duration (month)	N (treatment /control)	Study design	Age	Type of patient	Dose of n-3 PUFAs (g/d)	Treatment	Indication	Primary endpoint	Result
								2) placebo (olive oil)			
Kromhout 1985	Zutphen	240 (20 years)	1088	Observational	40-59 (for 852 men)	Middle-aged men in Zutphen (about 19% did not consume fish)	0.4 (average)	Subjects were divided into 5 categories based on the no. of grams of fish consumed per day. 1) 0; 2) 1-14; 3) 15-29; 4) 30-44; 5) 45+	Primary	CHD, death	An inverse dose-response relation between fish consumption in 1960 and death from coronary heart disease. CHD mortality was > 50% lower among those who consumed at least 30 g of fish per day than among those who did not eat fish

APPENDIX C - Summary of meta-analyses evaluating the cardiovascular effects of n-3 PUFAs

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
Casula 2013	≥12	11	15,348	up to Mar 2013	PubMed, Embase, Cochrane library	1) Randomized, double-blind, placebo controlled trial; 2) adult patients with a history of CVD; 3) Used n-3 fatty acid supplements at least 1 g/day dosage and for at least 1 year; 4) investigated outcomes such as total mortality, cardiac death, sudden death, myocardial infarction and/or stroke; 5) the studies reported quantitative estimates of the exposure-outcome association (odds ratio, rate ratio, or hazard ratio and their corresponding 95% CI or p-value) or sufficient data to calculate it.	Total mortality, cardiac death, sudden death, MI and/or stroke	Total mortality was not statistically significant (RR, 0.89; 95% CI, 0.78 to 1.02) and stroke (RR, 1.31; 0.90 to 1.90). Conversely, statistically significant protective effects were observed for cardiac death (RR, 0.68; 95% CI, 0.56 to 0.83), sudden death (RR, 0.67; 95% CI, 0.52 to 0.87), and myocardial infarction (RR, 0.75; 95% CI, 0.63 to 0.88).	Long-term effect of high dose n-3 PUFAs supplementation may be beneficial for the onset of cardiac death, sudden death and myocardial infarction in patients experienced CVD.

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
Kwak 2012	12-56 (1.0-4.7 years) (mean 2; SD 1.2)	14	20,485	before Apr 2011	PubMed (January 1, 1976, through April 30, 2011), Embase (January 1, 1985, through April 30, 2011), and the Cochrane Library (January 1, 1987, through April 30, 2011)	1) the trial studied adult patients (male or female aged 18 years) with a history of CVD; 2) the patients had used n-3 PUFAs for at least 1 year; 3) the design was a randomized, doubleblind, placebo-controlled trial; 4) the trial reported outcome measures like angina, unstable angina, CVD or events, sudden cardiac death, cardiovascular death, all-cause mortality, congestive heart failure, transient ischemic attack and stroke, or fatal or nonfatal myocardial infarction.	Total mortality, sudden cardiac death, MI, CHF, TIA and stroke	N-3 PUFAs did not reduce the risk of overall CV events (RR 0.99; 0.89-1.09; I^2=27.1%). Small reduction in CV death RR 0.91; 0.84-0.99) which disappear when the study which had problem on methodology was excluded.	The evidence of n-3 PUFAs as secondary prevention on overall cardiovascular events in patients experienced CVD was not sufficient.
Rizos 2012	> 1 year ave. 2 yrs (1.0-6.2)	20 (including 14	68,680	before Aug 2012	PubMed, Embase, and the	1) N-3 PUFAs supplements 2) diet or placebo	Total mortality, cardiac	Total mortality was not statistically significant (RR, 0.96 (0.91 to 1.02); risk	The addition of n-3 PUFAs did not reduce the risk of total

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
		studies in Kwak's meta-analysis)			Cochrane Central Register of Controlled Trials	2 studies used diet; 18 studies used supplements	death, sudden death, MI, and stroke	reduction [RD] −0.004 (−0.01 to 0.02)), cardiac death (RR, 0.91 (0.85 to 0.98); RD, −0.01 (−0.02 to 0.00)), sudden death (RR, 0.87 (0.75 to 1.01); RD, −0.003 (−0.012 to 0.006)), myocardial infarction (RR, 0.89 (0.76 to 1.04); RD, −0.002 (−0.007 to 0.002)), and stroke (RR, 1.05 (0.93 to 1.18); RD, 0.001 (−0.002 to 0.004))	mortality, cardiac death, sudden death, MI, or stroke. Only the risk of cardiac death was significantly reduced.
Chen 2011	≥ 6	10	33,429	1966-Dec 2010	PubMed, Embase, Cochrane database	1) Compared dietary or nondietary intake of n-3 PUFA with a controlled diet or placebo 2) minimum follow-up of 6 months 3) SCD as a cited end-point Excluded: case report, case study, letters , editorials	SCD, cardiac death, and all-cause mortality	In patients with guidelines-adjusted therapy, n-3 PUFAs did not reduce the risk ratio (RR) of SCD (RR,0.96; 95% CI, 0.84-1.10). In patients with non- guidelines-adjusted therapy, n-3 PUFAs reduced the RR of SCD (RR, 0.64; 95% CI,	In the era of guidelines-adjusted treatment for CVD secondary prevention, n-3 PUFAs do not appear to reduce SCD

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
								0.51-0.80). Overall, RR for cardiac death and all cause mortality were 0.81 (95% CI: 0.69-0.95) and 0.89 (95% CI: 0.79-1.01), respectively.	
Hooper 2009	≥ 6	48 RCTs, 41 cohort	36,913	before Feb 2002	5 (incl. CENTRAL,Medline,Embase)	RCT and cohort, omega-3 intake or advice, duration at least 6 months	All-cause mortality, combined CV event and cancer Secondary outcome: individual CV events, risk factor changes and quality of life	N-3 PUFAs did not reduce the risk of total mortality or combined cardiovascular events (with significant statistical heterogeneity). Sensitivity analysis, including only studies at low risk of bias, reduced heterogeneity also showed no significant effect of n-3 PUFAs. Subgroup analysis by dietary advice or supplementation, baseline risk of CVD or n-3 PUFAs dose demonstrated no clear	The evidence on effectiveness of n-3 PUFAs was not sufficient.

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
								effects of these factors on primary outcomes.	
Leon 2009	NA	12	32,779	before Nov 2006	Medline, Embase, the Cochrane Library, PubMed, CINAHL, IPA, Web of Science, Scopus, Pascal, Allied and Complementary Medicine, Academic OneFile, ProQuest Dissertations and	Tested fish oil as dietary supplements in humans in a randomised controlled trial setting. Excluded: did not report any of the outcomes of interest, were not randomised, included pregnant women or children, or lasted less than three months.	Arrhythmic end points of appropriate implantable cardiac defibrillator intervention (confirmed by electrogram) and sudden cardiac death	The risk of mortality reduced but not statistically significant. The risk reduction of cardiac death was significant.	N-3 PUFAs significantly reduced cardiac death but had no effect on arrhythmias or total mortality. Insufficient evidence to recommend an optimal formulation of EPA or DHA to reduce these outcomes. The optimal formulations for DHA and EPA remain unclear

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
					Theses, Evidence-Based Complementary Medicine, and LILACS				
Marik 2009	≥12	11	39,044	1966 - Dec 2008	Medline, Embase, the Cochrane Database of Systematic Reviews	1) Dietary supplements of EPA/DHA were given for at least 1 year 2) RCT	Cardiovascular death, sudden death, all-cause mortality, and nonfatal cardiovascular events (unstable angina, myocardial	N-3 fatty acids showed significantly reduction of the risk of cardiovascular deaths by 13% (p = 0.002), sudden cardiac death by 13% (p = 0.04), total mortality by 8% (p = 0.02), and nonfatal cardiovascular events by 8% (p = 0.02). The mortality benefit was largely due to the studies which enrolled high risk patients, while the reduction in nonfatal cardiovascular events was	Dietary supplementation with n-3 PUFAs should be considered in the secondary prevention of cardiovascular events.

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
							infarction, cardiac failure, arrhythmias)	noted in the moderate risk patients (secondary prevention only). Meta-regression failed to demonstrate a relationship between the daily dose of n-3 fatty acid and clinical outcome.	
Mozaffarian 2006	NA	15	20,369	before Apr 2006	Medline, governmental reports, and systematic reviews and meta-analyses	1) Intake of fish or fish oil and cardiovascular risk 2) effects of methylmercury and fish oil on early neurodevelopment 3) risks of methylmercury for cardiovascular and neurologic outcomes in adults 4) health risk of dioxins and polychlorinated biphenyls in fish	Death from CHD, neurologic development	Modest consumption of fish (eg, 1-2 servings/wk), especially species higher in the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduces risk of coronary death by 36% (95% CI, 20%-50%; P .001) and total mortality by 17% (95% confidence interval, 0%-32%; P=.046) and may	Consumption of 250 mg/day of EPA-DHA demonstrated 365 risk reduction of fatal coronary heart disease. More consumption did not show more benefits.

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
								favorably affect other clinical outcomes. Intake of 250 mg/d of EPA and DHA appears sufficient for primary prevention.	
Whelton 2004	NA	19 14 cohort, 5 case-control)	228,864 patients	before May 2003	Medline	1) conducted in adult humans, 2) used an observational case-control or cohort study design, 3) compared a group that consumed fish on a regular basis with a group that consumed little or no fish, 4) used CHD as an outcome, and 5) reported an association in the form of a relative risk (RR), hazard ratio (HR), or odds ratio (OR) of CHD by category of fish consumption.	CHD	Fish intake versus little to no fish intake had a relative risk of 0.83 (p <0.005) for fatal CHD and a relative risk of 0.86 (p<0.005) for total CHD.	Fish intake was associated with a significant risk reduction of fatal and total CHD

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
Brouwer 2004	NA	5	155,503	NA	Medline	1) Intake of a-linolenic acid (ALA) - n-3 PUFA from vegetable oils 2) mortality from heart disease 3) prostate cancer	Mortality from heart disease, prostate cancer	High ALA intake was associated with reduced risk of fatal heart disease in prospective cohort studies (RR 0.79, 95% CI, 0.6-1.04). Increased risk of prostate cancer in men with a high intake of ALA (RR 1.70, 95% CI, 1.12-2.58)	In subjects with low intake of ALA, 21% risk reduction of fatal coronary heart disease was demonstrated.
Bucher 2002	20 (6-46)	11 (2 dietary, 9 supplementation)	7,951 (intervention) and 7,855 (control)	1966-Aug 1999	Medline, Embase/Excerpta Medica, Pascal Biomed, Index Medicus, the Cochrane Library; and scanning	1) compared dietary or nondietary intake of n-3 PUFA with a controlled diet or placebo 2) reported fatal and non-fatal MI and overall mortality 3) followed patients with MI or angiographically established CAD for >=6 months Excluded: studies of restricted patients who had	Omega-3 FA reduced overall mortality, fatal MI and sudden cardiac death	Nonfatal MI (RR 0.8; 0.5-1.2), fatal MI (RR 0.7; 0.6-0.8), sudden death (RR 0.7; 0.6-0.9). Overall mortality (RR 0.8; 0.7-0.9). No difference in summary estimates between dietary and nondietary intervention of n-3 PUFA	Dietary and nondietary intake of n-3 polyunsaturated fatty acids reducesoverall mortality, mortality due to myocardial infarction, andsudden death in patients with coronary heart disease.

Author	Treatment duration (month)	No. of articles	No. of patients	Publication period	Search database	Selection Criteria	Endpoint	Result	Conclusion
					bibliographies of relevant publications	had coronary bypass surgery or heart transplantation.			

APPENDIX D - Summary of cost-effectiveness analyses of n-3 PUFAs

Author	Country	Perspective	Time horizon	Discount rate	End point	Result
Gerlier 2012	Ireland and Estonia	Public payer perspective	3.5 years and life time	4% for Ireland and 5% for Estonia were applied on outcomes and costs	ICER	Lifelong treatment with n-3 PUFAs ethyl esters yielded 0.26 LYG, 0.19 QALY gained (Ireland) and 0.24 LYG (Estonia). ICER of €6,223/LYG and €8,210/QALY gained (Ireland) and €5,079/LYG (Estonia). Respective ICERs at 3.5-years were €18,686/LYG, €23,527/QALY gained for Ireland and €28,797/LYG for Estonia
Lamotte 2006	Australia, Belgium, Canada, Germany, Poland	Healthcare payer	3.5 years but the effects of life expectancy through avoidance of cardiac events were calculated lifelong	5% of effects and costs	ICER	The ICER varied between €2788 (Canada) to €5097 (Belgium) per LYG
Quilici 2006	UK	Healthcare payer (NHS)	4 years and lifetime	3.5% of LYG, QALY and death (recommended by NICE)	Cost per QALY gained, cost per life years gained	Cost per QALY gained: £3,717 at 4 years and £15,189 over a lifetime. Cost per LYG: £2,812 and £12,011, respectively. The cost per death avoided at 4 years was £31,786.
Franzosi 2001	Italy	Third-party payer	3.5 years	5% of resources and effectiveness results	ICER, NNT	ICER = €24,603 per LYG (22646-26930). NNT = 172 at an annual cost of €68,000.

APPENDIX E - Consumer Price Index (CPI)

BE	AD	CPI (All commodities)	CPI (Medical care)
2543	2000	74.51	88.69
2544	2001	75.71	90.77
2545	2002	76.24	91.90
2546	2003	77.62	93.11
2547	2004	79.76	95.29
2548	2005	83.39	96.87
2549	2006	87.26	97.92
2550	2007	89.21	98.39
2551	2008	94.08	98.92
2552	2009	93.28	99.31
2553	2010	96.33	99.41
2554	2011	100.00	100.00
2555	2012	103.02	100.96
2556	2013	105.27	101.94

Source: Ministry of Commerce

APPENDIX F - MI cost calculation – direct health care cost in the first year

Patients	N	Average cost	SD	SE
STEMI	110	176,894	179,414	
NSTEMI	107	174,949	155,604	
Total MI	217	175,935	167,321	11,358.47

Source: Thai ACS Registry

APPENDIX G - Stroke cost calculation

Actual cost (Baht), mean(SD)	Unexposed group (N=90)		Exposed group (N=117)		Total group (N=207)			Total group (N=207) for 1 year		
	Cost	SD	Cost	SD	Cost	SD	SE	Cost	SD	SE
Direct Health care cost	**17,563**	**24,569**	**21,269**	**17,561**	**19,658**	**20,793**	**1,445**	**29,851**	**30,341**	**2,109**
Hospital cost	**11,401**	**16480**	**16,993**	**19509**	**14,562**	**18,167**	**1,263**	**14,562**	**18,167**	**1,263**
Direct health care cost after discharge	**6,162**	**18460**	**4,276**	**5433**	**5,096**	**12,769**	**888**	**15,289**	**24,845**	**1,727**
• Medical cost	4,178	18172	2,599	4242	3,286	12,331	857	9,857	36,994	2,571
• Alternative medicine	572	1325	590	1450	582	1,390	97	1,747	4,171	290
• Massage	632	1962	690	1112	665	1,532	107	1,994	4,597	320
• Rehabilitation	781	1356	397	1356	564	1,349	94	1,692	4,048	281

* The cost in 1 year was calculated by extrapolation of the cost at 4 months with the assumption of 1 hospitalization and 3 follow-up visits per patient

APPENDIX H - Result from survival analysis

```
streg age, dist(weibull) nohr

failure _d:  death == 1
  analysis time _t:  duration
Fitting constant-only model:
Iteration 0:   log likelihood = -713.42717
Iteration 1:   log likelihood = -698.98157
Iteration 2:   log likelihood = -698.39885
Iteration 3:   log likelihood = -698.39789
Iteration 4:   log likelihood = -698.39789
Fitting full model:
Iteration 0:   log likelihood = -698.39789
Iteration 1:   log likelihood = -672.75771
Iteration 2:   log likelihood = -670.23748
Iteration 3:   log likelihood = -670.23518
Iteration 4:   log likelihood = -670.23518

Weibull regression -- log relative-hazard form

No. of subjects =         1525
Number of obs   =         1525
No. of failures =          149
Time at risk    =       496860
LR chi2(1)      =        56.33
Log likelihood  =   -670.23518
Prob >      chi2        =     0.0000
```

_t	Coef.	Std. Err.	z	P>z	[95% Conf.	Interval]
age	0.0503961	0.0069719	7.23	0	0.0367315	0.0640607
_cons	-9.583858	0.5931454	-16.16	0	-10.7464	-8.421315
/ln_p	-0.3910318	0.0790599	-4.95	0	-0.5459863	-0.2360773
p	0.6763586	0.0534728			0.5792702	0.7897196
1/p	1.478506	0.1168905			1.266272	1.72631

. estat vce

	age	_cons	ln_p:
age	0.00004861		
_cons	-0.00347821	0.35182147	
ln_p:	0.00001331	-0.02546878	0.00625046

Modeling the hazard function for treatment failure (death)

explanatory variables

	coefficient	se	hazard ratio
lngamma	-0.39	0.08	0.676
cons	-9.58	0.59	0.000
age	0.05	0.01	1.052

Covariance matrix

	lngamma	cons	age
lngamma	0.0063		
cons	-0.0255	0.3518	
age	0.0000	-0.0035	0.00005

Correlation matrix

	lngamma	cons	age
lngamma	1		
cons	-0.543	1	
age	0.024	-0.841	1

Cholesky decomposition

	lngamma	cons	age
lngamma	0.0791		
cons	-0.3221	0.4980	
age	0.00017	-0.0069	0.0011

Random variables

	z	Tz	mu + Tz
lngamma	-1.4258	-0.1127	-0.5038
cons	-1.3290	-0.2026	-9.7864
age	0.1898	0.0091	0.0595

VITA

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