Literature Evaluation

beyond the basics

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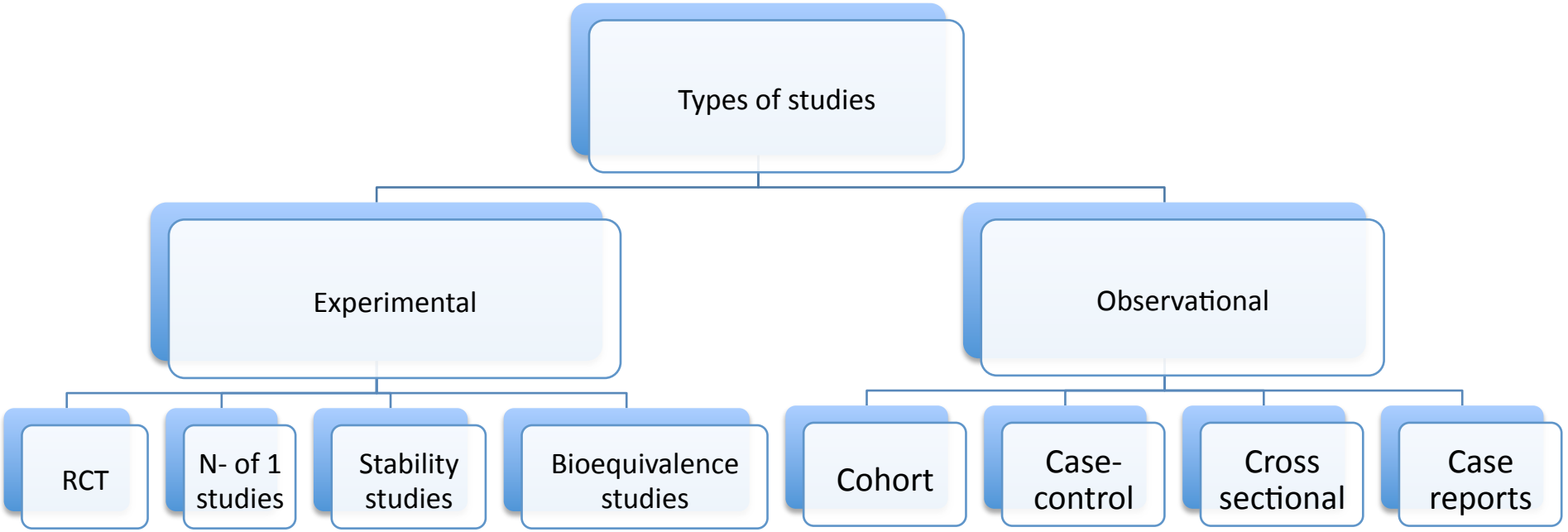
Learning Objectives

- **Describe** examples of other study designs besides the basic controlled clinical trial.
- **Describe** the characteristics, usefulness, advantages and disadvantages of various observational trial designs.
- **Differentiate** between the three types of literature reviews: narrative (nonsystematic) review, systematic review, and meta-analysis.
- **Discuss** the use of clinical practice guidelines (CPG).
- **list** general and specialized CPG resources.
- **Interpret** CPG recommendations.

Introduction

- ***Question:*** *Why is it important to understand principles of study design and evaluation beyond the prospective, randomized, controlled, clinical trial?*
- ***Answer:*** *Because* there are situations where other research designs are more effective in answering specific questions or provide the only data available to answer the questions.

Study designs



Comparison between Experimental and Observational studies

Experimental	Observational
Any research in which the investigator intervenes in a population for the sole purpose of evaluation.	The investigator makes no attempt to intervene in the study sample .

Experimental study design

Experimental study designs

- **Randomized clinical trials (RCT)**

also called “interventional trials”.

Experimental study designs

- **N-of-1 Trials**
- Apply the principles of clinical trials such as randomization and blinding to individual (single) patients.
- Used to compare effects of drugs to control during multiple observation periods in a single patients.

An N-of-1 randomized controlled trial ('N-of-1 trial') of donepezil in the treatment of non-progressive amnestic syndrome

Abstract

Introduction: a professional man sustained a residual, persisting, isolated impairment of short-term memory secondary to severe carbon monoxide poisoning. Informal, open trial of the cholinesterase inhibitor donepezil resulted in uncertain benefit.

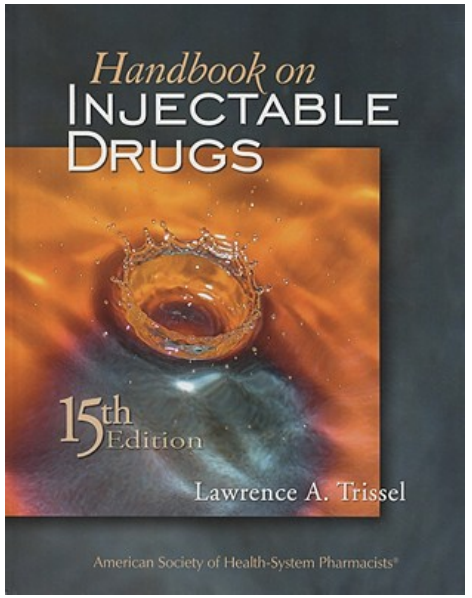
Protocol: an N-of-1 randomized, double-blind controlled trial of donepezil against placebo. Placebo-induced headache permitted evaluation of donepezil at only the 5 mg dose.

Results: there was no improvement in short-term memory.

Conclusion: the trial excluded significant benefit of donepezil 5 mg in this patient, preventing long-term unnecessary prescription. Beneficial effects in other similar patients or at higher dosage cannot be excluded.

Experimental study designs

- **Stability studies\in vitro studies**
- Determine the stability of drugs in various preparations (e.g. ophthalmic ,intravenous , topical and oral) under various conditions (e.g. heat ,freezing ,refrigeration and room temperature).
- Trissel et al prepared a stability studies guidelines and he is the author of the “handbook of injectable drugs”



Stability and compatibility of the mixture of tramadol, ketorolac, metoclopramide and ranitidine in a solution for intravenous perfusion

Abstract

Objective: To determine whether a mixture for intravenous perfusion containing tramadol (5 mg/ml), ranitidine (1.5 mg/ml), ketorolac (1.5 mg/ml) and metoclopramide (0.5 mg/ml) in a 0.9% sodium chlorides solution is compatible and stable at room temperature during a 48-hour period.

Methods: We tested the mixture for stability using the HPLC technique (high performance liquid chromatography), with parallel visual assessments of any changes in colour, appearance of precipitate or phase separation indicating incompatibilities between the components.

Results: At the end of the trial, chromatography data showed a mean metoclopramide concentration between 100% and 105% of the initial level, while concentrations of tramadol, ketorolac and ranitidine were between 99% and 102% of initial levels. There was no evidence of incompatibility between the drugs at any time during the study period.

Conclusions: The combination is stable as a solution and its components are physically and chemically compatible in the concentrations used in the study, during at least 48 hours at room temperature.

Experimental study designs

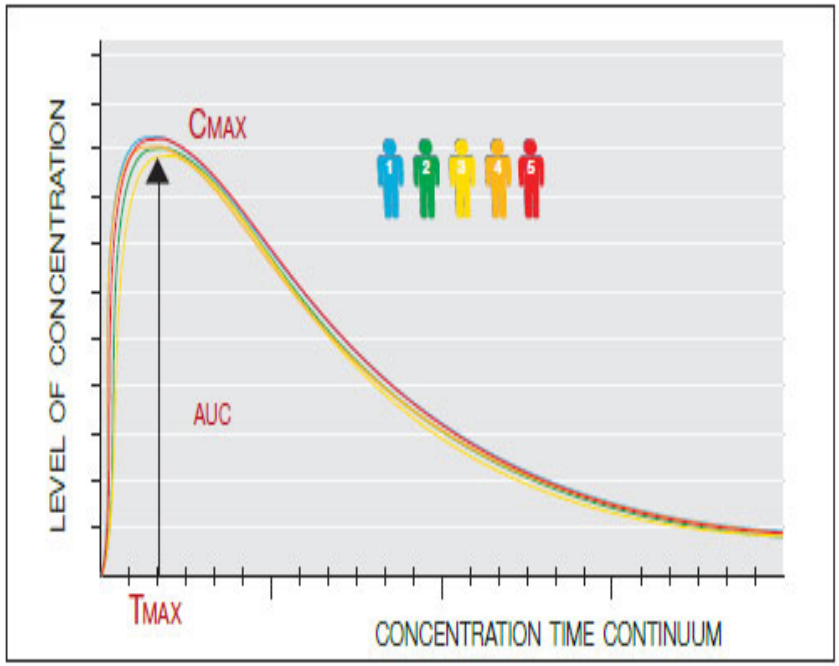
- **Bioequivalence studies**
- Due to the increasing number of generic products in the market, there is a need to establish that the Quality ,safety and efficacy of these generic drugs are the same as the brand name product.

Experimental study designs

- **Bioequivalence studies**
- These studies conducted under standardized condition in **small number of normal ,healthy** volunteers because of **availability and lack of confounding factors.**

Experimental study designs

- **Bioequivalence studies**
- Bioequivalent products are the products that are equivalent in Rate (C_{max}) and Extent of absorption (AUC).
- The rate and extent differ by ±20 % or less



Open Access Full Text Article

ORIGINAL RESEARCH

Bioequivalence assessment of two formulations of ibuprofen

Background: This study assessed the relative bioavailability of two formulations of ibuprofen. The first formulation was Doloraz®, produced by Al-Razi Pharmaceutical Company, Amman, Jordan. The second forumulation was Brufen®, manufactured by Boots Company, Nottingham, UK.

Methods and results: A prestudy validation of ibuprofen demonstrated long-term stability, freeze-thaw stability, precision, and accuracy. Twenty-four healthy volunteers were enrolled in this study. After overnight fasting, the two formulations (test and reference) of ibuprofen (100 mg ibuprofen/5 mL suspension) were administered as a single dose on two treatment days separated by a one-week washout period. After dosing, serial blood samples were drawn for a period of 14 hours. Serum harvested from the blood samples was analyzed for the presence of ibuprofen by high-pressure liquid chromatography with ultraviolet detection. Pharmacokinetic parameters were determined from serum concentrations for both formulations. The 90% confidence intervals of the ln-transformed test/reference treatment ratios for peak plasma concentration and area under the concentration-time curve (AUC) parameters were found to be within the predetermined acceptable interval of 80%–125% set by the US Food and Drug Administration.

Conclusion: Analysis of variance for peak plasma concentrations and AUC parameters showed no significant difference between the two formulations and, therefore, Doloraz was considered bioequivalent to Brufen.

Keywords: ibuprofen, bioequivalence study, pharmacokinetics

Bioequivalence assessment of two formulations of ibuprofen

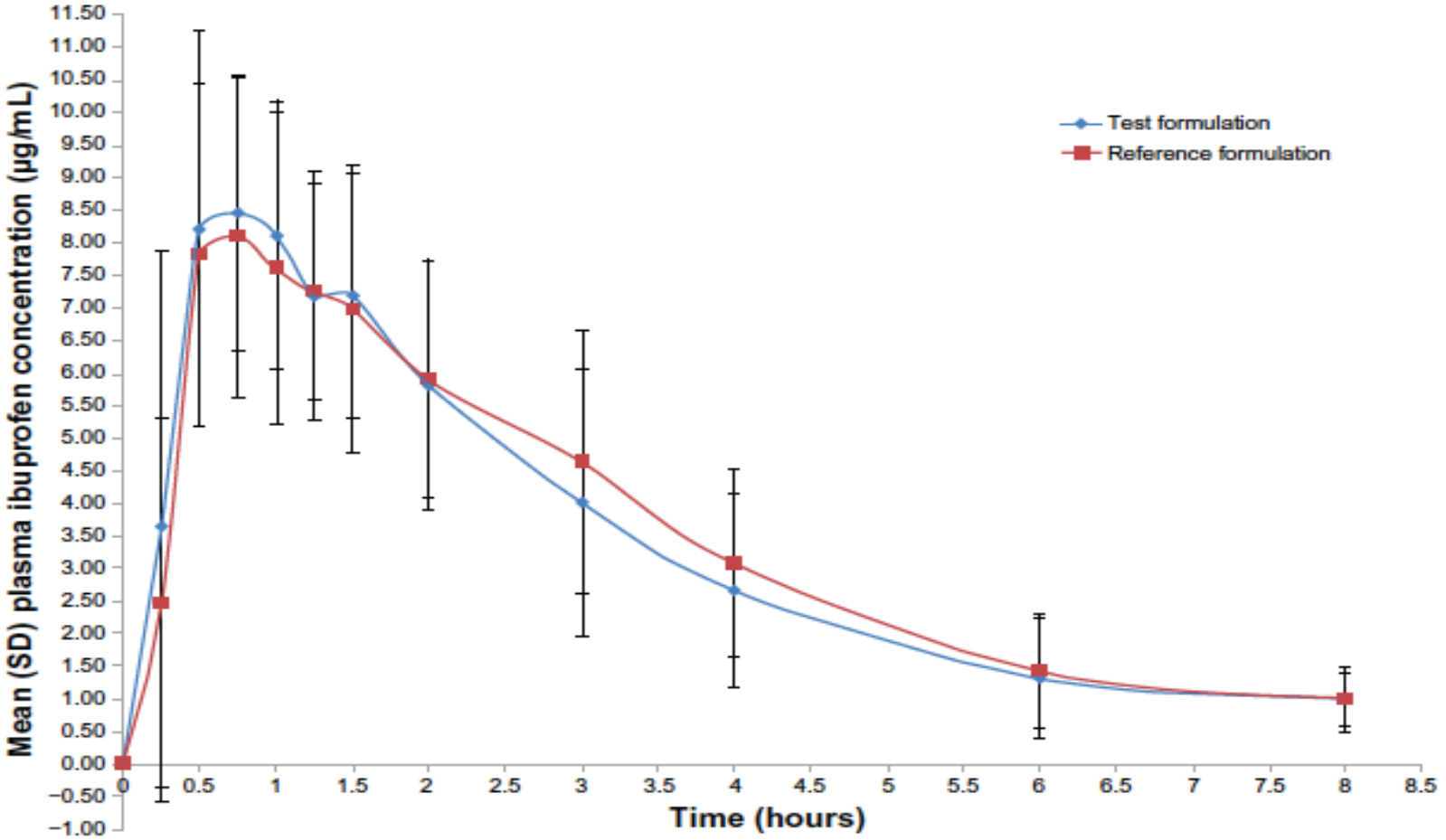


Figure 3 Serum concentration-time plots for 100 mg of ibuprofen after a single oral dose of the test and reference formulations in healthy adult male volunteers (n = 24). The lower limit of quantitation was 1.0 µg/mL.

Observational study design

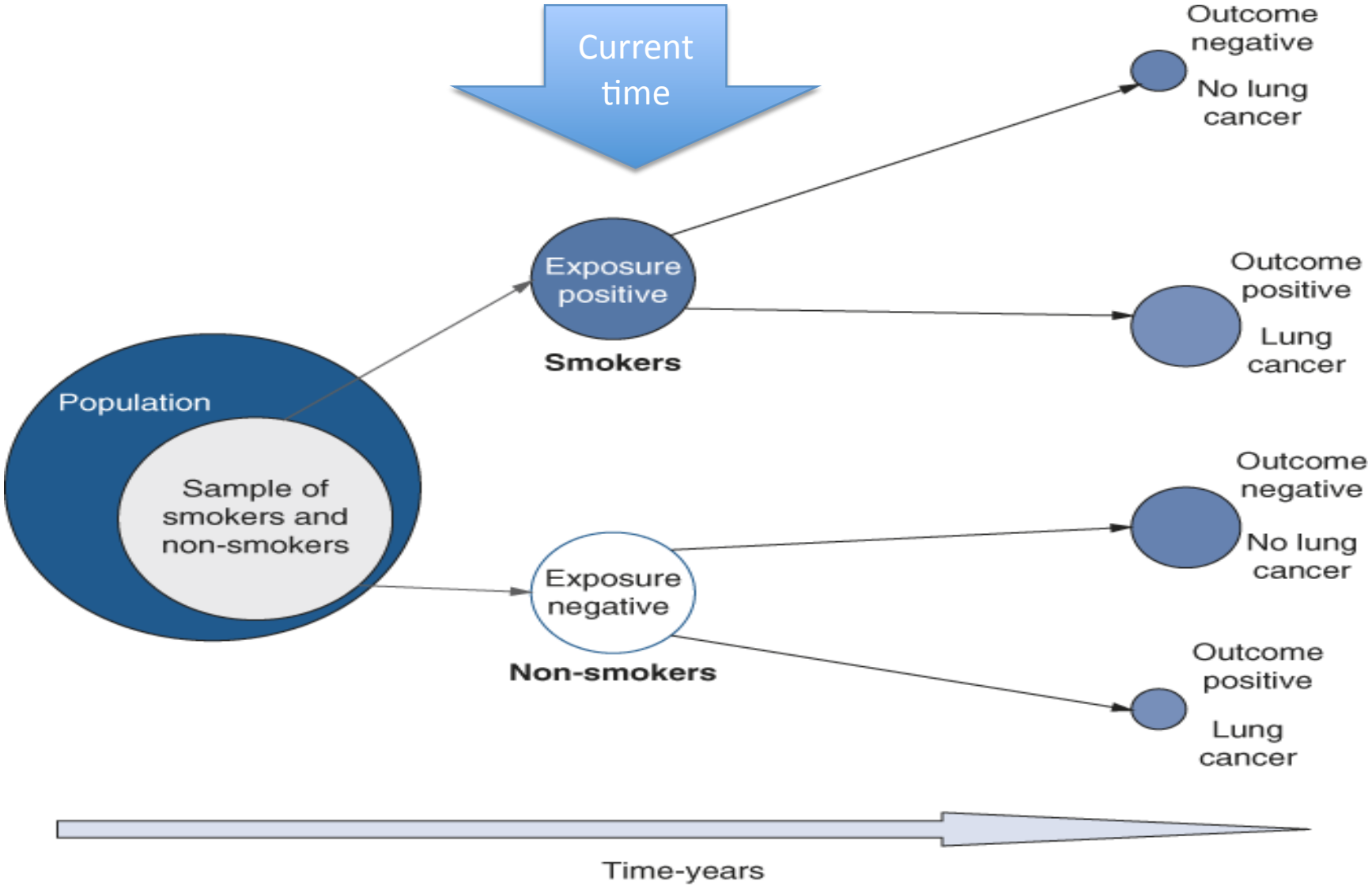
Observational study design

Cohort studies

- The term *cohort is derived from the Latin word cohors, which means a group of soldiers.*
- also called follow-up, longitudinal studies.
- The **strongest** observational study design.

Observational study design

- **Cohort studies**
- The investigator recruits a disease free subject population and divide them into two groups : Those Identified as either exposed and unexposed to a factor of interest .
- Subjects are then followed prospectively as development of a disease state of interest is observed during the study period.



Schematic diagram of a cohort study.

Observational study design

- **Cohort studies**
- **Advantages:**

This design is useful in investigating outcomes from rare exposures.

- **Disadvantages**:

Expensive and time consuming .

Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9

Abstract

Objective To assess the risk of venous thromboembolism from use of combined oral contraceptives according to progestogen type and oestrogen dose.

Design National historical registry based cohort study.

Setting Four registries in Denmark.

Participants Non-pregnant Danish women aged 15-49 with no history of thrombotic disease and followed from January 2001 to December 2009.

Main outcome measures Relative and absolute risks of first time venous thromboembolism.

Results Within 8 010 290 women years of observation, 4307 first ever venous thromboembolic events were recorded and 4246 included, among which 2847 (67%) events were confirmed as certain. Compared with non-users of hormonal contraception, the relative risk of confirmed venous thromboembolism in users of oral contraceptives containing 30-40 µg ethinylestradiol with levonorgestrel was 2.9 (95% confidence interval 2.2 to 3.8), with desogestrel was 6.6 (5.6 to 7.8), with gestodene was 6.2 (5.6 to 7.0), and with drospirenone was 6.4 (5.4 to 7.5). With users of oral contraceptives with levonorgestrel as reference and after adjusting for length of use, the rate ratio of confirmed venous thromboembolism for users of oral contraceptives with desogestrel was 2.2 (1.7 to 3.0), with gestodene was 2.1 (1.6 to 2.8), and with drospirenone was 2.1 (1.6 to 2.8). The risk of confirmed venous thromboembolism was not increased with use of progestogen only pills or hormone releasing intrauterine devices. If oral contraceptives with desogestrel, gestodene, or drospirenone are anticipated to increase the risk of venous thromboembolism sixfold and those with levonorgestrel threefold, and the absolute risk of venous thromboembolism in current users of the former group is on average 10 per 10 000 women years, then 2000 women would need to shift from using oral contraceptives with desogestrel, gestodene, or drospirenone to those with levonorgestrel to prevent one event of venous thromboembolism in one year.

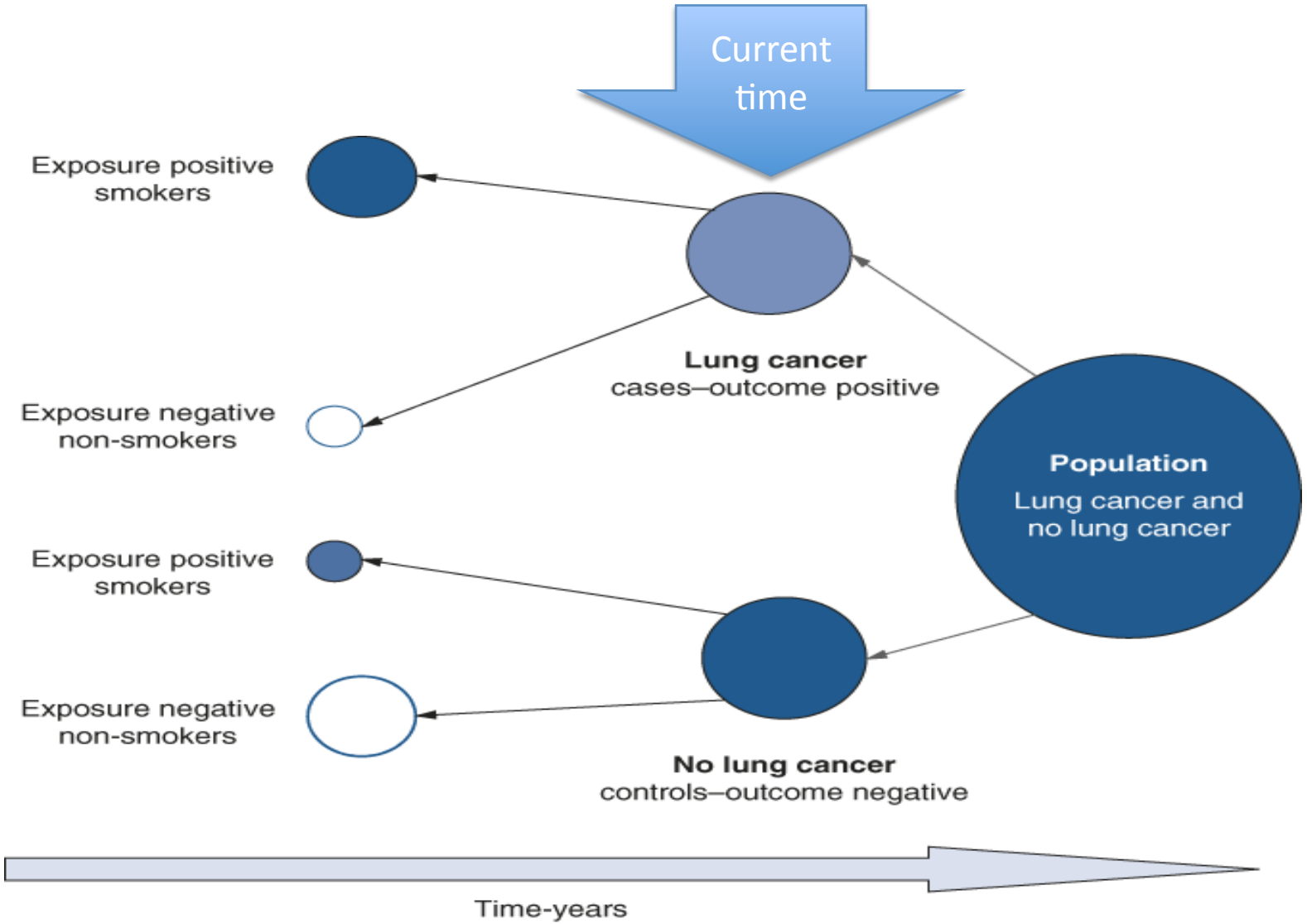
Conclusion After adjustment for length of use, users of oral contraceptives with desogestrel, gestodene, or drospirenone were at least at twice the risk of venous thromboembolism compared with users of oral contraceptives with levonorgestrel.

Observational study design

- **Case –control studies**
- Also known as retrospective or trohoc (cohort spelled backwards).
- Case-control studies seek to retrospectively identify potential risk factors of diseases or outcomes.
- In a case-control study, subjects (cases) with a particular characteristic or outcome of interest (e.g., disease) are recruited, matched with, and compared to a similar group of subjects (controls) who have not experienced the characteristic or outcome.

Observational study design

- **Case –control studies**
- Data regarding exposures are collected retrospectively via patient interviews or by reviewing subject data records, and the two groups are compared to identify possible risk factors or contributors for development of the disease or outcome of interest.



Schematic diagram of a case-control study.

Observational study design

- **Case –control studies**
- **Advantages**
- Useful when disease occur rarely or many years after exposure.
- Designed to determine the cause rather than effect.
- Inexpensive and can be accomplished in short time.
- Reduce the need for large sample size.
- **Disadvantages**
- Historical data used in case control studies may be inaccurate or incomplete.

Isotretinoin Use and the Risk of Inflammatory Bowel Disease: A Case Control Study

Abstract

Introduction—Isotretinoin is commonly prescribed for the treatment of severe acne. Though cases of inflammatory bowel disease (IBD) have been reported in isotretinoin users, a causal association remains unproven.

Methods—We performed a case-control study using a large insurance claims database. Incident cases of IBD were identified and matched to 3 controls on the basis of age, gender, geographical region, health plan, and length of enrollment. Isotretinoin exposure was assessed in a 12 month period prior to case ascertainment. Conditional logistic regression was used to adjust for the matching variables.

Results—The study population contained 8,189 cases (3,664 CD and 4,428 UC) and 21,832 controls. Sixty subjects (24 cases and 36 controls) were exposed to isotretinoin. Ulcerative colitis was strongly associated with prior isotretinoin exposure (OR 4.36, 95% CI 1.97, 9.66). However, there was no apparent association between isotretinoin and Crohn's disease (OR 0.68, 95% CI 0.28, 1.68). Increasing dose of isotretinoin was associated with elevated risk of UC (OR per 20 mg

Comparison between cohort and case control studies

Observational Study Design	Prospective Data Collection	Retrospective Data Collection	Exposure Known at Beginning of Study	Outcome Known at Beginning of Study	Study Determines Exposure Status	Study Determines Outcome Occurrence
Cohort	X		X			X
Case-control (trohoc)		X		X	X	

Observational study designs

- **Cross sectional studies**
- Also called prevalence studies can be thought of as **"snapshot"** because data are collected and evaluated at a single point in time.

Observational study designs

- **Cross sectional studies**
- Typical example of cross sectional studies are questionnaires and interviews that evaluate opinions or situations at a fixed point in time.

Questionnaires	Interviews
Cheap	Expensive
Low response rate	High response rate
Large sample size	Smaller sample size

Observational study designs

- **Cross sectional studies**
- **Advantages:**
- Relatively quick and easy to perform.
- Useful in measuring the prevalence of a current health status.

Disadvantages:

- Difficult to establish cause-effect relationship.

Perception of Pharmacy Students in Malaysia on the Use of Objective Structured Clinical Examinations to Evaluate Competence

Objectives. To assess bachelor of pharmacy students' overall perception and acceptance of an objective structured clinical examination (OSCE), a new method of clinical competence assessment in pharmacy undergraduate curriculum at our Faculty, and to explore its strengths and weaknesses through feedback.

Methods. A cross-sectional survey was conducted via a validated 49-item questionnaire, administered immediately after all students completed the examination. The questionnaire comprised of questions to evaluate the content and structure of the examination, perception of OSCE validity and reliability, and rating of OSCE in relation to other assessment methods. Open-ended follow-up questions were included to generate qualitative data.

Results. Over 80% of the students found the OSCE to be helpful in highlighting areas of weaknesses in their clinical competencies. Seventy-eight percent agreed that it was comprehensive and 66% believed it was fair. About 46% felt that the 15 minutes allocated per station was inadequate. Most importantly, about half of the students raised concerns that personality, ethnicity, and/or gender, as well as inter-patient and interassessor variability were potential sources of bias that could affect their scores. However, an overwhelming proportion of the students (90%) agreed that the OSCE provided a useful and practical learning experience.

Conclusions. Students' perceptions and acceptance of the new method of assessment were positive. The survey further highlighted for future refinement the strengths and weaknesses associated with the development and implementation of an OSCE in the International Islamic University Malaysia's pharmacy curriculum.

Observational study designs

- **Case studies, case reports and case series**
- Reports **describing observations made regarding a patient or patient group exposure** to a drug or technology can be valuable to record preliminary findings that will lead to further study.

Observational study designs

- **Case studies, case reports and case series**
- A key characteristic to these reports is the lack of a control or comparison group. .
- they do not take into consideration other influencing factors that may also have played a role in observed outcomes.

Observational study designs

- **Case studies, case reports and case series**
- also be useful for early recognition of drug toxicities and teratogenicity.
- A newly recognized value of case reports is utilization for understanding potential toxicities of dietary supplement products (botanical and non-botanical).

CLINICAL CASE REPORTS

Severe vancomycin-induced anaphylactic reaction

Summary. *Vancomycin is widely used against methicillin-resistant Staphylococcus aureus infections, but it is associated with many adverse effects such as nephrotoxicity, ototoxicity, gastrointestinal disturbances, blood disorders, and two types of hypersensitivity reactions – an anaphylactoid reaction known as "red man syndrome" and anaphylaxis. We report a case of a 23-year-old man who developed a vancomycin-induced anaphylactic reaction in the treatment of methicillin-resistant Staphylococcus aureus infection.*

Experimental study designs

What is the difference between N-of-1 trials and case reports ?

Table 5–2. Comparison of N-of-1 Trials and Case Studies

	N-of-1 Trial	Case Study
Design	Prospective	Retrospective (most often)
Predefined methods	Yes	No
Clearly defined outcome measures	Yes	No
Randomization	Yes	No
Blinding	Yes	No
Multiple treatment periods	Yes	Not usually

General review

Table 5–1. Commonly Encountered Biomedical Literature

Study Design	Study Purpose
Clinical study (true experiment)	Determine cause and effect relationships
N-of-1 study	Compare effects of drug to control during multiple observation periods in a single patient
Stability study	Evaluate stability of drugs in various preparations (e.g., ophthalmologic, intravenous, topical, and oral)
Bioequivalence study	Assess the bioequivalency of two or more products
Programmatic research	Determine the impact and/or economic value of clinical services
Cohort (follow-up) study	Determine association between various factors and disease state development
Case-control (trohoc) study	Determine association between disease states and exposure to various risk factors
Cross-sectional study	Identify prevalence of characteristics of diseases in populations
Case study, case report, or case series	Report observations in a single patient or series of patients
Survey research	Study the incidence, distribution, and relationships of sociologic and psychologic variables through use of questionnaires applied to various populations
Postmarketing surveillance study	Evaluate use and adverse effects associated with newly approved drug therapies
Narrative review	Nonsystematic, subjective summary of data from multiple studies
Systematic review	Systematic, qualitative, and objective summary of data from multiple studies
Meta-analysis	Combine, statistically evaluate, and summarize data from multiple studies
Outcomes studies (pharmacoeconomic and health related-QOL measures)	Compare outcomes (QOL) and costs (pharmacoeconomics) of drug therapies or services

Review articles

Review articles

- Review articles, with the exception of meta-analyses, that essentially consist of analysis and interpretation of previously conducted research studies, are classified as **tertiary** literature.
- However, Meta-analyses are classified as **primary** literature since they create new data.

Review articles

- Review articles discussing treatment of disease states or clinical aspects of drug therapy enable practitioners to gain insight into a topic or question of interest and may provide more current information than textbooks.
- the three types of literature reviews: narrative (nonsystematic) review, systematic review, and meta-analysis.

Narrative (Nonsystematic) Review

- Is a summary of research that lacks a description of systematic methods.
- considered **tertiary literature** because they provide information in much the same manner as found in textbooks.

N-acetylcysteine for Prevention of Contrast-Induced Nephropathy: A Narrative Review

ABSTRACT

Contrast-induced nephropathy (CIN) affects in-hospital, short- and long-term morbidity and mortality. It also leads to prolonged hospital stay and increased medical cost. Given the potential clinical severity of CIN, there has been considerable interest in the development of preventative strategies to reduce the risk of contrast-induced renal deterioration in at-risk populations. A number of pharmacologic and mechanical preventive measures have been attempted, but no method other than adequate periprocedural hydration has been conclusively successful. Since its introduction in 2000, N-acetylcysteine (NAC) has been widely investigated, albeit with conflicting findings for its nephroprotection capability in patients receiving contrast media procedures. However, there is still virtually no definitive evidence of effectiveness of NAC. Although the exact mechanism responsible for the protective action of NAC from renal function deterioration remains unclear, the antioxidant and vasodilatory properties of NAC have been suggested as the main mechanisms. This review summarizes the current status of NAC as a potential agent to prevent renal functional deterioration and its limitations. **(Korean Circ J 2011;41:695-702)**

Systematic Review: Qualitative

- Is a scientific investigations with predefined methods and original studies as their subjects.
- Contain a summary of results of primary studies where the results are **not** statistically combined.
- Specific criteria should be used to select articles from the primary literature to be included in the review.

Prediction Tools for Unfavourable Outcomes in *Clostridium difficile* Infection: A Systematic Review

Abstract

Context: Identifying patients at risk for adverse outcomes of *Clostridium difficile* infection (CDI), including recurrence and death, will become increasingly important as novel therapies emerge, which are more effective than traditional approaches but very expensive. Clinical prediction rules (CPRs) can improve the accuracy of medical decision-making. Several CPRs have been developed for CDI, but none has gained a widespread acceptance.

Methods: We systematically reviewed studies describing the derivation or validation of CPRs for unfavourable outcomes of CDI, in medical databases (Medline, Embase, PubMed, Web of Science and Cochrane) and abstracts of conferences.

Results: Of 2945 titles and abstracts screened, 13 studies on the derivation of a CPR were identified: two on recurrences, five on complications (including mortality), five on mortality alone and one on response to treatment. Two studies on the validation of different severity indices were also retrieved. Most CPRs were developed as secondary analyses using cohorts assembled for other purposes. CPRs presented several methodological limitations that could explain their limited use in clinical practice. Except for leukocytosis, albumin and age, there was much heterogeneity in the variables used, and most studies were limited by small sample sizes. Eight models used a retrospective design. Only four studies reported the incidence of the outcome of interest, even if this is essential to evaluate the potential usefulness of a model in other populations. Only five studies performed multivariate analyses to adjust for confounders.

Conclusions: The lack of weighing variables, of validation, calibration and measures of reproducibility, the weak validities and performances when assessed, and the absence of sensitivity analyses, all led to suboptimal quality and debatable utility of those CPRs. Evidence-based tools developed through appropriate prospective cohorts would be more valuable for clinicians than empirically-developed CPRs.

Meta-Analysis: Quantitative

- quantitative systematic review, or meta-analysis, has been described as a systematic review that uses **statistical methods to combine** the results of two or more studies to generate new data.
- **Meta-analyses** assist in:

(1) supporting or refuting lesser-quality evidence.

(2) overcoming reduced statistical power of small studies.

Interventions to Influence Consulting and Antibiotic Use for Acute Respiratory Tract Infections in Children: A Systematic Review and Meta-Analysis

Abstract

Background: Respiratory tract infections (RTIs) are common in children and generally self-limiting, yet often result in consultations to primary care. Frequent consultations divert resources from care for potentially more serious conditions and increase the opportunity for antibiotic overuse. Overuse of antibiotics is associated with adverse effects and antimicrobial resistance, and has been shown to influence how patients seek care in ensuing illness episodes.

Methodology/Principal Findings: We conducted a systematic review and meta-analysis to assess the effectiveness of interventions directed towards parents or caregivers which were designed to influence consulting and antibiotic use for respiratory tract infections (RTIs) in children in primary care. Main outcomes were parental consulting rate, parental knowledge, and proportion of children subsequently consuming antibiotics. Of 5,714 references, 23 studies (representing 20 interventions) met inclusion criteria. Materials designed to engage children in addition to parents were effective in modifying parental knowledge and behaviour, resulting in reductions in consulting rates ranging from 13 to 40%. Providing parents with delayed prescriptions significantly decreased reported antibiotic use (Risk Ratio (RR) 0.46 (0.40, 0.54); moreover, a delayed or no prescribing approach did not diminish parental satisfaction.

Conclusions: In order to be most effective, interventions to influence parental consulting and antibiotic use should: engage children, occur prior to an illness episode, employ delayed prescribing, and provide guidance on specific symptoms. These results support the wider implementation of interventions to reduce inappropriate antibiotic use in children.

Comparison of Different Types of Reviews

Feature	Nonsystematic Review	Qualitative Systematic Review	Quantitative Systematic Review
Clinical question	Often broadly defined	Clearly defined and focused	Clearly defined and focused
Literature search	Methods of literature search usually not explicitly described	Explicit description of predefined and comprehensive search strategy	Explicit description of predefined and comprehensive search strategy
Studies included	Methods for determining which studies to include not usually described	Predefined inclusion and exclusion criteria	Predefined inclusion and exclusion criteria
Includes unpublished literature	Not usually	Possibly	Possibly
Blinding of reviewers	No	Yes	Yes
Analysis of data	Variable and subjective	Rigorous and objective	Rigorous and objective
Results statistically evaluated	No	No	Yes
Types of results	Qualitative	Qualitative	Quantitative

Clinical practice guidelines

Practice guidelines

- Practice guidelines are created to:

1. facilitate clinical decision-making.
2. improve the quality of health care.
3. provide consistent treatment across environments.
4. decrease costs.
5. identify individualized alternative treatment.

Finding Guidelines on the web

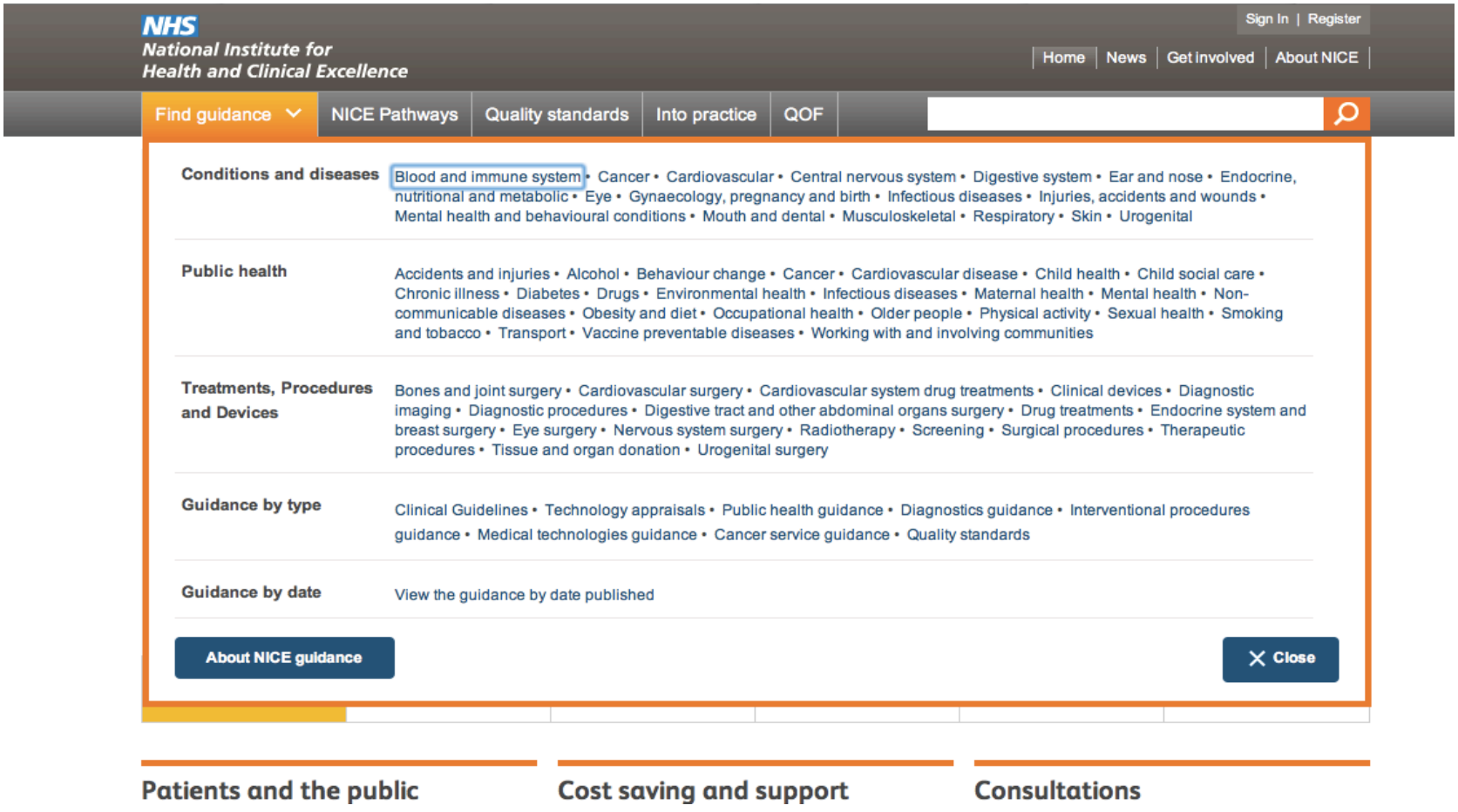
- National Institute for Health and Clinical Excellence (NICE)

  www.nice.org.uk
- Scottish Intercollegiate Guidelines Network (SIGN)

  www.sign.ac.uk
- NHS Evidence Guidelines Finder
  www.evidence.nhs.uk
- Turning Research Into Practice (TRIP)
  www.tripdatabase.com

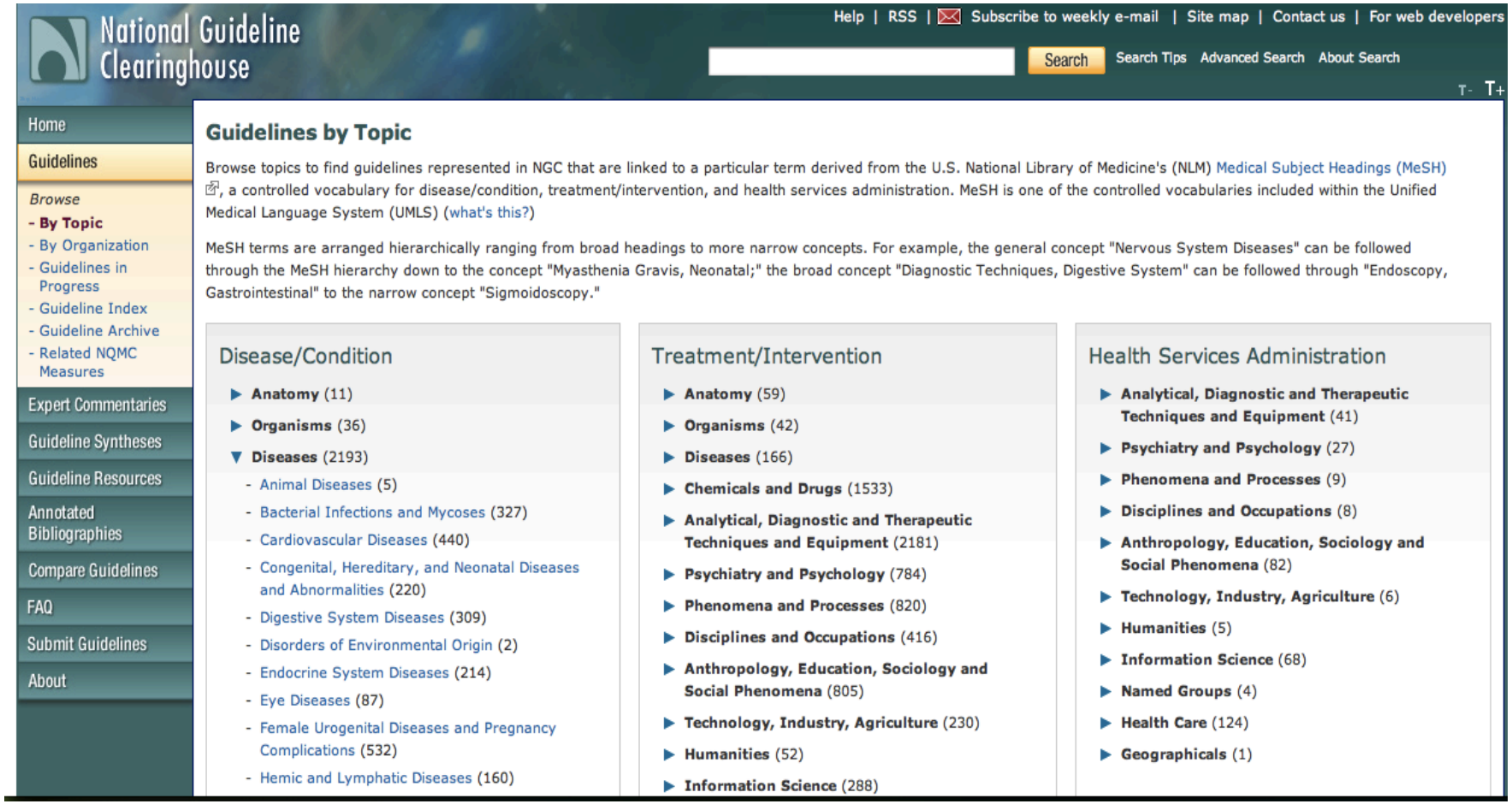
General CPG resources

- www.nice.org.uk



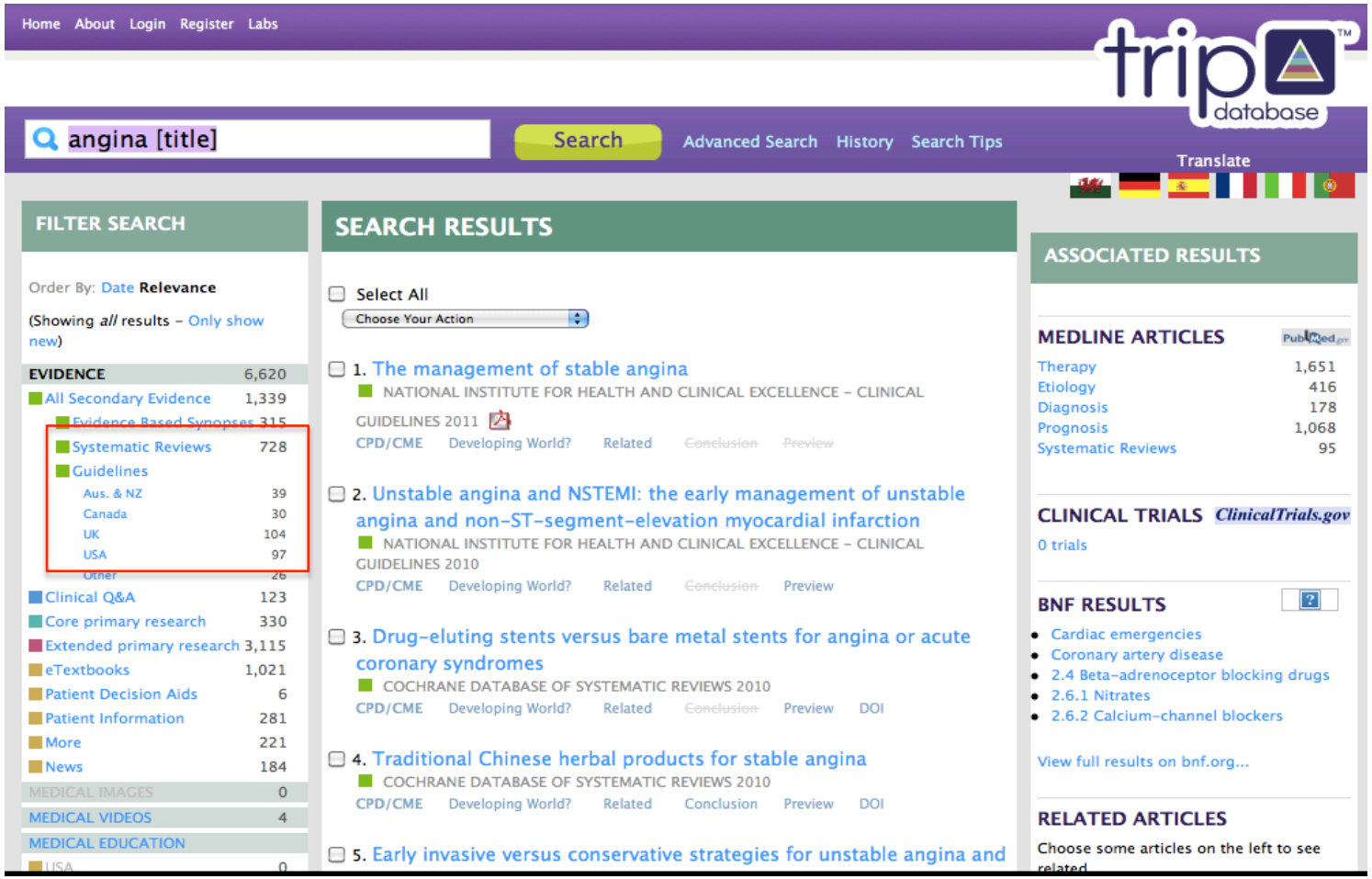
General CPG resources

- www.guideline.gov



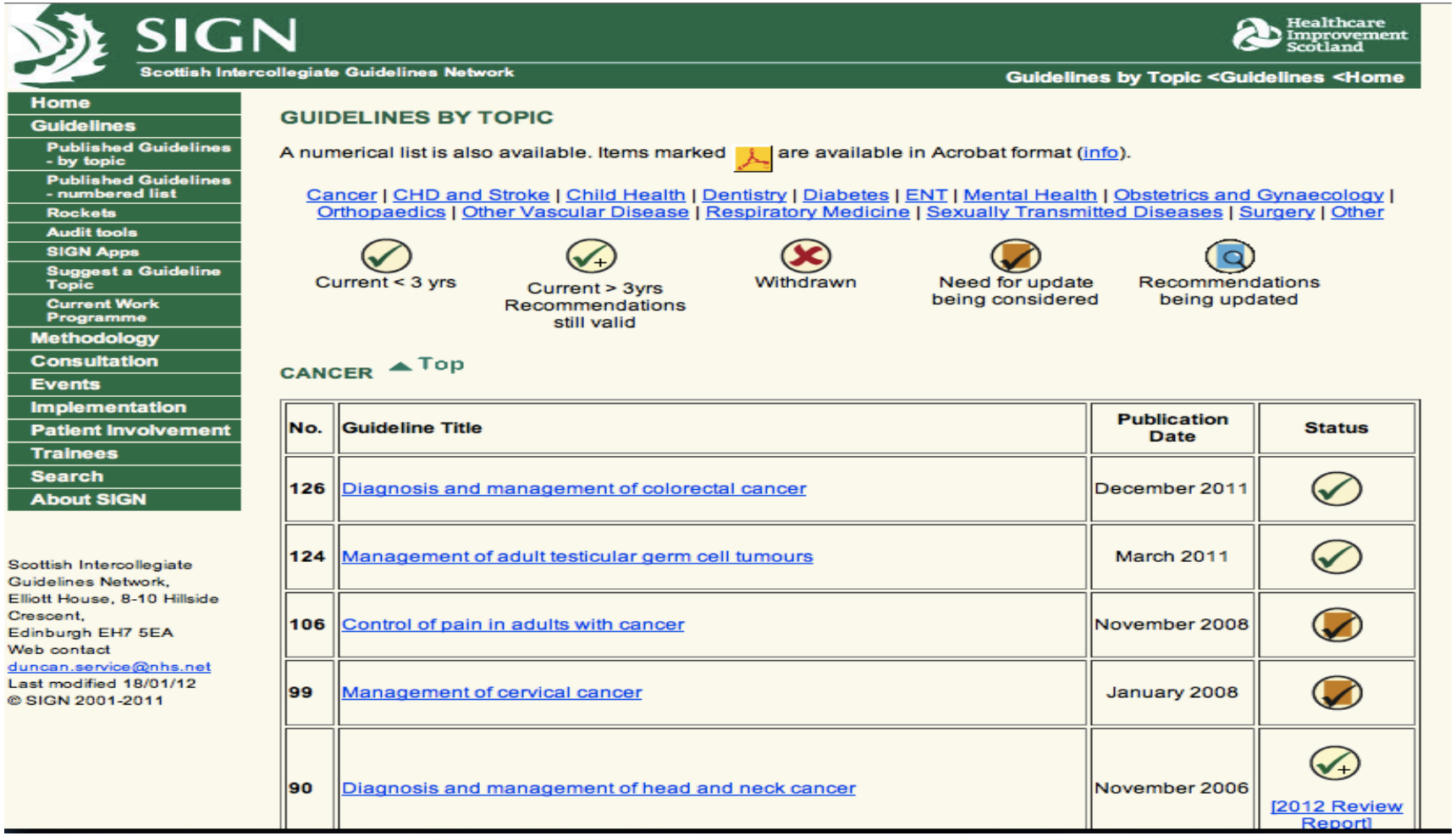
General CPG resources

- www.tripdatabase.com



General CPG resources

- www.sign.ac.uk



SIGN
Scottish Intercollegiate Guidelines Network
Healthcare Improvement Scotland
Guidelines by Topic <Guidelines <Home

Home
Guidelines
Published Guidelines - by topic
Published Guidelines - numbered list
Rockets
Audit tools
SIGN Apps
Suggest a Guideline Topic
Current Work Programme
Methodology
Consultation
Events
Implementation
Patient Involvement
Trainees
Search
About SIGN

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GUIDELINES BY TOPIC

A numerical list is also available. Items marked are available in Acrobat format (info).

Cancer | CHD and Stroke | Child Health | Dentistry | Diabetes | ENT | Mental Health | Obstetrics and Gynaecology | Orthopaedics | Other Vascular Disease | Respiratory Medicine | Sexually Transmitted Diseases | Surgery | Other

Current < 3 yrs
Current > 3yrs Recommendations still valid
Withdrawn
Need for update being considered
Recommendations being updated

CANCER Top

No.	Guideline Title	Publication Date	Status
126	Diagnosis and management of colorectal cancer	December 2011	
124	Management of adult testicular germ cell tumours	March 2011	
106	Control of pain in adults with cancer	November 2008	
99	Management of cervical cancer	January 2008	
90	Diagnosis and management of head and neck cancer	November 2006	[2012 Review Report]

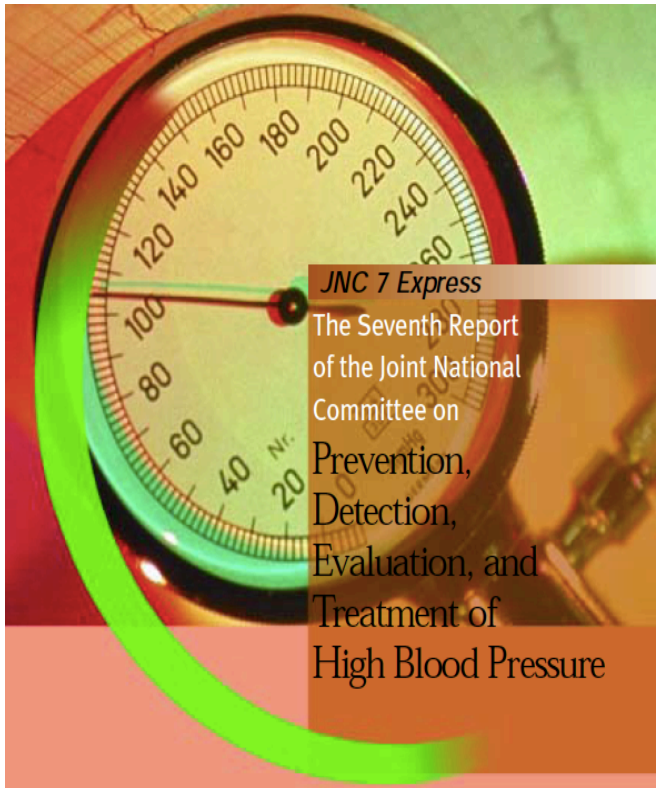
Specialized CPG resources

- Infectious diseases

- Diabetes mellitus

Specialized CPG resources

- Hypertension



- Cardiology

American Heart Association®
Learn and Live℠

Specialized CPG resources

- Asthma

- Pediatrics

Specialized CPG resources

- Rheumatology

BSR
The British Society for Rheumatology

AMERICAN COLLEGE OF RHEUMATOLOGY
EDUCATION • TREATMENT • RESEARCH

- Oncology

ASCO®
American Society of Clinical Oncology

NCCN National Comprehensive Cancer Network®

How to interpret CPG

European Heart Journal
doi:10.1093/eurheartj/ehl002

ESC Guidelines

Guidelines on the management of stable angina pectoris: full text‡

The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology

Level of evidence

- ***Level of evidence A:*** Data derived from multiple randomized clinical trials or meta-analyses

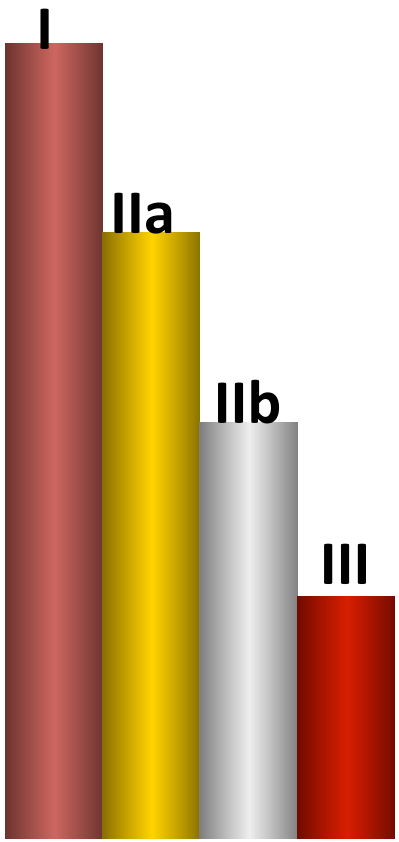
- ***Level of evidence B:*** Data derived from a single randomized trial or nonrandomized studies

- ***Level of evidence C:*** Only consensus opinion of experts, case studies, or standard of care

Hirsch AT et al. Available at: http://www.acc.org/clinical/guidelines/pad/summary.pdf. Accessed March 22, 2006.

Classification of recommendations

Class:



- **Class I:** Conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective
- **Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
  - **Class IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy
  - **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion
- **Class III:** Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful

Hirsch AT et al. Available at: http://www.acc.org/clinical/guidelines/pad/summary.pdf. Accessed March 22, 2006.

How to interpret CPG.. Example

Recommendations for pharmacological therapy to improve prognosis in patients with stable angina

Class I

(1) Aspirin 75 mg daily in all patients without specific contraindications (i.e. active GI bleeding, aspirin allergy, or previous aspirin intolerance) (level of evidence A)
(2) Statin therapy for all patients with coronary disease (level of evidence A)
(3) ACE-inhibitor therapy in patients with coincident indications for ACE-inhibition, such as hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes (level of evidence A)
(4) Oral beta-blocker therapy in patients post-MI or with heart failure (level of evidence A)

Class IIa

(1) ACE-inhibitor therapy in all patients with angina and proven coronary disease (level of evidence B)
(2) Clopidogrel as an alternative antiplatelet agent in patients with stable angina who cannot take aspirin (e.g. aspirin allergic) (level of evidence B)
(3) High dose statin therapy in high-risk (>2% annual CV mortality) patients with proven coronary disease (level of evidence B)

Class IIb

(1) Fibrate therapy in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome (level of evidence B)
(2) Fibrate or nicotinic acid as adjunctive therapy to statin in patients with low HDL and high triglycerides at high risk (>2% annual CV mortality) (level of evidence C)

Table 8 Summary of recommendations for revascularization in stable angina

Indication	For prognosis[a]		For symptoms[b]		Studies
	Class of recommendation	Level of evidence	Class of recommendation	Level of evidence	
PCI (assuming suitable anatomy for PCI, appropriate risk stratification, and discussion with the patient)					
Angina CCS classes I–IV despite medical therapy with one-vessel disease			I	A	ACME and MASS
Angina CCS classes I–IV despite medical therapy with multi-vessel disease (non-diabetic)			I	A	RITA 2 and VA-ACME
Stable angina with minimal (CCS class I) symptoms on medication and one-, two-, or three-vessel disease but objective evidence of large ischaemia	IIb	C			ACIP
CABG (assuming suitable anatomy for surgery, appropriate risk stratification, and discussion with the patient)					
Angina and LM stem disease	I	A	I	A	CASS, European Coronary Surgery study, VA Study, and Yusef meta-analysis
Angina and three-vessel disease with objective large ischaemia	I	A	I	A	
Angina and three-vessel disease with poor ventricular function	I	A	I	A	
Angina with two- or three-vessel disease including severe disease of the proximal LAD	I	A	I	A	
Angina CCS classes I–IV with multi-vessel disease (diabetic)	IIa	B	I	B	BARI, GABI, ERACI-I, SoS, ARTs, Yusef *et al.*, Hoffman *et al.*
Angina CCS classes I–IV with multi-vessel disease (non-diabetic)			I	A	
Angina CCS classes I–IV despite medical therapy and one-vessel disease including severe disease of the proximal LAD			I	B	MASS
Angina CCS classes I–IV despite medical therapy and one-vessel disease not including severe disease of the proximal LAD			IIb	B	
Angina with minimal (CCS class I) symptoms on medication and one-, two-, or three-vessel disease but objective evidence of large ischaemia	IIb	C			ACIP