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Unpublished but Available Clinical Trials: Pivotal Drug Studies and More

Drug companies submit unpublished clinical trial data to the U.S. Food and Drug Administration (FDA) along with each new drug application (NDA). Studies submitted include animal, Phase I, II and III, pharmacokinetic, drug interaction, and pivotal studies. There is no formal definition of a pivotal study, but they are typically Phase II or III studies that best show the safety and efficacy of a drug for its proposed indication.¹

Pivotal studies are found in FDA Approval Packages, Briefing documents from FDA Advisory Committee meetings and in the published medical literature. FDA Approval Packages, or Reviews, are a compilation of various sorts of information associated with an NDA (e.g., clinical and non-clinical studies, or administrative documents). Typically there are 15-18 different sections, including a Summary Review, Medical Review(s), and Statistical Review(s).

FDA Advisory Committees cover a number of different drug categories (e.g., anti-infective drugs, cardiovascular and renal drugs, oncologic drugs) and are made up of a group of external experts that provide the FDA with independent opinions and recommendations.² Based on summary information from an NDA and the FDA's review of application documents, Advisory Committees recommend approval or disapproval for an NDA. The FDA, however, is not obligated to abide by their recommendation. The Advisory Committees also address questions of drug safety, need for labeling changes, and other issues of importance related to FDA actions regarding medications. Before each Advisory Committee meeting, Briefing materials for the meeting are posted on the FDA web site. The Briefing materials from the Drug Sponsor and the FDA typically contain pivotal studies and may also contain information on pharmacokinetic and drug-interaction studies. A complete transcript of the meeting, and Summary Minutes for each meeting, are posted following the meeting. The materials from these meetings contain valuable insight into questions of efficacy and or safety of medications and areas in which additional investigation would be valuable. While every new drug approved by the FDA has an Approval Package there is not an FDA Advisory Committee meeting devoted to each new drug.

Not every clinical trial or pivotal study submitted with an NDA is published in the medical literature.¹ In a study of new drugs approved between 1998 and 2000, over half the trials submitted to the FDA for new drug review remained unpublished 5 years after approval.¹ Nine hundred and nine trials were identified in the FDA Approval packages for 90 newly approved drugs, of which 43% (394/909) were published in the medical literature. Of the 340 trails that were considered pivotal trials, 76% (257/340) could be found in the published medical literature. Pivotal studies and studies with statistically significant results and larger sample sizes were more likely to be published.

For one drug, none of the studies in the Approval Package were published in the medical literature. If a study was to be published it most likely occurred within the first 3 years after drug approval.

Comparative effectiveness data is also limited for newly approved, new molecular entity (NME) drugs. FDA Approval Packages are a source of comparative effectiveness data for NME drugs.³ Comparative effectiveness studies were identified in 51% (100/197) of FDA Approval Packages for 197 NMEs approved between 2000 and 2010.

Following FDA approval, there is incomplete and selective publication of trials supporting approved new drugs.¹ Trials with unfavorable results are less likely to be published than favorable trial results, resulting in bias in the published literature, and consequently bias in systematic reviews and meta-analyses.⁴ This publication bias may lead to an inappropriately favorable risk/benefit profile for a drug.¹

There can also be variance or bias in the interpretation of data from clinical trials that appears in the Approval Package, compared with what is published in the literature. O'Connor points out that 4 of the 5 randomized studies that appear in the Approval Package for pregabalin were published, and the published analyses overestimate the proportion of patients achieving a 50% reduction in pain by 20-28% compared to FDA statisticians review of the same data.⁴ Similarly, renal toxicity and mortality data present in the medical and statistical reviews of the FDA Approval Package for zoledronic acid (Zometa[®]; Novartis) did not appear in the labeling for Zometa[®].⁵ In another example, pertinent efficacy data found in the FDA Approval Package medical review for eszopiclone (Lunesta[®]; Sepracor) was absent in the labeling for Lunesta[®].⁵

As a source for comparative effectiveness data, and because there are unpublished studies and a significant potential for publication bias, it is important to seek out and utilize FDA Approval packages and Briefing Information from FDA Advisory Committee meetings. Tuttle et al., believe that information from FDA Approval packages and Briefing Documents from Advisory Committee meetings are essential in conducting thorough reviews of new drugs.⁶ Educating pharmacy students on the importance and use of these sources of drug information is recommended.⁷

FDA Approval Packages and information from FDA Advisory Committee meetings are publicly accessible on the FDA web site, but are challenging to find and navigate.^{4,7} FDA Approval Packages and Briefing Documents from FDA Advisory Committee meetings are included in the *IDIS* database. Pivotal studies, as well as other Phase I, II and III studies, drug-interaction and pharmacokinetic studies, appearing in the FDA Approval Packages and Briefing Documents can be easily found in the *IDIS* database using the following search terms combined with a specific drug term:

Descriptor: PIVOTAL STUDY 162
FDA APPROVAL PACKAGE 155
FDA ADVISORY COMMITTEE 164
OR
Journal: FDA APPROVAL PACKAGE
FDA ADVISORY COMMITTEE

In Approval Packages, the pivotal studies are typically found in the Statistical Review(s) and the Medical Review(s) sections. These sections also contain other Phase I, II and III studies. Studies of drug interactions, pharmacokinetics and pharmacodynamics are found in the Clinical Pharmacology and Biopharmaceutics Review(s) section. For FDA Advisory Committee meetings, the pivotal studies are found in the Briefing Information from Drug Sponsor and Briefing Information from FDA. Studies of drug-interactions and pharmacokinetics and other Phase I, II or III studies also often appear in these documents.

Below is an example of searching for the dabigatran etexilate pivotal studies.

On the main search screen, type the term “dabigatran” in the Drug Field.

Alternatively, you could use the Look Up button at the end of the Drug field or the Thesaurus to locate and enter the valid *IDIS* drug term in the Drug Field.

Next, click the Look Up button at the end of the Descriptor Field. A list of the *IDIS* Descriptor terms appears. The Pivotal Study descriptor is located under the heading **Government Document**. Click in the box next to PIVOTAL STUDY 162 and then click Submit.

The screenshot shows the IDIS search interface. At the top, there are navigation links: [search](#), [preferences](#), [saved searches](#), [help](#), and [log off](#). On the left side, there is a vertical menu with links: [IowaTeach](#), [IDIN Answers](#), [Thesaurus](#), [Journal](#), [Drug Hierarchy](#), [Drug A to Z List](#), [Disease Hierarchy](#), [Disease A to Z List](#), [Descriptor Definitions](#), [Index Notes](#), and [Email: idis@uiowa.edu](#). Below the menu is a **log off** button.

The main search area contains the following fields and controls:

- Buttons: [search](#) and [clear](#)
- Search criteria:
 - All Fields: [] and []
 - Drug: and [] [Look Up](#)
 - Disease: [] and [] [Look Up](#)
 - Descriptor: and [] [Look Up](#)
 - Title: [] and []
 - Author: [] and [] [Look Up](#)
 - Abstract: [] and []
 - Journal: [] and [] [Look Up](#)
 - Volume: []
 - Issue: []
 - Page: starting: []
 - Year: From: [] To: 2011
 - Only search records with abstracts
 - Article Number: []
 - Sequence Number: []
- Buttons: [search](#) and [clear](#)

The main search screen should now have “dabigatran” in the Drug Field and “PIVOTAL STUDY 162” in the Descriptor Field.

As a shortcut, once you become familiar with the descriptor terms you may find that it is convenient to enter only the number, in this case 162, for the descriptor in the Descriptor Field.

Click the “search” button and the index records for the articles matching the search criteria will appear on screen.

The screenshot shows the IDIS search results page. At the top, there are navigation links: [search](#), [preferences](#), [saved searches](#), [help](#), and [log off](#). On the left side, there is a vertical menu with links: [IowaTeach](#), [IDIN Answers](#), [Thesaurus](#), [Journal](#), [Drug Hierarchy](#), [Drug A to Z List](#), [Disease Hierarchy](#), [Disease A to Z List](#), [Descriptor Definitions](#), [Index Notes](#), and [Email: idis@uiowa.edu](#). Below the menu is a **log off** button.

The main results area contains the following elements:

- Buttons: [Show/Hide Details](#)
- Results summary: Results of Drug(s): dabigatran and Descriptor(s): "PIVOTAL STUDY 162"
- Display controls: [Display Amount: 25](#) [Output/Display Format: Full Results](#) [Adjust](#)
- Page information: **Items #1-#8 of 8**, **Total Pages: 1**, **PAGE: 1**
- Actions:
 - Select All On This Page
 - Save Query: [Perform](#)
 - E-Mail Results:
 - Bibliographic
 - Text
 - Email Address: [] [Perform](#)
 - Print Results: [Perform](#)
- Section header: **Full Results**
- Article details:
 - Article Number: [647630](#)
 - Sequence Number: 738595
 - 1 MEDICAL REVIEW(S). DABIGATRAN ETEXILATE MESYLATE, PRADAXA, FDA APPROVAL PACKAGE FOR NDA 22-512 (REF ART 647615-647630)**
 - Author(s): ANONYMOUS
 - FDA APPROVAL PACKAGE, vol , iss , p , yr 2010
 - Drug(s): **DABIGATRAN ETEXILATE 20120449**; WARFARIN 20120208
 - Disease(s): FIBRILLATION, ATRIAL 427.3; DISORDER, KIDNEY/URETER NEC 593.; PROPHYLAXIS NEC V07.; EMBOLISM/THROMBOSIS, VN NEC 453.; EMBOLISM/THROMBOSIS, CEREB 434.; DISEASE, CEREBROVASCULAR NEC 436.; DISEASE, LIVER, CHRONIC NEC 571.; RACE V87.

Scrolling through this list you will see the pivotal studies for dabigatran appear in the Medical Review(s) and Statistical Review(s) from the dabigatran FDA Approval Package, the Briefing Information from a FDA Advisory Committee meeting, and were also published in the Lancet and The New England Journal of Medicine.

To view any of these articles click on the Article Number link.

To return to the Main search screen, click on the search button near the top of the page or click the back arrow on your browser. Your original search terms should still be there.

We continually monitor the FDA web site and update the *IDIS* database monthly as Approval Packages and Advisory Committee meeting documents are posted on

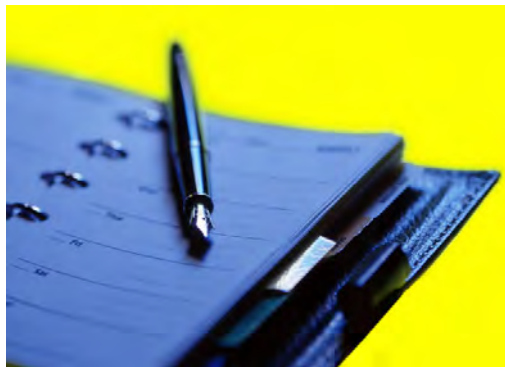
the FDA web site. The Iowa Drug Information Service (*IDIS*) has been adding FDA Approval Packages [formerly Summary Basis of Approvals (SBA)] to the *IDIS* database since 1998. FDA Advisory Committee meetings have been a part of the database since 2006.

References

1. Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: A literature analysis. *PLoS Med.* 2008;5:e191.
2. Available at: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/default.htm>. Accessed 09/08, 2011.
3. Goldberg NH, Schneeweiss S, Kowal MK, Gagne JJ. Availability of comparative efficacy data at the time of drug approval in the united states. *JAMA.* 2011;305:1786-1789.
4. O'Connor AB. The need for improved access to FDA reviews. *JAMA.* 2009;302:191-193.
5. Schwartz LM, Woloshin S. Lost in transmission--FDA drug information that never reaches clinicians. *N Engl J Med.* 2009;361:1717-1720.
6. Tuttle DA, Sasich LD, Sukkari SR. Improving access to FDA reviews and documents. *JAMA.* 2009;302:2204; author reply 2205.
7. Sasich LD, Sukkari SR, Cook GE, Tuttle DA. The importance of FDA approval packages and briefing documents in pharmacy education. *Am J Pharm Educ.* 2009;73:126.



Brad Gilchrist is a 1990 graduate of the University of Iowa College of Pharmacy (B.S., R.Ph.). His current position at DDIS is Drug Information Pharmacist. In addition to indexing articles for the database, his other main responsibility is overseeing the acquisition, formatting and indexing of the FDA Approval Packages.



It is time to renew your *IDIS* Database Subscription!

The 2012 *IDIS* subscription renewal materials were sent to the contact person on your account in mid-September. We urge you to notify us of your subscription renewal intentions as soon as possible. To avoid interruption of service, we do need to receive your renewal by January 1, 2012. Do not hesitate to contact our office if you have questions about your renewal idis@uiowa.edu. Thank you for your prompt attention to your 2012 *IDIS* subscription renewal and your continued interest in the *Iowa Drug Information Service*!

Remembering

Donna K. Brus

Division of Drug Information Service

Administrative Assistant II

January 1, 1952 – August 14, 2011



Donna started working at the Division of Drug Information Service (DDIS) in October of 1983; prior to coming to DDIS she worked at the Business Office and at University of Iowa Hospitals and Clinics in the Department of Obstetrics and Gynecology. She was the third “office manager” for DDIS and left in 2008 due to health reasons. The position fit her well and during her tenure she facilitated many changes in products and production and eased many new staff members in and out of their positions. She kept the group connected with the rest of the University, and, above all, she was a strong advocate for *IDIS* subscribers. Donna brought continuity and strength to DDIS during four changes in division directors and one interim director. Through her work at DDIS she developed many relationships throughout the University and beyond.

Donna was an avid Hawkeye fan and especially enjoyed tailgating with her “Hawkeye” friends. She looked forward to her yearly fishing trips to Canada and was a twenty-six year member of the North Liberty American Legion Auxiliary. She was a trusted and reliable colleague and friend.

Iowa Drug Information Service Travels to India

2011 International Pharmaceutical Federation (FIP) Meeting—Hyderabad

Dr. Kevin Moores, Director, Division of Drug Information Service, University of Iowa College of Pharmacy, attended the 71st World Congress of Pharmacy and Pharmaceutical Sciences of the International Pharmaceutical Federation (FIP) from September 3-8 in Hyderabad, India. Almost 2000 delegates from around the world representing pharmacy education, pharmacy practice, pharmacy professional associations and other professionals from various fields in the pharmaceutical sector attended this Congress. The theme of the program centered on increasing safety and quality of medicines on a global level. Dr. Moores also attended the workshop on Pharmacovigilance and Medicines Information to Enhance Patient Safety organized by the Pharmacy Information Section of FIP, of which Dr. Moores is a member. During the Congress, Dr. Moores represented the Division of Drug Information Service and demonstrated the **Iowa Drug Information Service (IDIS)** database in the exhibit program. On September 2nd he was a guest at the Inauguration Ceremony for the new USP—India Private Limited Building in IKP Knowledge Park, Hyderabad, India.



Dr. Kevin G. Moores,
Director, Division of Drug
Information Service

IDIS Participates in International Experiential Education in Pharmacy Practice Seminar

Dr. Kevin Moores, Director, Division of Drug Information Service, University of Iowa College of Pharmacy, provided a presentation and 3 hour workshop on Incorporating Evidence-Based Medicine into Clinical Practice and Practical Tools for Information Mastery, as part of an International Seminar on Experiential Education in Pharmacy Practice, September 10-11, sponsored by the JSS College of Pharmacy, Mysore, India and the Pharmacy Council of India. Approximately 200 delegates of pharmacy faculty and students from across India attended the two-day event, where the theme was Developing Practice Skills Through Experiential Education. During the opening ceremony for this seminar, Dr. Moores had the honor of launching the Poison Information Centre website for the first time in public to inaugurate the opening of this new service from JSS College of Pharmacy, Mysore.



Pictured: JSS University Vice-Chancellor Dr. B. Suresh inaugurating the International Seminar on 'Experiential Education in Pharmacy Practice' at JSS College of Pharmacy September 10. Others seen are (from left) Dr. H.G. Shivakumar, Principal, Dr. Mruthyunjaya P. Kulenur, Registrar, Dr. Kevin Moores, Mr. Mike Rouse, Dr. Lucinda Maine, Dr. Wafa Dahdal and Dr. G. Parthasarathi.

Dr. Moores Presents at JSS University Staff Development Program

Dr. Kevin Moores, Director, Division of Drug Information Service, University of Iowa College of Pharmacy, provided an 8 hour workshop on September 13 as part of a 2-week Staff Development Program, at JSS University College of Pharmacy, Mysore. The topic of Dr. Moores' workshop was drug therapy research methods and clinical interpretation of the primary literature covering randomized, controlled trials, cohort studies, case control studies and meta-analysis. The workshop was attended by approximately 50 faculty and students from colleges of pharmacy in India.

New Molecular Entities & Biologicals

*FDA Approvals
June 2011-August 2011*

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor 155 FDA APPROVAL PACKAGE in combination with the valid drug term to retrieve these documents from the *IDIS* database.

For some newly approved drugs, the FDA Approval Package may not yet be available. If the medication has been reviewed by one of the FDA Advisory Committees, you may still access data from pivotal studies, even those that have not been published in peer reviewed literature. These Committee reports are indexed in the *IDIS* database using the descriptor "FDA ADVISORY COMMITTEE 164". In addition to access to data from pivotal studies, these reports provide critical commentary from the Advisory Committee members, and specific, important questions related to the use and safety of the medication.

Generic Name Trade Name (FDA Review Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Brentuximab Vedotin <i>Adcetris</i> (BIOL)	Seattle Genetics (August 19, 2011)	BRENTUXIMAB VEDOTIN 10120945 FDA Approved Indication (2 citations) Total (2 citations)	Refractory lymphomas. Injection.	Lympho-/Reticulosarcoma 200. Hodgkin's Disease 201.
Crizotinib <i>Xalkori</i> (P)	Pfizer (August 26, 2011)	CRIZOTINIB 10120949 FDA Approved Indication (12 citations) Total (23 citations)	Lung cancer. Oral Capsule.	NEOP, MGN- Bronchus/Lung 162.
Ezogabine <i>Potiga</i> (S)	Valeant Pharms (June 10, 2011)	EZOZABINE 28122039 FDA Approved Indication (11 citations) Total (21 citations)	Partial-onset seizures. Oral Tablet.	Epilepsy, Part No Impair Consc 345.5 Epilepsy, Part W Impair Consc 345.4
Icatibant acetate <i>Firazyr</i> (O)	Shire Orphan Therapies (August 25, 2011)	ICATIBANT 95000097 FDA Approved Indication (30 citations) Total (49 citations)	Hereditary angioedema. Injection.	Disorder, Metabolic NEC 277.
Indacaterol maleate <i>Arcapta Neohaler</i> (S)	Novartis (July 1, 2011)	INDACATEROL 12120057 FDA Approved Indication (18 citations) Total (21 citations)	Chronic obstructive pulmonary disease (COPD). Inhalation Powder.	Obstruction, Air, Chr NEC 496.
Rivaroxaban <i>Xarelto</i> (S)	Johnson & Johnson (July 1, 2011)	RIVAROXABAN 20120451 FDA Approved Indication (47 citations) Total (169 citations)	Prevent blood clots, deep vein thrombosis, and pulmonary embolism following knee or hip replacement surgery. Oral Tablet.	Embolism/Thrombosis, VN NEC 453. Embolism, Pulmonary 415.1 Prophylaxis NEC V07.

Ticagrelor <i>Brilinta</i> (S)	Astrazeneca LP (July 20, 2011)	TICAGRELOR 20120673 FDA Approved Indication (99 citations) Total (141 citations)	Acute coronary syndrome. Oral Tablet.	Infarction, Myocard, Acute 410.
Vemurafenib <i>Zelboraf</i> (S)	Hoffman-La Roche (August 17, 2011)	VEMURAFENIB 10120939 FDA Approved Indication (9 citations) Total (12 citations)	Metastatic melanoma. Oral Tablet.	Melanoma, Malignant, Skin 172.

Review Classification:

S=Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA=Accelerated Approval

FT=Fast Track

P=Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL=Biological

O=Orphan

Selected Bibliography

Ezogabine

French JA, Abou-Khalil BW, Leroy RF, et al. Randomized, double-blind, placebo-controlled trial of ezogabine (Retigabine) in partial epilepsy. *Neurology*. 2011; 76:1555-1563. (IDIS Article Number 656330)

This multicenter trial randomized 305 patients with drug-resistant partial onset seizures to oral ezogabine at doses titrated to 1200 mg/day in 3 divided doses (n = 153), or placebo (n = 152). Titration took place during an 18-week treatment period, followed by a 12-week maintenance period. Results showed a median percent reduction in total partial seizure frequency of 44.3% vs 17.5% (p<0.001) for ezogabine and placebo respectively during the treatment period, and 54.5% and 18.9% (p<0.001) respectively during the maintenance period. Side effects more common in the study drug group were dizziness, somnolence, fatigue, confusion, dysarthria, urinary tract infection, ataxia and blurred vision.

Icatibant acetate

Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med*. 2010; 363:532-541. (IDIS Article Number 642259)

Two double-blind, randomized, multicenter trials evaluated the effect of icatibant in patients with hereditary angioedema presenting with cutaneous or abdominal attacks. The For Angioedema Subcutaneous Treatment (FAST) 1 trial randomized 56 patients to subcutaneous icatibant 30 mg (n = 27), or placebo (n = 29). The FAST 2 trial randomized patients to the same icatibant dose (n = 36), or 3 gm daily of oral tranexamic acid for 2 days (n = 38). The primary end point was median time to clinically significant relief of the index symptom. In FAST 1, primary end point was reached in 2.5 hours with icatibant and in 4.6 hours with placebo (p = 0.14), and for FAST 2 in 2.0 hours with icatibant and 12.0 hours with tranexamic acid (p<0.001). Three recipients of icatibant and 13 recipients of placebo required treatment with rescue medication. No serious adverse events were reported with icatibant.

Indacaterol maleate

Chapman KR, Rennard SI, Dogra A, et al. Long-term safety and efficacy of indacaterol, a long-acting β_2 -agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest*. 2011; 140:68-75. (IDIS Article Number 660541)

In this 2-part study, patients with moderate to severe chronic obstructive pulmonary disease (COPD) were randomized to 26-weeks of 150 μ g (n = 144) or 300 μ g (n = 146) inhaled indacaterol once daily, tiotropium, or placebo (n = 125). Consenting patients who had received indacaterol or placebo then continued on to a 26-week extension period. Data presented in the study was derived from the 415 patients who completed the entire 52-week study period. Indacaterol had no significant effects on ECG findings, on serum potassium or on plasma glucose levels. Results showed that, compared with placebo, indacaterol increased trough FEV1 throughout the study, and showed significant reductions on COPD exacerbations (p<0.05), and reductions in as-needed albuterol use (p<0.001). No tolerance to the bronchodilator effect of indacaterol was observed.

Rivaroxaban

Turpie AG, Lassen MR, Davidson BL, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *Lancet*. 2009; 373:1673-1680. (IDIS Article Number 617088)

Efficacy of rivaroxaban was assessed in 3148 patients undergoing knee arthroplasty in this randomized, double-blind Phase III trial. Patients received oral rivaroxaban (n = 1584, n = 965 included in primary efficacy outcomes) once daily starting 6-8 hours after surgery, or

subcutaneous enoxaparin (n = 1564, n = 959 included in primary efficacy outcomes) 30 mg every 12 hours starting 12-24 hours after surgery. The primary efficacy end point was the composite of any deep vein thrombosis, non-fatal pulmonary embolism, or death from any cause up to day 17 post surgery. Investigators found that the primary efficacy outcome occurred in 67 (6.9%) of 965 patients in the rivaroxaban group and in 97 (10.1%) of 959 in the enoxaparin group, (absolute risk reduction 3.19%, 95% CI 0.71-5.67; p = 0.0118). Major bleeding occurred in 10 (0.7%) of 1526 patients in the rivaroxaban group and in 4 (0.3%) of 1508 patients in the enoxaparin group, (p = 0.1096).

Ticagrelor

Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009; 361:1045-1057. (IDIS Article Number 623769)

A total of 18,624 patients with an acute coronary syndrome, with or without ST-segment elevation, were included in this multicenter, double-blind, randomized trial that compared ticagrelor at doses of 180 mg loading dose and 90 mg twice daily thereafter, and clopidogrel at 300-600 mg loading dose and 75 mg daily thereafter. The primary end point was the composite of death from vascular causes, myocardial infarction, or stroke. Results showed that at 12 months the primary end point occurred in 9.8% of patients in the ticagrelor group and in 11.7% of those in the clopidogrel group (HR, 0.84; 95% CI, 0.77-0.92; p<0.001). The death rate from any cause was less in the ticagrelor group compared with clopidogrel, 4.5% vs 5.9% respectively (p<0.001). There was no significant difference in the rate of major bleeding between the groups, but in the ticagrelor group there was a higher rate of major bleeding not related to coronary artery bypass grafting (4.5% vs 3.8%; p = 0.03), including more cases of fatal intracranial bleeding, but fewer cases of other types of fatal bleeding.

Vemurafenib

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011; 364:2507-2516. (IDIS Article Number 660208)

This Phase III randomized trial compared vemurafenib 960 mg orally twice/day (n = 337) with intravenous dacarbazine 1000 mg/square meter of body surface area every 3 weeks (n = 338) in previously untreated patients with metastatic melanoma and the BRAF V600E mutation. Rates of overall and progression-free survival were co-primary end points. At 6 months, the overall survival in the vemurafenib group was 84% (95% CI, 78-89) and 64% (95% CI, 56-73) in the dacarbazine group. Response rates were 48% for vemurafenib and 5% for dacarbazine. An independent data and safety monitoring board recommended a crossover from dacarbazine to vemurafenib after a review of the interim analysis. Adverse effects associated with vemurafenib were arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous-cell carcinoma, photosensitivity, nausea and diarrhea.

Dr. Nicola Sarrazin is a 1984 graduate of the University of Iowa (B.A. in Anthropology and Asian Studies) and a 1997 graduate of the University of Iowa College of Pharmacy (Pharm.D.). Since that time she has been a pharmacist in the College of Pharmacy's Division of Drug Information Service. Nickie's responsibilities include indexing articles for the IDIS database, overseeing the Drug vocabulary and contributing articles for the *World of Drug Information* newsletter.

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