Strategies for future drugs

- Individualized therapy
- Safety
- Risk assessment
- Novel etiologies
- Drug delivery & biopharma
- Chronobiology
- Novel biomarkers
- Supplemental & alternative medicine
- Tissue engineering

Spending in 2016

Source: IMS Institute for Healthcare Informatics, May 2012

Revenue-Generating Power of Orphan Drugs

Orphan drugs =Treatment for rare diseases

Average Present Value (2010)

Orphan Drugs=
$637 Million

Non-Orphan Control Drugs=
$638 Million

Top 10 Orphan Drugs

40% Oncology Drugs
EALRP = **$70** billion/per drug

60% Treat Other Diseases
EALRP = **$41** billion/per drug

EALRP = Estimated Average Lifetime Revenue Potential

Compound Annual Growth Rate (2001-2010)

Orphan Drugs
25.8%

Non-Orphan Drugs
20.1%

Source:
Thomson Reuters Cortellis

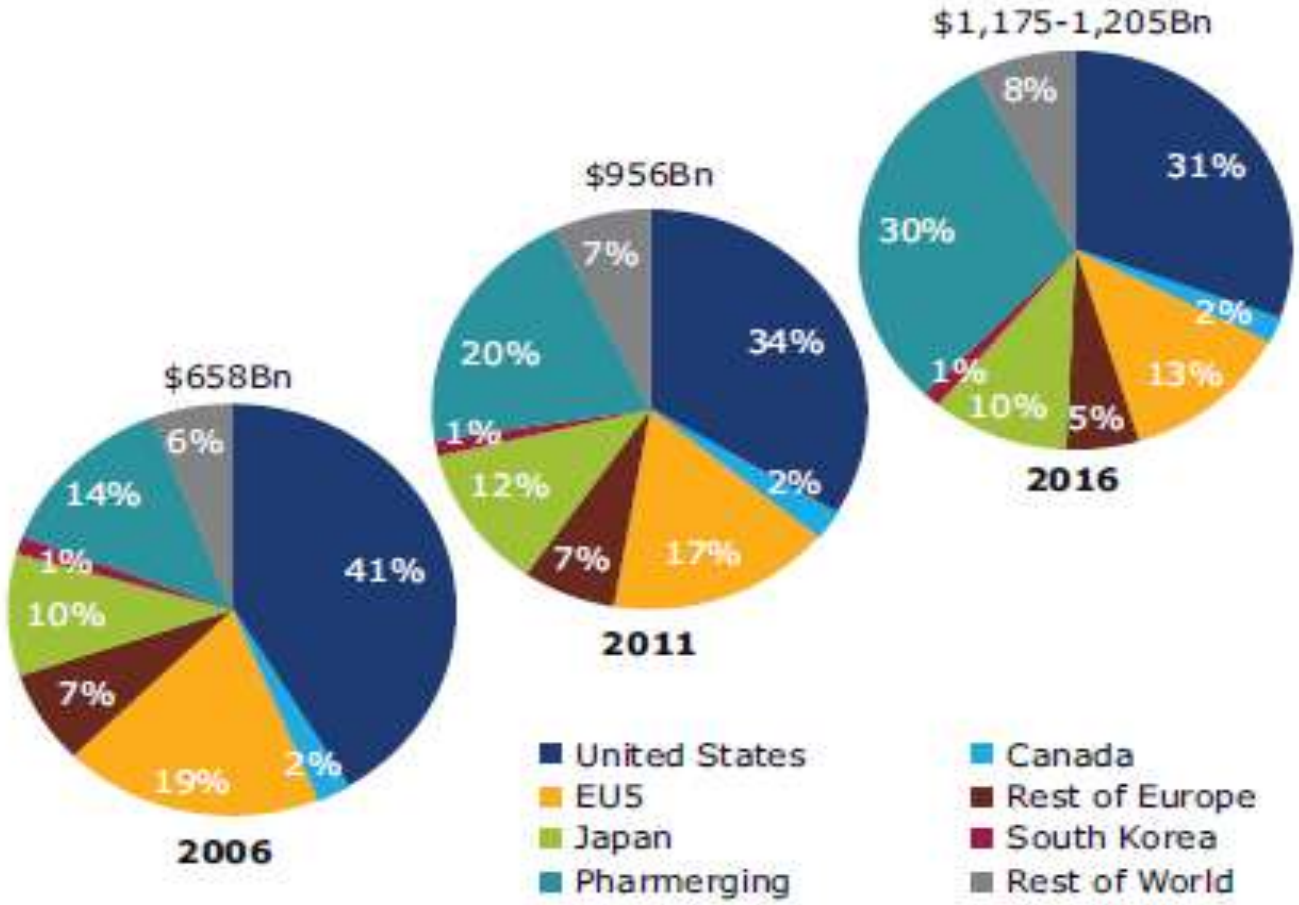
THOMSON REUTERS

TOP REVENUE GENERATING ORPHAN DRUGS

GENERIC NAME	THERAPY AREA	DISCOUNT PV (B)	PRESENT DAY PEAK SALES VALUE (B)
Rituximab	Oncology	$154	$7
Ranibizumab	Ophthalmology	$74	$5
Somatropin (epr)	Metabolism	$62	$3
Lenalidomide	Oncology	$60	$5
Imatinib mesylate	Oncology	$42	$5
Filgrastim	Hematology	$42	$2
Glatiramer Acetate	MSP	$40	$4
Recombinant Factor VIII; Octocog alfa	Hematology	$28	$1
Bosentan (monohydrate)	Cardiovascular	$27	$2
Bortezomib	Oncology	$24	$2

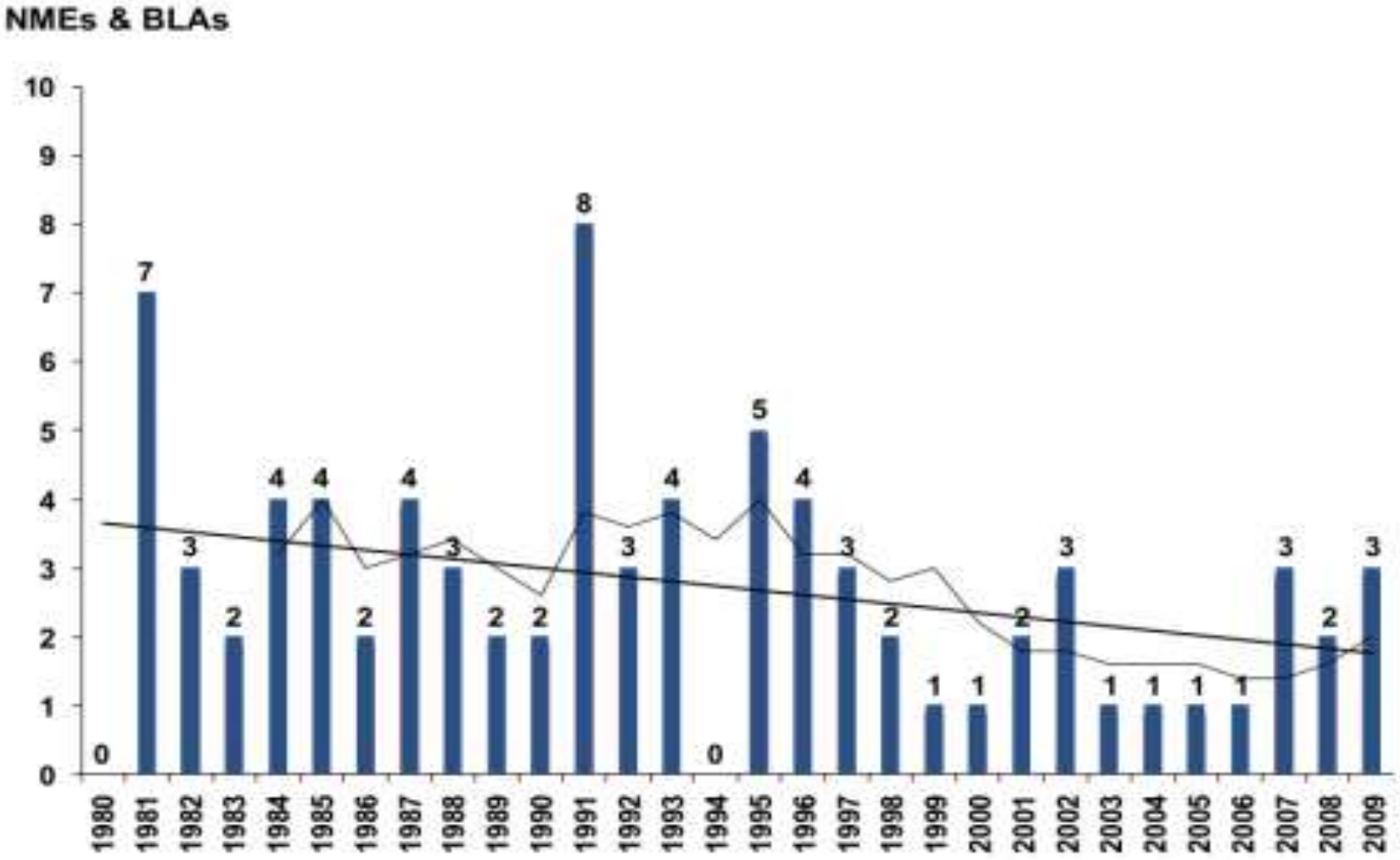
Source: Thomson Reuters Cortellis

Spending by Geography

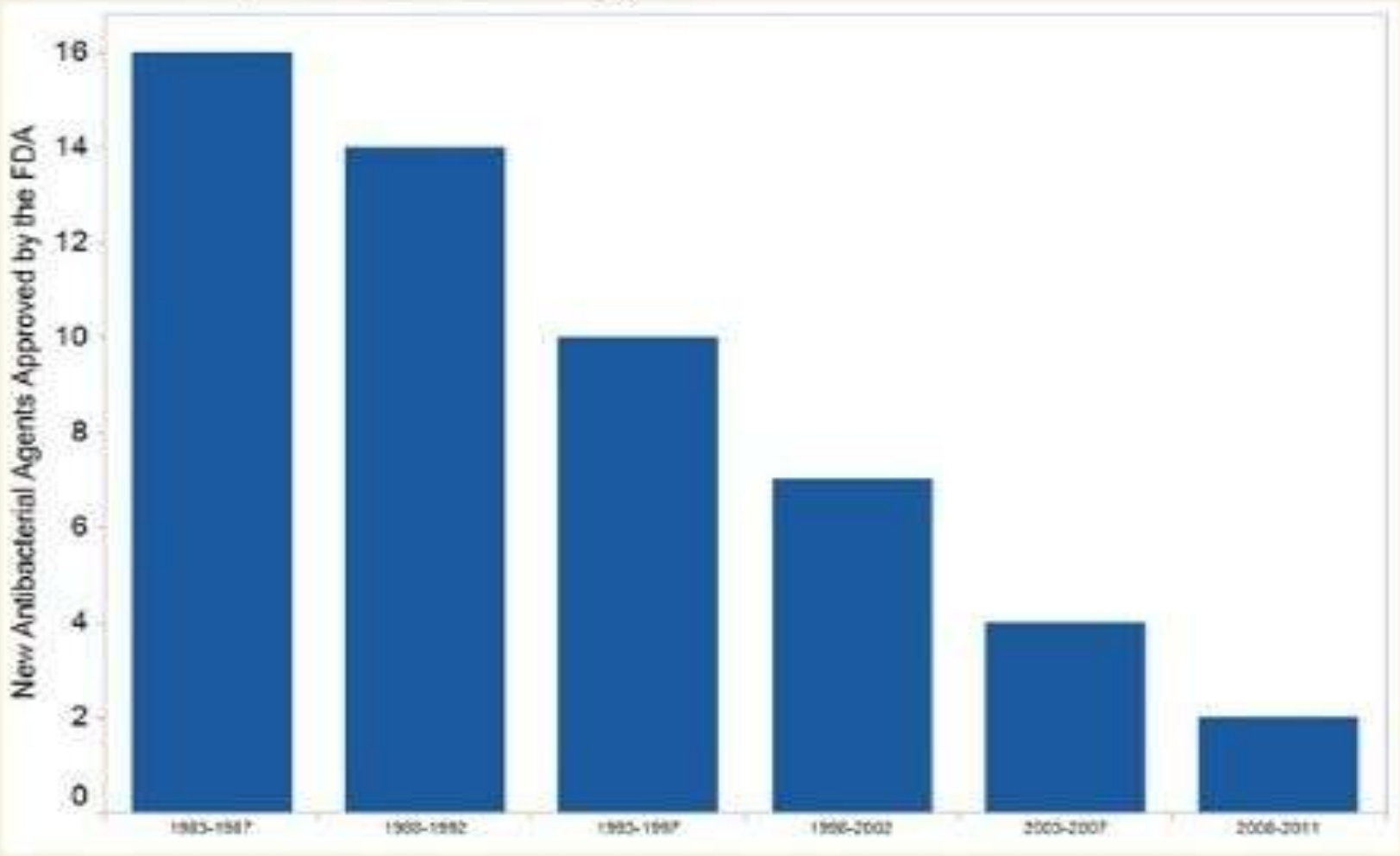


Source: IMS Market Prognosis, May 2012

Chart 29. Cardiovascular System Drugs Approved by the FDA (1980-2009).
Marketed Drugs, Linear Trend & 5 Year Moving Average

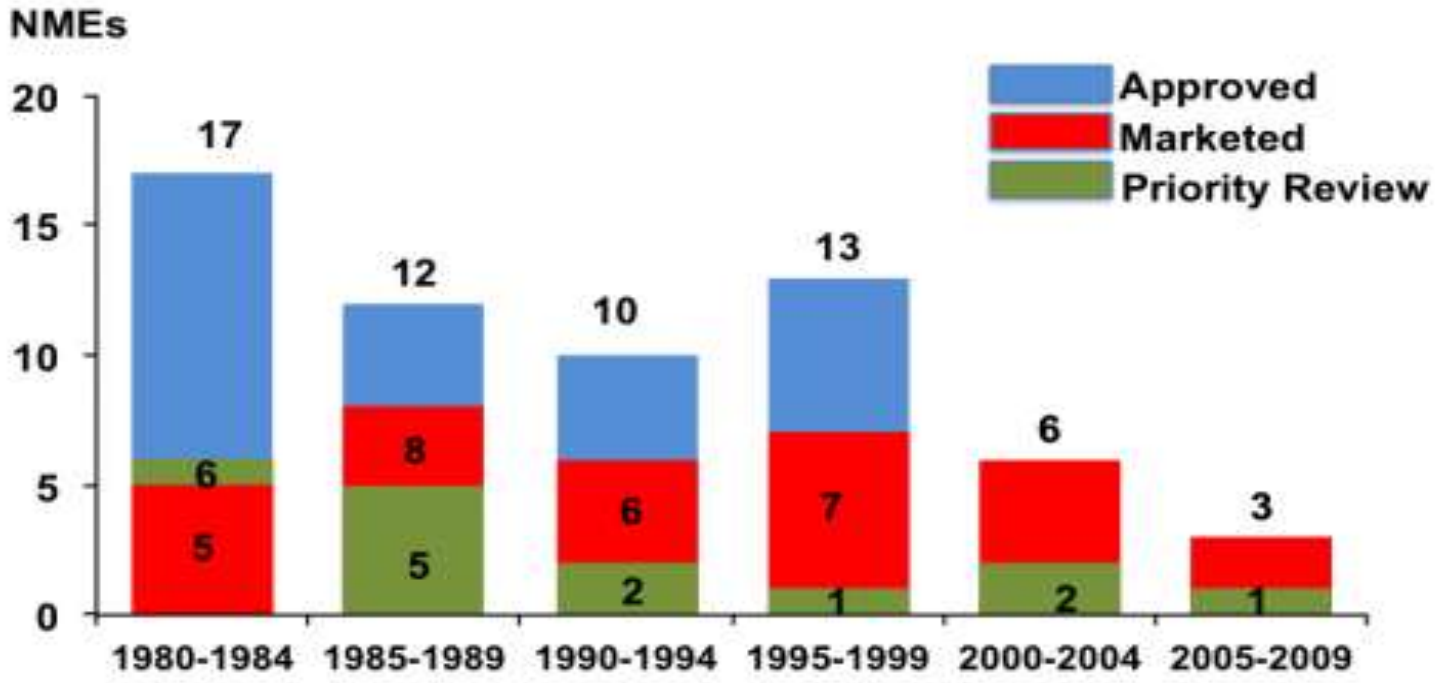


Decline in FDA approval of new antibiotic agents



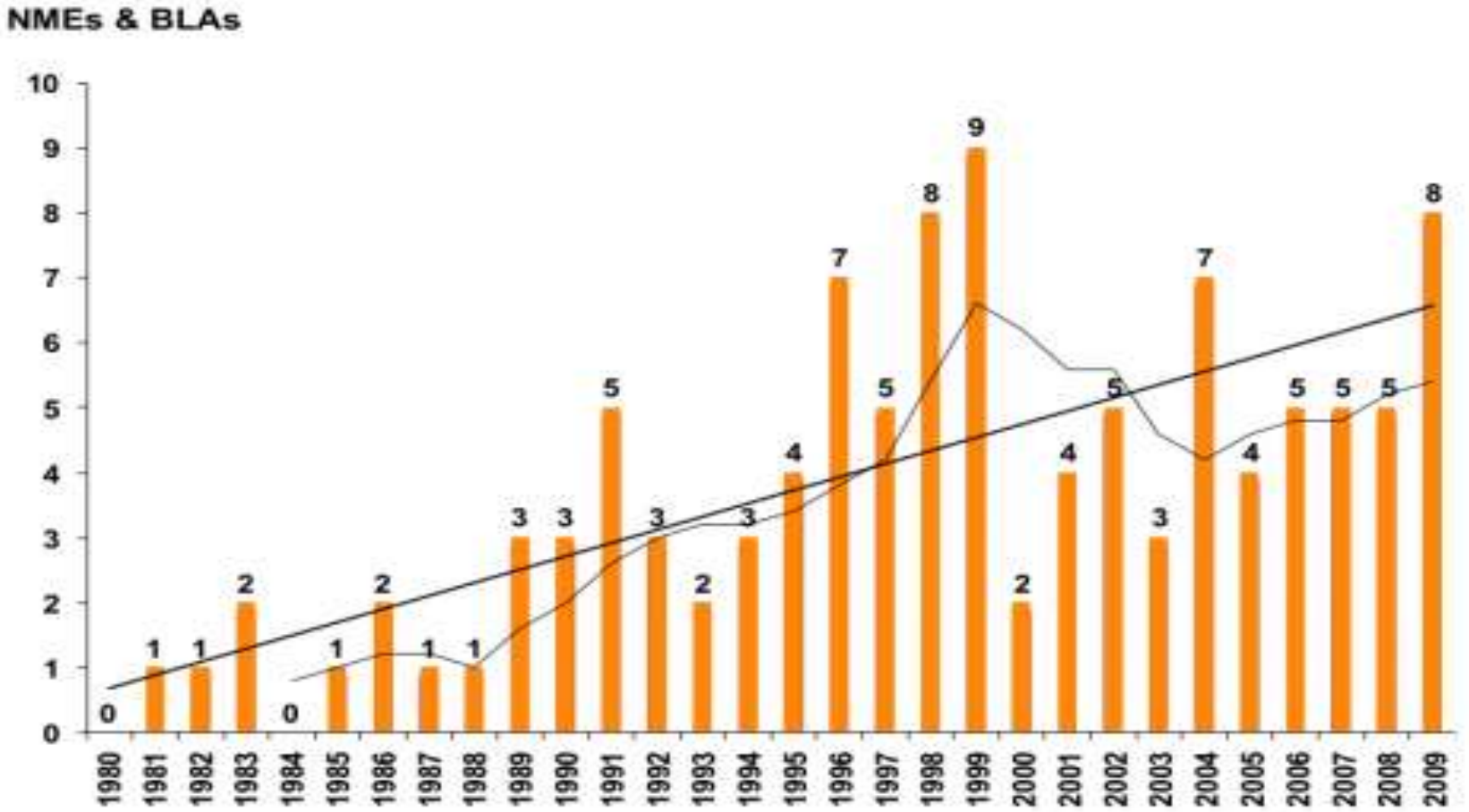
Source: Infectious Diseases Society of America

Chart 3b. Systemic Antibacterial NMEs Approved by the FDA (1980-2009)



Marketed = Products still in the market in August 1, 2010.

Chart 27. Antineoplastic & Immunomodulating Agents Approved by the FDA (1980-2009). Marketed Drugs, Linear Trend & 5 Year Moving Average



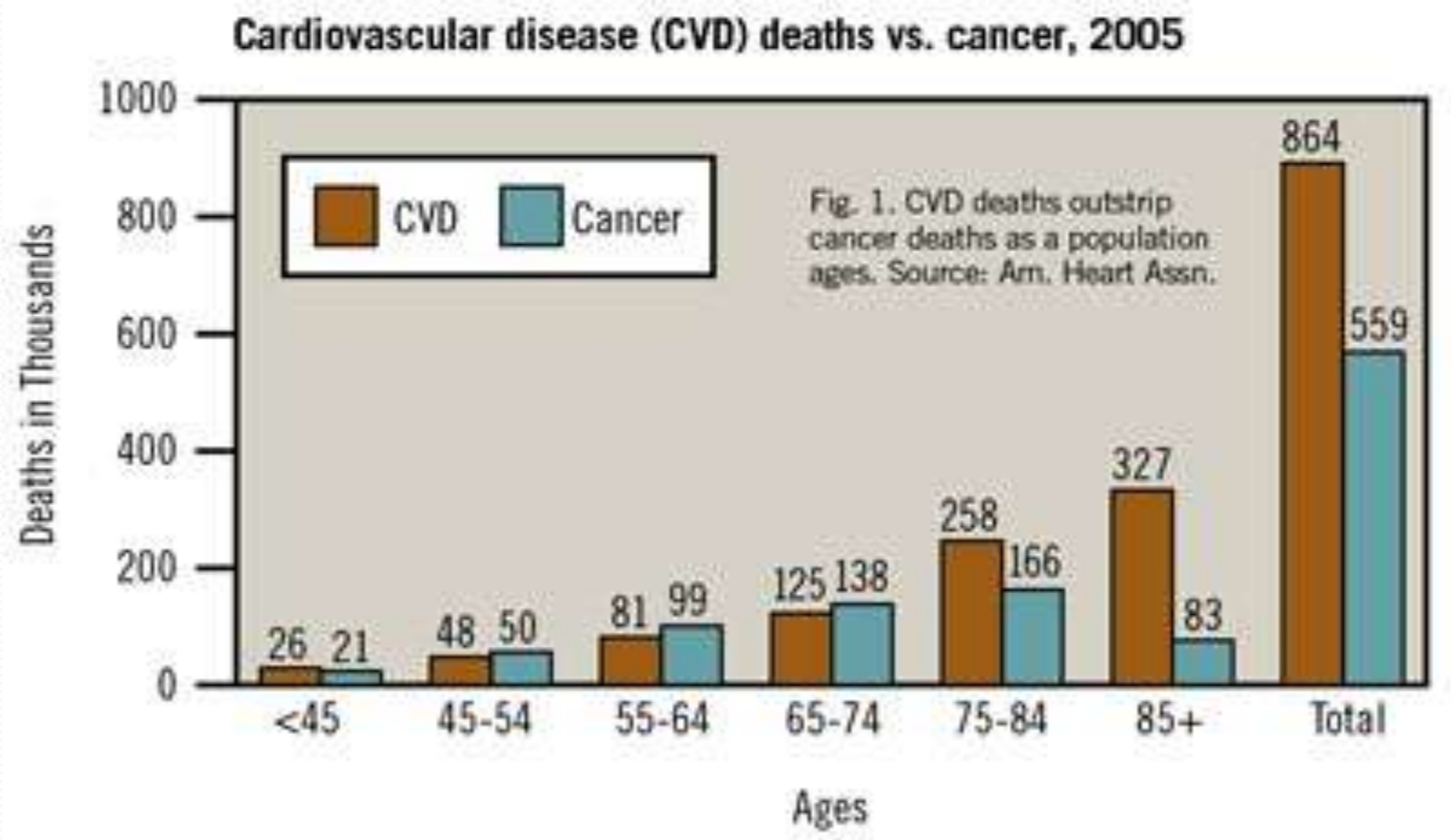
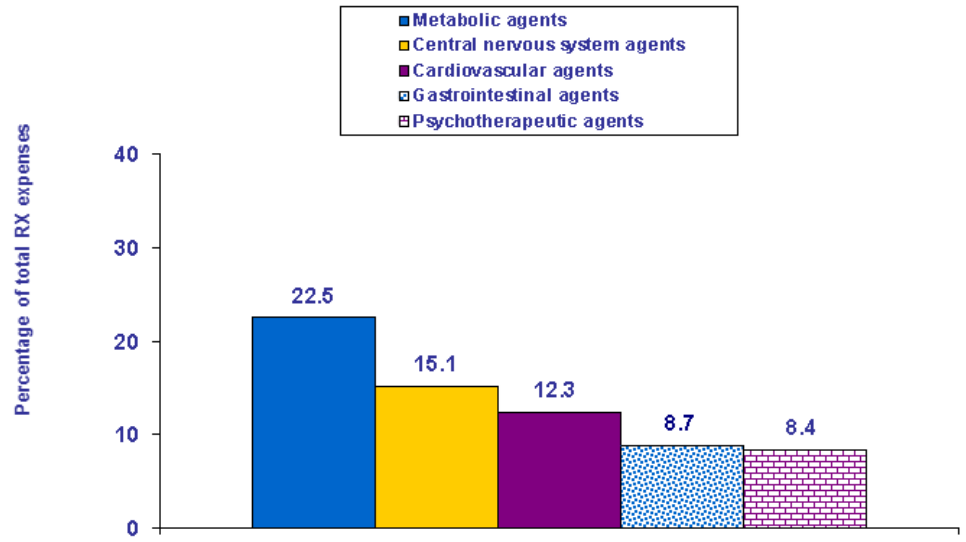
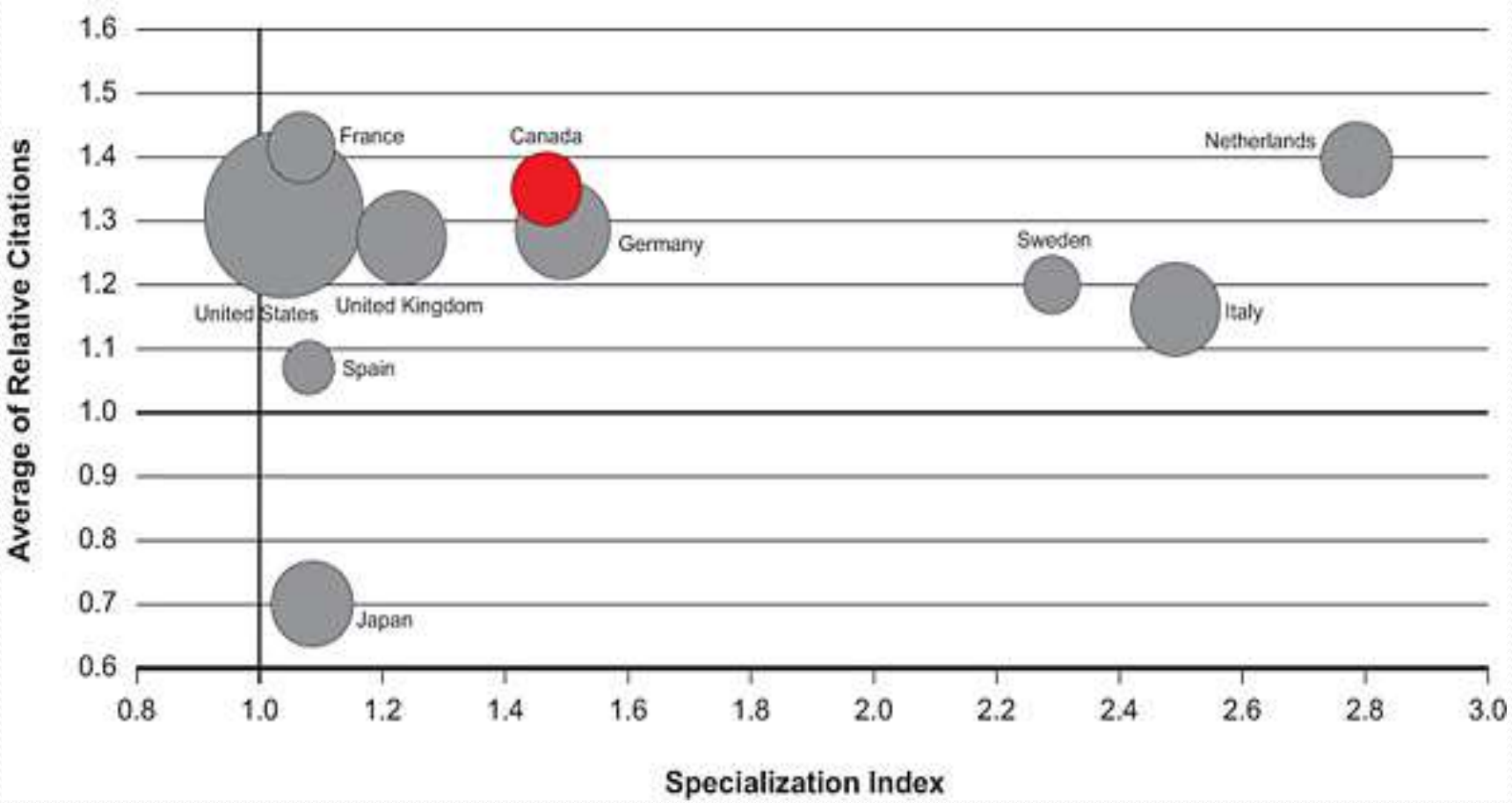

Cardiovascular disease (CVD) deaths vs. cancer, 2005
Deaths in Thousands
1000
800
600
400
200
0
CVD
Cancer
Fig. 1. CVD deaths outstrip cancer deaths as a population ages. Source: Am. Heart Assn.
26
21
48
50
81
99
125
138
258
166
327
83
864
559
<45
45-54
55-64
65-74
75-84
85+
Total
Ages

Figure 3. Top five therapeutic classifications as percentages of total prescribed drug expenses for adults age 18 and older, 2008



Source: Center for Financing, Access, and Cost Trends, AHRQ, Household and Pharmacy Components of the Medical Expenditure Panel Survey, 2008


Average of Relative Citations
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
France
Canada
Netherlands
Germany
Sweden
United States
United Kingdom
Italy
Spain
Japan
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
Specialization Index

Drug name	Molecule	Maker	Type	Sales, $ million
Lipitor	(atorvastatin calcium)	Pfizer	anti-dyslipidemic	$13,530
Plavix	(clopidogrel bisulfate)	Sanofi Aventis/Bristol-Myers Squibb	anti-platelet agent	$8,073
Diovan	(valsartan)	Novartis	anti-hypertensive	$5,012
Lovenox	(enoxaparin sodium injection)	Sanofi Aventis	anti-coagulant	$3,576
Cozaar/Hyzaar	(losartan potassium and losartan potassium with hydrochlorothiazide)	Merck	anti-hypertensive	$3,350
Norvasc	(amlodipine besylate)	Pfizer	anti-hypertensive	$3,001
Crestor	(rosuvastatin calcium)	AstraZeneca	anti-dyslipidemic	$2,887
Vytorin	(ezetimibe/simvastatin)	Merck/Schering-Plough	anti-dyslipidemic	$2,838
Zetia	(ezetimibe)	Merck/Schering-Plough	anti-dyslipidemic	$2,373
Micardis	(tolmisartan)	Boehringer Ingelheim	anti-hypertensive	$2,085

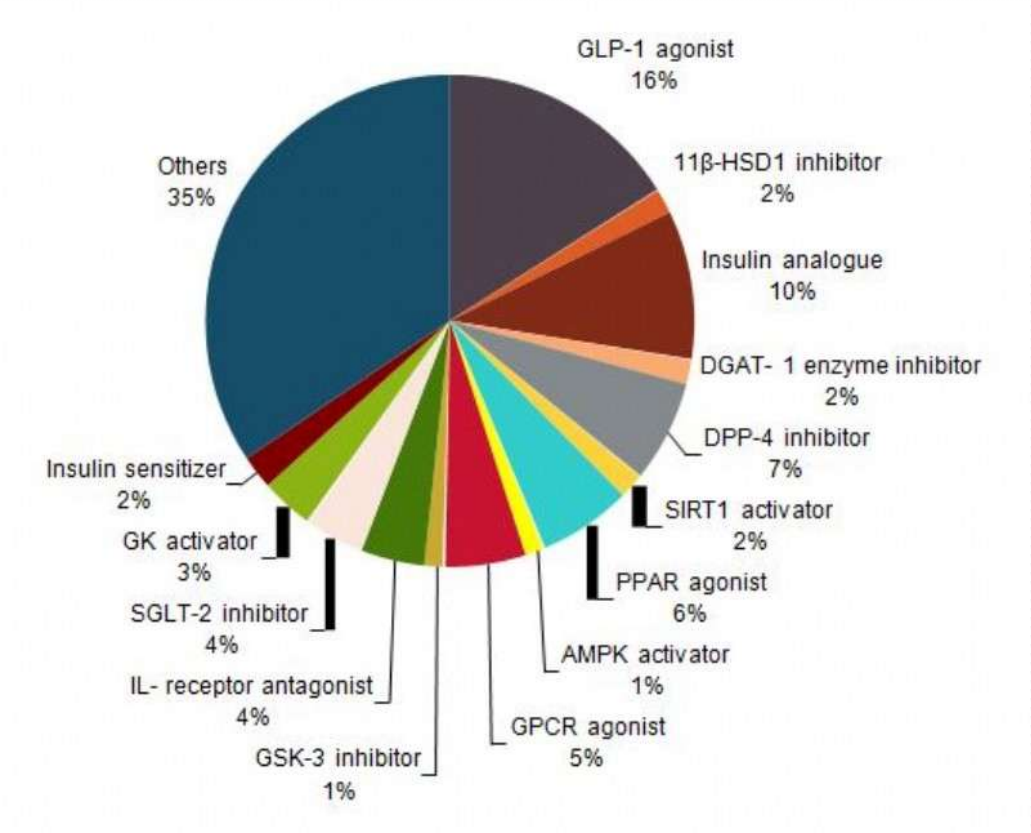
Fig. 3. Top Ten Cardiovascular Drugs, 2007, source: Decision Resources

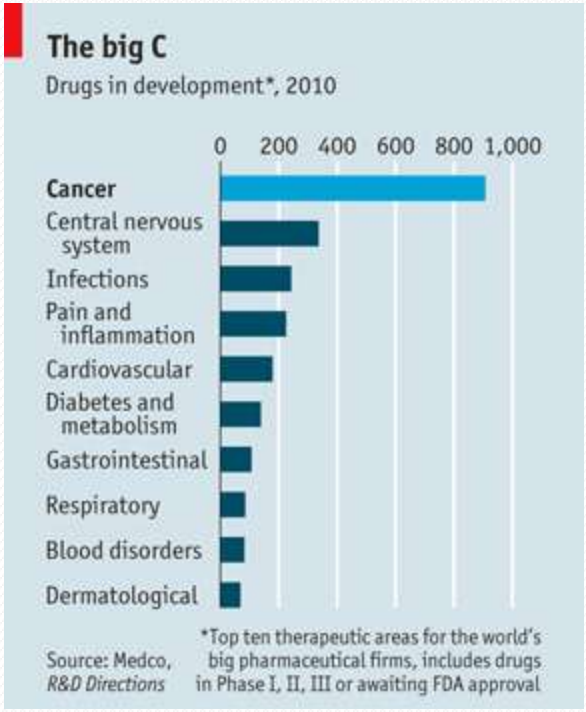
PROTECTION EXPIRY YEAR	US		JAPAN	UK	FRANCE	GERMANY
2012	Plavix® Seroquel® Singulair® Actos® Lexapro®	Diovan® Diovan HCT® Geodon® Viagra® Boniva®	Nu Lotan Myslee® Preminent Haigou Seroquel®	Lipitor® Amias Seroquel® Aricept® Singulair®	Tahor Singulair® Pariet® Ixprim Aprovel	Seroquel® Atacand® Atacand® Plus Sortis® Aricept®
2013	Oxycontin® Aciphex® Zometa®	Xeloda® Opana® ER Asacol®	Diovan® Plavix® Livalo® Elplat®	Viagra® Xeloda®	Seretide® Coaprovel Xeloda® Micardis® Viagra®	Viani® Zometa® Atmadisc® Coaprovel Viagra®
2014	Nexium® Cymbalta® Celebrex® Symbicort®	Lunesta® Restasis® Evista® Sandostatin® LAR Actonel®	Prograf® Glivec® Abilify®	Abilify® Cipralex® Risperdal® Consta®	Seroplex® Abilify® Ebixa® Risperdal® Consta® LP	Axura Risperdal® Consta® Blopress Plus®
2015	Abilify® Copaxone® Gleevec® Namenda®	Provigil® Combivent® Zyvox® Prezista® Avodart®	Zyprexa® Adoair® Alimta® Spiriva® Symbicort®	Spiriva® Cymbalta® Alimta®	Alimta® Spiriva® Copaxone® Protelos® Cymbalta®	Spiriva® Copaxone® Alimta® Cymbalta®
2016	Crestor® Benicar® Benicar HCT® Cubicin®		Blopress Baraclude®	Glivec® Vfend®	Glivec® Cancidas® Vfend®	Glivec® Zyvoxid Vfend®

Source: IMS MIDAS, May 2012

Appendix notes

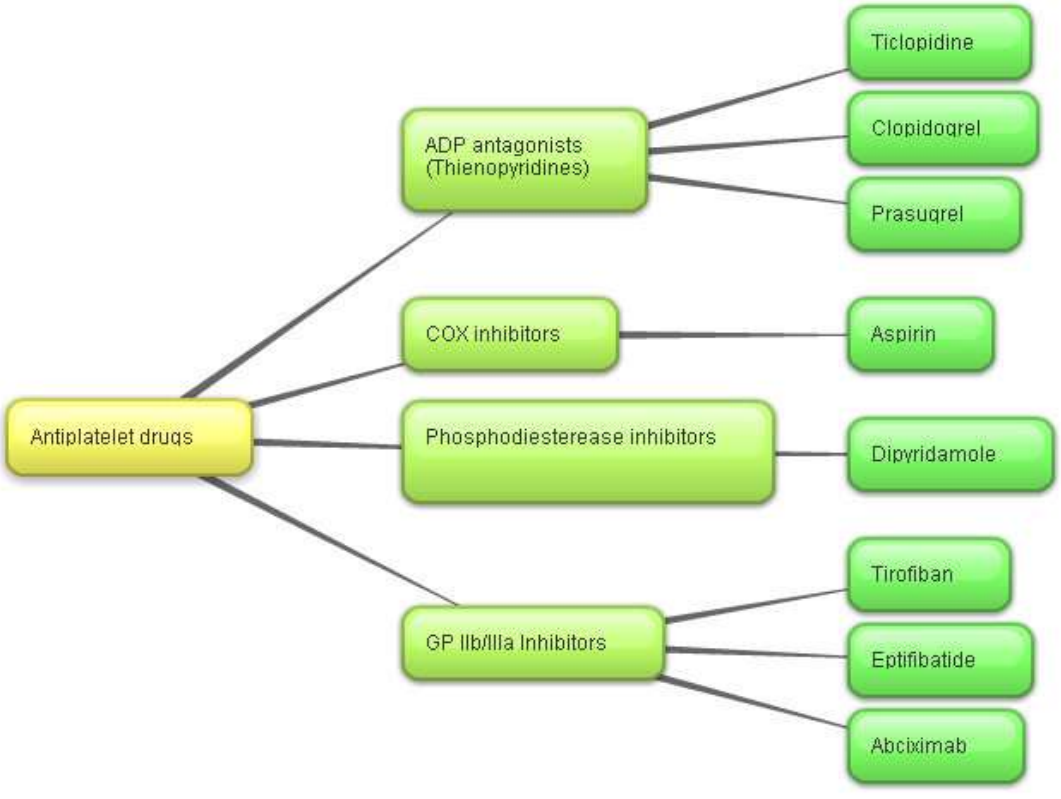
Largest products (U.S.:>=$500Mn, Others: Top 2-5) with protection expiries in the 2012-2016 period, listed in descending order by country sales in constant US$ at Q4 2011 exchange rates. Estimates of protection expiry from information available as of March 31, 2012.


GLP-1 agonist
16%
11β-HSD1 inhibitor
2%
Insulin analogue
10%
DGAT- 1 enzyme inhibitor
2%
DPP-4 inhibitor
7%
SIRT1 activator
2%
PPAR agonist
6%
AMPK activator
1%
GPCR agonist
5%
GSK-3 inhibitor
1%
IL- receptor antagonist
4%
SGLT-2 inhibitor
4%
GK activator
3%
Insulin sensitizer
2%
Others
35%

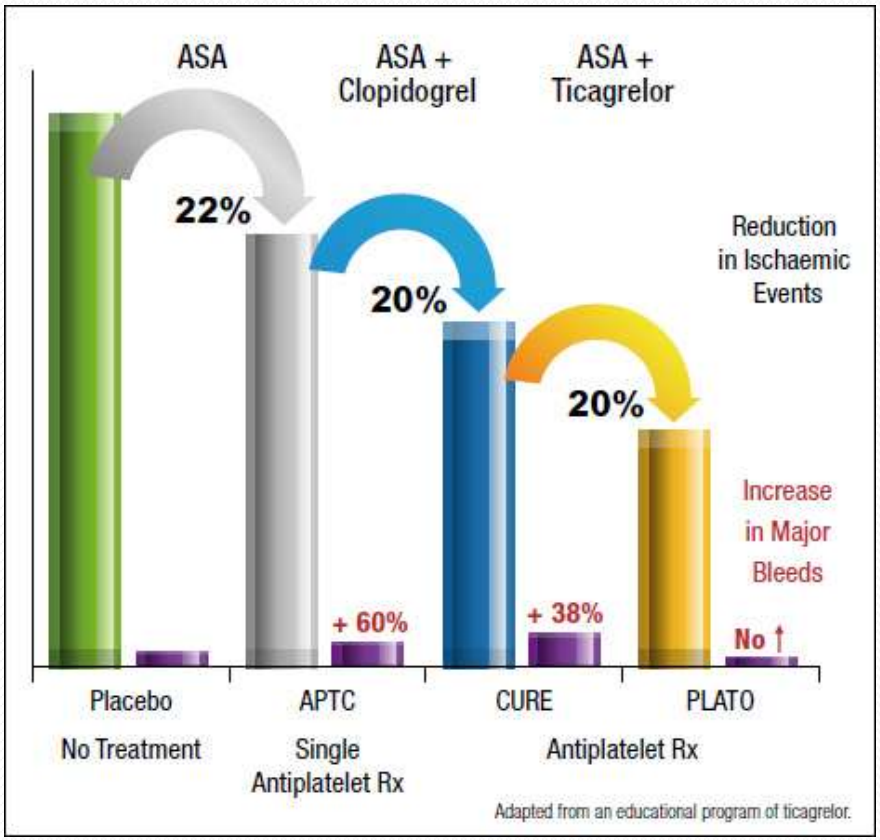

The big C
Drugs in development*, 2010
0
200
400
600
800
1,000
Cancer
Central nervous system
Infections
Pain and inflammation
Cardiovascular
Diabetes and metabolism
Gastrointestinal
Respiratory
Blood disorders
Dermatological
Source: Medco, R&D Directions
*Top ten therapeutic areas for the world's big pharmaceutical firms, includes drugs in Phase I, II, III or awaiting FDA approval

New heart Failure drugs 2012

- Eplerenon
- Ivabradin
- Omega 3
- Coenzyme q


Antiplatelet drugs
ADP antagonists (Thienopyridines)
Ticlopidine
Clopidogrel
Prasugrel
COX inhibitors
Aspirin
Phosphodiesterease inhibitors
Dipyridamole
GP IIb/IIIa Inhibitors
Tirofiban
Eptifibatide
Abciximab


NDC 0186-0777-60
60 tablets
BRILINTA™
ticagrelor tablets
90 mg
Rx only


ASA
ASA + Clopidogrel
ASA + Ticagrelor
22%
20%
20%
Reduction in Ischaemic Events
Increase in Major Bleeds
+ 60%
+ 38%
No ↑
Placebo
No Treatment
APTC
Single Antiplatelet Rx
CURE
PLATO
Antiplatelet Rx
Adapted from an educational program of ticagrelor.

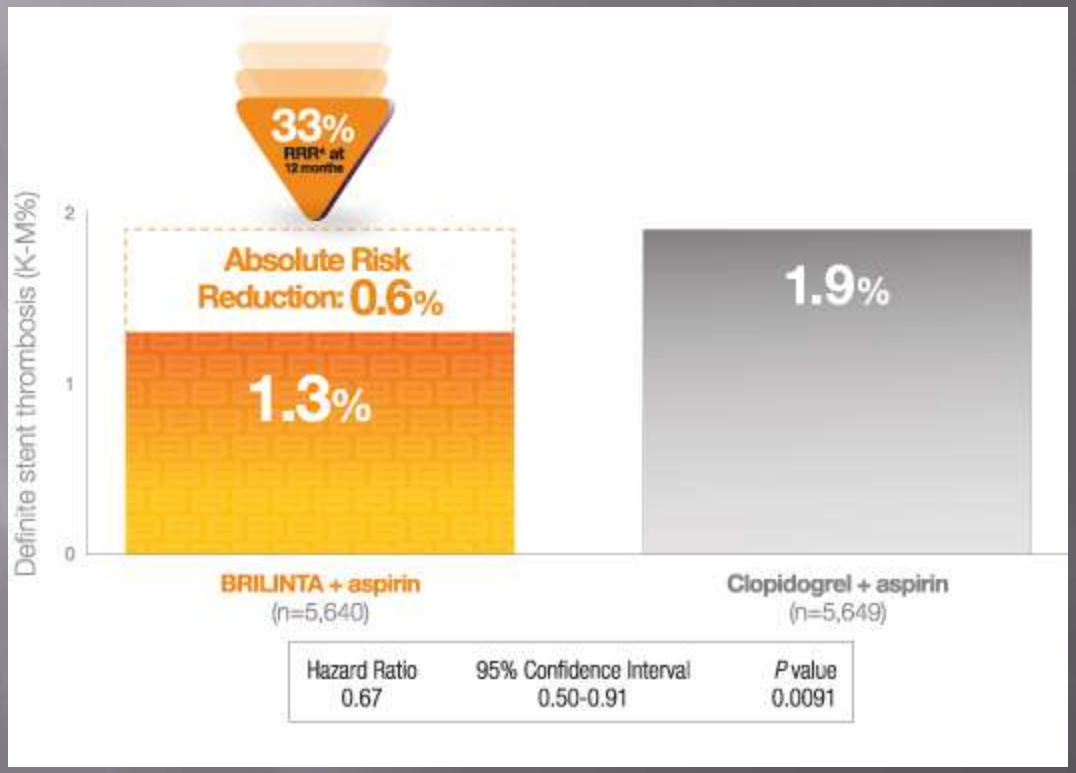

33%
RRR* at
12 months
Definite stent thrombosis (K-M%)
2
1
0
Absolute Risk
Reduction: 0.6%
1.3%
1.9%
BRILINTA + aspirin
(n=5,640)
Clopidogrel + aspirin
(n=5,649)
Hazard Ratio
0.67
95% Confidence Interval
0.50-0.91
P value
0.0091

Table 1. Comparison among major $P2Y_{12}$ inhibitors.

	Clopidogrel	Prasugrel	Ticagrelor
Activation	Prodrug, limited by metabolization	Prodrug, NOT limited by metabolization	Active drug
Receptor Binding	Irreversible	Irreversible	Reversible
Onset (50% IPA*)	2–4 hour	30 min	30 min
Duration of effect	3–10 days	5–10 days	3–4 days
Non-responder	Yes	No	No
Withdrawal before major surgery	5 days	7 days	5 days

* 50% inhibition of platelet aggregation

Modified from the original table of Hamm C W et al. Eur Heart J 2001; eurheartj.ehr236.

Glycoprotein IIb/IIIa receptor inhibitors

- Inhibits the GP IIb/IIIa receptor in the membrane of platelets
- Inhibits final common pathway activation of platelet aggregation
- Available approved agents
  - Abciximab (ReoPro)
  - Eptifibitide (Integrilin)
  - Tirofiban (Aggrastat)

Top 10 Biopharma Companies

based on 2011 biopharma revenues

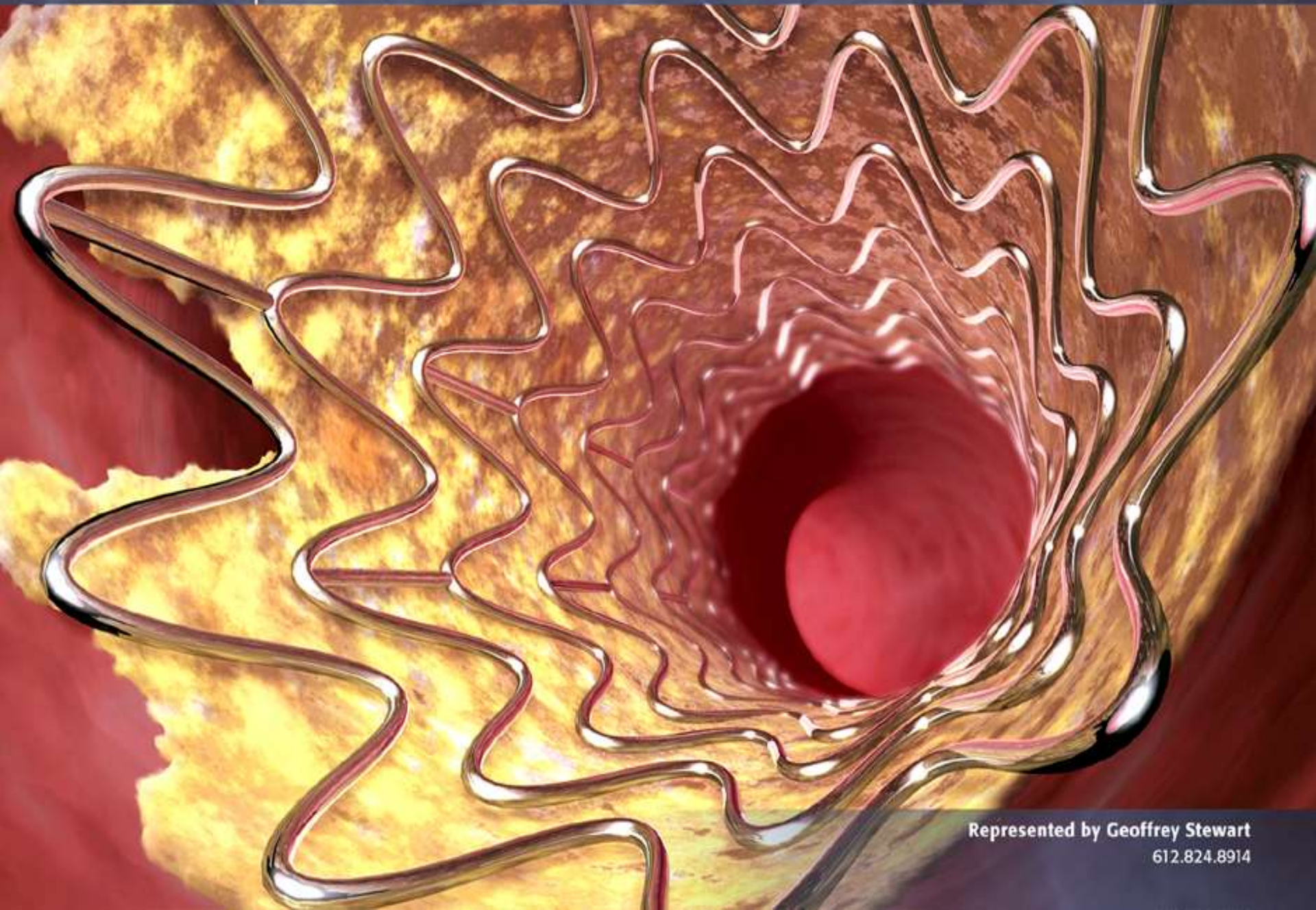
1	Roche	$37,110
2	Amgen	$15,582
3	Novo Nordisk	$12,400
4	Merck Serono	$8,243
5	Baxter BioScience	$6,053
6	Biogen Idec	$4,833
7	CSL Ltd.	$4,145
8	Allergan	$1,595
9	Alexion	$783
10	Dendreon	$214

2011 R&D Expenditures

1	Roche	$9,148
2	Amgen	$3,167
3	Novo Nordisk	$1,799
4	Merck Serono	$1,706
5	Biogen Idec	$1,220
6	Baxter	$946
7	Allergan	$903
8	CSL Ltd.	$322
9	Alexion Pharma	$137
10	Dendreon	$74

Comparison of Approved Fibrinolytic Agents

	Streptokinase	Anistreplase	Alteplase	Reteplase
Dose	1.5 MU in 30-60 min	30 mg in 5 min	100 mg in 90 min	10U x 2 over 30 min
Bolus administration	NO	Yes	No	Yes
Antigenic	Yes	Yes	No	No
Allergic reactions (mostly hypotension)	Yes	Yes	No	No
Systemic fibrinogen depletion	Marked	Marked	Mild	Moderate
90-min patency rate	~50%	~65%	~75%	~75%
TIMI-3 flow	32%	43%	54%	60%
Mortality rate	7.3%	10.5%	7.2%	7.5%
Cost /dose (US)	$294	$2116	$2196	$2196



Represented by Geoffrey Stewart
612.824.8914

Drug-Eluting Stents - Pharmacology

Anti-Inflammatory Immunomodulators	Anti-Proliferative	Migration Inhibitors ECM-Modulators	**Promote Healing & Re-Endothelialization**
Dexamethasone	QP-2, Taxol	Batimastat	**BCP671**
M-prednisolone	Actinomycin	Prolyl hydroxylase inhibitors	**VEGF**
Interferon γ-1b	Methothrexate	Halofuginone	**Estradiols**
Leflunomide	Angiopeptin	C-proteinase inhibitors	**NO donors**
Sirolimus (and analogues)	Vincristine	Probucol	**EPC antibodies**
Tacrolimus	Mitomycine		**Biorest**
Mycophenolic acid	Statins		**Advanced coatings**
Mizoribine	C MYC antisense		
Cyclosporine	Sirolimus (and analogs)		
Tranilast	RestenASE		
Biorest	2-chloro-deoxyadenosine		
	PCNA Ribozyme		

Many agents have Multiple actions

Table 1. Types of Drug-Eluting Stents

Manufacturer	Series	FDA Approval	Platform	Diameters Available (mm)	Lengths Available (mm)	Coating and Drug	Trials
Sirolimus stents							
Johnson & Johnson and Cordis	Cypher	4/23/03	316L stainless steel Bx Velocity stent (140-µm struts, 1.1176-mm crimped profile)	2.25, 2.50, 2.75, 3.00, 3.50	8, 13, 18, 23, 28, 33	12.6-µm 3-layer coating (2-µm Parylene C base coat, 10-µm main coat of PEVA, PBMA, and sirolimus, 0.6-µm top coat of PBMA). 80% of sirolimus elutes over ~30 days; remainder released by end of 90 days	RAVEL, SAPPHIRE, and SIRIUS
Paclitaxel stents							
Boston Scientific	Taxus	3/4/04	316L stainless steel Express2 stent (132-µm struts)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	8, 12, 16, 20, 24, 28, 32, 38	16-µm single-layer Translute SIBS co-polymer (nonresorbable elastomeric) coating containing paclitaxel, which elutes over ~90 days	ELUTES, TAXUS II,[a] and ASPECT
Boston Scientific	Ion	4/22/11	316L stainless steel platinum chromium alloy (81-µm struts for diameters 2.25-3.50 mm, 86-µm struts for 4.00 mm)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	8, 12, 16, 20, 24, 28, 32, 38	Triblock copolymer (composed of polystyrene and polyisobutylene units) coating containing paclitaxel	PERSEUS[b]
Everolimus stents							
Boston Scientific	Promus	11/22/11	L605 cobalt chromium alloy ML Vision stent (81-µm struts, 1.0668-mm stent profile)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	8, 12, 15, 18, 23, 28	PBMA, PVDF-HFP, and everolimus; 100% drug elution over 120 days	SPIRIT[c]
Guidant and Abbott	Xience V	7/2/08	L605 cobalt chromium ML Vision stent (81-µm struts)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	8, 12, 15, 18, 23, 28	7.6-µm fluoropolymer multilayer coating with 100 mcg/cm^2 everolimus	SPIRIT
Guidant and Abbott	Xience Prime	11/2/11	L605 cobalt chromium ML Vision stent (81-µm struts)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	8, 12, 15, 18, 23, 28, 33, 38	7.6-µm fluoropolymer multilayer coating with 100 mcg/cm^2 everolimus	SPIRIT
Zotarolimus stent							
Medtronic	Endeavor	2/1/08	Cobalt chrome Driver stent (91-µm struts)	2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50	8, 12, 18, 24, 30	4.3-µm phosphorylcholine coating (includes zotarolimus) on 1-µm base coat	ENDEAVOR

[a] TAXUS II used clopidogrel 75 mg/day or ticlopidine 250 mg bid for ≥6 mo. Acetylsalicylic acid >75 mg, which was mandated for ≥12 mo after procedure, was recommended.
[b] PERSEUS trial used clopidogrel 75 mg/day or ticlopidine for 6 mo or 12 mo if no risk of bleeding. Aspirin 325 mg was used for 6 mo; later, 81 mg was used indefinitely.
[c] SPIRIT subjects were maintained on clopidogrel bisulfate daily for a minimum of 3 mo and aspirin daily for duration of trial (1 y).
ASPECT: ASian Paclitaxel-Eluting stent Clinical Trial; ELUTES: European evaLUation of pacliTaxel Eluting Stent; HFP: hexafluoropropylene; PBMA: poly (n-butyl methacrylate); PEVA: poly(ethylene-co-vinyl acetate); PVDF: polyvinylidene fluoride; RAVEL: RAndomized study with sirolimus-eluting Bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions; SAPPHIRE: Stenting and Angioplasty with Protection in Patients at HIgh Risk for Endarterectomy trial; SIBS: poly(styrene-b-isobutylene-b-styrene); SIRIUS: SIRolImUS-eluting Bx Velocity balloon expandable stent trial; TAXUS II: paclTAXel-eUting Stent trial-II.
Source: References 1, 9, 25, 35.

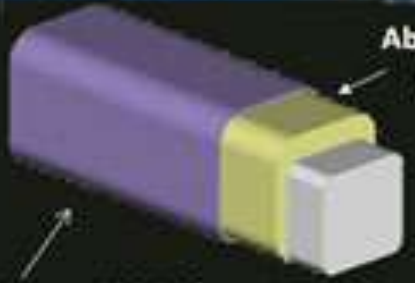
Platforms With Bioabsorbable Polymers

BioMatrix™: Abluminal Release

- Biolimus A9™ / PLA 50:50 mix

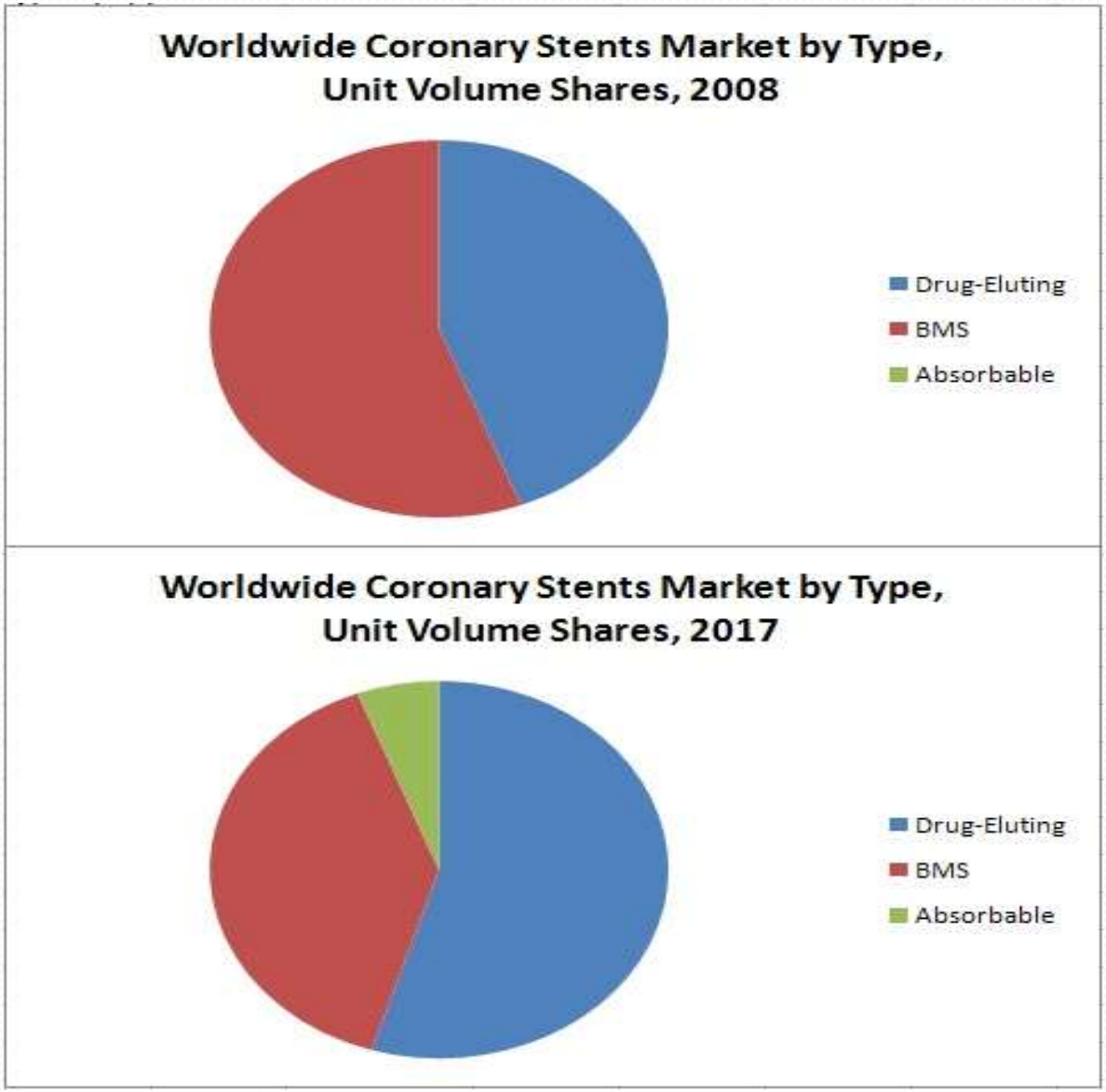
Nevo™: Sirolimus-Eluting Stent

- Bioresorbable PLGA polymer
- Exclusively housed in reservoirs

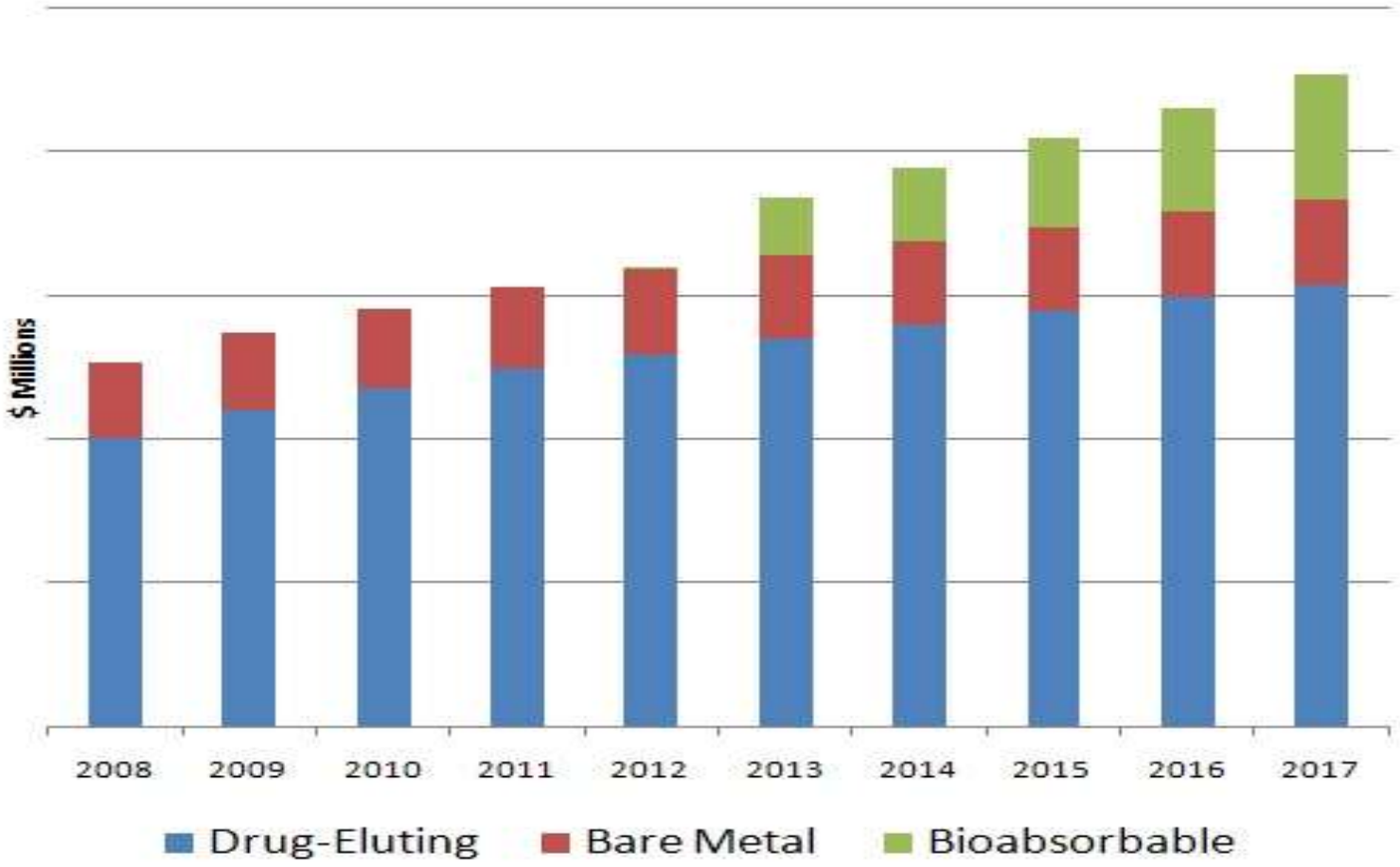


Genous™-DES Technology:

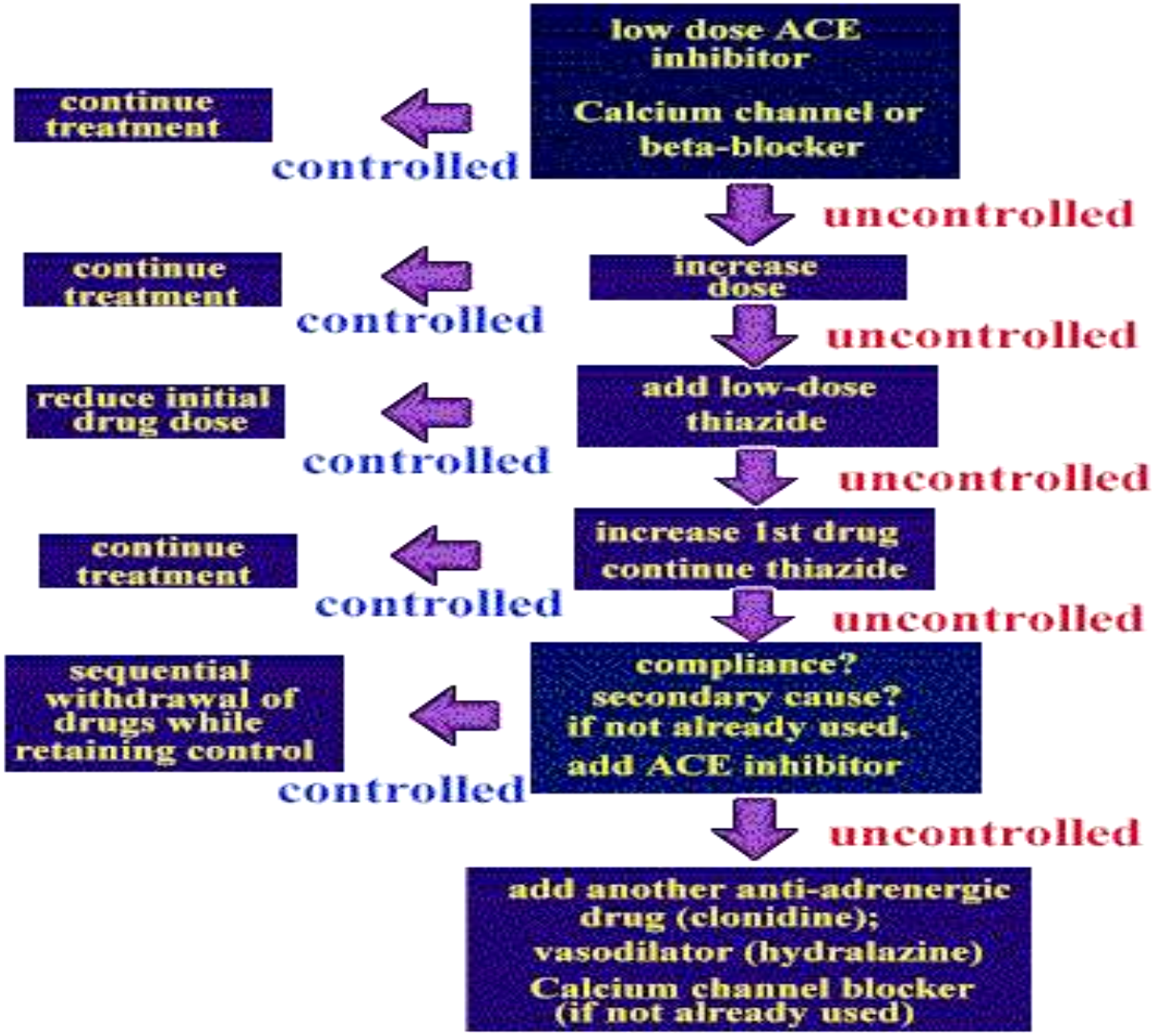
- Rapamycin (5 µg/mm) applied in biodegradable SynBiosys™ polymer on the abluminal side


Worldwide Coronary Stents Market by Type, Unit Volume Shares, 2008
Drug-Eluting
BMS
Absorbable
Worldwide Coronary Stents Market by Type, Unit Volume Shares, 2017
Drug-Eluting
BMS
Absorbable

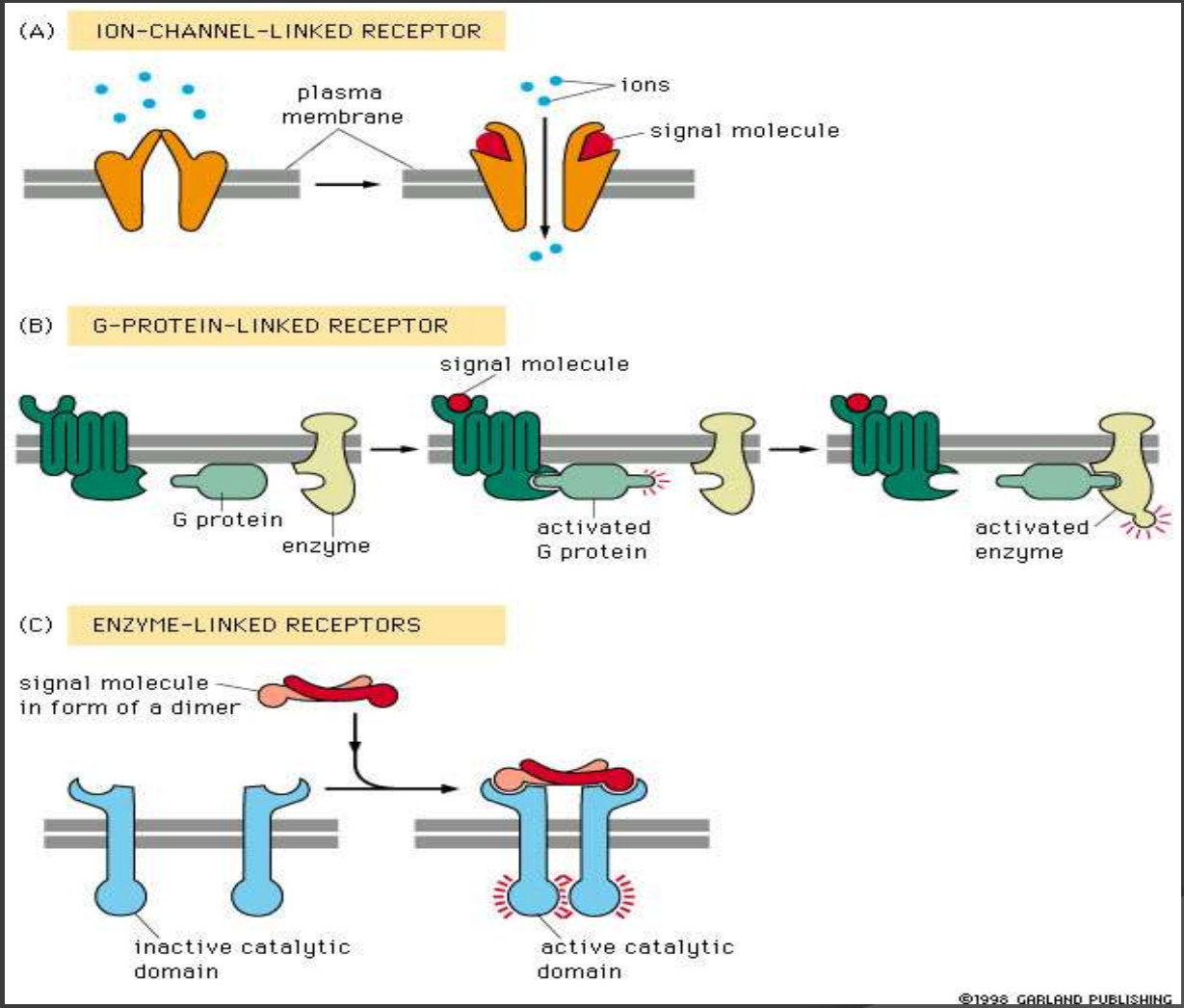
Asia/Pacific Coronary Stents Market, 2008-2017



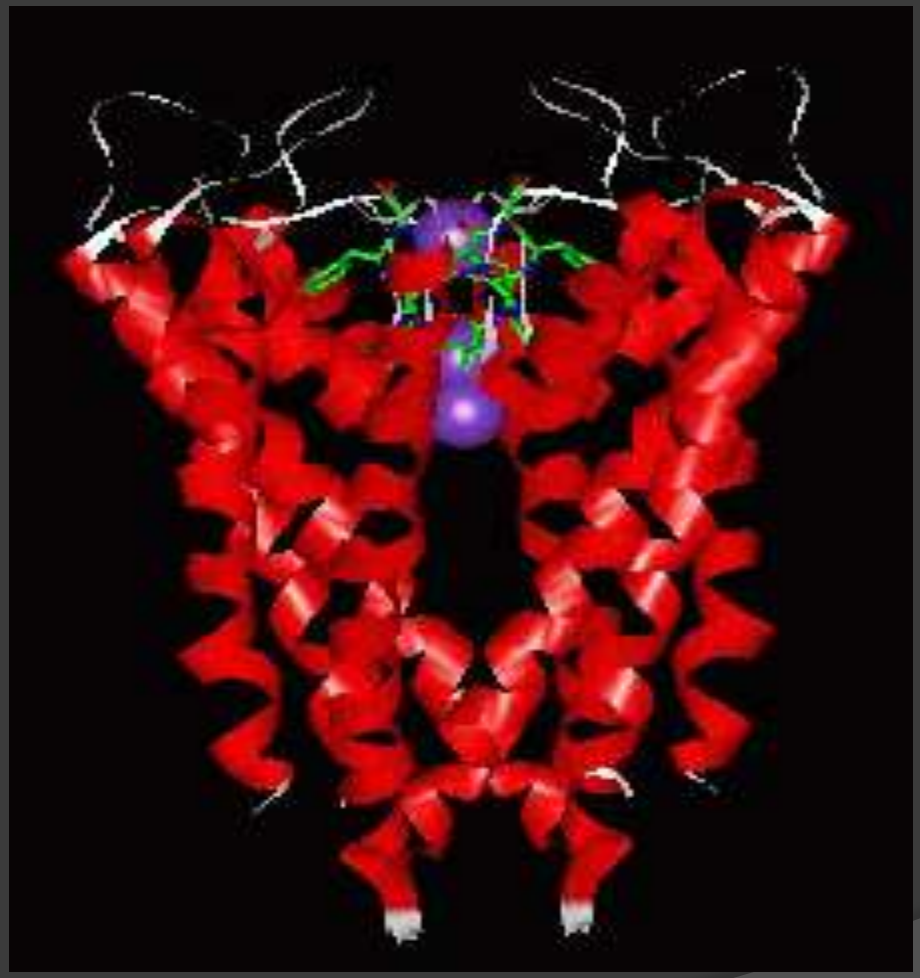
Hypertension update



Receptor Subclasses



K Channel Structure at 3Å Resolution



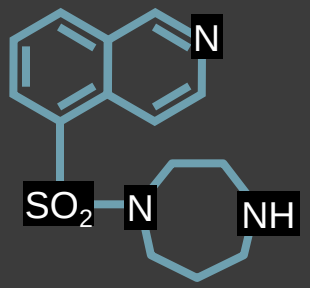
Doyle et al, 1998

Nicorandil at a glance

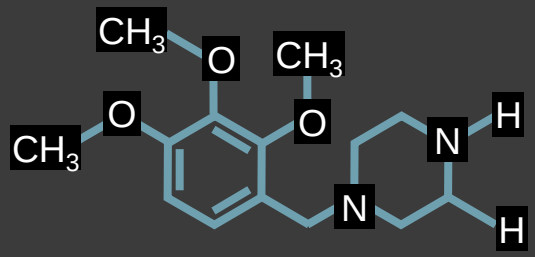
- Orally and parenterally available
- Hepatically metabolized and eleminated
- Peak plasma level 0.3-1h after oral administration
- Less pro arrythmic than other PCO's
- Antiplatelet activity
- Antioxidant activity
- Immunomodulating properties

New mechanistic approaches to chronic stable angina

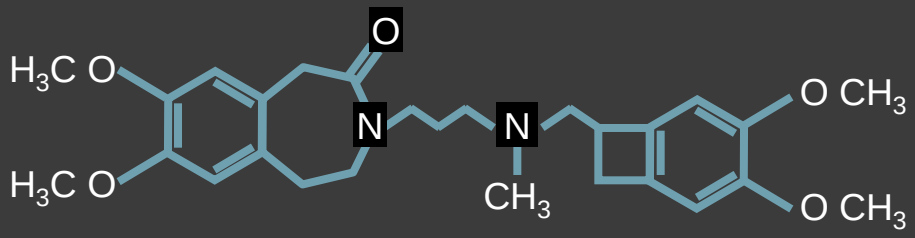
Rho kinase inhibition (fasudil)



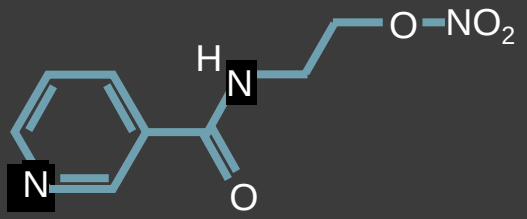
Metabolic modulation (trimetazidine)



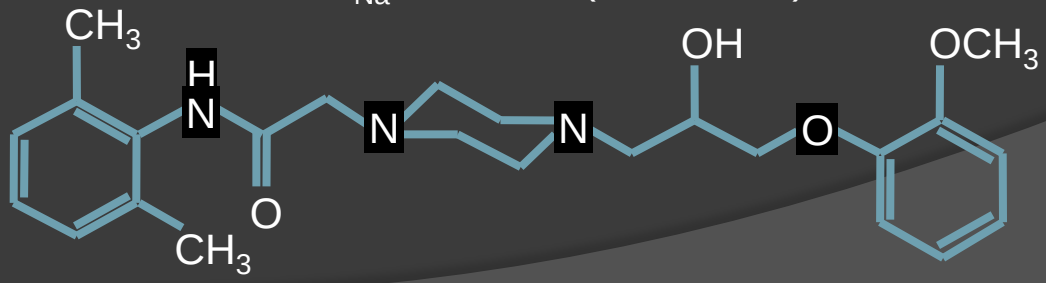
Sinus node inhibition (ivabradine)



Preconditioning (nicorandil)

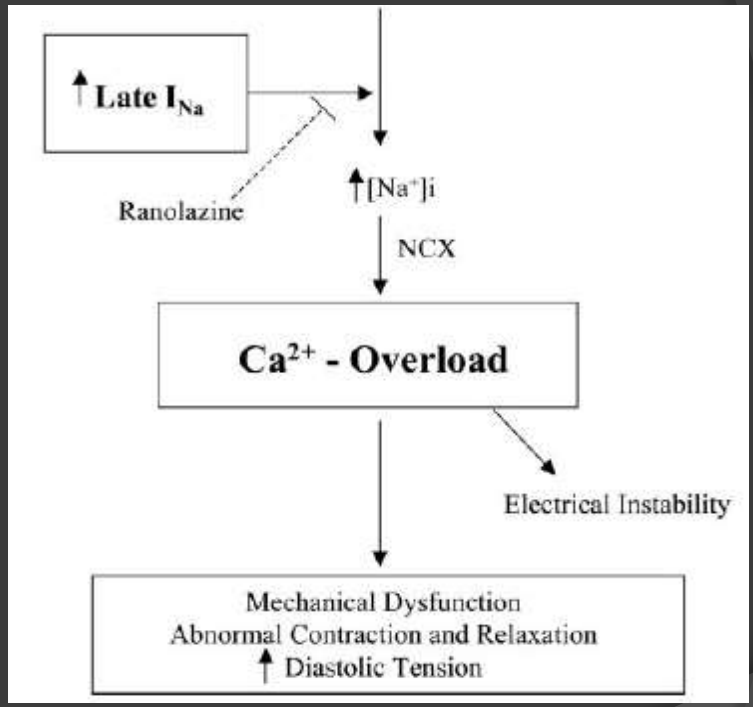


Late I_{Na} inhibition (ranolazine)



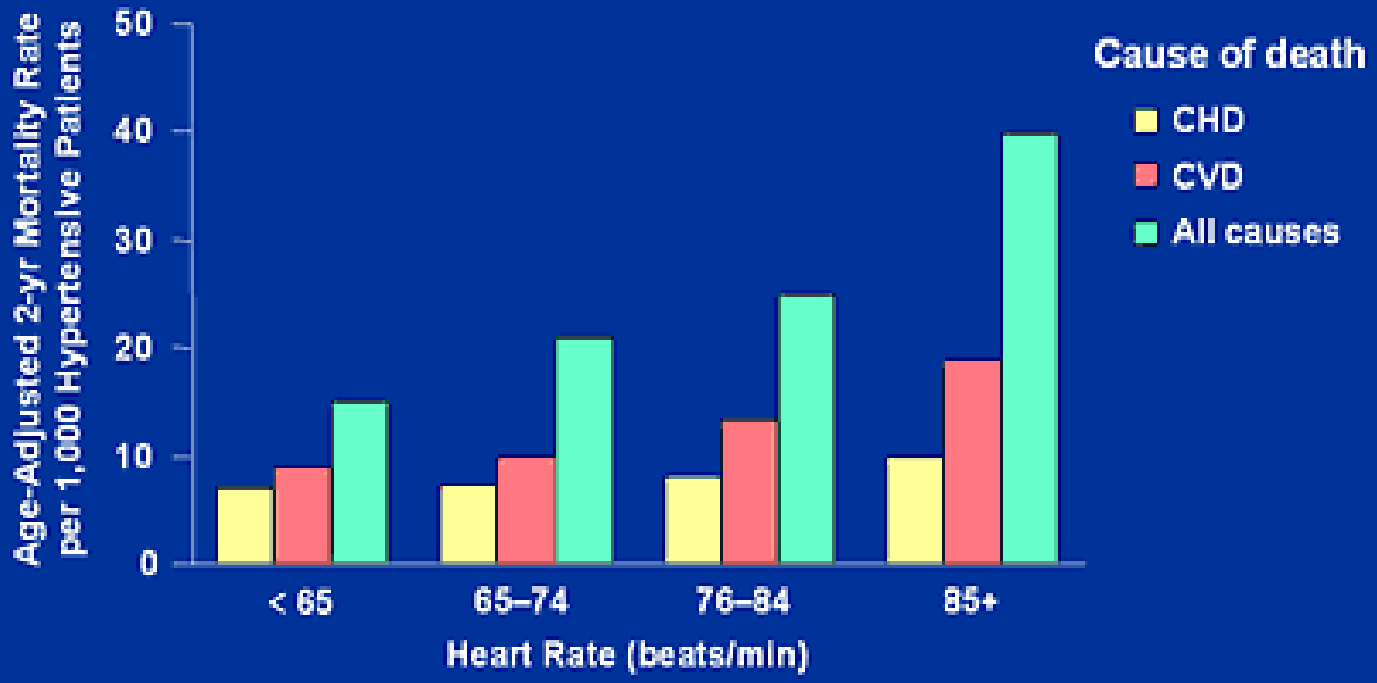
Ranolazine: Most recent Anti-anginal

- Piperazine derivative
- Anti-ischemic effect without effect on heart rate or blood pressure
- Inhibits late I_{na} (slowly inactivating component of sodium current) = reduce intracellular calcium and sodium overload



High Heart Rates Predict Hypertensive Mortality

Framingham Study (36-Year Follow-up Data)



n = 2,037 hypertensive males; 2,493 hypertensive females
CHD = coronary heart disease; CVD = cardiovascular disease
Gillman MW et al. *Am Heart J.* 1993;125:1148–1154.

Chronobiology

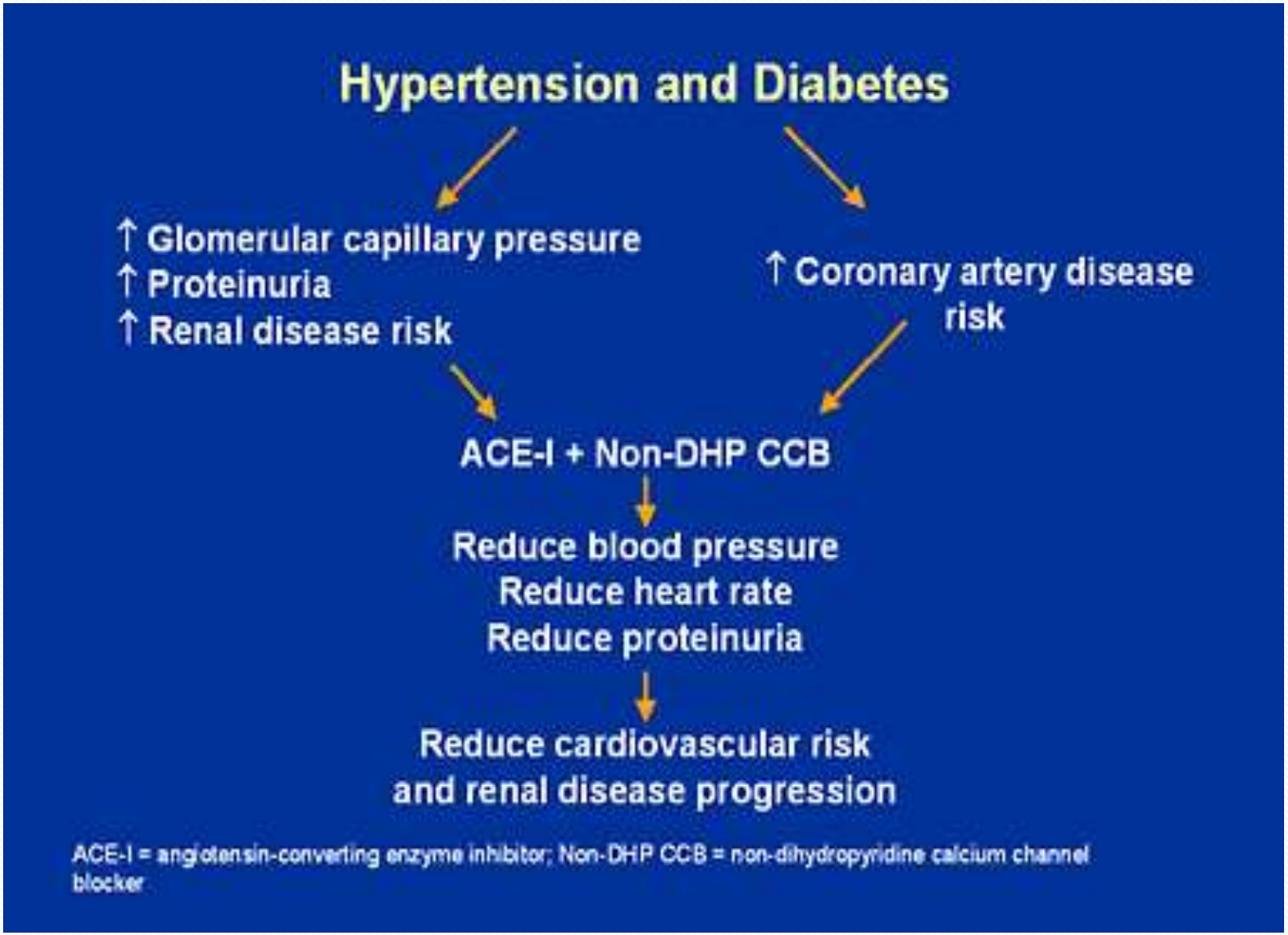
Peak Times of Cardiovascular Complications

- Sudden death[1]
- Acute myocardial infarction[1]
- Typical angina pectoris[2]
- Silent ischemia[1]
- Total ischemic burden[1]
- Ischemic stroke[3]

6 AM–noon

- Variant angina pectoris (2 AM–4 AM)[4]
- Platelet aggregability[5,6]

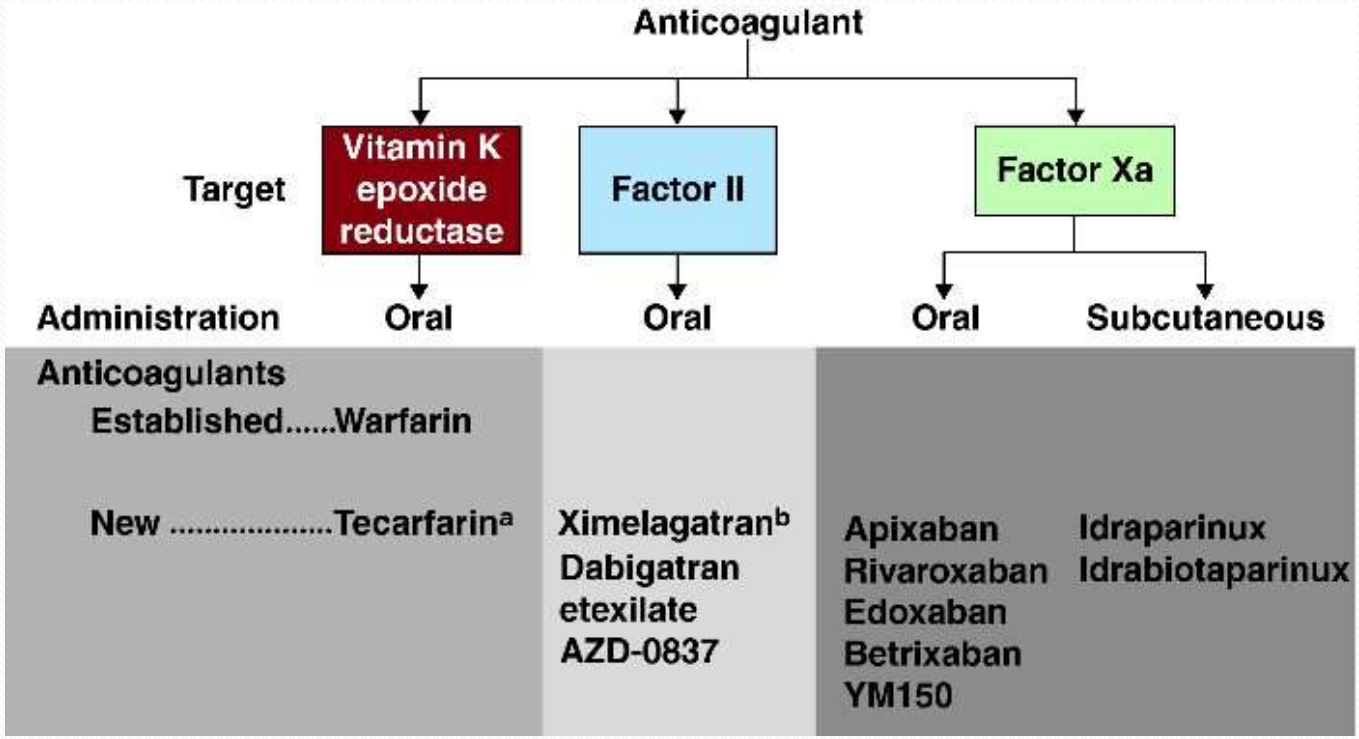
1. Mulcahy D et al. *Lancet*. 1988;2(8614):755–759; 2. Taylor CR et al. *Am Heart J*. 1969;118:1096–1099; 3. Marler JR et al. *Stroke*. 1989;20:473–476; 4. Ogawa H et al. *Circulation*. 1989;80(6):1617–1626; 5. Portaluppi F et al. In: White WB, ed. *Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics*. Totowa, NJ: Humana Press. 2000;104–110; 6. Toffler GH et al. *N Engl J Med*. 1987;316:1514–1518.


Hypertension and Diabetes
↑ Glomerular capillary pressure
↑ Proteinuria
↑ Renal disease risk
↑ Coronary artery disease risk
ACE-I + Non-DHP CCB
Reduce blood pressure
Reduce heart rate
Reduce proteinuria
Reduce cardiovascular risk and renal disease progression
ACE-I = angiotensin-converting enzyme inhibitor; Non-DHP CCB = non-dihydropyridine calcium channel blocker

Albuminuria

- Associated with myocardial infarction and stroke
- Reflects endothelial damage
- Part of the cardiometabolic syndrome
- Progression of micro-* to macroalbuminuria predicts progression of renal disease

*Microalbuminuria: 30–300 mg/d


Anticoagulant
Target
Vitamin K epoxide reductase
Factor II
Factor Xa
Administration
Oral
Oral
Oral
Subcutaneous
Anticoagulants
Established.....Warfarin
New .....Tecarfarin[a]
Ximelagatran[b]
Dabigatran etexilate
AZD-0837
Apixaban
Rivaroxaban
Edoxaban
Betrixaban
YM150
Idraparinux
Idrabiotaparinux

Dabigatran and renal function: atrial fibrillation

Renal function	CrCl (mL/min)	Dabigatran (Europe, e.g. Germany)	Dabigatran (US)
Normal	80>	150 mg bid	150 mg bid
Mild impairment	80- 50	No adjustment necessary	No adjustment necessary
Moderate impairment	50-30	110 mg bid dose reduction in pts with ↑bleeding risk	No adjustment necessary
Severe renal impairment	15-30	contraindicated	75 mg bid
Renal failure	<15	contraindicated	not recommended

Pradaxa ® product information US 2010 and Germany 2011

Rivaroxaban: indication specific dosing

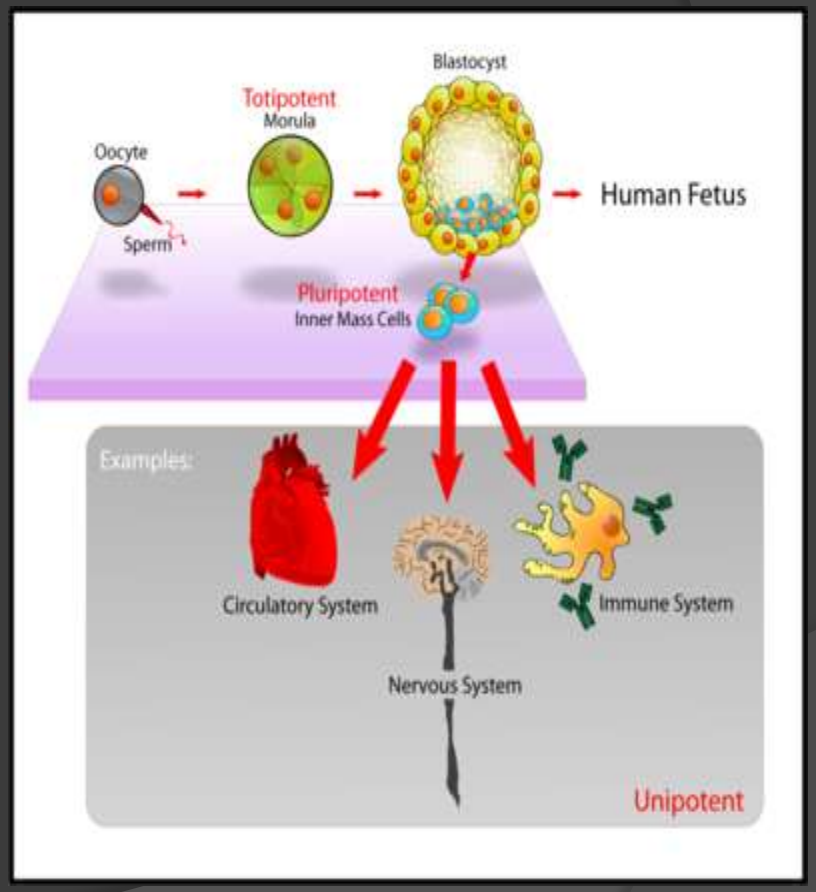
Indication	Dosing schedule
VTE prevention after major orthopaedic surgery	
5 weeks (elective hip replacement surgery)	10 mg od
2 weeks (elective knee replacement surgery)	10 mg od
Treatment of DVT and prevention of recurrent DVT and PE	
Days 1–21 (3 weeks)	15 mg bid
Day 22 and onwards*	20 mg od (CrCl ≥50 ml/min) 15 mg od (CrCl 15–49 ml/min)#
Stroke prevention in patients with non-valvular AF*	
Continuous administration	20 mg od (CrCl ≥50 ml/min)
Continuous administration	15 mg od (CrCl 15–49 ml/min)#

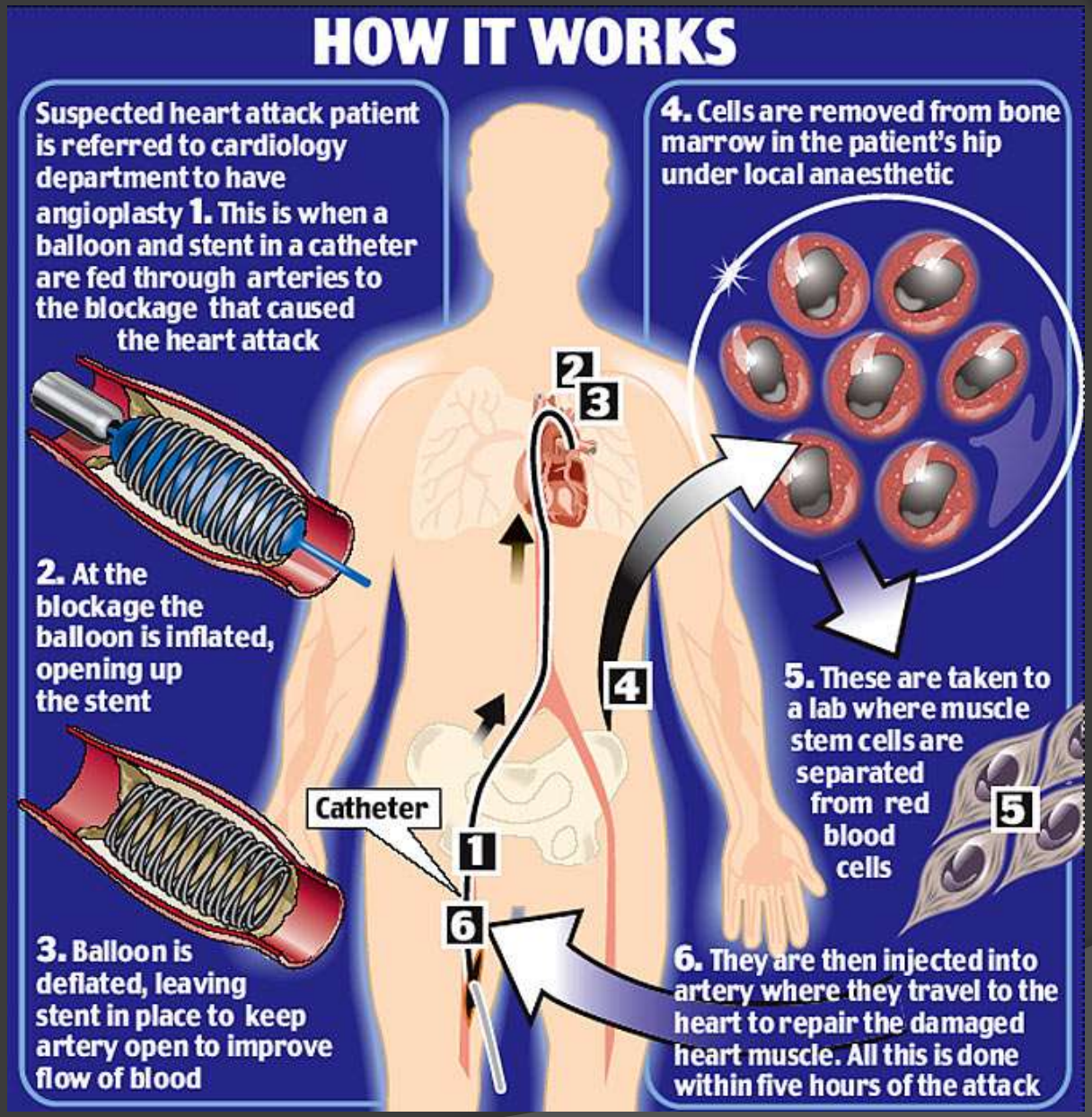
#In patients with CrCL 15–29 ml/min, limited data indicate that rivaroxaban plasma concentrations are significantly increased, therefore, rivaroxaban should be used with caution (a reduced dose of 15 mg od) and the benefit–risk should be assessed before initiating rivaroxaban in these patients
AF, atrial fibrillation; bid, twice daily; CrCl, creatinine clearance; DVT, deep vein thrombosis; od, once daily; PE, pulmonary embolism; VTE, venous thromboembolism.

Brand name	Generic name	First FDA approval	Half-life	Lipophilic or lipophobic	Manufacturer and derivation
Mevacor	Lovastatin	1987	Less than 2 hours	Lipophilic	Merck, natural compounds
Zocor	Simvastatin*	1991	Less than 2 hours	Lipophilic	Merck, natural compounds
Pravachol	Pravastatin	1991	2 hours	Lipophobic	Bristol-Myers Squibb, natural compounds
Lescol	Fluvastatin	1993	Less than 3 hours	Lipophilic	Novartis, synthetic
Lipitor	Atorvastatin	1996	14 hours	Lipophilic	Pfizer, synthetic
Crestor	Rosuvastatin	2003	19 hours	Lipophobic	IPR Pharmaceuticals, synthetic

*Low-dose pill approved for over-the-counter sales in U.K.

Stem Cell therapy




HOW IT WORKS
Suspected heart attack patient is referred to cardiology department to have angioplasty 1. This is when a balloon and stent in a catheter are fed through arteries to the blockage that caused the heart attack
2. At the blockage the balloon is inflated, opening up the stent
3. Balloon is deflated, leaving stent in place to keep artery open to improve flow of blood
4. Cells are removed from bone marrow in the patient's hip under local anaesthetic
5. These are taken to a lab where muscle stem cells are separated from red blood cells
6. They are then injected into artery where they travel to the heart to repair the damaged heart muscle. All this is done within five hours of the attack
Catheter
1
2
3
4
5
6

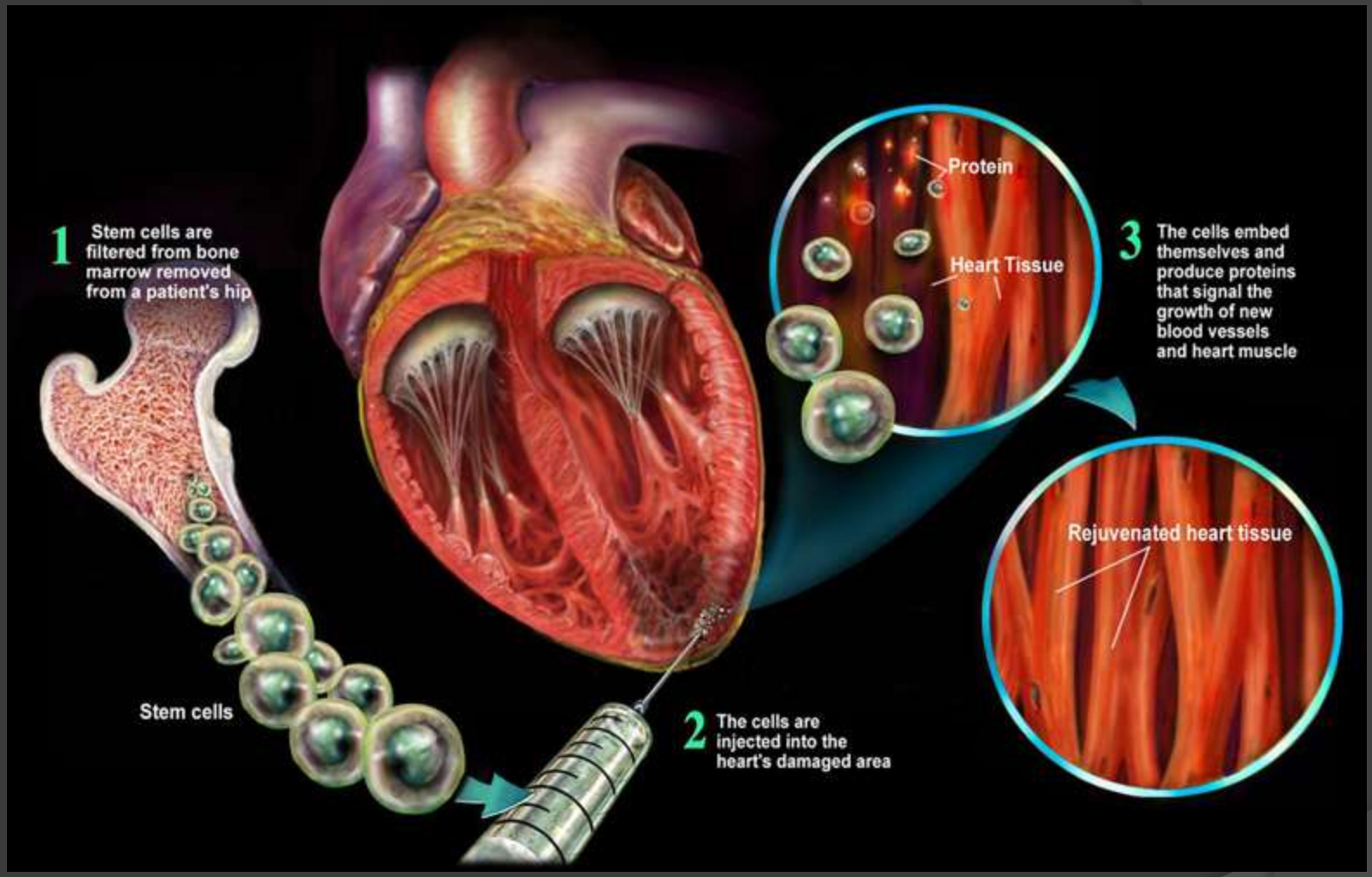
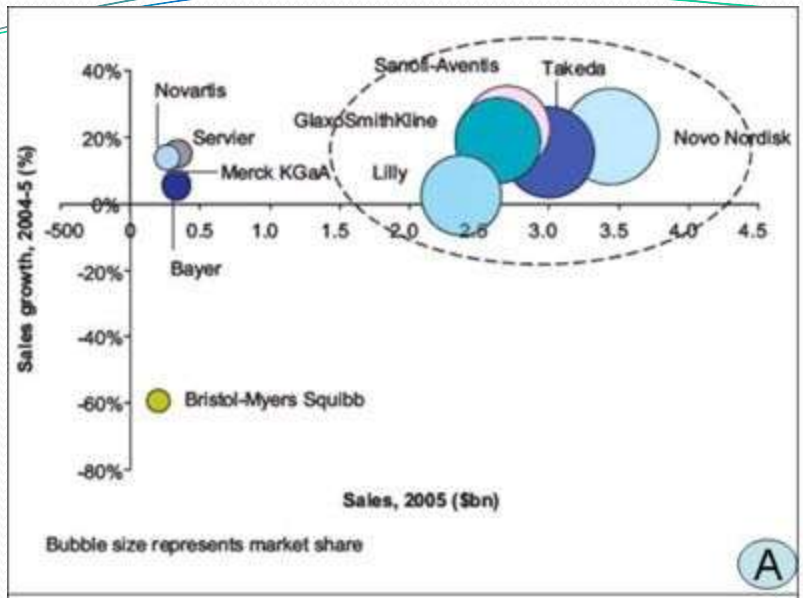
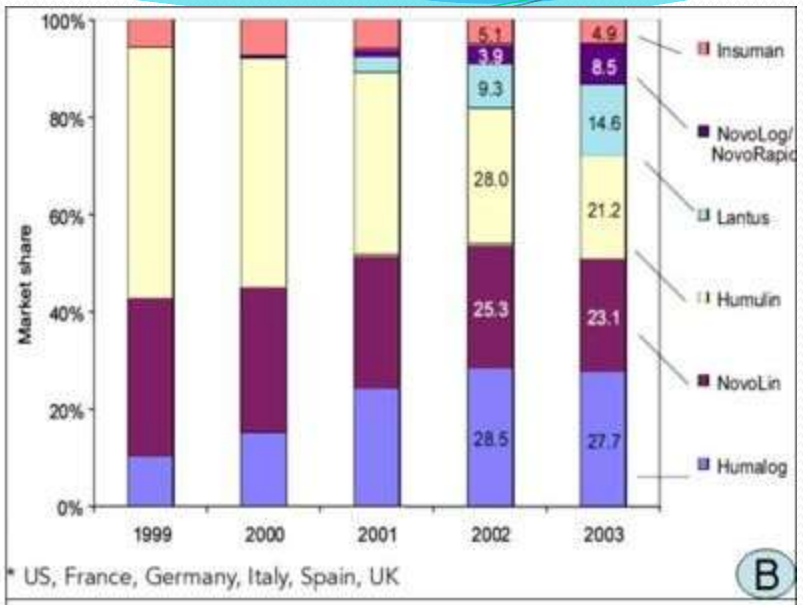

1 Stem cells are filtered from bone marrow removed from a patient's hip
Stem cells
2 The cells are injected into the heart's damaged area
Protein
Heart Tissue
3 The cells embed themselves and produce proteins that signal the growth of new blood vessels and heart muscle
Rejuvenated heart tissue

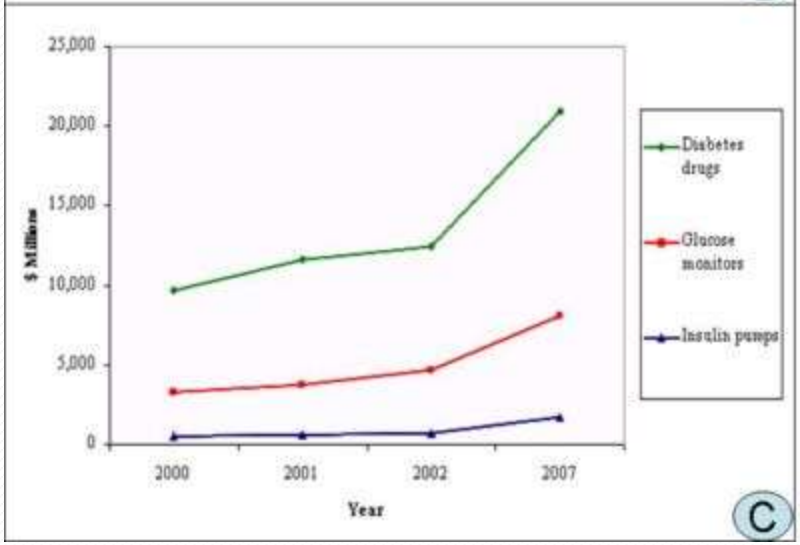
Table 1 – Non-insulin agents available for treatment of diabetes in the United States

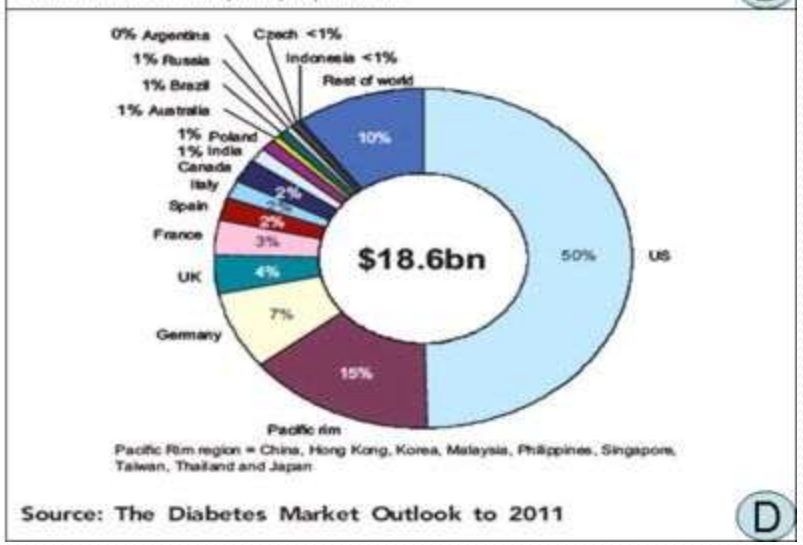
Drug class	Route of administration	Advantages	Disadvantages
Biguanides (metformin)	Oral	Effectively lowers HbA_{1c}, low cost, does not cause weight gain	GI complaints, minimal risk of lactic acidosis (contraindicated in patients older than 80 y and in those with elevated creatinine levels)
Sulfonylureas (tolbutamide, glyburide, glipizide, glimepiride)	Oral	Available as generics (low cost)	Can cause weight gain
Disaccharidase inhibitors (acarbose, meglitol)	Oral	Do not promote weight gain; safe in patients with renal failure; reinforce carbohydrate restriction through averse response	Flatulence, abdominal discomfort, diarrhea; relatively high cost
Thiazolidinediones (rosiglitazone, pioglitazone)	Oral	May preserve beta cells from ongoing destruction	Cause fluid retention (sometimes leading to heart failure); stimulate accumulation of adipose tissue
Meglitinides (repaglinide, nateglinide)	Oral	Rapid disappearance time results in lower risk of hypoglycemia than with sulfonylureas	Much shorter duration of action than sulfonylureas; thus, these agents must be taken before meals; moderately high cost
GLP analogs (exenatide)	Parenteral	May result in progressive weight loss in some patients	Nausea (often severe); must be injected twice daily; high cost
Amylin analogs (pramlintide)	Parenteral	Weight loss can occur	Nausea; unpredictable hypoglycemia; high cost
DPP-IV inhibitors (sitagliptin)	Oral	No prominent side effects, low risk of hypoglycemia	Does not lead to weight loss; high cost

HbA_{1c}, glycosylated hemoglobin; GLP, glucagonlike peptide; DPP-IV, dipeptidyl peptidase IV


Sales growth, 2004-5 (%)
40%
20%
0%
-20%
-40%
-60%
-80%
-500
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
Novartis
Servier
Merck KGaA
Bayer
Sanofi-Aventis
GlaxoSmithKline
Lilly
Takeda
Novo Nordisk
Bristol-Myers Squibb
Sales, 2005 ($bn)
Bubble size represents market share
A


Market share
100%
80%
60%
40%
20%
0%
1999
2000
2001
2002
2003
5.1
3.9
9.3
28.0
25.3
28.5
4.9
8.5
14.6
21.2
23.1
27.7
Insuman
NovoLog/ NovoRapid
Lantus
Humulin
NovoLin
Humalog
* US, France, Germany, Italy, Spain, UK
B


$ Millions
25,000
20,000
15,000
10,000
5,000
0
2000
2001
2002
2007
Year
Diabetes drugs
Glucose monitors
Insulin pumps
C


0% Argentina
1% Russia
1% Brazil
1% Australia
Czech <1%
Indonesia <1%
Rest of world
1% Poland
1% India
Canada
Italy
Spain
France
UK
Germany
Pacific Rim
10%
2%
2%
3%
4%
7%
15%
50%
US
$18.6bn
Pacific Rim region = China, Hong Kong, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand and Japan
Source: The Diabetes Market Outlook to 2011
D

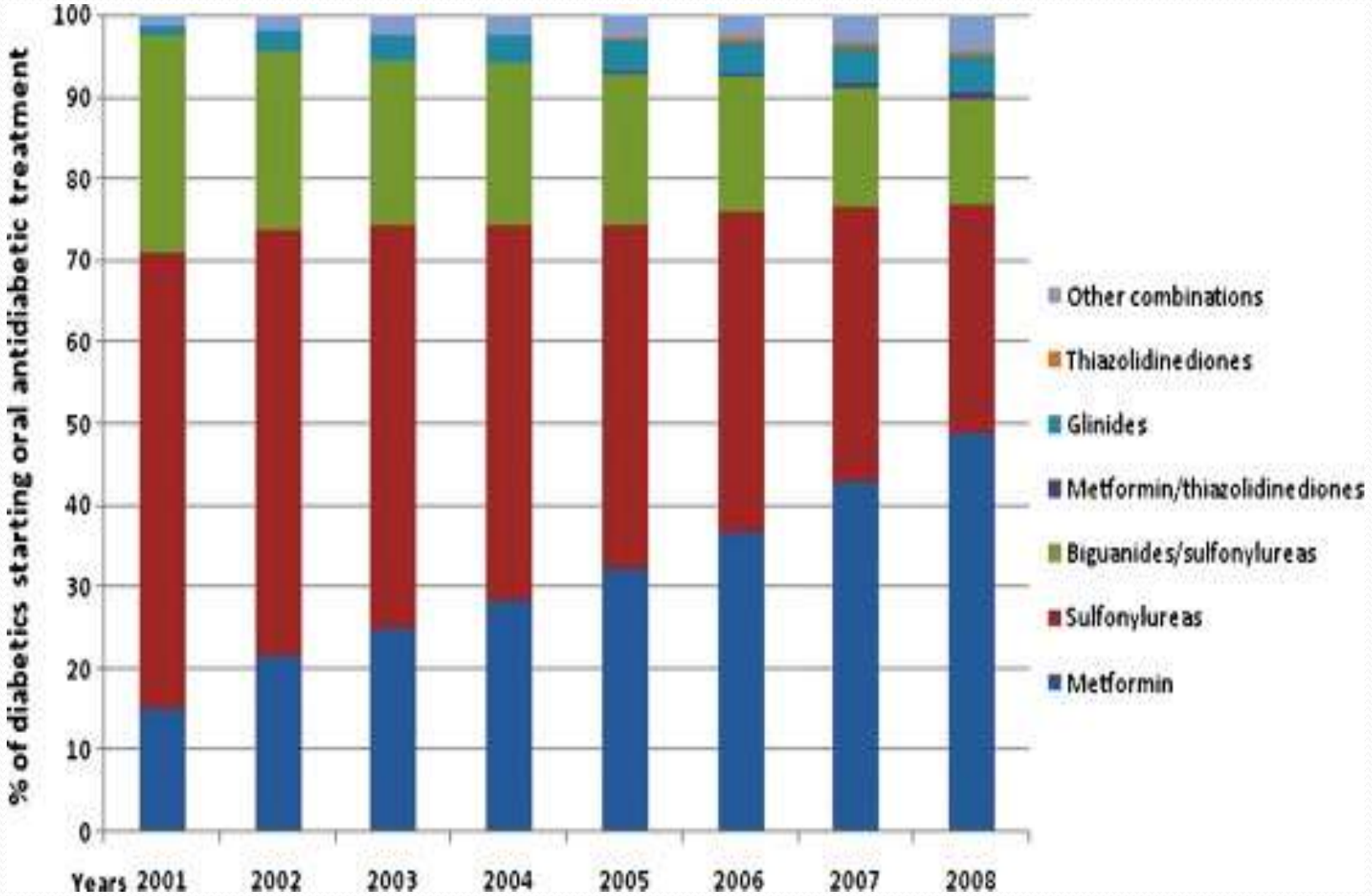

% of diabetics starting oral antidiabetic treatment
100
90
80
70
60
50
40
30
20
10
0
Years 2001
2002
2003
2004
2005
2006
2007
2008
Other combinations
Thiazolidinediones
Glinides
Metformin/thiazolidinediones
Biguanides/sulfonylureas
Sulfonylureas
Metformin

Table 1: Antidiabetic Agents with Reported Hepatotoxicity

Class	Drug (Trade Name)
Sulfonylureas	First-generation: Chlorpropamide (Diabinese) Tolazamide (Tolinase) Tolbutamide (Orinase) Second-generation: Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (DiaBeta, Glynase, Micronase)
Alpha-glucosidase inhibitors	Acarbose (Precose)
Biguanides	Metformin (Fortamet, Glucophage, Riomet)
Thiazolidinediones (TZDs)	Pioglitazone (Actos) Rosiglitazone (Avandia) Troglitazone (Rezulin)[a]

[a] *No longer available; pulled from the U.S. market in 2000.*