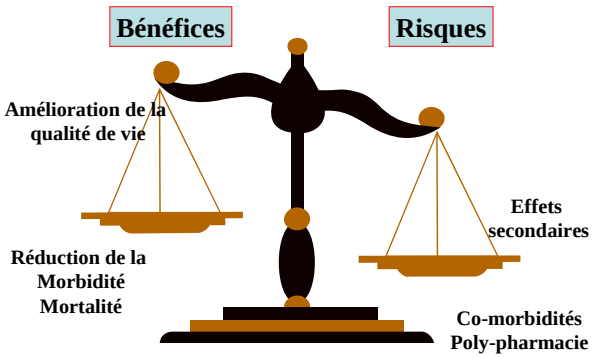
Quoi de neuf sur le plan thérapeutique ?

Pr Benoît DE WAZIERES
CHU Nîmes

Quoi de Neuf en Gériatrie

Pr B de WAZIERES
Service de Médecine Interne et Gériatrie
Centre Hospitalier Universitaire
NIMES

Traitement du sujet âgé

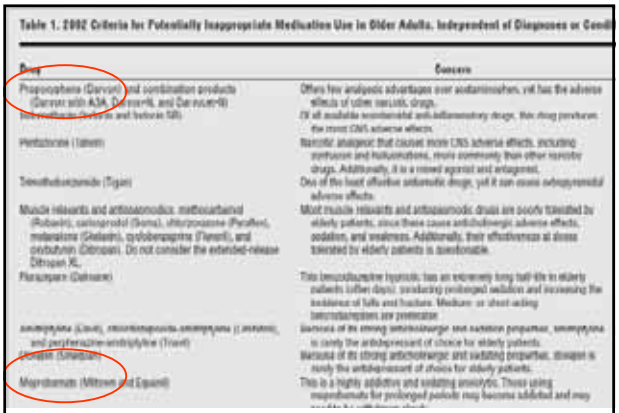


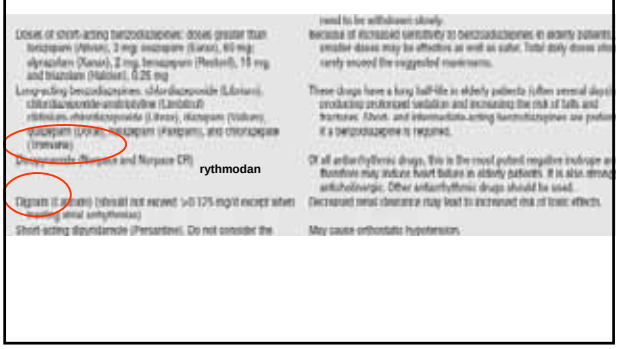
Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

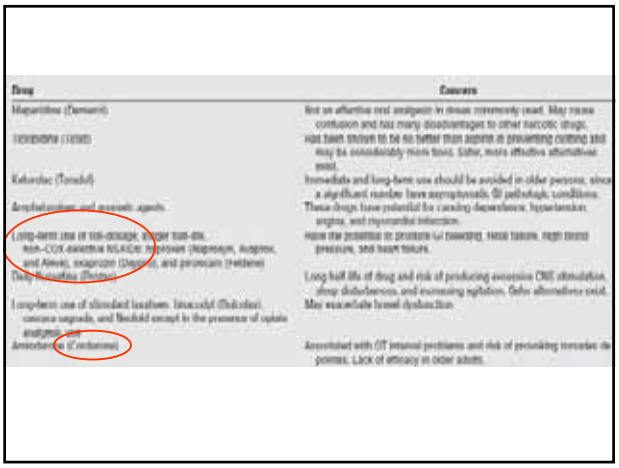
Results of a US Consensus Panel of Experts

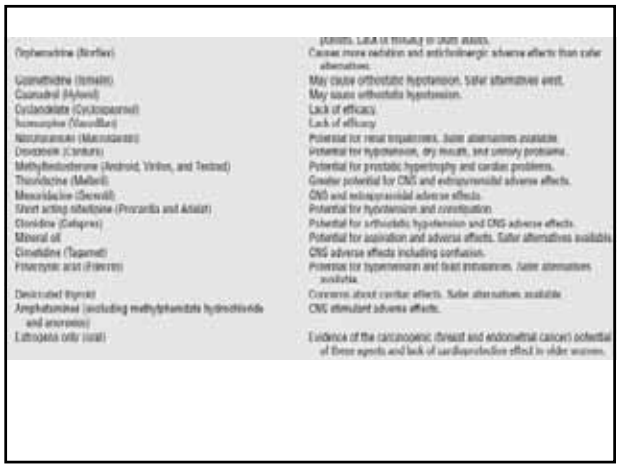
Donna M. Fick, PhD, RN; James W. Cooper, PhD, RPh; William E. Wade, PharmD, FASHP, FCCP; Jennifer L. Waller, PhD; J. Ross Maclean, MD; Mark H. Beers, MD

Arch Intern Med. 2003;163:2716-2724









Agitation

- Parfois possibilité de contact et examen clinique, maintient de la relation avec contact oral
- Dans les cas extrêmes : Contention physique
- Sédation médicamenteuse
  - La voie orale est souvent suffisante
  - Injectable si nécessaire
    - Par voie IM car pratique (mais pas plus rapide!)

Agitation

- Trois critères de choix du médicament
  - Rapidité d'action
  - Absence d 'effet indésirable grave après une injection unique
  - Facilite d'emploi, conditionnement urgence

Neuroleptique Injectable

- Butyrophenone. Droleptan® Haldol®
- Phenothiazines. Nozinan®
- Benzamides. Tiapridal® Solian ®
- Diazepine. Loxapac®

Neuroleptiques

- Effets anticholinergique
  - Rétention urinaire
  - Glaucome
  - Délire toxique
- Effets cardiovasculaires
  - Hypotension
  - Bradycardie
  - Torsades de pointes/Trouble du rythme Vent.
- Troubles extrapyramidaux
  - akathisie « incapacité de s'asseoir »
  - Dystonies

Confusion
Malaise et chutes

Benzodiazépines Injectable

- Clorazepate (tranxene®)
- Diazepam (valium®)
- Lorazepam (temesta® ref. mais pas en France)

Meprobamate Equanil®
Hydroxyzine Atarax®

Benzodiazépines

- Dépression respiratoire
- Confusion
- Sédation

Choix dans l'urgence

Revue Prescrire 2004

- Déments
  - Haldol® 1 mg (0.7 à 2.4)
  - Tiapridal®
- Psychotiques
  - Haldol® 5 mg
- Etats confusionnels
  - Haldol® 1 à 2 mg toute les deux à quatre heures

Les Nouveaux Antipsychotiques

- Clozapine Leponex®
- Tiapride Tiapridal®
- Risperidone Risperdal®
- Olanzapine Zyprexa®
- Quetiapine

Les Nouveaux Antipsychotiques

- Clozapine Leponex®
  - Agranulocytose
    - Parkinson

Les Nouveaux Antipsychotiques

- Olanzapine Zyprexa ®
  - Demi vie longue(51 h chez la PA saine!)
  - Peu de travaux gériatrique
  - Forme galénique
    - Velotab
    - Pas de goutte!
    - Injectable
- Mise en garde de l'AFFSAP 2004
  « surmortalité » et donc contre indication chez le sujet âgé dément

Les Nouveaux Antipsychotiques

- Risperidone Risperdal®
  - X publications chez la personne âgées
  - Demi vie courte (3 à 24 h)
  - Tolérance (parkinson?)
  - Dose consensuelles
    - 0.25 mg à 2 mg/j

Mise en garde sur les AVC

Les Nouveaux Antipsychotiques

- Les précautions restent les mêmes
  - Syndromes malin
  - Démence a corps de Lewy
  - Jamais de forme retard
  - Dyskinésie, syndrome extrapyramidal

Les Nouveaux Antipsychotiques

- Discuter l'indication
- Bien connaître la molécule
- Faible posologie
- Et réévaluer le tt
- Arrêt si Tp°
- Attention aux associations!
  - Primperan®,motilium®,plitican®,agreal®

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study

Sudeep S Gill, Paula A Rochon, Nathan Herrmann, Philip E Lee, Kathy Sykora, Nadia Gruneir, Shamoul Jaffer T Normand, Jerry H Gurwitz, Connie Marras, Walter P Wodchis, Muhammad Mamdani

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study
Sudeep S Gill,

- **Objective** To compare the incidence of admissions to hospital for stroke among older adults with dementia receiving atypical or typical antipsychotics.

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study
Sudeep S Gill,

- **Patients** 32 710 older adults (≥ 65 years) with dementia (17 845 dispensed an atypical antipsychotic and 14 865 dispensed a typical antipsychotic).

Design Population based retrospective cohort study.
Setting Ontario, Canada.

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study
Sudeep S Gill,

- **Main outcome measures** Admission to hospital with the most responsible diagnosis (single most important condition responsible for the patient's admission) of ischaemic stroke. Observation of patients until they were either admitted to hospital with ischaemic stroke, stopped taking antipsychotics, died, or the study ended

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study
Sudeep S Gill,

- **Results** After adjustment for potential confounders, participants receiving atypical antipsychotics showed no significant increase in risk of ischaemic stroke compared with those receiving typical antipsychotics (adjusted hazard ratio 1.01, 95% confidence interval 0.81 to 1.26). This finding was consistent in a series of subgroup analyses, including ones of individual atypical antipsychotic drugs (risperidone, olanzapine, and quetiapine) and selected subpopulations of the main cohorts.

Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study
Sudeep S Gill,

- **Conclusion** Older adults with dementia who take atypical antipsychotics have a similar risk of ischaemic stroke to those taking typical antipsychotics.

Characteristics	Atypical antipsychotics cohort (n=17 845)	Typical antipsychotics cohort (n=14 865)
Mean (SD) age (years)	82.5 (7.5)	82.7 (7.4)
Men	6431 (36.0)	5727 (38.5)
Long term care	8495 (47.5)	7682 (51.7)
Low income	6688 (37.5)	5807 (39.1)
Urban residence	2807 (15.7)	2673 (18.0)
Mean (SD) frequency of medical contact (days)*	33.3 (25.4)	34.3 (26.8)
Year of entry to cohort:		
1997	598 (3.4)	5452 (36.7)
1998	1588 (8.9)	4570 (30.7)
1999	3696 (20.7)	2680 (18.0)
2000	5589 (31.3)	1321 (8.9)
2001	6374 (35.7)	842 (5.7)
Chronic users†	13792 (77.3)	9929 (66.8)

Table 2 Event rates and hazard ratios for older adults with dementia receiving atypical or typical antipsychotics

Main analysis (full cohorts)	Atypical antipsychotic cohort (n=17 845)	Typical antipsychotic cohort (n=14 865)
No (%) of new admissions for ischaemic stroke	284 (1.6)	227 (1.5)
Mean (SD) duration of follow up (days)	227.2 (264.0)	209.1 (336.4)
Crude event rate (No of events per 1000 person years)*	25.5	22.5
Unadjusted hazard ratio (95% CI)	1.00 (0.89 to 1.27)	1.00
Adjusted hazard ratio (95% CI)†	1.01 (0.81 to 1.26)	1.00

*(No of events/total No of days per 365 days)×1000.
†Adjusted for age; sex; low income status; residence in long term care; frequency of medical contact; year of entry to cohort; history of stroke in past five years; history of atrial fibrillation; hypertension; diabetes mellitus; acute myocardial infarction in past three months; congestive heart failure; number of distinct drugs; chronic use (≥7 consecutive prescriptions) of antipsychotics; and baseline use of warfarin, antiplatelet drugs, antihypertensive drugs, angiotensin converting enzyme inhibitors, lipid lowering drugs, antidiabetic drugs, and hormone replacement therapy.

What is already known on this topic

Atypical antipsychotics are commonly used to manage behavioural and psychological symptoms of dementia (BPSD)

Recent evidence from clinical trials suggests an association between atypical antipsychotic use and cerebrovascular events (including stroke) among older adults with BPSD

These data prompted the UK Committee on Safety of Medicines to recommend against the prescribing of atypical antipsychotics to patients with BPSD

The choice of atypical or typical antipsychotics to manage BPSD should not be based on concerns about the risk of stroke

Findings were consistent for a series of subgroup analyses including ones for patients at high baseline risk of stroke

The choice of atypical or typical antipsychotics to manage BPSD should not be based on concerns about the risk of stroke

Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis

John Hippisley-Cox, Carol Coupland

9218 cases with a first ever diagnosis of myocardial infarction during the four year study period
86 349 controls matched for age, calendar year, sex, and practice.

A significantly increased risk of myocardial infarction was associated with current use of rofecoxib (adjusted odds ratio 1.32) compared with no use within the previous three years; with current use of diclofenac (1.55); and with current use of ibuprofen (1.24).

What is already known on this topic

The VIGOR study found that rofecoxib was associated with an increased risk of myocardial infarction compared with naproxen

Uncertainty existed as to whether this reflected a true increase or an apparent increase due to a cardioprotective effect of naproxen

Rofecoxib has been withdrawn, but uncertainty persists about the cardiovascular safety of the other selective non-steroidal anti-inflammatory drugs (NSAIDs)

What this study adds

Rofecoxib, diclofenac, and ibuprofen were associated with a higher risk of myocardial infarction; no evidence of a cardioprotective effect for naproxen was found

The increased risk with rofecoxib in the VIGOR study was genuine; the toxicity of conventional NSAIDs and newer selective NSAIDs is also of concern

No clinically important interactions occurred between any NSAID and either aspirin or coronary heart disease

Annals of Internal Medicine | ARTICLE

The Risk for Myocardial Infarction with Cyclooxygenase-2 Inhibitors: A Population Study of Elderly Adults

Linda E. Levesque, BSc(Pharm), MSc, Samy H. Brophy, BSc, PhD, and Bin Zhang, MSc

Ann Intern Med. 2005;142:481-489.

Participants: 113 927 elderly persons without previous MI and newly treated with an NSAID between 1 January 1999 and 30 June 2002.

Annals of Internal Medicine | ARTICLE

The Risk for Myocardial Infarction with Cyclooxygenase-2 Inhibitors: A Population Study of Elderly Adults

Linda E. Levesque, BSc(Pharm), MSc, Samy H. Brophy, BSc, PhD, and Bin Zhang, MSc

Ann Intern Med. 2005;142:481-489.

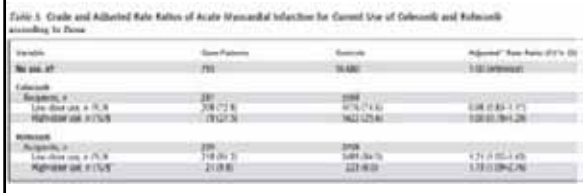
Conclusions: Those results provide evidence of an increased risk for acute MI in current users of rofecoxib among elderly persons with no history of MI. This risk appears greater at higher doses. Aspirin use mitigates the risk associated with low-dose but not high-dose rofecoxib. There was no evidence of an increased risk with the other NSAIDs.

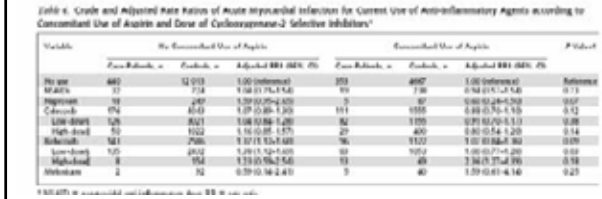
Annals of Internal Medicine | ARTICLE

The Risk for Myocardial Infarction with Cyclooxygenase-2 Inhibitors: A Population Study of Elderly Adults

Linda E. Levesque, BSc(Pharm), MSc, Samy H. Brophy, BSc, PhD, and Bin Zhang, MSc

Ann Intern Med. 2005;142:481-489.





Inclusion aux grandes études: L'exemple de l'insuffisance cardiaque

- Sur 20388 patients (Medicare) de plus de 65 ans (78 ans) avec ICC, seuls
  - 18% étaient éligibles pour SOLVD
  - 13% étaient éligibles pour MERIT-HF
  - 25% étaient éligibles pour RALES

Masoudi: Am Heart J 2003;146:250

Etudes de mortalité: Moyenne d'âge

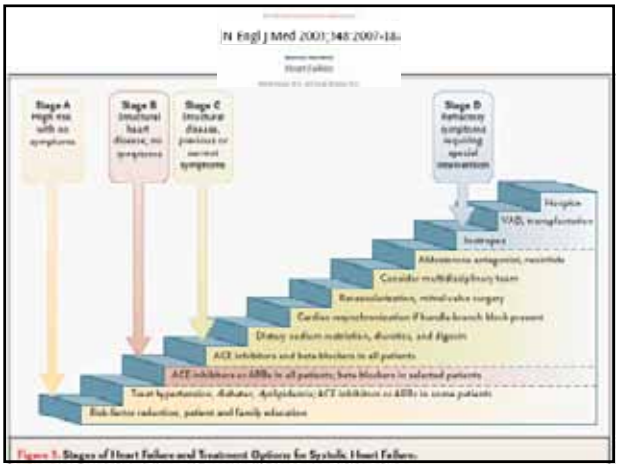
• SOLVD Prevention:	59 ans
• SOLVD Treatment:	61 ans
• VeHeFT-II:	60 ans
• SAVE:	59 ans
• AIRE:	65 ans
• TRACE:	67 ans
• DIG:	63 ans
• RALES:	65 ans
• CIBIS II:	61 ans
• MERIT-HF:	64 ans
• COPERNICUS:	63 ans
• Val HeFT:	63 ans
• CHARM-added:	64 ans
• CHARM-preserved	67 ans

Hyperkalaemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study

BMJ 2003;327:1141–2

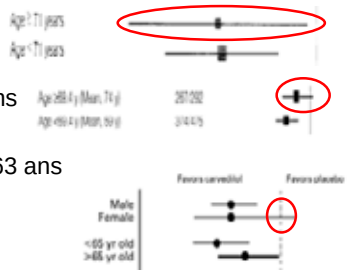
Comment

Taking spironolactone for congestive heart failure is associated with considerably more frequent side effects than previously thought. Age, lower LVEF, and higher NYHA FC are predictors of hyperkalaemia and azotaemia.



Bêta-bloquants

- CIBIS II: 61 ans
  Bisoprolol
- MERIT-HF: 64 ans
  Métoprolol
- COPERNICUS: 63 ans
  Carvédilol



Inclusion aux grandes études:
L'exemple de l'insuffisance cardiaque

COMORBIDITES
(pourcentage)

Démence	36
Chutes	30
Diabète	23
Anémie	20
BPCO	19
Dépression	17
Cancer	9
Parkinson	4
Néphropathie	1

Gambassi G ; Am Heart J 2000 ; 139 : 85 - 93

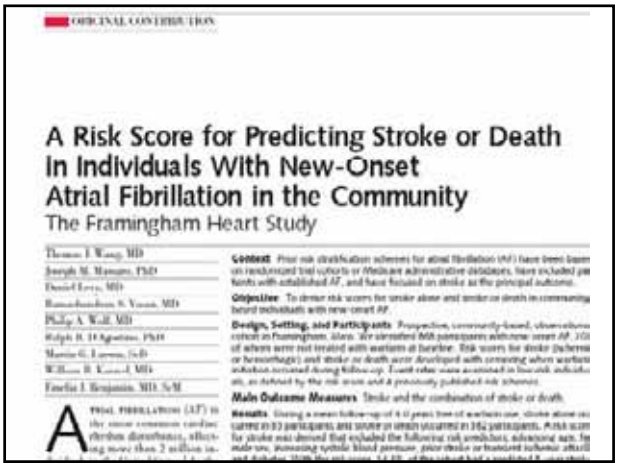
Inclusion aux grandes études:
L'exemple de l'insuffisance cardiaque

- Donc pour le traitement de l'insuffisance cardiaque du sujet âgé, le clinicien est en permanence hors AMM

Traitement anticoagulant dans la fibrillation auriculaire

La FA est un modèle de la problématique bénéfice risque car

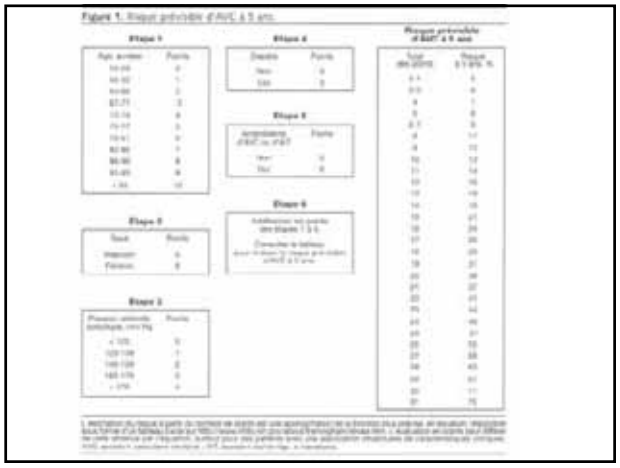
- Le risque d'AVC est bien connu mais variable selon certains facteurs de risques dont l'age…
- Les effets secondaires des AVK sont aussi bien connu mais variable selon certains facteurs de risques dont l'age…

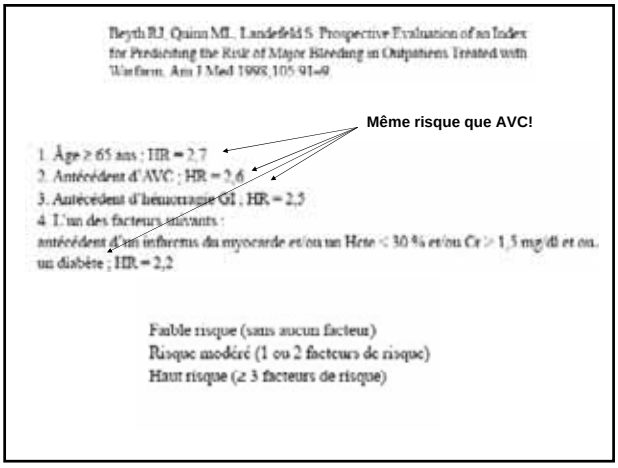


ORIGINAL CONTRIBUTION

A Risk Score for Predicting Stroke or Death In Individuals With New-Onset Atrial Fibrillation in the Community

The Framingham Heart Study



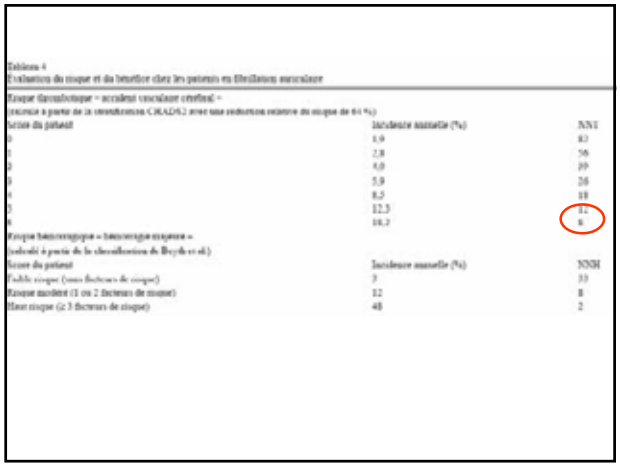


Beyth RJ, Quinn LM, Landefeld CS. Prospective Evaluation of an Index for Predicting the Risk of Major Bleeding in Outpatients Treated with Warfarin. Am J Med 1998;105:91-99.

Même risque que AVC!

1. Âge ≥ 65 ans ; HR = 2,7
2. Antécédent d'AVC ; HR = 2,6
3. Antécédent d'hémorragie GI ; HR = 2,5
4. L'un des facteurs suivants :
antécédent d'un infarctus du myocarde et/ou un Hcte < 30 % et/ou Cr > 1,5 mg/dl et ou, un diabète ; HR = 2,2

Faible risque (sans aucun facteur)
Risque modéré (1 ou 2 facteurs de risque)
Haut risque (≥ 3 facteurs de risque)

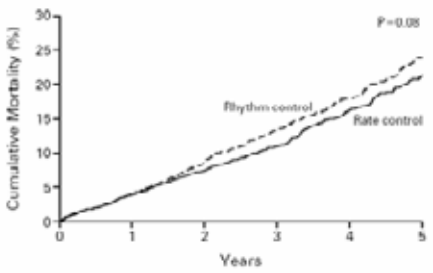


A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

None of the presumed benefits of rhythm control noted above were confirmed in this study. The implication is that rate control should be considered a primary approach to therapy and that rhythm control, if used, may be abandoned early if it is not fully satisfactory. Our data also suggest that continuous anticoagulation is warranted in all patients with atrial fibrillation and risk factors for stroke, even when sinus rhythm appears to be restored and maintained.

N Engl J Med, Vol. 347, No. 23 · December 5, 2002



No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	176 (9)	267 (13)	314 (16)	362 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	276 (16)	306 (21)

Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.
Time zero is the day of randomization. Data have been truncated at five years.

THE NEW ENGLAND JOURNAL of MEDICINE

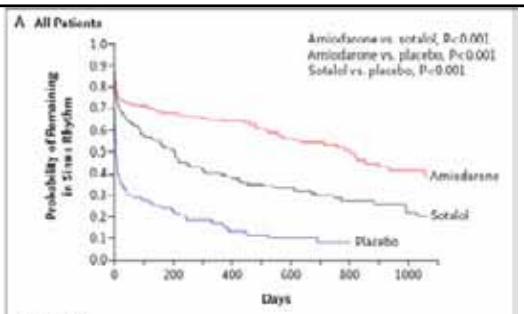
ORIGINAL ARTICLE

Amiodarone versus Sotalol for Atrial Fibrillation

Bramah N. Singh, M.D., D.Sc., Steven N. Singh, M.D., Domenic J. Reda, Ph.D., X. Charlene Tang, M.D., Ph.D., Becky Lopez, R.N., Crystal L. Harris, Pharm.D.,

Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T)

N Engl J Med 2005;352:1861-72.



No. at Risk						
Amiodarone	206	131	98	60	38	18
Sotalol	195	97	61	38	21	13
Placebo	90	21	11	8	5	2

Figure 2. Kaplan–Meier Estimates of the Time to Recurrence of Atrial Fibrillation among Patients in Whom Sinus Rhythm Was Restored on Day 28.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Amiodarone Group (N=267)	Sotalol Group (N=262)	Placebo Group (N=137)	P Value†
Age — yr	67.3±9.4	66.8±9.9	67.7±9.8	0.48
Male sex — no. (%)	265 (99.3)	257 (98.5)	136 (99.3)	0.27

ORIGINAL INVESTIGATION

Oral Cyanocobalamin Supplementation in Older People With Vitamin B_{12} Deficiency

A Dose-Finding Trial

Simone J. P. M. Eussen, MSc; Lisette C. P. G. M. de Groot, PhD; Robert Clarke, MD; Jörn Schneede, MD; Piet M. Ueland, MD; Wilfred H. F. Hustinx, MD, PhD; Wijda A. van Staveren, PhD

Arch Intern Med. 2005;165:1167-1172

Daily doses of 647 to 1032 µg of cyanocobalamin

Conclusion: The lowest dose of oral cyanocobalamin required to normalize mild vitamin B_{12} deficiency is more than 200 times greater than the recommended dietary allowance, which is approximately 3 µg daily.

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H.,

N Engl J Med 2005;352.

CONCLUSIONS

Vitamin E had no benefit in patients with mild cognitive impairment. Although after three years, the rate of progression to Alzheimer's disease was not lower among patients treated with donepezil than among those given placebo, donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment.

Role of multivitamins and mineral supplements in preventing infections in elderly people: systematic review and meta-analysis of randomised controlled trials

Alex F Kardinaal, Alexander J Nelson

BMJ 2005;330:871–, originally published online 31 Mar 2005.

Conclusion The evidence for routine use of multivitamin and mineral supplements to reduce infections in elderly people is weak and conflicting. Study results are heterogeneous, and this is partially confounded by outcome measure.

Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial

Lancet 2005; 365: 755–63

The FOOD Trial Collaboration*

Interpretation We could not confirm the anticipated 6% absolute benefit for death or poor outcome from routine oral nutritional supplements for mainly well nourished stroke patients in hospital. Our results would be compatible with a 1% or 2% absolute benefit or harm from oral supplements. These results do not support a policy of routine oral supplementation after stroke.

Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial

The FOOD Trial Collaboration*

Interpretation Early tube feeding might reduce case fatality, but at the expense of increasing the proportion surviving with poor outcome. Our data do not support a policy of early initiation of PEG feeding in dysphagic stroke patients.

Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial

Lancet 2005; 365: 764–72

The FOOD Trial Collaboration*

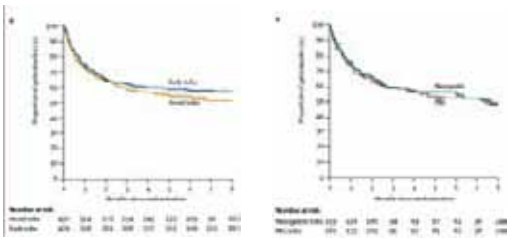


Figure 5: Kaplan-Meier survival curves
(A) early versus avoid and (B) PEG versus nasogastric tube

Prise en charge des cancers solides et des hémopathies malignes du sujet âgé : l'oncogériatrie, une discipline en devenir. Seconde partie : traitement des cancers solides (partie 2) et des hémopathies malignes du sujet âgé

S. Ludwig, F. Stanglein, P. Mankowski, R.O. Casanovas, E. Solary, J.F. Beaucaire, P. Pfitzenmeyer

la revue de médecine interne

PNEUMONIE ET IPP

Albumin, Length of Stay, and Proton Pump Inhibitors: Key Factors in *Clostridium difficile*–Associated Disease in Nursing Home Patients

(J Am Med Dir Assoc 2005; 6: 105–108)

Objectives: To identify risk factors for *Clostridium difficile*–associated disease (CDAD) in nursing home patients.

The third significant risk factor was the use of proton pump inhibitors, 60% versus 32%, respectively (2 4.137; *df* 1; *P* .05). Levofloxacin was the most frequently prescribed antibiotic (37%).

VACCIN CHEZ L'ENFANT
DIMINUTION DES PNEUMONIES CHEZ LES SENIORS

The NEW ENGLAND JOURNAL of MEDICINE

MAY 1, 2003

Decline in Invasive Pneumococcal Disease after the Introduction of Protein–Polysaccharide Conjugate Vaccine

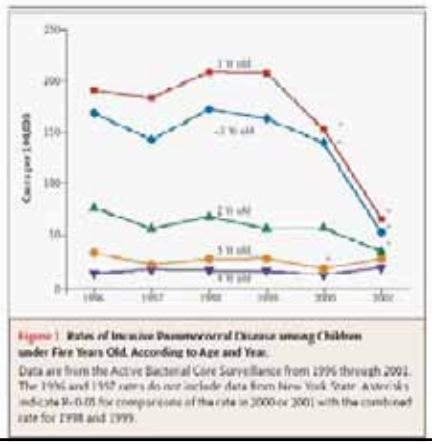


Figure 1. Rates of Invasive Pneumococcal Disease among Children under Five Years Old, According to Age and Year.

Data are from the Active Bacterial Core Surveillance from 1996 through 2001. The 1996 and 1997 rates do not include data from New York State. Asterisks indicate P<0.05 for comparisons of the rate in 2000 or 2001 with the combined rate for 1998 and 1999.

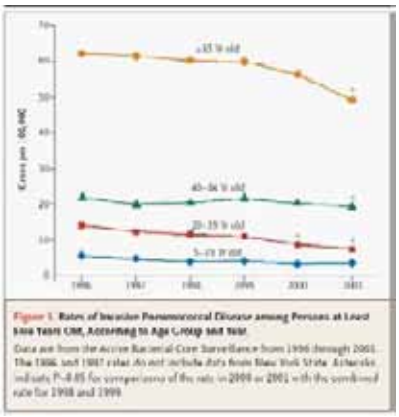


Figure 3. Rates of Invasive Pneumococcal Disease among Persons at Least [illegible], According to Age Group and Year.

Data are from the Active Bacterial Core Surveillance from 1996 through 2001. The 1996 and 1997 rates do not include data from New York State. Asterisks indicate P<0.05 for comparisons of the rate in 2000 or 2001 with the combined rate for 1998 and 1999.

Obesite Fragilite

CHOLESTÉROL
NOUVELLE RECOMMANDATION

Community-acquired meticillin-resistant *Staphylococcus aureus*: an emerging threat

Nimalan Chambers, John S Francis, Eric L Nuermberger, William R Bishai

Lancet Infect Dis 2005; 5: 275–86

New strains of *S aureus* displaying unique combinations of virulence factors and resistance traits have been associated with high morbidity and mortality in the community.
Severe invasive pulmonary infections in young, otherwise healthy people have been particularly noteworthy.

Community-acquired pneumonia as the initial manifestation of serious underlying diseases

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ORIGINAL INVESTIGATION

A Prescribing Cascade Involving Cholinesterase Inhibitors and Anticholinergic Drugs

Arch Intern Med. 2005;165:808-813

Methods: A population-based retrospective cohort study was carried out in Ontario, Canada. Participants included 44 804 older adults with dementia (20 491 were dispensed a cholinesterase inhibitor and 24 303 were not), enrolled between June 1, 1999, and March 31, 2002. Sub-

- Adults with dementia who were dispensed cholinesterase inhibitors had an increased risk of subsequently receiving an anticholinergic drug (4.5% vs 3.1%; *P*.001; adjusted hazard ratio, 1.55; 95% confidence interval, 1.39- 1.72), relative to those not receiving cholinesterase inhibitors.

Affiche Vaccin Pneumocoque