the current analysis, older patients had significantly lower BMI values than young and middle-aged patients (mean BMI $24.7 \text{ kg/m}^2 < 65$ vs $23.7 \text{ kg/m}^2 \geq 65$) and included fewer obese patients. Thus, candesartan did not show significant differences from amlodipine with respect to a lower incidence of new-onset diabetes mellitus in elderly patients, who generally have lower RAS activity.

Although the morbidity of diabetes mellitus increases with aging, the contribution of aging to new-onset diabetes mellitus remains controversial. Differences in study design and in the statistical analysis set may influence the incidence of new-onset diabetes mellitus related to aging. Elderly patients with hypertension in our series who did not have diabetes mellitus at the time of enrollment in the CASE-J trial were considered to represent a population surviving the onset of diabetes mellitus. Therefore, older patients with hypertension but without diabetes mellitus may represent individuals with less susceptibility to new-onset diabetes mellitus and may differ from younger patients with hypertension with new-onset diabetes mellitus in terms of the presence of risk factors for new-onset diabetes mellitus and in glucose metabolism function. This may also be a reason why the older subgroup of patients was less sensitive to the preventive effects of candesartan against new-onset diabetes mellitus.

In conclusion, the ARB candesartan prevented new-onset diabetes mellitus significantly more effectively than the CCB amlodipine in the CASE-J trial in high-risk patients with hypertension, although there was a significant difference between ARB and CCB in the incidence of new-onset diabetes mellitus stratified according to age only for the younger subgroup (< 65) and not for the older subgroup (≥ 65).

Toshio Ogihara, MD, PhD
Osaka General Medical Center
Osaka, Japan

Akira Fujimoto, MS
EBM Research Center
Kyoto University Graduate School of Medicine
Kyoto, Japan

Kazuwa Nakao, MD, PhD
Department of Medicine and Clinical Science
Kyoto University Graduate School of Medicine
Kyoto, Japan

Takao Saruta, MD, PhD
Keio University Graduate School of Medicine
Tokyo, Japan

ACKNOWLEDGMENTS

Conflict of Interest: TO, TS, and KN have received honoraria for lectures from Takeda Pharmaceutical Co Ltd. and Pfizer Japan Inc. AF has no conflict of interest.

Author Contributions: TO and AF: study concept and design, analysis and data interpretation, preparation of the manuscript. TS and KN: study concept and design, analysis.

Sponsor's Role: No sponsor.

REFERENCES

1. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997.
2. Lindholm LH, Ibsen H, Borch-Johnsen K et al, for the LIFE study group Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. *J Hypertens* 2002;20:1879–1886.
3. Niklason A, Hednet T, Captopril Prevention Project Study Group et al. Development of diabetes is retarded by ACE-inhibition in hypertensive patients — a subanalysis of the Captopril Prevention Project (CAPPP). *J Hypertens* 2004;22:645–652.
4. Kjeldsen SE, Julius S, VALUE Trial Investigators et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: The VALUE trial. *J Hypertens* 2006;24:1405–1412.
5. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: A network meta-analysis. *Lancet* 2007;369:201–207.
6. Fukui T, Rahman M, Hayashi K et al. Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: Rationale, design, and methods. *Hypertens Res* 2003;26:979–990.
7. Ogihara T, Nakao K, Fukui T et al. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: Candesartan Antihypertensive Survival Evaluation in Japan trial. *Hypertension* 2008;51:393–398.
8. Ogihara T, Fujimoto A, Nakao K et al. for the CASE-J trial group ARB candesartan and CCB amlodipine in hypertensive patients: The CASE-J Trial. *Expert Rev Cardiovasc Ther* 2008;6:1195–1201.
9. Messerli FH, Sundgaard-Riise K, Ventura HO et al. Essential hypertension in the elderly: Haemodynamics, intravascular volume, plasma rennin activity, and circulating catecholamine levels. *Lancet* 1983;2:983–986.
10. Karlsson C, Lindell K, Ottosson M et al. Human adipose tissue expresses angiotensinogen and enzymes required for its conversion to angiotensin II. *J Clin Endocrinol Metab* 1998;83:3925–3929.

PNEUMOCOCCAL COLONIZATION IN OLDER PERSONS IN A NONOUTBREAK SETTING

To the Editor: *Streptococcus pneumoniae* is a leading cause of bacteremia, meningitis, and pneumonia in older persons and causes the highest mortality in this age group.¹ Asymptomatic pharyngeal colonization precedes respiratory or systemic disease and plays an important role in horizontal spread in the community. The highest colonization rates have been documented in children.² Colonization is seldom reported in older subjects.

A prospective epidemiological study was performed to establish the prevalence, risk factors, and dynamics of pneumococcal colonization in community-dwelling ($n = 109$) and institutionalized (296 nursing home residents and 98 hospitalized) older persons using bacteriological culture and molecular diagnostic (polymerase chain reaction (PCR)) techniques on nasopharyngeal swabs (NPSs).

Two NPSs, one from each nares, were obtained per participant using Dacron polyester-tipped swabs on an aluminium shaft. The first NPS was plated directly on a selective agar containing polymyxin B and incubated for 48 hours. The second NPS was wringed in Todd-Hewitt (TH) broth, preincubated for 18 to 24 hours, plated on a blood agar, and then processed like the first NPS. When identified, pneumococci were serotyped.

The overall pneumococcal colonization rate was 4.2% (21/503) (5.5% (6/109) in the community, 4.1% (12/296) in nursing homes, and 3.1% (3/98) in the hospital, $P = .69$) (Table 1). Fourteen of 21 colonizing pneumococci were recovered by direct plating on a selective agar and seven of 21 after enrichment in TH broth.

Table 1. Subject Characteristics and Pneumococcal Colonization Rate

Characteristic	Total N = 503	Community n = 109	Nursing Home n = 296	Hospital n = 98	P-Value
Age, mean $\pm$ SD	80.3 $\pm$ 10.0	66.2 $\pm$ 4.5	84.3 $\pm$ 7.4	83.8 $\pm$ 6.4	.001
Male:female	0.52	0.43	0.54	0.58	.57
Comorbidities, mean $\pm$ SD	2.5 $\pm$ 1.8	1.0 $\pm$ 1.1	2.7 $\pm$ 1.4	3.6 $\pm$ 2.4	.001
Antibiotic use within the previous 3 months, n (%)	139 (27.6)	8 (7.3)	93 (31.4)	39 (39.8)	.001
Hospitalization within the previous year, n (%)	162 (32.2)	11 (10.1)	102 (34.5)	51 (52)	.001
Influenza vaccine within the previous year, n (%)	376 (73)	43 (39.4)	258 (87.2)	66 (67.3)	.001
Pneumococcal vaccine, n (%)	187 (37.2)	14 (12.8)	148 (50)	25 (25.5)	.001
Katz score, mean $\pm$ SD	14.7 $\pm$ 7.2	8.0 $\pm$ 0.2	16.4 $\pm$ 7.1	17.6 $\pm$ 6.8	.001
Pneumococcal colonization, n (%)	21 (4.2)	6 (5.5)	12 (4.1)	3 (3.1)	.69

SD = standard deviation.

No significant differences in age and sex distribution, presence of comorbidities, vaccination status, hospitalization or antibiotic use history, or functionality (Katz score) were evident between colonized and noncolonized subjects.

Ten colonized and 30 noncolonized nursing home residents were reswabbed after 1, 2, 4, 8, and 12 weeks. During these 3 months after the primary sampling, pneumococcal carriage occurred in five of the 10 subjects colonized at first sampling (50.0%), compared with eight of the 30 (26.7%) subjects not colonized at first sampling ($P = .25$). Colonization could be detected only once (2/13), intermittently (4/13), or for longer periods (1/13 during 2 weeks, 6 during ≥ 1 month). The pneumococci recovered per resident during primary sampling and follow-up belonged to the same serotype.

In a subset of nursing home residents ($n = 199$), deoxyribonucleic acid was extracted from the NPSs and amplified using real-time fluorescence PCR with a *lytA* gene (encoding for autolysin) probe with a high sensitivity and specificity for *S. pneumoniae* as described previously.³ The pneumococcal colonization rate detected using PCR was 2.0% (4/199) in this group. When PCR was taken as the criterion standard, the bacteriological culture technique had a sensitivity, specificity, and positive and negative predictive values for detecting nasopharyngeal colonization of 50%, 100%, 100%, and 99%, respectively.

This is the first study that specifically describes prevalence and dynamics of pneumococcal colonization in older subjects in a nonoutbreak setting. The overall prevalence of nasopharyngeal pneumococcal colonization was low (4.2%). Higher colonization rates in older subjects have been described in families with small children (4.6%), during respiratory tract infections (6.5–8.7%), and during outbreaks of pneumococcal disease in nursing homes (23%).^{4–6}

During the 3-month follow-up, more than one-quarter of nursing home residents carried a pneumococcus. It is likely that family visits with young children and healthcare personnel with young children, acting as intermediary carriers, can transmit pneumococci to institutionalized older adults.

No specific risk factor for pneumococcal carriage in older adults could be identified in this study. Neither colonization nor its risk factors by themselves but rather immunosenescence (reduced and deficient immunological response) and comorbid illness (cardiopulmonary disease, smoking, alcoholism) contributes to the high susceptibility of elderly persons to pneumonia and invasive pneumococcal disease.^{7,8}

The broth enrichment technique augmented the recovery of colonizing pneumococci by 33%, although the combination of direct inoculation and broth enrichment in the recovery of colonizing pneumococci is likely to underestimate the true pneumococcal carriage rate. In adults, a supplementary oropharyngeal swab can yield 30% more carriers.⁹ Compared with PCR with a *lytA* probe, the bacteriological culture technique resulted in a good specificity (100%) but low sensitivity (50%) for detecting pneumococci. These results suggest that the pneumococcal colonization rate detected using *lytA*-PCR is twice that of the culture technique that relies on the recovery of viable pneumococci.

In conclusion, the prevalence of nasopharyngeal carriage of pneumococci in older persons is low, although over a period of 3 months, pneumococcal colonization was a frequent event. The origin, dynamics, risk factors, and optimal detection method of pneumococcal colonization in older persons need further study.

Johan Flamaing, MD, PhD
Department of Geriatric Medicine

Willy E. Peetermans, MD, PhD
Department of General Internal Medicine and Infectious Diseases

Jos Vandeven, Techn
Jan Verhaegen, MD, PhD
Department of Microbiology
University Hospitals Leuven
Leuven, Belgium

ACKNOWLEDGMENTS

We would like to acknowledge Marc Van Ranst, virologist of the department of microbiology of the University Hospitals Leuven, Belgium, for his expert advice on the application of molecular diagnostics by PCR on the nasopharyngeal samples.

The results of this study were partially presented at the 18th European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, April 19 to 22, 2008 (abstract P1708).

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has

determined that the authors have no financial or any other kind of personal conflicts with this paper.

This study was partially funded by a clinical PhD grant from the Research Foundation Flanders (FWO-Vlaanderen) granted to Johan Flamaing.

Author Contributions: All authors participated in the design, analysis and interpretation of the data, and preparation of the manuscript. J. Flamaing was responsible for acquisition of subjects, NPSs, and laboratory work.

Sponsor's Role: The Research Foundation Flanders (FWO-Vlaanderen) had no role in the design, methods, subject recruitment, data collection, analysis, or preparation of the letter.

REFERENCES

- Centers for Disease Control and Prevention. 2004. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, *Streptococcus pneumoniae*, 2004 [on-line]. Available at <http://www.cdc.gov/ncidod/dbm/d/abcs/survreports/spneu04.pdf> Accessed August 20, 2009.
- Bogaert D, De Groot R, Hermans PW. *Streptococcus pneumoniae* colonization: The key to pneumococcal disease. *Lancet Infect Dis* 2004;4:144–154.
- McAvlin JC, Reilly PA, Roudabush RM et al. Sensitive and specific method for rapid identification of *Streptococcus pneumoniae* using real-time fluorescence PCR. *J Clin Microbiol* 2001;39:3446–3451.
- Regev-Yochay G, Raz M, Dagan R et al. Nasopharyngeal carriage of *Streptococcus pneumoniae* by adults and children in community and family settings. *Clin Infect Dis* 2004;38:632–639.
- Konno M, Baba S, Mikawa H et al. Study of upper respiratory tract bacterial flora: First report. Variations in upper respiratory tract bacterial flora in patients with acute upper respiratory tract infection and healthy subjects and variations by subject age. *J Infect Chemother* 2006;12:83–96.
- Nuorti JP, Butler JC, Crutcher JM et al. An outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents. *N Engl J Med* 1998;338:1861–1868.
- Hakim FT, Gress RE. Immunosenescence: Deficits in adaptive immunity in the elderly. *Tissue Antigens* 2007;70:179–189.
- Kyaw MH, Rose CE Jr, Fry AM et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. *J Infect Dis* 2005;192:377–386.
- Watt JP, O'Brien KL, Katz S et al. Nasopharyngeal versus oropharyngeal sampling for detection of pneumococcal carriage in adults. *J Clin Microbiol* 2004;42:4974–4976.

ANTICOAGULATION VERSUS ASPIRIN FOR GERIATRIC PATIENTS WITH ATRIAL FIBRILLATION: IS THERE STILL ANY DOUBT?

To the Editor: The latest American and European guidelines recommend oral anticoagulation (OA) unless contraindicated, targeting an international normalized ratio between 2 and 3 for patients aged 75 and older with atrial fibrillation (AF) and associated risk factors (arterial hypertension, heart failure, systolic dysfunction according to echocardiography, or diabetes mellitus) and for secondary prevention.¹ Aspirin may be used when other risk factors are absent or when OA is contraindicated,¹ although even recent cross-sectional studies have shown that only half of patients with AF at a high risk of stroke effectively receive anticoagulants and that this proportion declines with age.^{2,3}

Guidelines are based on a meta-analysis⁴ of five unblinded randomized controlled trials (Table 1). In these trials, OA resulted in a 36% lower risk of stroke (14–52%) than aspirin. Three randomized trials have been published since the latest guidelines were issued, namely the Atrial Clopidogrel Trial with Irbesartan for prevention of Vascular Event (ACTIVE W),⁵ the Warfarin Versus Aspirin for Stroke Prevention in Octogenarians with Atrial Fibrillation (WASPO)

trial,⁶ and the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study⁷ (Table 1). ACTIVE W compared OA with aspirin (75–100 mg) plus clopidogrel and showed that OA was significantly more effective. WASPO focused on primary prevention in octogenarians with permanent AF but was interrupted prematurely. In the BAFTA study, patient screening and recruitment were organized systematically across general practitioner practices in the United Kingdom. Patients could be excluded if their physician thought, in view of their ischemic and hemorrhagic risk factors, that they should, or should not, receive warfarin. How the general practitioners formed their judgment is not specified. The results favored OA.

To examine the external validity of these trials with respect to a population of frail elderly patients with AF, they were critically analyzed, with a focus on the inclusion and exclusion criteria, to assess the potential eligibility of a population of geriatric subjects.

During a period of 6 consecutive months, all patients (n = 83) admitted to an acute geriatric unit with permanent or paroxysmal AF were identified. Their mean age was 89, and they were at a high risk of ischemic events (mean CHADS2 score⁸ = 2.7 ± 1.2) and bleeding (mean HEM-ORR2HAGES score⁹ = 3.0 ± 1.3). Seventeen of these patients (20%) could have been included in at least one of the eight trials, because they fit the published inclusion and exclusion criteria (Table 1). The main factors that would probably have excluded the patients in the current study was their limited life expectancy in 15 cases (11 because of severe dementia), poor adherence to treatment in 13 cases, and progressive cancer in eight cases.

Recruitment was organized systematically in only two of the eight published studies, and the attending physicians were allowed to refuse anticoagulation for their patients, regardless of any explicit exclusion criteria, in at least five of the eight trials (Table 1). These two facts would have resulted in selection biases, the most fragile and oldest patients likely being excluded.

Dans' method was used to assess external validity.¹⁰ It consists of posing six questions aimed at identifying a possible difference in the risk–benefit ratio of a treatment between a trial population and a population to which one wishes to apply the trialists' conclusions. Six negative responses are required for the trial results to be applicable to another population. With respect to the population of the current study, the answer would be yes to the third question: “Are there important differences in patient compliance that may diminish the treatment response?” and to the fifth question: “Do my patients have comorbid conditions that significantly alter the potential benefits and risks of treatment?” Dans' approach,¹⁰ without casting doubt on the superiority of anticoagulation over aspirin for thrombotic prevention, calls into question the reported difference in the risk–benefit ratios of the two treatments in the geriatric setting.

New trials involving very frail elderly patients are difficult to envisage, for practical and ethical reasons. Centralized registers recording the outcomes of all patients with AF receiving OA could provide clinicians with assistance when weighing the potential risks and benefits of this treatment in elderly patients at the highest risk.

These results thus highlight the poor external validity, with respect to frail elderly patients, of clinical trials comparing OA with aspirin in patients with AF. For such pa-

Copyright of Journal of the American Geriatrics Society is the property of Blackwell Publishing Limited and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.