Author's response to reviews

Title: Impact of valvular heart disease on daily living activity of nonagenarians: The Leiden 85-plus study

Authors:

Thomas van Bemmel (t.van_bemmel@lumc.nl)
Victoria Delgado (v.delgado@lumc.nl)
Jeroen J Bax (j.j.bax@lumc.nl)
Jacobijn Gussekloo (j.gussekloo@lumc.nl)
Gerard J Blauw (g.j.blauw@lumc.nl)
Rudi G Westendorp (r.g.j.westendorp@lumc.nl)
Eduard R Holman (e.r.holman@lumc.nl)

Version: 2 Date: 13 September 2009

Author's response to reviews: see over
Reviewer's report

Title: Prevalence of valvular heart disease in nonagenarians from the general population: The Leiden 85-plus study
Version: 1 Date: 3 June 2009
Reviewer: FULVIO LAURETANI

Reviewer's report:

The manuscript entitled “Prevalence of valvular heart disease in nonagenarians from the general population: The Leiden 85-plus study” suggested that significant valvular disease was highly prevalent in older persons, but the presence of significant valvular disease does not impact negatively on the functional status assessed with the GARS score.

The manuscript is accurately written, concise and well organized.

Major issues:

1) Should be important for well describe the functional status of this study population, report other functional tests, such as 4-meter walking test at usual or fast pace, or even score of the 400-meter walking test, which are objective walking tests, highly validated in older persons.

We agree with the reviewer that a 4-meter walking test would add valuable information. However, the participants did not perform that test at age 90. We have added this as a limitation in the discussion. (page 13)

2) Details of the study characteristics such as cognitive status, depressive symptoms and other characteristics of the functional status such as ADL and IADL disability, could better describe this population, reinforcing the conclusion of the study.

As suggested by the reviewer we have added more detailed information about the characteristics of the study population. Table one now contains information about cognition, depression, IADL and ADL disability.
Changes made to the manuscript: 5109993402713548

Reviewer's report

Title: Prevalence of valvular heart disease in nonagenarians from the general population: The Leiden 85-plus study
Version: 1 Date: 19 June 2009
Reviewer: Giovanni Gambassi

Reviewer's report:

DISCRETIONARY REVISIONS

1)The title focuses only on the prevalence of valvular disease whereas a more appropriate one would integrate the relation with activities of daily living or with physical function in some way.

We thank the reviewer for this important suggestion. The title has been changed into: Impact of valvular heart disease on daily living activity of nonagenarians: The Leiden 85-plus study

2)The word “competence” to describe the performance of an individual in the activities of daily living is a bit awkward.

We have changed competence into performance. (page 4)

3)The introduction section in my opinion should be focused more on the specific topic rather than give an account of the effect of age on anatomical and functional parameters. It reads more as a textbook rather than a scientific manuscript.

We agree with the reviewer and accordingly, the introduction section has been changed in order to highlight the focus of the study on the impact of valvular heart disease on the daily living activities and physical function of nonagenarians (page 3).

4)In describing the study protocol, the authors mention that “...performance tests were conducted” when person become 90 years old. To what exactly do they refer to. The GARS is only a questionnaire. Do the authors have available data on functional performance tests (6 min WT)??

Unfortunately we do not have a six-minute walking test. The Performance tests refered to several cognitive tests that were taken. In table one we have added the results of the Mini Mental State Examination on request of the other reviewer. Therefore we have not changed the phrase in the methods section.

MAJOR COMPULSORY REVISIONS

1) A paragraph on the limitations of the current study seems warranted. In particular, the authors need to mention and justify several problems arising from the study. First, 705 85+ individuals were asked to participate and then later the cohort is suddenly down to
599 individuals. Clarify this aspect. Following, 290 individuals reached 90 years which would translated in 50% of the initial cohort dying.

As suggested we have clarified the numbers of included participants. Of the initial 705 eligible participants at the Leiden 85–plus study, 14 died before they could be enrolled and 92 refused to participate, resulting in a cohort of 599 participants who could be enrolled at age 85 (87% response). (page 8)

2) The authors should convince the reader that their study is not affected by an evident survivorship effect. For example, a prevalence of only 48% for cardiovascular comorbidity seems to lend support to such bias. Could equally prevalent and severe valvular heart disease have been associated with reduced physical performance in individuals who died before reaching 90 years? Do baseline characteristics of the dead (at their initial or last? Available assessment) resemble those of the study sample?

Also, the authors should provide evidence that those who did not show up and did not receive echocardiography were not different, at least based on the parameters continuously collected. This is of fundamental importance in order to be able to exclude a dramatic selection bias.

Certainly our results can be affected by a survivorship effect. We do not have longitudinal data on echocardiographic examinations. Additionally despite having a population based character the present analysis is limited due to the inclusion of relatively vital participants. The differences in general performance, cognitive performance (MMSE) and activities of daily living (ADL) between the participants with versus those without an echocardiography underlined this bias towards health. We have added these limitations in the discussion section, page 13.

Study Limitations

The present study population represents a selected group of outpatient nonagenarians and therefore, the results may not apply to the general population of nonagenarians.

3) Of the 290 individuals reaching 90 years, 81 underwent echocardiography. The authors state that the “remaining 175 …were not able to visit the study center.” Clearly, 81+175 does not add to 290!!!

We thank the reviewer for this important remark. We have corrected the mistake and the sentence has been changed into: Some 277 participants survived up to age 90 years and were in principle eligible for the study. Among them, 81 outpatient individuals underwent echocardiography. The remaining 196 individuals were not able to visit the study center. (page 9)
4) The authors should also discuss the limitations of their measure of the outcome. ADL, IADL or the GARS score which combines them might not be the most appropriate measurement and other performance test could prove more sensitive and accurate. Or, it could be just that the performance of the individuals in this cohort was too skewed towards very little impairment (bias??).

The reviewer correctly noticed that the GARS score might not be the most accurate to measure physical limitations due to valve dysfunction. However, the GARS score is a validated score reflecting the limitations in daily life. We believe that in this aged population quality of life must be the first treatment goal. Therefore the GARS score can give a valuable insight in the limitations of daily life related to valve dysfunction. That there is no apparent difference in those with versus those without significant valve dysfunction is therefore remarkable. We have added these considerations in the discussion section in section Study Limitations. (page 13)

5) A very confusing issue regards the definition of what the authors refer to as either “significant”, “clinically relevant” valvular heart disease. This seems to have different meaning in different section of the manuscript. Also, it does appear to have a variable relation with the severity of the disease based on the ACC/AHA guidelines. As clearly stated in the methods section on page 6, the authors considered that significant (clinically relevant) were Mitral stenosis of any severity, Aortic stenosis of any severity, Mitral regurgitation of only moderate-to-severe severity, Aortic stenosis of any severity, Tricuspid regurgitation of only moderate-to-severe severity. All this requires a clear and convincing explanation. Why didn’t the authors adopt a common definition? Do the results change if they select only those with moderate-to severe valvular disease individuals?

According to the European, multicenter registry Euro Heart Survey on Valvular Heart Disease (Iung et al. Eur Heart J 2003), significant valvular heart disease, as defined by echocardiography, included:

- Aortic stenosis with a maximal jet velocity $\geq 2.5$ m/s
- Mitral stenosis with a valve area $\leq 2$ cm$^2$
- Aortic regurgitation with grade $\geq 2/4$
- Mitral regurgitation with grade $\geq 2/4$

According to the ACC/AHA/ESC guidelines for the management of patients with valvular heart disease, the above mentioned definitions correspond to:

- Any aortic stenosis severity: mild (maximal jet velocity < 3 m/s), moderate (maximal jet velocity 3-4 m/s) and severe (maximal jet velocity >4 m/s).
- Any mitral stenosis severity: mild (valve area $>1.5$ cm$^2$), moderate (valve area 1-1.5 cm$^2$) and severe (valve area $<1$ cm$^2$)
- Moderate (grade 2) and severe (grades 3-4) aortic regurgitation
- Moderate (grade 2) and severe (grades 3-4) mitral regurgitation
Therefore, significant valvular heart disease was defined as any mitral or aortic stenosis severity, moderate or severe mitral regurgitation, and moderate or severe aortic regurgitation.
In addition, moderate (grade 2) and severe (grade 3-4) tricuspid regurgitation were considered also significant valvular heart disease. When valve leaflets are not diseased, the presence of moderate/severe tricuspid regurgitation usually coexists with significant left-sided valvular heart disease, pulmonary hypertension and right ventricular dysfunction with tricuspid annular dilatation. The presence of moderate/severe tricuspid regurgitation have a poor long-term prognosis (Hollins et al. Br J Surg 1989). Therefore, we considered moderate and severe tricuspid regurgitation as significant valvular heart disease.

We thank the reviewer for this important suggestion and accordingly, a common definition of significant valvular heart disease has been used throughout the manuscript (page 3, line 17; page 6, line 20).

In addition, differences in functional status as assessed by the GARS score were evaluated between individuals with and without moderate or severe valvular heart disease. Patients with and without moderate or severe valvular heart disease showed comparable GARS score: 34.8 ± 13.4 vs. 34.8 ± 9.4, p = 0.97. These data has been added to the manuscript (page 9, line 16).

6) On the same line, authors should refrain from assuming that their data refer to only moderate-to-severe disease (as in discussion, page 12).

We thank the reviewer for this suggestion and accordingly, the discussion has been changed.

MINOR ESSENTIAL REVISIONS

1) The abstract in its present form reads rather generic since it refers continuously to “significant valvular disease…” for which no definition is given. So, for a general readership the abstract is hard to follow.

Definition of significant valvular heart disease has been added to the abstract.

2) The numbers presented in the abstracts are at odds with those presented in the results section. Authors should check them very carefully and possibly provide an explanation for such inconsistencies. A significant valvular disease is reported to occur in 57 (70%) individuals while in the result section this becomes 61 and 75%.

We thank the reviewer for this remark and accordingly the abstract has been corrected (page 8, line 22).
3) In the introduction section, the authors state that the aim of the study was to “evaluate … the prevalence of significant (moderate to severe) left-sided …” This is not true. First, although the authors state throughout the manuscript that they are studying “significant valvular disease” this is not equivalent to moderate to severe. In fact, in the methods section at page 6, it is clearly reported that mitral stenosis and aortic regurgitation were considered significant even if mild according to ACC/AHA guidelines. Secondly, the paper will then constantly consider tricuspid valve as well, thus, including right ventricle.

We thank the reviewer for this remark. In the introduction section, definition of significant valvular heart disease, according to the Euro Heart Survey on Valvular Heart Disease (Iung et al. Eur Heart J 2003), has been added. The term “left-sided” has been removed, since moderate and severe tricuspid regurgitation is also included in the definition of significant valvular heart disease.

4) It is the opinion of the reviewer that much information about the study population should be given in a revised table 1. Since the GARS score combines info on IADL as well, table 1 should include living and social descriptors. Also, information on clinically relevant conditions should also be mentioned. Performance on activities of daily living is clearly a mono-dimensional estimated of cardiac function. Similarly, if the authors have available information on medications those would be much informative. GARS scores ranged from 18 to 69, a quite substantial span. Could the data be analyzed according to tertiles of baseline function?

As suggested by the reviewer we have changed table one, adding more relevant information, see revised table one. Additionally we have presented the data on ADL, IADL, MMSE, GDS with medians and interquartile range. We have added these modifications in the methods section (page 4 and 5) and in the revised table 1.

5) A figure with the prevalence of the most common combination of valvular disease would be helpful.

We thank the reviewer for this suggestion and accordingly, a bar-graph illustrating the prevalence of valvular heart disease has been added (page 9, line 1 and page 16).
Mitral valve regurgitation and calcific aortic stenosis are the most common valvular heart diseases in the Western countries (Nkomo et al. Lancet 2006; Iung et al. Eur Heart J 2003). However, only 0.5% of the patients included in the Euro Heart Survey on Valvular Heart Disease were ≥ 90 years old and the prevalence of each type of valvular heart disease is not reported for this range of age. In addition, data on the prevalence of valvular heart disease in very old individuals are scarce and based mostly on in-hospital series (Sadiq et al. Am J Cardiol 2007), introducing an important selection bias. In contrast, the present study population included 81 outpatients nonagenarians who were able to come to the hospital for echocardiography examination. Therefore, the prevalence of type of valvular heart disease may differ from the published registries. Nonetheless, in line with the study of Nkomo et al. (Lancet 2006), mitral regurgitation was the most common valvular heart disease in the present study.

In the study limitations section, we acknowledge that the present study population represents a selected group of outpatient nonagenarians and therefore, the results may not apply to the general population of nonagenarians (page 13, line 1).