



Comments on GUIDE-IT, a randomized study of natriuretic peptide-guided therapy in high-risk patients with heart failure and reduced ejection fraction

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The topic of guiding therapy in heart failure patients with natriuretic peptide levels is not new: eleven trials have been performed and several meta-analyses have been published including one with individual patient data (1). The GUIDE-IT trial should have been the trial that confirmed the meta-analyses that guiding therapy with natriuretic peptides in patients with heart failure would reduce the primary endpoint of heart failure readmissions and cardiovascular mortality by 20% (2,3). The patients in GUIDE-IT were selected as having a reduced ejection fraction (<40%) and a recent admission for heart failure (within 12 months), so that there was a combination of higher risk and disease treatable with current heart failure medication; most (82%) patients were <75 years, all factors that would favor a positive result from a heart failure guiding trial. However, the results of GUIDE-IT show no difference in the composite 1-year outcome in the biomarker guided group versus in the control group [33.8% versus 36.0%, a treatment difference of -2.2% (95% CI, -9.1% to 4.6%, adjusted HR 0.98)] (2). For the secondary outcome of all-cause mortality 12-month Kaplan-Meier event rates are reported of 9.8% for biomarker-guided group and 14.1% in the usual care group with adjusted HR 0.86 (95% CI, 0.62–1.20; P=0.37). The 1-year composite outcome in the control group in GUIDE-IT is a little less than the predicted 40% from the EVEREST study (4), but the patients were followed-up for a maximum of 24 months, and results were not different from those at 12 months. The 1-year all-cause mortality of around 10% is low compared

to 1-year mortality of 25% after discharge from hospital in the EVEREST population of 2005 (4). The outcome is therefore mainly determined by readmissions for heart failure.

Concepts and designs in guiding trials and in GUIDE-IT

The concept of GUIDE-IT and previous guiding trials is that guideline-directed care for heart failure patients is not fully being practiced and that it should be improved in such a way that more patients with heart failure are treated with target (sometimes called optimal) doses of all appropriate heart failure medications. There is evidence for a risk-treatment paradox, i.e., that patients at highest risk are often treated submaximally, partly because of contraindications, partly because of non-adherence to guidelines (5,6). So, we know that there is prognosis to gain, the only question is: how? Improved care is deemed possible if physicians are made aware of the risks of heart failure patients and opportunities to improve care (7). The simple answer is thus to follow the guideline better, or in other words change usual care to standard of care. In GUIDE-IT preference was given to neurohumoral modulating heart failure medication over diuretics in both arms of the trial. One of the remaining questions in GUIDE-IT is to what extent the risk-treatment paradox was present, so as to confirm the assumption the GUIDE-IT was based on. If guidelines are followed however, is it still possible to further improve

outcomes with biomarker guided treatment? It may depend on risk stratification and risk evaluation, since the guidelines do not risk stratify or reevaluate risk in the way that it would be possible, but treat every patient in the same way (depending on ejection fraction and NYHA class). The added-on-standard of care—value of a biomarker approach would then be that patients who are or remain at higher than expected risk would receive intensified treatment or intensified visits. Patients on lower than expected risk (those with low biomarker levels) would still be treated with target doses of medications as standard of care.

The different concept(s) of design for guiding treatment with natriuretic peptides are (I) that natriuretic peptide levels are used as risk indicators for entry into improvement programs—identify risk if you are not able to follow all patients intensively, (II) that they are used as surrogate outcome targets which can be set in time well before a predefined follow-up period and (III) as possible monitors of heart failure risk to return to option 1, but still on top of the guideline direction that all patients should be treated with optimal dosing of heart failure medication. In a summary of the natriuretic peptide guiding trials, those trials that set a target and were able to reduce the natriuretic peptides more in the biomarker guided care groups than in the standard of care groups, had positive outcome results while monitoring strategies did not (8,9).

A guiding strategy can however not be better than the therapies available for such a strategy. There are limited therapeutic possibilities of improving heart failure outcome, and although the PARADIGM study was able to improve the outcome by 20% (10) the patients in the GUIDE-IT trial were (albeit mentioned as possibility) not treated with sacubitril/valsartan. So, the main focus of the GUIDE-IT trial was to improve the adherence to guideline directed care of heart failure with the medications available until 2014.

What is not part of our guideline directed prescription of heart failure medication—unlike the lipids and hypertension guidelines—is the target we aim for (apart from prognosis and symptom relief), with subsequent questions in what time frame the target should be attained, and whether this target needs further monitoring. There is no doubt that risk can be predicted by the natriuretic peptides, and in the population at hand—ejection fraction <40% and well treated with ICD's and CRT-D—natriuretic peptide levels are highly predictive of outcome (11). Here I disagree with the editorial accompanying the GUIDE-IT trial, in which it is stated that lowering natriuretic peptide levels may not be a direct aim of treatment such as lowering blood

pressure (12). We are becoming aware that for a given therapy, different reductions in natriuretic peptide levels translate into different outcomes (13), and that reaching a target natriuretic peptide level by either an improved therapy or on old therapy may still have the same prognostic result, although the target will be reached more often in the newer therapy, such as was demonstrated in substudies of the Val-HEFT (13,14) and the PARADIGM study (15).

A point that has to be taken into consideration is that risk can be predicted for a longer term by a single measurement of natriuretic peptides, but has to be re-assessed and can then be used as target for treatment in order to try and keep the risk low (13,14). A target should however be set and verified until accomplished. Every patient in GUIDE-IT had a NT-proBNP level of >2,000 ng/L before entry of the study. A minor design flaw was that this could be a value measured during the previous hospital admission, but also a value measured after admission; the question is how many patients had this entry criterion of >2,000 ng/L at randomization. The risk in GUIDE-IT seems to have been more defined by the inclusion criterion of a previous hospital admission. After randomization, NT-proBNP levels were measured per protocol at week 2 and at week 6, and then every three months in both groups, blinding results of the biomarker levels in the standard of care group. As the first (qualifying) natriuretic peptide measurement in GUIDE-IT was available in both groups of the trial, risk assessment was not different in either group of the trial. The additional measurements are therefore the focus of the remainder of the trial, and the trial should probably be interpreted as such: a trial with a predefined risk assessment in both groups of the trial, in which the intensity of adaptations in medications for heart failure in patients with a previous heart failure admission was made following guidelines in both of randomized groups. In GUIDE-IT there was not a predefined time point (other than the end of the study) that the NT-proBNP levels had to be on target. Would this have been possible, and when would one then expect to observe a difference between the two groups, adding information from a biomarker?

Following the target

The target in GUIDE-IT was set on NT-proBNP levels of below 1,000 ng/L, as initiated from the Val-Heft trial results including patients with ejection fraction <40%. The predictive value of the NT-proBNP level of 1,000 ng/L was obtained in the Val-Heft trial in the placebo

group at 4 months from baseline, and subsequent mortality was <10% for 20 months after the initial 4 months (14). The target of 1,000 ng/L was confirmed in the PROTECT pilot study to have a low 10-month cardiovascular event rate; PROTECT pilot study patients had a median baseline NT-proBNP level of 2,118 pg/mL similar as in GUIDE-IT with a baseline NT-proBNP level of 2,632 pg/mL (8). In GUIDE-IT (nor in PROTECT), we do not know whether it was the biomarker target strategy that initiated the medication changes or that was the visit itself. We do know that there were more visits in the NT-proBNP guided strategy arm than in the standard of care arm (in GUIDE-IT per patient 12 versus 10 visits in standard of care, with 6 medication adjustments made versus 4 medication adjustments, respectively). In GUIDE-IT, the statement is that any change in medication was followed by additional visits; was this done differently in the biomarker guided group (additional visits specifically for attaining the target)? From the number of medication changes, less than the number of visits, we may assume that there were visits made without previous medication changes. Still, it does not seem that attaining the target NT-proBNP level of <1,000 pg/mL was very important in the trial. In fact, although the mean NT-proBNP levels during the visits in both groups are reported, appraisal of the target of 1,000 pg/mL is only given at 12 months follow up: in the guided group target levels were reached in 46% of patients, and in the control group in 40% ($P=0.21$). In PROTECT, at the end of study at 10 months 44.3% of patients were on target of <1,000 ng/L in the NT-proBNP arm, versus 35.6% in the standard of care arm (8). From this perspective, the GUIDE-IT trial did better in improving care in the standard of care group than the PROTECT study. From the perspective of the 'guideline only' protagonist, we would only have to look at the number of medication changes and final medication given to see whether the protocol to increase or change medication was followed successfully and we do not need another target than that. After the GUIDE-IT trial, the 'guideline only' view has been sharpened, but biomarker protagonists are still wondering what was done to attain the biomarker target.

What effect is expected on NT-proBNP levels within what time frame

From the perspective of the biomarker protagonists, the success of guiding trials should be evaluated by the success in which the targets were reached, to be able to interpret

the results. To come back to the question before: when would one expect to observe a difference between the two groups in GUIDE-IT, may only have been answered if the target of <1,000 ng/L was actually set for example at 3 months. If this target would then not have been reached more in the biomarker guided group than in the standard of care group, the trial would already have been regarded as failing as biomarker guided study. From this perspective, evaluating why the biomarker target was not attained more often in the guided group is the real question. Regarding the target of 1,000 pg/mL, what is possible to attain? In the Val-Heft trial, including similar patients with ejection fraction <40%, the placebo group was followed, and in those patients with baseline levels >1,079 pg/mL, target levels of 1,079 pg/mL were attained in 17% of patients at 4 months without any discernible interventions but with improved outcomes; there were 11% of patients who increased NT-proBNP levels from low levels to values above the target with more than doubling of mortality risk (14). So, these are more or less spontaneously occurring decreases and increases in risk. When treated with valsartan, the percent decrease in NT-proBNP after 4 months determined outcome (13). When guided with various medications, the target of 1,300 pg/mL can be followed in both arms of the BATTLESCARRED study (16). At baseline, already 45% of patients in the guided NT-proBNP group and 35% of patients in the control group were on target (16). After 3 months, there is little improvement in patients on target, and after 6 months still only 48% of patients in the NT-proBNP group are on target versus 47% of patients in the control group (16). So, in BATTLESCARRED, it was difficult to improve care in terms of lowering NT-proBNP levels. Results of the GUIDE-IT and PROTECT have improved results, as baseline levels were all above target levels, in both studies attaining target NT-proBNP levels of <1,000 ng/L in 45% of patients after 10 to 12 months. For a guiding outcome trial however, the target should probably be reviewed earlier than 10 to 12 months, and the results of guiding should then be compared with the success of reaching the target. Only then can we answer the question whether setting a biomarker target in heart failure care is useful or not. In a recent substudy of the PARADIGM study, in patients who had baseline levels >1,000 pg/mL, a NT-proBNP level of <1,000 pg/mL was attained after 1 month in 31% of patients on ARNI, compared to in 17% of patients on enalapril (15). Outcome was better with a HR of 0.41 when patients attained a level <1,000 pg/mL irrespective of treatment allocation (HR in ARNI group 0.44

and in the enalapril group 0.38). From these studies, we may conclude that it is possible to shorten the time (likely at 3 months) within which medication is initiated and titrated towards a desired target of NT-proBNP. It would be helpful if the GUIDE-IT investigators provide insight into the possibility of having (and especially also not having) reached targets at 3 months.

Overall view of the GUIDE-IT trial

The GUIDE-IT trial was set up well with 894 patients studied, with an appropriate population at risk and the therapies available to improve the outcome of patients; patients in the standard of care arm were very well treated following guideline directions, making it difficult for a biomarker guided approach to improve outcome. The biomarker guided approach should probably be changed from how it is done so far, towards a preset period of time in which the biomarker target level has to be reached well before the end of the study. For any future biomarker guided study, information is necessary for what is an expected response in biomarker levels after a medication change, so as to be able to preview the difficulty of attaining the targets on time. Additional interest into the biomarker approach will be the prediction of various risk categories of sudden death and death due to end-stage heart failure, ischemic heart disease problems or events related to ischemic cerebral disease (17), for which several different therapies may be started to prevent the outcome. The remaining question for future trials is whether attaining a specific target of 1,000 ng/L is the best target. In patients who may never reach such levels (more than 50% of patients in the trial), despite reaching optimal medications and interventions, perhaps an expected (predicted) target is more realistic (for example in patients with baseline levels of 5,000 ng/L the target is 3,000 ng/L, for patients with 2,000 ng/L a target of 1,000 ng/L may be appropriate). The investigators may have a look into the various relative changes from the true baseline (at randomisation), to see what would have been possible. Although absolute values of NT-proBNP serve well as risk stratifying levels, relative changes may be preferred as attainable targets (15,18,19).

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