Rationale

The pathophysiology of macrovascular and cardiac alterations is quite different to those of microvascular changes (especially retinopathy) in diabetes. The following hypothesis is primarily based on macrovascular and cardiac alterations.

The prevalence of diabetes mellitus (DM) is increasing worldwide. In 2011 approximately 360 million people were estimated to have DM, 95% having type 2 DM (T2DM). This number is projected to increase to 552 million by 2030. [1]

More than half of the mortality and most of the morbidity of this affection is related to cardiovascular disease (CVD). [1]

Whether those numbers are accurate is not formally proven, but only based on demographic estimations. The worldwide increase of people with DM is at least partly based on the changing definition of diabetes in regard to lower diagnostic thresholds. [2] Most studies that had demonstrated a beneficial treatment effect for DM were performed in populations where the current definitions of the diagnosis do not apply. Overdiagnosis and corresponding overtreatment is accordingly a topic of increased interest recently. Especially for the very common conditions like hyperlipidemia, hypertension and DM there is increasing concern in how far expanding the definition has any beneficial consequence for the patient. Regarding DM, a recent publication states "there is an imminent need to balance stigma and costs of mistakenly identifying individuals as diabetic against the minimal clinical consequences of delaying the diagnosis in someone with HbA_{1c} level 6.5%". [3] *More importantly, there is increasing evidence that "medicine is harming healthy people through ever earlier detection and ever wider definition of disease".* [4] *Beside the fact that there is incomplete evidence if a minimally increased risk is clinically meaningful, two other important concerns remain. Firstly, there are competing interests between low-risk and high-risk patients. In times of limited resources treating low-risk patients will take time, effort, and money, which will be not available for high-risk patients. Thus the treatment options for patients with the highest need for therapy will decrease. Secondly, diagnosis, and treatment of low risk-patients might be potentially harmful. Beside over-suppression of endogenous*

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[1] ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD European Heart J 2013 pubahead.

[2] Schwarz l et al. Eff Clin Pract. 1999 Mar-Apr;2(2):76-85.

[3] *Moynihan RN, et al. PLoS Med2013;*10*(8):e1001500.*

[4] *Moynihan R. BMJ 2012;344:e3502.*

systems there are also behavioral and psychological consequences if patients are labeled to be diseased. [5] *These concerns have led to the "Too much medicine campaign" (*http://www.bmj.com/too-much-medicine*) of the British Medical Journal to fight against overdiagnosis and overtreatment,* [6] *and recently the first conference about the consequences of overdiagnosis was held in Dartmouth US (*http://www.preventingoverdiagnosis.net/*) and will be carried forward in Oxford in 2014.*

Therefore intensified collaboration between diabetologists and cardiologists is mandatory to understand, select, and treat appropriately those patients, who are in need for a cardiac treatment like RAS-Antagonists and possibly Beta-blocker therapy and more importantly to exclude those, where this treatment is ineffective or even harmful. Treatment efficacy has to be proven in three distinct populations:

1. The entire unselected population of people with DM (primary and secondary prevention).
2. The population of people with DM and a preexisting cardiac disease (secondary prevention).
3. The population of people with DM without evidence of a cardiac disease (primary prevention).

Evidence of treatment success in different populations

1) Total unselected diabetes population

Despite the known relationship between HbA_{1c} levels and cardiovascular events, there is no sound evidence that lowering blood glucose is related to a reduction of macrovascular events. Blood pressure lowering is recommended for all diabetic patients although there is only one study, which demonstrated a benefit. [7] The ACCORD sub-study found no benefit of lowering SBP below 130mmHg and actually noticed a trend towards harmful side effects. Two other studies demonstrated that treatment with Angiotensin Converting Enzyme (ACE)-inhibitors reduces macrovascular events unlike to calcium channel blockers. Notably, blood pressure

[5] *Macdonal LA, et. J Chronic Dis 1984;37:933-42.*
[6] *Glasziou P, et al. BMJ 2013;347:f4247.*
[7] UKPDS 38 BMJ. 1998 Sep 12;317(7160):703-13.

lowering was equal in treatment and control arms of these studies. [8] [9] The bulk of the data on this topic are derived from sub-analysis and therefore of limited value. Thus, there is more evidence about distinct drug effects, than global blood pressure lowering effects.

Regarding lipid lowering therapy, there are also only few studies exclusively looking at diabetic patients. Nevertheless, sub-analysis and meta-analysis of large RCTs imply that there is a comparable effect in diabetic and non-diabetic populations. Likewise, there is no compelling evidence about the effects of aspirin in this population, as it is still not clear if potential benefits outweigh harm such as antithrombotic effects and bleeding complications. [10] Only one small prospective randomized trial found a benefit of a multifactorial intervention on macrovascular complications. [11] These data could not be confirmed in a primary care setting. [12]

2) Diabetic population with a preexisting cardiac disease

Similar to the total unselected diabetic population there is no evidence that glucose lowering therapy is effective in reducing cardiac events such as hospitalization or death. Regarding blood pressure lowering agents, lipid lowering agents and antithrombotic agents, there is consensus that the treatment is equally effective in patients with and without diabetes.

3) Diabetic population without known cardiac disease

In this population information derived from prospective randomized clinical trials (RCT) is lacking almost entirely. Only one small recent trial focused on whether use of therapies such as RAS-antagonist or beta blockers may reduce risk. [13] In this randomized trial, NT-proBNP concentrations were used to pre-select patients at risk among patients without a known cardiac disease. This group of patients benefited from an aggressive treatment with RAS-antagonists and beta-blockers regarding strong

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[8] Tatti et al .Diabetes care 1998;21:597-603.

[9] Estacio et al. N Engl J Med 1998;338:645-652.

[10] Cleland. Eur Heart J. 2013 Aug 1.

[11] Gaede et al. N Engl J Med. 2003 Jan 30;348(5):383-93.

[12] Simmons et al. Diabet Med. 2012 Nov;29(11):e409-16.

[13] Huelsmann et al. J Am Coll Cardiol. 2013 Oct 8;62(15):1365-72.

cardiac endpoints. Regarding the combined endpoint of a cardiac hospitalization and/or a cardiac death a 63% risk reduction could be achieved.

Risk assessment in diabetes

The development of means to assess risk in patients with T2DM (such as biomarkers or scores) is valuable not only for the identification of a high-risk collective within a population with a specific disease, but more importantly to define low-risk subpopulations. It is evident that patients with low or no risk for further events will not benefit from any therapy, but might even suffer from harmful side effects of treatment. If this group of patients is large, this might also have important economic implications; this is not a small consideration as the health care expenditures of DM are estimated to amount to 75 billion € in Europe.

T2DM is known to be a very heterogeneous disease. In this context it is presumed, that cardiac risk is also unevenly distributed. In an unselected population with longstanding T2DM of about 10 years on average the prevalence of manifest cardiac disease was only around 20%. [14] In other words, 80% of T2DM patients did not develop any cardiac disease over a time period of 10 years. Identifying patients with low risk and withholding intensified therapy to prevent cardiovascular events might reduce costs substantially. On the other hand, targeting only patients with a high risk might be very effective regarding treatment success. Matching these assumptions, the current treatment options in more or less unselected diabetic populations are not only very cost-intensive, but as described above, have been quite ineffective in the prevention of cardiac events. In some studies cardiac event rates even increased. [15] [16] These inhomogeneous results are discussed to be at least in part due to differences in the investigated populations regarding baseline cardiovascular risk. [1]

Biomarkers

Many biomarkers and risk scores have been developed for the risk assessment in diabetes. Risk scores are currently discussed very controversially in the field of T2DM care. [17]

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[14] Huelsmann et al. Eur Heart J. 2008 Sep;29(18):2259-64.

[15] Gerstein et al. N Engl J Med 2011; 364:818-824.

[16] Haller et al. N Engl J Med 2011;364:907-17.

[17] Chamnan et al. Diabetologia. 2009 Oct;52(10):2001-14.

Proteinuria was the only biomarker to reach a level of evidence B in the current ESC guidelines.[1] Beside proteinuria, elevated levels of NT-proBNP are also recommended as strong predictors for excess mortality. Beside some retrospective analysis,[18] [19] [20] [21] there are several prospective data and confirmation studies, [14] [22] [23] [24] [25] which prove the importance of NT-proBNP. These data are calculated after adjustment for the most important clinical biomarkers for risk assessment. Very important in this context is the fact that the studies by Gaede, Clodi and Bruno showed that proteinuria, the current gold standard for cardiovascular prediction in diabetes, has only predictive power if NT-proBNP is also elevated. This means that proteinuria reveals additional information in higher-risk patients defined by NT-proBNP, but proteinuria is not prognostically relevant if NT-proBNP concentrations are low. To identify low-risk patients, NT-proBNP remains the best variable.

The natriuretic peptides

BNP and its hormonal inactive precursor NT-proBNP are activated in case of volume or pressure overload of the heart. Physiologically BNP acts as a vasodilator and increases natriuresis. It is increasingly accepted that natriuretic peptide release may be detected at a stage of pre-clinical functional impairment of the heart, long before morphologic changes can be detected.

NT-proBNP is a well-established marker of cardiac disease. It was first established for the diagnosis and risk-stratification of heart failure, but is currently used across the whole spectrum of cardiac disease. As importantly, NT-proBNP concentrations mirror the individual risk of developing and worsening cardiac disease. The value of cardiac risk-assessment is proven across the whole cardiac continuum from apparently healthy patients [26] to intensive care patients. [27]

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[18] Gaede et al. Diabetologia. 2005 Jan;48(1):156-63.
[19] Tarnow et al. Diabetologia. 2006 Oct;49(10):2256-62.
[20] Bhalla et al. *J Am Coll Cardiol* 2004*;*44*:*1047-1052.
[21] *Dawson et al.* Am J Cardiol. 2005 Oct 1;96(7):933-4.
[22] Clodi et al. Eur J Prev Cardiol. 2012 Oct;19(5):944-51.
[23] Neuhold et al. Eur J Clin Invest. 2011 Dec;41(12):1292-8.
[24] Gruden et al. Diabetes Care. 2012 Sep;35(9):1931-6.
[25] Bruno et al. Diabetes Care. 2013 Sep;36(9):2677-82.
[26] Wang et al. N Engl J Med. 2004 Feb 12;350(7):655-63.
[27] Meyer et al. Crit Care Med. 2007 Oct;35(10):2268-73.

Concordant vs. discordant treatment effects

As outlined above, for the very large group of patients with no evidence of manifest cardiac disease, evidence for a treatment success targeting cardiac disease is lacking almost entirely. There are two possible scenarios: It is possible that the treatment effect is concordant to the severity of the disease and might be lost in low-risk patients. In this case treatment would be ineffective in distinct diabetic populations. It is also possible that there is a discordant relationship. This would mean, that over-suppression of the neurohumoral systems by therapy might be harmful for the patients or that side effects of treatment might weigh more heavily than marginal positive treatment effects. This is already discussed intensively [4] and such negative effects are shown also in clinical trials. [16] In T2DM patients the individual risk can be remarkably estimated using NT-proBNP. In this population, we have previously shown in our preliminary work that an NT-proBNP concentration of 125pg/ml separates those with higher risk (about 40% of patients) from those with low imminent risk for developing a cardiac event such as hospitalization and/or death in the near and intermediate future (about 60% of patients). [14] From a therapeutic point of view, it seems intuitively attractive to specifically treat the highest risk patients and to do so at a stage where morphologic alterations are still not detectable. As discussed above, concentrations of NT-proBNP appear to be an attractive surrogate for deciding whether the patient is in need for therapy. This approach could theoretically help identify a large group of patients (40%), where early targeted treatment would be able to mitigate cardiac disease at a stage before organ damage becomes apparent. At the same time, the remaining 60% of patients with low risk (below 125pg/ml NT-proBNP) might be not in need for therapy. In this group, we absolutely do not know if a treatment effect is concordant to patients with elevated NT-proBNP or if there is a discordant behavior.

The PONTIAC study

In this prospective study Huelsmann et al. investigated the primary preventive effect of neurohumoral therapy in diabetic patients that were free from cardiac disease but identified to be at risk by elevated NT-proBNP.[13] A cut-point of NT-proBNP > 125pg/ml was chosen as it was convincingly shown priorly that above this level the event rate dramatically increased. [14] The authors used RAS-antagonist and beta-blockers, as those medications are recommended

for the most important cardiac diseases occurring in T2DM: CAD and chronic heart failure (CHF). A blood pressure goal was not targeted, as it was never proven that lowering blood pressure is beneficial for primary prevention of a cardiac disease in T2DM. The beneficial effects of RAS-antagonists seem to be independent of the blood pressure achieved, as mentioned above. [8 9] In the PONTIAC study 300 patients were randomized to receive either standard diabetic care or an additional aggressive up-titration of RAS-antagonists and beta-blockers to dosages recommended in the ESC-guidelines for heart failure. Beside an excellent safety profile, there was a significant reduction in cardiac event rates defined as hospitalization or death to a cardiac reason already after two years. This was the first study in a diabetic population, which formally proved a primary preventive effect of cardiac events.

Limitations of PONTIAC:

PONTIAC was designed as a proof of concept study. The number of patients included was low and accordingly confirmation in a larger cohort is mandatory. Secondly, the hypothesis that the treatment effect is restricted to patients with high NT-proBNP levels cannot be deduced from the data. In this context a concordant relationship between risk and treatment efficacy can be assumed. This would result in an increasing number needed to treat up to a point of ineffectiveness, depending on underlying risk. But, also a discordant relationship is possible as side effects or over-suppression of neurohumoral systems can lead to a preponderance of side effects over small or non-existing treatment effects. Such a discordant treatment effect is called “interaction effect” in statistical methodology. A cohort of patients without any evidence of a cardiac disease, independent of NT-proBNP is mandatory to test for such interactions. All these populations have to be evaluated in regard to safety and efficacy. As both investigated groups of drugs are registered, the design for a further study will be a post-authorization efficacy study (PAES) and a post-authorization safety study (PASS) in distinct populations.

Purpose and Rationale

The purpose of this study is to evaluate the effect of high dose RAS-antagonists and beta-blocker treatment for the primary prevention of cardiac events in a population of patients with Type 2 diabetes mellitus (T2DM) with no evidence of a preexisting cardiac disease. This

will be done in patients with NT-proBNP concentrations > 125pg/ml and the whole study population. An additional aim is to demonstrate the dependency of the treatment efficacy on the level of amino-terminal pro-B type natriuretic peptide (NT-proBNP) as a surrogate of imminent cardiac risk (so called interaction between NT-proBNP and treatment). A health economic analysis will objectify the impact on health care costs in accordance to the endpoints.