The main question of this thesis is ‘How can UTMD be used to increase cardiac uptake of miRNA inhibitors to the heart?’ This can be achieved by binding antagomiR to cationic MB through electrostatic interaction, injecting these MB intravenously, and applying US to the heart using a clinical US device with an mechanical index between 1.4 and 1.9 and a frequency between 1.5 MHz and 7 MHz in Power Doppler mode. Important considerations that have to be taken into account are:

1. Results on delivery of miRNA-inhibitors in vitro and to skeletal muscle are not predictive of delivery to the heart;
2. MiRNA-inhibitors are delivered directly into cardiomyocytes;
3. UTMD has no beneficial effect on delivery directly after ischemia-reperfusion, and is likely most suitable for treatment of chronic cardiac diseases like heart failure;
4. A combination of accurate imaging of the heart while applying UTMD greatly improves the reproducibility of UTMD;
5. UTMD causes bio-effects to the heart, which are very similar to bio-effects caused by ischemia-reperfusion;
6. The bio-effects of UTMD on the heart are transient and UTMD is a safe method for delivery of miRNA-inhibitors to the heart; and
7. The mechanism of UTMD is not driven by sonoporation alone.

UTMD is a promising technique to increase the cardiac uptake of miRNA-inhibitors. However, the effect and mechanism of UTMD in the heart are still not sufficiently clear in order to select the specific cell-types, miRNA-targets and treatment-timing for treatment. After the mechanism of UTMD in the heart is elucidated, optimal machines for UTMD have been developed, relevant in vitro models to screen miRNA-targets have been established, and we know exactly how UTMD changes the pharmacokinetic profile of miRNA-inhibitors, we can translate the use of UTMD from the lab to the clinic.