could be beneficial to reduce the likelihood of heart failure and improve the prognosis of patents with, or at risk of, heart failure.

In work leading up to the present invention, it was surprisingly determined that it is possible to rescue hypoxic cardiomyocytes from apoptosis by exposing the cells to low energy shockwaves. Notably, the inventor has established that treatment of hypoxic cardiomyocytes with shockwaves increases the phosphorylation, i.e. activation, of Protein kinase B (also known as Akt). Akt is a key regulator of apoptosis and activated Akt phosphorylates and inhibits various pro-apoptotic proteins, including Bcl-2 family members Bad, Bax, caspase-9, GSK-3, and FoxO1. However, application of an inhibitor of the PI3K/Akt pathway (LY294002) did not affect the anti-apoptotic effect caused by the application of shockwaves, i.e. the anti-apoptotic effect of shockwave treatment is independent of the PI3K/Akt pathway (see Example 5). Furthermore, the inventor has demonstrated that expression of SDF1, which is known to be anti-apoptotic, is not increased in cardiomyocytes exposed to shockwaves. Interestingly however, shockwave treatment of whole cardiac tissue does result in an increase of various anti-apoptotic proteins, including SDF1, MCP1, ANG1, VEGF-A, NOS3 and TAC-1. These findings have led the inventor to propose new therapies for the treatment of various heart disorders using shockwave therapies, particularly in the treatment of damage caused by hypoxia followed by normoxia, i.e. cardiac ischaemic reperfusion injuries.

Thus, the present disclosure generally relates to methods and agents for reducing or minimising apoptosis (i.e. cell death) of cells in heart tissue (e.g. cardiomyocytes). More specifically, the present disclosure relates to the use of shockwave therapy (i.e. extracorporeal cardiac shockwave therapy) alone or in combination with other therapies, particularly pharmaceutical or pharmacological therapies (referred to herein as combination therapies or combined therapies), to inhibit, prevent or minimise apoptosis of cardiac cells, particularly cardiomyocytes. Additionally, such therapeutic methods and pharmaceutical agents may be combined with cellular therapies to repair and/or restore cardiac tissue and function.

For instance, the present disclosure provides methods for treating subjects suffering from acute myocardial infarction by administering extracorporeal cardiac shockwave therapy, particularly as an adjuvant treatment alongside coronary angioplasty and stenting. It is advantageous to commence the extracorporeal cardiac shockwave therapy of the present disclosure as soon as possible after a

myocardial infarction. However, for patients admitted to hospital following a delay and who do not qualify for acute revascularisation or have contraindications for the procedure, the extracorporeal cardiac shockwave therapy of the present disclosure may be used alone. Whilst not wishing to be bound by theory, it is thought that the extracorporeal cardiac shockwave therapy of the present disclosure may delay the progressive loss of the remaining cardiomyocytes via the prevention of apoptosis, which may be particularly advantageous in patients with established infarctions, i.e. to prevent, reduce or minimise the probability of heart failure.

Thus, at its broadest, the disclosure can be seen to provide a method of reducing, preventing or minimising cellular apoptosis in heart tissue comprising administering shockwave therapy to said heart tissue. In particular, the disclosure provides a method reducing, preventing or minimising apoptosis of cardiomyocytes in heart tissue (e.g. a heart) comprising administering shockwave therapy to said heart tissue (e.g. heart).

Alternatively viewed, the disclosure relates to shockwave therapy for use in reducing, preventing or minimising cellular apoptosis in heart tissue. In particular, the disclosure relates to shockwave therapy for use in reducing, preventing or minimising apoptosis of cardiomyocytes in heart tissue (e.g. a heart) comprising administering shockwave therapy to said heart tissue (e.g. heart).

As noted above, it has been found that the shockwave therapy of the disclosure is effective as an anti-apoptotic therapy for cardiomyocytes *in vitro*, e.g. at preventing, reducing or minimising apoptosis of cardiomyocytes *in vitro*. Accordingly, the present disclosure may be seen also to provide new methods and means for preventing, reducing or minimising apoptosis of cardiomyocytes *in vitro* (e.g. in culture, such as in the cultivation of cardiomyocytes for the production of artificial or synthetic tissues) or *ex vivo* (e.g. in heart tissue removed from a subject, e.g. in a heart or heart tissue, e.g. valve, for transplantation).

In a particularly preferred embodiment, the disclosure provides new methods and means for preventing, reducing or minimising apoptosis of cardiomyocytes *in vivo*, i.e. in a subject. For instance, methods and means for preventing, reducing or minimising apoptosis of cardiomyocytes for use in the treatment of a subject following a myocardial infarction, e.g. to reduce, prevent or minimise cardiac ischaemic reperfusion injury and/or heart failure or, alternatively viewed, to improve the prognosis of heart failure patients. In this respect, it will be evident that the shockwave therapy need not be administered *in vivo* in order to have an effect on

the viability of cells (e.g. cardiomyocytes) *in vivo* (i.e. in the subject to be treated). Thus, in preferred embodiments of the disclosure, the shockwave therapy is administered outside the body of the subject, i.e. the shockwave administration is non-invasive. Alternatively viewed, the shockwave therapy of the present disclosure is preferably extracorporeal cardiac shockwave therapy.

Thus, in some embodiments, the disclosure may be seen to provide a method of treating, preventing or minimising cardiac ischaemic reperfusion injury comprising administering extracorporeal cardiac shockwave therapy to a subject in need thereof. Thus, in some embodiments, the disclosure may be seen to provide a method of improving the prognosis of a subject with, or at risk of, heart failure comprising administering extracorporeal cardiac shockwave therapy to said subject. As noted above, the method can be used in combination with angioplasty and stenting therapies.

Alternatively viewed, the disclosure provides extracorporeal cardiac shockwave therapy for use in treating, preventing or minimising cardiac ischaemic reperfusion injury. Thus, in some embodiments, the disclosure may be seen to provide extracorporeal cardiac shockwave therapy for use in improving the prognosis of a subject with, or at risk of, heart failure.

In yet another embodiment, the disclosure provides the use of extracorporeal cardiac shockwave therapy for treating, preventing or minimising cardiac ischaemic reperfusion injury. Thus, in some embodiments, the disclosure may be seen to provide the use of extracorporeal cardiac shockwave therapy for improving the prognosis of a subject with, or at risk of, heart failure.

As mentioned above, the inventor has established that the exposure of heart tissue to shockwaves increases the secretion of various chemokines, particularly pro-survival chemokines such as SDF-1 (stromal cell-derived factor 1, also known as C-X-C motif chemokine 12 (CXCL12), MCP1 (monocyte chemoattractant protein 1, also known as CCL2), substance P and IGF1 (Insulin-like growth factor 1), i.e. shockwaves increase the pro-survival “secretome” in heart tissue. Notably, it is thought that the secretome may be in the form of one or more exosomes, e.g. cell-derived vesicles containing one or more chemokines. Whilst the increase in the pro-survival secretome (or exosomes) does not explain the anti-apoptotic effect of shockwaves on cardiomyocytes, it is thought that the increase in these pro-survival chemokines may enhance the survival of cardiac cells exposed to the stress conditions associated with cardiac ischaemia and reperfusion. Notably however,

the rapid turnover of chemokines means that the increased pro-survival secretome caused by shockwave therapy may be transient, meaning that repeated shockwave treatments might be necessary to maximise the effects of shockwave therapy described above. However, in some instances, repeated shockwave therapy may be or become impractical. Generally, it is preferable to avoid the need for repeated and regular visits to the clinic as this creates a burden both for the patient and healthcare professionals. Moreover, repeated shockwave treatments may cause discomfort resulting in missed treatments, which may reduce the overall efficacy of the treatment.

The rapid turnover of chemokines is a result of their degradation and/or inactivation. Various enzymes are involved in the degradation of chemokines *in vivo*, such as dipeptidyl peptidase-IV (DPP-IV or DPP-4), which is also known as adenosine deaminase complexing protein 2 or cluster of differentiation 26 (CD26). DPP-4 is an antigenic enzyme expressed on the surface of most cell types. It is an intrinsic membrane glycoprotein and a serine exopeptidase that cleaves X-proline dipeptides from the N-terminus of polypeptides. Thus, DPP-4 has a diverse range of substrates, including SDF-1, MCP1, substance P and IGF1.

Accordingly, the inventor has determined that shockwave therapy may advantageously be combined with one or more protease inhibitors to reduce, prevent or minimise the degradation and/or inactivation of chemokines induced by shockwave therapy, i.e. to prolong the half-life of the pro-survival secretome (which may be in the form of one or more exosomes) of heart tissue resulting from shockwave therapy (referred to herein as a combination therapy or combined therapy). For instance, DPP-4 inhibitors are well-known in the art and can be combined readily with the shockwave therapy methods and uses described above. Thus, DPP-4 inhibitors may potentiate the effect of shockwave therapy in the methods and uses described above, i.e. may potentiate or enhance the anti-apoptotic effect of shockwaves on heart tissue, particularly cardiomyocytes, thereby improving the treatment of cardiac ischaemic reperfusion injury or minimising or preventing the damage of heart tissue, particularly heart muscle, caused by cardiac ischaemia and reperfusion, e.g. further improving the prognosis of a subject with, or at risk of, heart failure. Notably, the combined therapy (combination therapy) may function to reduce the size of the final infarct and/or prevent, retard or delay the progression to heart failure. Accordingly, in some embodiments the disclosure provides a method of treating or preventing heart failure or treating cardiac

ischaemic reperfusion injury comprising administering extracorporeal cardiac shockwave therapy and a DPP-4 inhibitor, or a pharmaceutical composition comprising said inhibitor, to a subject in need thereof, wherein said inhibitor or composition is administered prior to, simultaneously with, and/or after administration of said shockwave therapy. Thus, in some embodiments, the disclosure provides a method of improving the prognosis of a subject with, or at risk of, heart failure comprising administering extracorporeal cardiac shockwave therapy and a DPP-4 inhibitor, or a pharmaceutical composition comprising said inhibitor, to a subject in need thereof, wherein said inhibitor or composition is administered prior to, simultaneously with, and/or after administration of said shockwave therapy.

Alternatively viewed, the disclosure provides a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, for use in:

(a) treating or preventing heart failure; or

(b) treating cardiac ischaemic reperfusion injury,

in a subject, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor or composition is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy. Thus, the disclosure provides a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, for use in improving the prognosis of a subject with, or at risk of, heart failure, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor or composition is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy.

In one aspect, there is provided use of a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a pharmaceutical composition containing said inhibitor, in the manufacture of a medicament for: (a) treating or preventing heart failure; or (b) treating cardiac ischaemic reperfusion injury, in a subject, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor is to be administered prior to, simultaneously with, and/or after administration of said shockwave therapy.

In another aspect, there is provided a kit or product containing: (i) a DPP-4 inhibitor or composition comprising said inhibitor; and (ii) a pharmacological agent for mobilising stem cells, such as parathyroid hormone or fragment thereof, or a pharmaceutical composition comprising said pharmacological agent and at least one pharmaceutically acceptable carrier, diluent or excipient; and optionally (iii) an

additional agent, e.g. an agent for treatment of heart failure or glucose, or a pharmaceutical composition comprising said additional agent and at least one pharmaceutically acceptable carrier, diluent or excipient.

In another aspect, there is provided use of the kit or product as described herein in the manufacture of a medicament for: (a) treating or preventing heart failure; or (b) treating cardiac ischaemic reperfusion injury, in a subject, wherein (i), (ii) and optionally (iii) are provided as a combined preparation for simultaneous, sequential or separate use, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor and/or hormone is to be administered prior to, simultaneously with, and/or after administration of said shockwave therapy.

In a further embodiment, the disclosure provides the use of a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, in the manufacture or a medicament for:

(a) treating or preventing heart failure; or

(b) treating cardiac ischaemic reperfusion injury,

in a subject, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said medicament is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy.

Thus, the disclosure provides the use of a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, in the manufacture of a medicament for improving the prognosis of a subject with, or at risk of, heart failure, wherein said subject has been administered extracorporeal cardiac shockwave therapy and

wherein said inhibitor or composition is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy.

Advantageously, the inventor has also determined that the combination of shockwave treatment and DPP-4 inhibitor therapy also functions to promote angiogenesis in heart tissue, which may be particularly beneficial in the treatment of subjects with heart failure (e.g. chronic ischaemic heart disease or chronic myocardial ischemia) or cardiac ischaemic reperfusion injury.

Thus, in some embodiments, the disclosure provides a method of inducing (e.g. increasing or improving) angiogenesis in the heart tissue of a subject comprising administering extracorporeal cardiac shockwave therapy and a DPP-4 inhibitor, or a pharmaceutical composition comprising said inhibitor, to said subject, wherein said inhibitor or composition is administered prior to, simultaneously with, and/or after administration of said shockwave therapy. In particularly preferred embodiments, the subject has heart failure (e.g. chronic ischaemic heart disease or chronic myocardial ischemia) or cardiac ischaemic reperfusion injury.

Thus, in some embodiments, the disclosure provides a method of treating or preventing heart failure (e.g. chronic ischaemic heart disease or chronic myocardial ischemia) or treating cardiac ischaemic reperfusion injury in a subject by inducing angiogenesis in the heart tissue of said subject, said method comprising administering extracorporeal cardiac shockwave therapy and a DPP-4 inhibitor, or a pharmaceutical composition comprising said inhibitor, to a subject in need thereof, wherein said inhibitor or composition is administered prior to, simultaneously with, and/or after administration of said shockwave therapy.

Alternatively viewed, the disclosure provides a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, for use in inducing angiogenesis in the heart tissue of a subject (e.g. a subject with heart failure (e.g. chronic ischaemic heart disease or chronic myocardial ischemia) or cardiac ischaemic reperfusion injury), wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor or composition is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy. Thus, the disclosure provides a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, for use in treating or preventing heart failure (e.g. chronic ischaemic heart disease or chronic myocardial ischemia) or treating cardiac ischaemic reperfusion injury in a subject by inducing angiogenesis in the heart tissue of said subject, wherein said subject has

been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor or composition is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy.

In a further embodiment, the disclosure provides the use of a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, in the manufacture or a medicament for inducing angiogenesis in the heart tissue of a subject (e.g. a subject with heart failure (e.g. chronic ischaemic heart disease or chronic myocardial ischemia) or cardiac ischaemic reperfusion injury), wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said medicament is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy. Thus, the disclosure provides the use of a DPP-4 inhibitor, or a pharmaceutical composition containing said inhibitor, in the manufacture of a medicament for treating or preventing heart failure (e.g. chronic ischaemic heart disease or chronic myocardial ischemia) or treating cardiac ischaemic reperfusion injury in a subject by inducing angiogenesis in the heart tissue of said subject, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor or composition is for administration prior to, simultaneously with, and/or after administration of said shockwave therapy.

It will be evident that the methods and uses described above for inducing angiogenesis in the heart tissue of a subject may also be used for improving the prognosis of a subject with, or at risk of, heart failure.

Stem cells are also known to secrete paracrine factors that have anti-apoptotic effects that could be beneficial in patients suffering from heart attacks and/or heart failure, particularly heart failure caused by ischaemic reperfusion injury. However, as discussed above, the administration of stem cells to the heart is very invasive, expensive and associated with poor cell retention. Moreover, whilst the shockwave therapies described above (including the combined therapy) may minimise the damage to heart tissue caused by a myocardial infarction, e.g. cardiac ischaemic reperfusion injury, they do not provide any functional benefit to the heart in terms of the improvement of the ejection fraction, i.e. the shockwave therapies described above do not restore the function of the heart or repair damage caused by a myocardial infarction, e.g. cardiac ischaemic reperfusion injury.

Thus, the inventor has further determined that the methods and uses of the disclosure described above may be further enhanced by providing subjects with

stem cells or progenitor cells that can replace cardiac cells, particularly cardiomyocytes, that died as a consequence of the stress conditions associated with myocardial infarction, e.g. ischaemic reperfusion injury. In this respect, it is thought that the pro-survival secretome (which may be in the form of one or more exosomes) induced in heart tissue on exposure to shockwaves may function to attract or recruit stem cells to the damaged tissue, thereby enhancing the retention of the cells within the heart and enabling the effective repair of damaged tissue (i.e. restoring, at least some of, the lost cardiac function). In other words, the shockwave therapy of the disclosure may be seen to provide an environment that facilitates or potentiates the retention of stem cells within heart tissue and subsequent engraftment of said cells within the heart tissue. Whilst the stem cells may be administered to the heart tissue directly, e.g. via intravenous, intracoronary, transendocardial and/or intramyocardial injection as described above, it will be evident from the discussion below that the present disclosure removes the need for invasive administration of stem cells.

In this respect, in addition to providing an environment that facilitates or potentiates the retention of stem cells within heart tissue, the heart tissue secretome (which may be in the form of one or more exosomes) induced by the shockwave therapy of the disclosure may function to attract or recruit stem cells from sites other than the heart, e.g. stem cells that are present in blood. In other words, the method of the disclosure may facilitate the homing of stem cells to the heart. This may enable stem cells to be administered non-invasively, i.e. by injection at a site other than the heart, e.g. injection into the peripheral blood circulation. Thus, the present disclosure obviates the need for open heart surgery and direct injection of stem cells to heart tissue, e.g. using catheters into the coronary blood supply, is not necessary.

Advantageously, the present disclosure supports the use of endogenous stem cells, e.g. stem cells that are present in the blood of the subject to be treated. Thus, in some embodiments, the shockwave therapy of the disclosure may result in the non-invasive homing (i.e. recruitment and subsequent engraftment) of stem cells in the peripheral circulation to the heart tissue. In this respect, it may be useful to increase the number of stem cells present in the blood, e.g. using a pharmacological stem cell mobiliser, such as parathyroid hormone as discussed in more detail below.

Thus, in some embodiments, the method of the disclosure may further comprise administering a pharmacological stem cell mobiliser, e.g. parathyroid hormone or a fragment thereof, to said subject (a so-called combination therapy).

Alternatively viewed, the inhibitor (e.g. DPP-4 inhibitor) or pharmaceutical composition comprising said inhibitor is provided as a combined preparation with a pharmacological stem cell mobiliser, e.g. parathyroid hormone or a fragment thereof, for separate, simultaneous or sequential use or administration to the subject (a so-called combination therapy). Thus, in still further embodiments the disclosure provides the use of the inhibitor (e.g. DPP-4 inhibitor) or pharmaceutical composition comprising said inhibitor in the manufacture of a combined preparation with a pharmacological stem cell mobiliser, e.g. parathyroid hormone or a fragment thereof, for separate, simultaneous or sequential use or administration to the subject (a so-called combination therapy).

In some subjects (i.e. patients), it may be beneficial to harvest stem cells from the subject (e.g. prior to the start of treatment) and administer said cells to the subject (e.g. via injection into the peripheral circulation) at the most appropriate time, e.g. prior to shockwave therapy as discussed in more detail below. For instance, it may be necessary to harvest or obtain stem cells from a subject if the subject is unresponsive to agents used to mobilise the stem cells, e.g. parathyroid hormone, or if such agents are contraindicated. In some embodiments it may be useful to expand the population of stem cells *in vitro* (i.e. to culture the subject's endogenous stem cells *in vitro*) prior to administration. Such expansion methods are well-known in the art.

Thus, in some embodiments the method of the disclosure may further comprise administering stem cells to said subject (a so-called combination therapy). In particular, the method may comprise a step of obtaining or harvesting stem cells from a subject (e.g. the subject to be treated) and optionally expanding the population of stem cells *in vitro*, prior to administration.

Alternatively viewed, the inhibitor (e.g. DPP-4 inhibitor) or pharmaceutical composition comprising said inhibitor is provided as a combined preparation with stem cells for separate, simultaneous or sequential use or administration to a subject (a so-called combination therapy). Thus, in still further embodiments the disclosure provides the use of the inhibitor (e.g. DPP-4 inhibitor) or pharmaceutical composition comprising said inhibitor in the manufacture of a combined preparation

with stem cells for separate, simultaneous or sequential use or administration to a subject (a so-called combination therapy).

Thus, in some embodiments, the stem cells are obtained from said subject and optionally expanded *in vitro* prior to administration. Thus, in some embodiments, the stem cells are exogenous stem cells, e.g. autogeneic stem cells.

In still further embodiments, stem cells may be used in combination with pharmacological agents suitable for mobilising stem cells, such as parathyroid hormone or a fragment thereof (a so-called combination therapy).

In some instances, it may be desirable or necessary to use stem cells from a donor subject. Thus, in some embodiments the method may comprise a step of obtaining or harvesting stem cells from a donor subject and optionally expanding the population of stem cells *in vitro*, prior to administration to the subject to be treated. Thus, in some embodiments, the stem cells are exogenous donor stem cells, i.e. allogeneic stem cells.

It will be evident that the stem cells obtained or harvested from a subject may not be suitable for immediate administration, i.e. it may be necessary or advantageous to modify the stem cells prior to administration. For instance, as mentioned above, it may be useful to expand or cultivate the stem cells *in vitro* to increase the number of stem cells for administration. Additionally or alternatively, it may be useful to isolate or separate different stem cell types prior to administration. Furthermore, in some embodiments the stem cells may be treated to differentiate the cells to make them more suitable for use in the methods and uses of the disclosure, e.g. to differentiate the cells into cell types that may be particularly advantageous in the therapies of the disclosure, e.g. M2c macrophage cells as discussed below. For instance, the step of harvesting or obtaining stem cells may involve isolating blood progenitor cells from a subject (e.g. the subject to be treated or a donor subject), such as bone marrow–derived mononuclear cells, and cultivating said cells *in vitro* under conditions suitable to the preferred stem cells or populations of stem cells described in more detail below. However, in some embodiments, the blood progenitor cells do not undergo differentiation *in vitro*, i.e. in some embodiments the stem cells for administration in the method and uses of the disclosure are blood progenitor cells, e.g. bone marrow–derived mononuclear cells.

As discussed in more detail in the Examples below, the inventor has determined that exposure of vascular endothelial cells to shockwaves results in the

Claims

1. Use of a dipeptidyl peptidase-4 (DPP-4) inhibitor, or a pharmaceutical composition containing said inhibitor, in the manufacture of a medicament for:

(a) treating or preventing heart failure; or

(b) treating cardiac ischaemic reperfusion injury,

in a subject, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor is to be administered prior to, simultaneously with, and/or after administration of said shockwave therapy.

2. The use according to claim 1, wherein said inhibitor or composition is provided as a combined preparation with a pharmacological agent suitable for mobilising stem cells for separate, simultaneous or sequential use or administration.

3. The use according to claim 2, wherein said pharmacological agent suitable for mobilising stem cells is parathyroid hormone or a fragment thereof.

4. The use according to claim 3, wherein said parathyroid hormone fragment comprises teriparatide.

5. The use according to any one of claims 1 to 4, wherein said inhibitor or composition is to be administered prior to said shockwave therapy administration and continues throughout the course of the shockwave therapy.

6. The use according to any one of claims 2 to 5, wherein the pharmacological agent suitable for mobilising stem cells is to be administered at least 8 hours before the shockwave therapy.

7. The use according to claim 1, wherein said inhibitor is provided as a combined preparation with stem cells for separate, simultaneous or sequential use or administration.

8. The use according to claim 7, wherein said stem cells are derived from or comprise bone marrow–derived mononuclear cells.

9. The use according to claim 6 or 7, wherein the stem cells are to be administered at least 8 hours before the shockwave therapy.

10. The use according to any one of claims 1 to 9, wherein the DPP-4 inhibitor is Sitagliptin, Linagliptin, Vildagliptin, Gemigliptin, Anagliptin, Teneligliptin, Trelagliptin, Dutogliptin, Omarigliptin, Lupeol or a combination thereof.

11. The use according to any one of claims 1 to 10, wherein said heart failure is chronic heart failure or post-infarction heart failure.

12. The use according to any one of claims 1 to 10, wherein said shockwave therapy comprises administration of shockwave pulses with energy of about 0.05-0.25 mJ/mm^2.

13. The use according to any one of claims 1 to 12, wherein said shockwave therapy comprises administration of at least about 500 shockwave pulses, preferably at least about 1000 shockwave pulses.

14. The use according to any one of claims 1 to 13, wherein said shockwave therapy comprises administration of a dose of about 500-2000 shockwave pulses.

15. The use according to any one of claims 1 to 14, wherein said shockwave therapy comprises administration of shockwave pulses during the isovolumic contraction and/or isovolumic relaxation periods of the cardiac cycle.

16. The use according to any one of claims 1 to 15, wherein the focal point of the shockwave pulses is targeted to a specific region of the heart.

17. The use according to claim 16, wherein the region of the heart to be targeted is determined by echocardiography (Echo) visualisation and/or electrocardiogram (ECG) pattern recognition.

18. The use according to claim 16, wherein the region of the heart to be targeted is determined by magnetic resonance imaging.

19. The use according to any one of claims 16 to 18, wherein specific region of the heart to be targeted comprises scar tissue.

20. The use according to any one of claims 1 to 19, wherein the dose of shockwave pulses is to be administered over more than one session.

21. A kit or product containing:

(i) a DPP-4 inhibitor or composition comprising said inhibitor; and

(ii) a pharmacological agent for mobilising stem cells, such as parathyroid hormone or fragment thereof, or a pharmaceutical composition comprising said pharmacological agent and at least one pharmaceutically acceptable carrier, diluent or excipient; and optionally

(iii) an additional agent, e.g. an agent for treatment of heart failure or glucose, or a pharmaceutical composition comprising said additional agent and at least one pharmaceutically acceptable carrier, diluent or excipient.

22. Use of the kit or product of claim 21 in the manufacture of a medicament for:

(a) treating or preventing heart failure; or

(b) treating cardiac ischaemic reperfusion injury,

in a subject, wherein (i), (ii) and optionally (iii) are provided as a combined preparation for simultaneous, sequential or separate use, wherein said subject has been administered extracorporeal cardiac shockwave therapy and wherein said inhibitor and/or hormone is to be administered prior to, simultaneously with, and/or after administration of said shockwave therapy.

23. The use of claim 22, wherein said a DPP-4 inhibitor, pharmacological agent for mobilising stem cells and/or shockwave therapy is as defined in any of the aforementioned claims.