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非胰島素類降血糖藥物與心血管疾病之安全性

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摘　要

在本篇文獻回顧，我們主要在探討口服降血糖藥物 (雙胍類 (Metfornin)、磺醯尿素類 (Sulfonylurea)、美格替耐類 (Meglitinide)、噻唑烷二酮類衍生物 (Thiazolidinedione)、甲型醣苷酶抑制劑 (α-glucosidase inhibitors)、雙肽基肽酶 -4 抑制劑 (Dipeptidyl Peptidase-IV inhibitors) 和第二型鈉 - 葡萄糖轉運蛋白抑制劑 (Sodium-Glucose Co-transporter 2 inhibitors)) 及注射劑型降血糖藥物 (類升糖素肽 -1 受體促效劑 (Glucagon-Like Peptide-1 Receptor Agonists)) 長遠在心血管安全之影響。現有的證據顯示雙胍類 metformin 在第二型糖尿病患並沒有產生心血管疾病負面的影響；因為它可以改善一些心血管危險因子及可能減少心血管疾病的發病率和死亡率。目前磺醯尿素類與心血管疾病增加與否的關係仍是眾說紛紜。許多研究其中大部分是大型資料庫的回溯性分析，但是有些是前瞻性研究，顯示使用磺醯尿素類來治療第二型糖尿病會增加心血管疾病的風險。但是包括 UKPDS (United Kingdom Prospective Diabetes Study)、ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) 和 ACCORD (Action to Control Cardiovascular Risk in Diabetes) 等大型臨床試驗，發現磺醯尿素類並沒有增加第二型糖尿病患心血管疾病的死亡率或者發病率。最近幾年的統合分析也呈現相互矛盾的結果，有些顯示磺醯尿素類有增加心血管死亡率，但另有結論認為沒有增加心血管疾病的風險。或許要等到目前進行中的 CAROLINA (The Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients with Type 2 Diabetes) trial 結果出爐，這些藥物對於心血管安全的釐清及定義也許有所幫助。研究顯示美格替耐類對於傳統心血管疾病危險因子貢獻度顯得比較弱，雖然有研究指出 repaglinide 可以減少脂蛋白 (a)。單一藥物治療第二型糖尿病，研究發現相較於 metformin，repaglinide 不論病患過去是否有心肌梗塞病史，並沒有增加主要心血管事件、心因性死亡率或總死亡率。Rosiglitazone 有顯著增加心肌梗塞風險及增加心血管死亡率風險。Pioglitazone 對於一些心血管危險因子的改善是有幫助的，同時可以延緩動脈粥樣硬化與減少心血管事件。在 IRIS (the Insulin Resistance Intervention after Stoke) 試驗，對於有胰島素阻抗合併最近有缺血性腦中風或短暫性腦缺血發作非糖尿病患者，pioglitazone 則有降低腦中風或心肌梗塞的風險。ACE (the Acarbose Cardiovascular Evaluation) trial 結果顯示 acarbose 並沒有減少心血管疾病的風險。DPP-4 抑制劑 (saxagliptin, alogliptin 和 sitagliptin) 對於有高風險心血管疾病的第二型糖尿病人既沒有增加也沒有顯著改善心血管事件。Saxagliptin 意外地發現有高風險引起心臟衰竭住院。Lixisenatide 在有急性冠心症的第二型糖尿病患身上並沒有得到心血管的益處。緩釋型 exenatide 對心血管的 outcomes 也沒有顯著有更好的結論。相較之下，長效型 liraglutide 與超長效型 semaglutide 則可以減少

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主要心血管事件和死亡的發生率。Empagliflozin 和 canagliflozin 等兩種 SGLT-2 抑制劑顯示有明顯降低三重主要心血管事件、總死亡率與心臟衰竭住院的風險，另外 empagliflozin 則可以減低心血管的死亡率。CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) 研究，SGLT-2 抑制劑是可以減少心臟衰竭住院及總死亡率的風險。更進一步的 CVD-REAL 次級分析顯示 SGLT-2 抑制劑具有一定程度減少心肌梗塞及中風的風險。CVD-REAL 2 研究也顯示 SGLT-2 抑制劑有顯著減少心血管疾病之風險。總之，對於第二型糖尿病的治療，除了應個別化考量之外，也應該評估降糖尿病藥物是否會增加心血管事件的風險。

關鍵詞：第二型糖尿病 (Type II diabetes mellitus)
糖尿病藥物 (Anti-diabetic drugs)
心血管疾病 (Cardiovascular disease)
心臟衰竭 (Heart failure)

前言

隨著社會的變遷，我國人的飲食與生活習慣已有明顯的改變，而糖尿病的盛行率也有逐年增加的趨勢，持續幾年時間均位居國人十大死因第五名。根據世界衛生組織的統計，2014 年全球年齡大於 18 歲以上約有四億二千萬人罹患有糖尿病，全球糖尿病盛行率從 1980 年的 4.7% 上升至 2014 年的 8.5%，幾乎是成倍數成長 [1]。另外根據國際糖尿病聯盟 (International Diabetes Federation, IDF) 的統計，到了 2040 年全球糖尿病人口將會達到六億四千兩百萬，大約每 10 個人當中就有一人罹患有糖尿病 [2]。糖尿病是一種複雜及慢性的疾病，病患需要長期使用藥物來控制血糖，而糖尿病患者若長期血糖控制不佳，會伴隨多重併發症，包括血管病變、神經病變和視網膜病變等，因此唯有良好的血糖控制才能避免這些併發症的發生。多數的臨床醫師認為一個理想的降血糖藥物應該同時具備有效的控制血糖、低血糖風險、藥效持續性、不會增加體重負擔甚至可以減少體重、沒有水腫副作用、沒有增加心血管疾病風險甚至有心血管及腎臟功能保護的好處等等，然而像這樣的理想降血糖藥物，至少截至目前為止，臨床上仍然尋找不到如此完美的治療糖尿病用藥。而 2007 年 Steven E. Nissen 匯集 42 個臨床試驗的整合分析，發現 Rosiglitazone 有增加心肌梗塞及增加心血管事件的死亡率 [3]。因而美國藥物食品管理局在 2008 年 12 月 8 日發布一篇白皮書，往後治療第二型糖尿病藥物新藥必須先進行心血管疾病風險評估，證明不會增加心血管疾病事件才准上市 [4]。此後，有愈來愈多的議題探討有關降血糖藥物與心血管疾病之安全性。而從臨床醫師的角度，我們希望藉由降血糖藥物的使用來控制病患的血糖，避免後續大小血管疾病併發症的產生，同時也應該考量在藥物治療的同時，避免不必要的副作用，尤其是心血管疾病的發生。

糖尿病和心血管疾病之病理及生理學

一、高血糖 (hyperglycemia)

第二型糖尿病患者相對於一般正常人會有相當高的風險出現心血管疾病。許多的臨床研究指出長期處於高血糖環境會導致大小血管併發症的產生和死亡率的增加 [5,6]。高血糖會透過不同的代謝路徑作用在粒線體的電子傳遞鏈促使活性氧化物質 (reactive oxygen species, ROS) 的堆積 [7]。ROS 能直接改變蛋白質、脂質或去氧核醣核酸 (deoxyribonucleic acid, DNA) 和改變細胞內訊號傳遞路徑，導致不可逆的氧化性修飾。過多的 ROS 堆積的結果導致氧化壓力 (oxidative stress) 的產生，而過多的氧化壓力和

糖尿病各種的併發症有密切關係，如大小血管病變和心肌細胞病變等等。許多研究指出氧化壓力在心血管疾病扮演其中一個重要角色[8,9]。高血糖也會藉由增加血液循環中的細胞激素 (cytokines)、生長因子 (growth factors)、內皮素 - I (endothelin-I) 和血管收縮素 II (angiotensin II) 等，進而活化蛋白激酶 C (protein kinase C)，使得血管內皮細胞一氧化氮合成減少，誘發血管受損並影響血管功能[10-15]。研究指出餐後高血糖會提高心血管疾病的風險[16-18]，特別是當餐後血糖有明顯波動伴隨餐後高三酸甘油脂血症時，容易引起血管內皮細胞功能異常進而增加動脈粥狀硬化的風險[19]。Hanefeld 等學者針對初診斷第二型糖尿病所做的前瞻性臨床試驗在 11 年追蹤研究，顯示餐後血糖與心肌梗塞及死亡率有密切相關[20]。

二、胰島素阻抗 (insulin resistance)

胰島素阻抗是代謝症候群的核心也是導致第二型糖尿病的病因之一，許多大型的前瞻性研究顯示胰島素阻抗導致的高胰島素血症 (hyperinsulinemia) 是其中一個冠狀動脈疾病的預測因子[21-24]。最近的研究也發現胰島素阻抗時，某些胰島素訊號蛋白會抑制葡萄糖的攝取和胰島素在心肌細胞和心臟內皮細胞的其他功能，進一步導致心血管疾病的產生[25]。

三、腸泌素失調 (incretin dysfunction)

腸泌素的分泌不足和阻抗也是造成高血糖的原因之一。許多研究發現第二型糖尿病患者腸泌素的效用有明顯減少的趨勢，同時高血糖也會增加二肽基肽酶 -4 (dipeptidyl peptidase-4, DPP-4) 的活性[26-28]。許多的動物研究和小型的臨床研究發現腸泌素，尤其是胰高血糖素樣肽 -1 (glucagon-like peptide 1, GLP-1) 有促胰島素和類胰島素的效果，尤其可以增加心肌細胞對葡萄糖的攝取 , 似乎對心臟衰竭是有保護作用。一項研究以狗為模式探討在誘發心肌病變的情況下，輸注人工合成的 GLP-1 超過 48 小時明顯改善心輸出量、血管阻力和左心室的血流動力學[29]。在慢性心臟衰竭的病人也發現輸注人工合成的 GLP-1 可以改善心臟功能[30]。此外缺少 GLP-1 受體的老鼠會影響心肌結構和功能，暗示了 GLP-1 在心臟生理學扮演重要角色[31]。然而，另有些動物試驗發現心血管事件之後，腸泌素並沒有改善心肌功能[32,33]。綜合來說，腸泌素對人體是否有心血管保護作用，需要更多的臨床研究來佐證。

四、貝他細胞功能失調 (β cell dysfunction)

胰臟貝他細胞功能的失調亦為導致高血糖的原因之一。在一群有急性心肌梗塞而伴有高血糖的非糖尿病病患，發現其胰島素分泌量減少，顯示初期貝他細胞的功能失調在急性心肌梗塞的過程中扮演重要病理和生理上的角色[34]。此外貝他細胞功能的失調的結果，會造成前胰島素 (proinsulin) 濃度的增加，在一項超過 27 年的追蹤研究顯示前胰島素濃度升高會增加兩倍心血管的死亡率和發病率的風險[35]。在 11 年追蹤研究的 Hoorn study 也發現空腹的前胰島素濃度的增加在調整年齡和性別之後，增加 21% 的整體死亡率和 33% 的心血管疾病死亡率[36]。

五、心血管疾病的危險因子 (risk factors of cardiovascular disease)

根據台灣健保資料庫分析統計，自 2000 年至 2009 年台灣第二型糖尿病人口中有超過 56% 以上是合併有體重過重或肥胖[37]。除了飲食生活型態之外，有許多的降血糖藥物在高劑量使用之下也會造成體重增加的負擔，進而增加心血管疾病的風險。在一篇大型的統合分析研究，發現體重每增加 1 公斤會增加 7.1% 心臟衰竭的風險[38]。另外，肥胖也會加速體內臟器脂肪組織的分解，提升血液中游離脂肪酸、纖溶酶原激活物抑製劑 -1 (plasminogen activator inhibitor-1, PAI-1) 及一些發炎反應物質，進而造成心血管疾病風險的增加。根據台灣健保資料庫分析統計，自 2000 年至 2009 年台灣第二型糖尿病人口中，有超過 60% 以上合併高血壓和超過 40% 合併高血脂[39]。高血壓和高血脂乃是導致心血管疾病的重要因子。積極的血

壓控制，可以減少糖尿病的大小血管併發症風險[40]。慢性發炎狀態和心血管疾病的發生有關，同時也可以預測第二型糖尿病的發展[41,42]。慢性發炎時，C- 反應蛋白 (C-reactive protein, CRP)、纖維蛋白原 (Fibrinogen)，唾液酸 (Sialic acid)、介白素 -6 (Interleukin-6, IL-6) - 和 PAI-1 等的血中濃度均會上升。此外高血糖會造成血小板的活化、結構改變、聚集增加和凝血傾向等結果，進一步造成血管的阻塞[43,44]。高血壓是台灣糖尿病病人發生心血管疾病與心臟衰竭的重要危險因子。利用台灣健保資料庫，2007 年，台大曾慶孝醫師收集 1995 至 2002 年糖尿病患者共 89857 位，研究指出隨著年齡和身體質量係數的增加，高血壓盛行率有顯著上升的趨勢，且身體質量係數每增加 1 kg/m^2，男性和女性高血壓風險分別增加 1.16 倍和 1.13 倍[45]。2008 年，台大曾慶孝等醫師收集共 1296 位第二型糖尿病患者，研究指出缺血性心臟病盛行率在有高血壓、肥胖、血脂異常和代謝症候群病人有顯著上升的趨勢[46]。2011 年，台大曾慶孝醫師分析 2692 位心臟衰竭住院病人，尤其是老年人 (≧ 65 years) 比青壯年 (20 － 64 years) 有 25 倍心臟衰竭住院風險，合併症中又以高血壓所占的比例最高[47]。

六、低血糖 (hypoglycemia)

低血糖是臨床醫師在治療糖尿病患者心中永遠的痛，也是糖尿病患者達成理想控制血糖的一大障礙。英國低血糖研究小組的一個大型前瞻性研究，發現在以胰島素治療的第二型糖尿病患者嚴重低血糖是一個常見問題，而且隨著胰島素治療時間愈久嚴重低血糖出現的事件也有增加的趨勢[48]。短期低血糖的結果患者可能會有不愉快的症狀，而長期低血糖對患者健康的生活品質會有負面的衝擊[49]。根據美國 2007 年至 2009 年的統計，六十五歲以上的老年人因藥物的副作用至急診就診的前四名藥物中，其中胰島素和口服降血糖藥分居第 2 名和第 4 名，主要與這些藥物導致病患低血糖的結果有關[50]。根據台灣健保資料庫分析統計，自 1998 至 2009 年間低血糖仍有較高風險的比率出現心血管疾病、住院和整體死亡率[51]。嚴重低血糖也是造成心血管疾病的危險因子，其機轉可能包括交感腎上腺系統活化 (sympathoadrenal activation)、心臟再極化異常 (abnormal cardiac repolarization)、心臟自主神經功能失調 (cardiac autonomic neuropathy)、血栓形成增加 (increased thrombogenesis)、發炎反應增加 (enhanced inflammation) 以及內皮細胞功能失調 (endothelial dysfunction)[52]。雖然 1932 年已有人提出低血糖與心血管疾病的關係[53]，但兩者之間的關聯性至今仍被廣泛討論，尚無明確定論。大型的臨床試驗包括早期針對初診斷的糖尿病患者的英國前瞻性糖尿病研究 (UK Prospective Diabetes Study, UKPDS)、ACCORD (Action to Control Cardiovascular Risk in Diabetes)、ADVANCE (Action in Diabetes and Vascular Disease: Pretreat and Diamicron Controlled Evaluation) 和 VADT (Veterans Affairs Diabetes Trial) 等 5 大型臨床試驗系統性分析，發現嚴格的血糖控制組，其嚴重低血糖發生率是有意義的增加。雖然嚴格控制血糖對於非致死性疾病如心肌梗塞的減少是有意義的，但對於心血管疾病死亡率和任何原因的死亡率統計學上卻是沒有意義的[54]，也許此與每個臨床試驗所選擇的個體條件不盡相同有關。但從這些大型臨床試驗，顯示嚴重低血糖與心血管事件或死亡率似乎仍缺乏明顯的因果關係，因此糖尿病治療過程中產生的低血糖，是否會導致死亡率增加抑或抵銷嚴格血糖控制的好處，仍受到廣大的討論。儘管如此，目前有愈來愈多的共識認為低血糖是一個心血管疾病的危險因子[55-58]，特別是原本就屬於高風險心血管疾病的族群。最近的一個世代研究，收集了 3260 位第一型糖尿病患者和 10422 位第二型糖尿病患者，在第一型糖尿病患者本身同時有或著沒有罹患心血管疾病情況下，低血糖造成心血管疾病的風險比分別為 1.51 和 1.61；而在第二型糖尿病患者本身有或沒有罹患心血管疾病情況下，低血糖造成心血管疾病的風險比分別為 1.60 和 1.49，顯示低血糖造成心血管疾病的風險是增加的[59]。但整體來說，積極控制血糖對

糖尿病患者是有好處的，只是每個病患血糖的控制目標應該考量個別化[60]。臨床上，盡其所能把糖尿病患者血糖控制在理想的範圍內並免低血糖，以期能使糖尿病患者得到最佳的好處和避免相關併發症的產生。

七、微量白蛋白尿 (microalbuminuria)

對糖尿病的患者而言，微量白蛋白尿在臨床上暗示腎絲球血管的損傷，且目前已普遍被視為心血管疾病的一個獨立危險因子[61,62]。Dinneen 和 Gerstein 兩位學者在一篇系統性文獻回顧，發現第二型糖尿病患者一旦出現微蛋白尿會顯著增加 2.4 倍的整體死亡率及 2 倍的心血管死亡率[63]。微量白蛋白尿是一個糖尿病腎病變的指標，也暗示著增加血管疾病的風險[64]，且有研究指出微量白蛋白尿與冠狀動脈粥狀硬化嚴重程度呈正相關[65]。微量白蛋白尿也暗示著廣泛輕微發炎反應的進展、血管內皮細胞失調與凝血功能活化有關，進而提高心血管疾病之風險[66]。近期發表的 Steno-2 研究，對於第二型糖尿病併有微量白蛋白尿在積極的行為與藥物控制 7.8 年，在追蹤 21.2 年發現分別能顯著減少冠狀動脈疾病、腦血管疾病及心血管疾病[67]。總括來說，微量白蛋白尿是糖尿病腎病變的指標，也暗示增加心血管疾病之風險，唯有積極控制血糖、血壓、血脂、體重及生活型態的調整，才能有效改善微量白蛋白尿，進而減少心血管疾病的發生。至於微量白蛋白尿與心血管壁間交互作用的真正致病機轉目前仍沒有定論，需要更多的研究來探討。

非胰島素降血糖藥物與心血管疾病安全性之文獻分析

一、雙胍類 (Biguanides)

在目前所有的口服降血糖藥物中，Metformin 屬於具有降糖效果、少低血糖風險、低體重增加及價格便宜等諸多優勢，不僅是目前世界上使用最多的口服降血糖藥，同時也是包括美國糖尿病學會與歐洲糖尿病學會建議的第一線的口服降血糖藥物[68]，也是美國臨床內分泌專家學會建議的第一線的口服降血糖藥物之一[69]。學理上，Metformin 似乎有諸多血管保護作用，包括減少發炎反應和氧化壓力、避免血管纖維和重塑化 (remodeling)、促進巨嗜細胞分化以達到抗炎反應[70-74]。關於 Metformin 是否會影響心肌細胞電為活動、在第一型糖尿病的小鼠實驗，發現 Metformin 可以避免 QT 的延長[75]。在另一個誘發急性心肌梗塞的大鼠實驗，短期給予 Metformin 治療，有顯著避免心電圖上病態性的改變[76]。不過在臨床上，只有一個研究顯示 Metformin 可以減少第二型糖尿病患者在矯正 QT 約 12 微秒，且臨床上是沒有意義的[77]。綜合來說，目前仍沒有明確證據指出 Metformin 對心肌細胞的電位活動有直接的影響。在 1998 年，UKPDS 34 針對第二型糖尿病肥胖患者，發現 Metformin 相對於胰島素或磺醯尿素 (sulfonylurea)，儘管血糖控制結果相似，但 Metformin 可以減少 10 年整體死亡率和糖尿病相關死亡率分別為 36% 和 42%，且相對於常規治療可以降低 39% 心肌梗塞的相對風險[78]。更重要的是，Metformin 在該研究結束後的 10 年追蹤這樣的好處仍持續著[79]。相似的另一個臨床試驗，在以胰島素治療第二型糖尿病患者為前提之下，額外加入 Metformin 治療，追蹤 4.3 年的結果發現 Metformin 可以減少 39% 大血管病變[80]。Mellbin 等學者在觀察性的研究[81]，發現相對於其它口服降血糖藥，Metformin 可以改善第二型糖尿病患者在 ST 上升的心肌梗塞後的存活率。對於急性心肌梗塞的第二型糖尿病患者，Metformin 相對於非 Metformin 降血糖藥物的治療，可以明顯減少心肌細胞凋亡尖峰值的指數，包括肌酸激酶 (Creatine Kinase)，肌鈣蛋白 (troponins) 和肌酸激酶 -MB (Creatine Kinase-MB)[82]。此外在離體心臟和動物實驗，Metformin 相對於控制組，在缺血 - 再灌流心肌損傷之前或期間，Metformin 可以減少心肌梗塞面積 22%[83] 至 65%[84]。不過在臨床運用上，Metformin 是否能有效降低心肌梗塞的面積，可能要後續更多研究來佐證。不過，最近 Messaoudi 等學者針對心臟繞道手術之非糖尿病患者探討 Metformin 對心肌損傷之效果[85]，以隨機雙盲方式分為兩組，一組接受每日 Metformin

1500mg，另一組則接受安慰劑，分別在術前的前 3 天開始至術前 3 小時前給藥，發現短期術前 Metformin 雖然安全但似乎沒有效減少術中造成的心肌損傷。至於有心臟血管疾病非糖尿病患者，多數的研究發現在心肌梗塞之後 Metformin 並沒有心血管保護作用 [85,86]。最近一項 DPPOS (Diabetes Prevention Program Outcome Study) 研究，有 2029 人參與冠狀動脈硬化測量，平均追蹤 14 年，比較接受 Metformin 組和安慰劑組在罹患有高風險糖尿病 (prediabetes) 和早期糖尿病的男性患者，Metformin 對於冠狀動脈硬化具有保護作用，不過在女性 Metformin 並沒有呈現這樣抗冠狀動脈硬化的效果 [87]，其中的可能解釋是在這個研究中，女性冠狀動脈硬化嚴重程度相對是比較輕微的，或在研究之初有 36% 的女性尚未停經，而停經前的冠狀動脈硬化速度是比較緩慢的，尤其在沒有糖尿病的人身上，又或 Metformin 會影響賀爾蒙有關，如 Metformin 只會在男性但不會在女性減少睪固酮的量 [88,89]。截至目前為止，並沒有回溯性臨床試驗探討 Metformin 是否會引起心臟衰竭的問題。 Romero 等學者所進行超過 1500 位初診斷糖尿病合併有初診斷心臟衰竭的患者，在 2 年的追蹤發現 Metformin 不但可以減少整體死亡率和心血管疾病造成的死亡率，同時可以減少因心臟衰竭而住院的比率 [90]。在一篇大型的觀察性研究系統性文獻回顧中，對於有心臟衰竭的患者而言，即使有嚴重的左心室功能失調，Metformin 至少和其它降血糖藥物一樣是安全的 [91]。雖然 Metformin 對心血管疾病的這些發現和證據為大多數人所接受，但近年來有些研究提出不一樣的觀點，其中一篇匯集了 13 個研究的統合分析，比較了 Metformin 分別與飲食控制、安慰劑、合併其它降血糖藥物等治療，探討糖尿病患者死亡率和心血管疾病相關死亡率之影響，結果並未發現 Metformin 呈現有統計學上顯著的優勢 [92]。或許在某些情況之下，我們並不能完全排除 Metformin 對於心血管疾病可能隱藏負面的影響，需要更多研究投入來進一步釐清真相。

二、磺醯尿素類 (Sulfonylurea)

關於磺醯尿素類和心血管疾病死亡的關係，最早溯及 1970 年代的 University Group Diabetes Program 研究發現，第一代磺醯尿素類藥物 tolbutamide，會增加心血管死亡風險 [93]。磺醯尿素類所造成體重增加和低血糖風險一直是糖尿病患者揮之不去的陰影，同時也與心血管疾病風險增加有關 [94,95]。最近 Anthony 等學者所做的世代研究 [96]，分析 143635 位接受 Sulfonylurea 治療的糖尿病患者發現，每百人年發生急性心肌梗塞、心臟衰竭和中風事件分別為 1.53、4.26 和 1.92，顯示低血糖和體重增加是磺醯尿素類造成心血管疾病事件的原因之一。至目前為止，磺醯尿素類是否會引起心血管事件的增加尚無定論，此也許與每個臨床試驗所選擇的個體條件不盡相同有關。許多大型回溯性的分析 [97-101]，發現使用磺醯尿素類治療第二型糖尿病患者會增加心血管疾病的風險。但是包括 ACCORD[102]、UKPDS[103] 和 ADVANCE[104] 等大型臨床試驗，發現磺醯尿素類並沒有增加第二型糖尿病患心血管疾病的死亡率或者發病率。最近一篇系統性文獻回顧及統合分析 [105]，發現磺醯尿素類有顯著增加糖尿病患者的心血管死亡率和心血管事件，分析中也比較磺醯尿素類和雙胍類相關的心血管死亡率 (R.R. =1.26, [95% CI 1.17–1.35]) 和心血管事件 (R.R. = 1.18, [95% CI 1.13–1.24])。過去也有一些前瞻性的研究顯示磺醯尿素類會增加心血管疾病的風險 [106]。至此，磺醯尿素類與心血管疾病增加與否的關係仍是眾說紛紜，或許部分疑惑要等到目前進行中的 CAROLINA 試驗 (The Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Patients with Type 2 Diabetes) 結果出爐 [107]，才會有比較明確的答案。

三、美格替耐類 (Meglitinide)

美格替耐類屬於短效胰島素促分泌劑，控制糖尿病患者餐後血糖，這點與磺醯尿素類主要是控制病患的空腹血糖不同。相對於磺醯尿素類，美格替耐類較少有低血糖和體重增加等副作用 [108-111]。至今沒有大型長期臨床試驗

證實美格替耐類是否會增加心血管事件。美格替耐類和磺醯尿素類均藉由關閉貝他細胞表面腺核甘三磷酸敏感鉀離子通道 (ATP-dependent potassium channels，KATP) 來刺激胰島素分泌，但心肌細胞和血管平滑肌細胞有豐富的 KATP 通道 [112]，一旦心肌細胞表面的 KAPT 通道被關閉，進而抑制心肌缺血前制約效應 (ischemic preconditioning) 的保護作用，反而會增加對心肌細胞的傷害。所以磺醯尿素類在 DIGAMI 研究 (Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction) 的分析發現會對心血管有負面的影響 [113]，不過在 UKPDS 研究並沒有支持此結果 [103]。由於美格替耐類結合在 KATP 通道位置不同於磺醯尿素類和相對於磺醯尿素類有較短的半衰期，對心血管的負面作用會相對比較來得少 [114,115]。一篇丹麥的回溯性研究，發現相較於雙胍類 Metformin，美格替耐類 Repaglinide 用於第二型糖尿病治療時，不論病患過去是否有心肌梗塞病史，均不會增加主要心血管事件、心因性死亡率或總死亡率 [116]。研究也發現美格替耐類對於傳統心血管疾病危險因子貢獻度顯得比較弱 [117,118]。根據台灣健保資料庫分析，自 2000 年至 2010 年 5586 位第二型糖尿病合併有末期腎臟疾病患者，初次使用美格替耐類患者相對於沒有使用美格替耐類患者有 1.9 倍風險出現低血糖，特別發生在年齡大於 62 歲或小於等於 33 歲的患者)[119]，而低血糖將導致心血管事件、總住院率和總死亡率的增加 [120]。

四、噻唑烷二酮類衍生物 (Thiazolidinedione)

Thiazolidinedione (TZD) 主要藉由活化 PPAR-γ (peroxisome proliferator-activated receptors-γ) 來改善胰島素敏感性，增加胰島素分泌和控制血糖 [121]。由於腎絲球含有豐富的 PPAR-γ，TZD 能夠促進腎臟對鈉離子和水分的吸收 [122]。所以 TZD 有可能因水分滯留體內而造成心臟衰竭的風險，特別在有心臟衰竭後期的患者。至今 TZD 類衍生物對心血管疾病的功過倍受爭議。在 2007 年，由 Nissen 和 Wolski 兩位學者針對 Rosiglitazone 所做的統合分析，顯示其心肌梗塞風險為 1.43 以及心因性死亡風險則為 1.64[123]。之後，許多研究顯示 TZD 可能增加心血管疾病的風險，Schernthaner 等學者針對 TZD 所做的統合分析，顯示 Rosiglitazone 造成心血管疾病的 H.R. >1.0[124]，因此歐美等國家紛紛的禁止 Rosiglitazone 的使用。不過在另一篇分析 RECORD study[125] (the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes)，顯示 Rosiglitazone 會增加心臟衰竭的風險，但對於心肌梗塞，心因性死亡率和整體死亡率，Rosiglitazone 和控制組之間均沒有顯著差別。此外最近一篇 VADT (The Veterans Affairs Diabetes Trial) 重新檢視 Rosiglitazone 治療和心血管疾病之間的關係 [126]，4mg 或 8mg Rosiglitazone 反而有明顯減少心血管疾病風險，及降低心因性死亡風險，至於在心肌梗塞風險方面就沒有顯著的影響。另外美國食品藥物管理局在 2013 年重新再次檢視 RECORD 研究，顯示 Rosiglitazone 並沒有增加整體心血管疾病風險 [127]。由於整體分析目前仍缺乏一致性的結論，需後續更多的臨床研究才能有較明確的答案。

就學理上來說，相較於 Rosiglitazone，Pioglitazone 似乎有減少發炎指數 (inflammatory markers) 和改善心血管風險因子，包括降低三酸甘油脂、提升高密度膽固醇 [128]、減少自由脂肪酸、C- 反應蛋白和改善內皮細胞擴張功能 [129]、減緩頸動脈內膜中層厚度 [130]、改善腫瘤壞死因子 α 所誘導胰島素阻抗 [131] 和降低血壓 [132]、降低胰島素阻抗 [133] 等。就臨床上來說，一個大型的前瞻性臨床試驗 (PROspective pioglitAzone Clinical Trial In macroVascular Events)[134]，針對先前有大血管疾病的第二型糖尿病患者，Pioglitazone 顯示可以減少 16% 主要不良心血管事件。另外，雖然 Pioglitazone 增加因心臟衰竭而住院的風險，但其死亡率並沒有隨著心臟衰竭而增加。

2006 年 Mazzone 等學者所做的 CHICAGO 試驗 (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone)，顯示 Pioglitazone 相較於 Glimepiride 可以明顯減緩第二型糖尿

病患者頸動脈內膜中層厚度增厚的進展[135]。2007 年 Lincoff 等學者匯集 19 個臨床試驗所做的統合分析，顯示 Pioglitazone (排除 PROactive study) 增加了 44% 嚴重心臟衰竭，但可以減少 25% 心血管疾病[136]。在 2008 年，Nissen 等學者所做的 PERISCOPE 隨機臨床試驗 (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)，對於第二型糖尿病合併冠狀動脈疾病的患者，發現 Glimepiride 組動脈粥樣硬化體積百分比增加 0.73%，但是 Pioglitazone 組則可減少 0.16%，兩者差別有意義[137]，顯示 Pioglitazone 可以改善冠狀動脈粥樣硬化的程度，對於心血管疾病有保護作用的。2015 年日本的一篇 6 年觀察性世代研究，顯示 Pioglitazone 對於第二型糖尿病患者的心血管疾病是有保護作用[138]。2016 年 Keman 等學者針對 3876 位患有胰島素阻抗的缺血性腦中風或短暫性腦缺血發作的患者，顯示 Pioglitazone 能夠減少 24% 心血管事件，同時也發現 Pioglitazone 沒有增加心臟衰竭或因此而住院的比例[139]。2017 年，Liao 等學者收集 9 個臨床試驗所做的統合分析[140]，顯示 Pioglitazone 分別在胰島素阻抗患者和糖尿病患者可以減少主要不良心血管事件，但是卻增加了心臟衰竭的風險，推測可能與 Pioglitazone 造成病患液體滯留、體重增加和過去有心臟衰竭病史有關。

五、甲型醣苷酶抑制劑 (α-glucosidase inhibitors)

甲型醣苷酶抑制劑主要藉由抑制腸道中的多醣和雙醣分解為單醣，故可延遲腸道中糖分的吸收，可能會有胃腸症狀包括腹脹排氣及腹瀉等副作用，主要用於控制餐後血糖。許多研究資料指出，餐後高血糖會增加心血管疾病和死亡風險[141-145]。所以藉由甲型醣苷酶抑制劑的治療，其對心血管疾病的保護好處包括有降低三酸甘油脂[146-149]、減輕體重[150-153]、提升胰島素敏感性或減少胰島素阻抗[154-156]、減少血漿 PAI-1 和纖維蛋白原[157]、減少餐後凝血因子活化[158] 和改善高血壓[159,160]。

有研究顯示 Acarbose 減少體重方面在亞洲族群比西方族群來的明顯，也許與東西方飲食文化和基因等不同因素有關[150]。臨床上，甲型醣苷酶抑制劑關於心血管疾病的影響少有大型長期的臨床研究。在 2003 年，STOP-NIDDM 試驗中[161]，針對 1429 位葡萄糖耐受不良患者，相對於安慰劑，Acarbose 降低飯後高血糖的結果，可以減少心血管事件相對風險 49%，其中以心臟梗塞風險減少 91% 最為顯著 (H.R.= 0.09, [95% CI 0.01– 0.72], P=0.02)。在另一篇 STOP-NIDDM 的分析，發現腹部肥胖和葡萄糖耐受不良的惡化是導致高血壓的最主要的相關危險因子，而 Acarbose 的治療則可以減少 41% 高血壓風險[162]。在 2004 年 Hanefeld 等學者收集 7 個隨機雙盲的臨床試驗，相對於安慰劑，統合分析結果顯示 Acarbose 明顯減少 64% 心肌梗塞風險和 35% 心血管事件風險，同時其在血糖控制、三酸甘油脂、體重和收縮壓也有顯著的改善[163]。Chen 等學者利用台灣健保資料庫收集在 2003 年至 2008 年新診斷第二型糖尿病但沒有罹患心血管疾病的患者共 644792 位[164]，追蹤了 7 年時間，發現 Acarbose 在使用的最初第一年的心血管疾病風險有暫時性的增加，但其後隨著使用時間拉長則有明顯減少心血管疾病的風險，其詳細的機轉目前仍不明，需後續更多研究資料來探討。在 2015 年，由台大張以承等學者根據台灣健保資料庫分析在 Metformin 之後加上第二線口服降血糖藥 Acarbose，發現可以明顯降低急性心肌梗塞風險[165]。不過由台大張家勳等醫師在 2015 年同樣根據台灣健保資料庫分析[166]，以 Acarbose 做為第一線口服降血糖藥與多數治療指引建議的第一線口服降血糖藥 Metformin 相比，Acarbose 反而比 Metformin 增加 5% 心血管事件、增加 8% 心臟衰竭和增加 5% 缺血性中風，顯示以 Acarbose 做為第一線口服降血糖藥，可能有增加心血管疾病之風險，不過兩者參與人數相差懸殊，是否能反應真正的結果，值得商榷。另外 2005 年由 van de Laar 等學者針對第二型糖尿病患者單獨使用甲型醣苷酶抑制劑的一篇統合分析[167]，對死亡率或罹病率並沒有充分證據顯示有顯著影響。於 2017 年，由中國大陸和香港所做的 ACE trial (the

Acarbose Cardiovascular Evaluation)[168]，以大型前瞻的隨機雙盲設計來評估 Acarbose 對於心血管疾病所做的次級預防，結果顯示甲型醣苷酶抑制劑並沒有減少心血管疾病的風險。總歸來說，甲型葡萄糖酶抑制劑對於心血管疾病的風險評估目前仍缺乏較大規模前瞻性的研究，故其對心血管事件之預後尚無一致性的結論。

六、雙肽基肽酶 -4 抑制劑 (Dipeptidyl Peptidase-IV Inhibitors)

Dipeptidyl Peptidase-IV Inhibitors (DPP-4 抑制劑)，藉由抑制雙肽基肽酶 -4 分解酶，提高血液中活性的類升糖素胜肽 -1 (glucagon-like peptide 1) 來刺激胰島素分泌和抑制升糖素 (glucagon) 分泌來改善血糖的控制 [169]。在臨床研究，DPP-4 抑制劑長期可藉由抑制單核細胞活化 / 趨化性來減少血管的硬化和發炎反應 [170,171]，Sitagliptin 與 Vildagliptin 可以改善第二型糖尿病患者動脈硬化、血壓、血脂、發炎係數和頸動脈內膜中層厚度 [172,173]，Alogliptin 研究顯示可以延緩頸動脈內膜中層厚度的增厚、改善胰島素阻抗和致動脈粥樣化脂質 [174,175]，Sitagliptin 可以改善內皮細胞機能失調 [176]、降低餐後脂蛋白 [177]、延緩頸動脈內膜中層厚度的增厚 [178]。在一篇包含 17 個臨床試驗的統合分析顯示 DPP-4 抑制劑可以減少總膽固醇 [179]。最近的一篇文獻回顧分析，顯示 DPP-4 抑制劑可藉由許多訊號路徑傳遞，有利於血管生成或新生血管，推測對於心血管疾病治療尤其是缺血性心臟病或周邊動脈疾病是有幫助的 [180]。一些薈萃分析或統合分析顯示 DPP4 抑制劑可以減少心血管事件的發生 [181-186]，但這些主要都是回溯性的分析，並不是一開始就設計用來探討其與心血管疾病發生與否的關係，所以並不能真正反映出兩者之間的關聯性。DPP-4 抑制劑在心血管疾病危險性評估的縱向性研究，三大型臨床試驗包括 2013 年的 SAVOR-TIMI 53 (The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53)[187]、EXAMINE (The Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care)[188] 和 2015 年的 TECOS (The results of Trial Evaluating Cardiovascular Outcomes with Sitagliptin)[189] 等結果顯示既沒有增加也沒有顯著改善心血管事件。不過在 SAVOR-TIMI 53 Saxagliptin 病患因心臟衰竭而住院比例增加，就 SAVOR-TIMI 53 次分析來看，Saxagliptin 造成的心臟衰竭主要是使用的前六個月出現，其後的後六個月起其與安慰劑相比較，Saxagliptin 並沒有顯著增加心臟衰竭風險，事後分析發現在接受 Saxagliptin 前，若病患的 NT-ProBNP (N-terminal Pro-Brain Natriuretic Peptide) 有顯著偏高的族群，其血糖治療後心臟衰竭風險是增加的。另外其事後分析 (post hoc analysis) 也發現：（一）Saxagliptin 在沒有慢性腎臟疾病的患者並不會增加心臟衰竭的風險，但有慢性腎臟疾病的患者則會增加其風險；（二）有心臟衰竭病史的患者，使用 Saxagliptin 並不會增加心臟衰竭的風險，而原先沒有心臟衰竭並使得患者，使用 Saxagliptin 後則有 1.3 倍增加心臟衰竭的風險 [190]，推論這組群應該至少有 25% 左右潛藏有心臟衰竭風險，只是沒有被診斷出來，所以這一族群是屬於心臟衰竭的高風險，使用 Saxagliptin 後就比較會因心臟衰竭而住院。在 EXAMINE 次分析也有類似的結果，病患在急性冠心症之後，若有被診斷出心臟衰竭，因為有再接受相關治療，日後接受 Alogliptin 並不會增加心臟衰竭的風險，相反的，在急性冠心症之後，若沒有被診斷出心臟衰竭，其後接受 Alogliptin 則會增加 1.76 倍心臟衰竭的風險，尤其容易出現在原先就有較高 BNP (Brain Natriuretic Peptide) 的族群 [191]。總括來說，若第二型糖尿病患者本身就屬於心臟衰竭高風險組群，如有心血管疾病病史、心臟衰竭病史、肥胖、低血糖、高齡和血糖控制不佳等等，在使用 Saxagliptin 或 Alogliptin 前應該先排除是否有潛在的心臟衰竭，以免增加病患使用後因心臟衰竭而住院的風險。另外在 TECOS 的次分析，不論過去有無心臟衰竭或慢性腎臟病，顯示 Sitagliptin 並沒有增加因心臟衰竭而住院的風險 [189,192]。其實這三個大型臨床試驗由於納入研究的條件不同，我們只看到有無心血

管風險而沒有進一步分析是否有心臟衰竭的風險以及這些病患大都有在使用抗血壓藥、抗血脂藥和抗凝血藥，所以無法進一步比較其各自的優劣。長庚醫院陳東藝醫師等人在 2015 年根據台灣健保資料庫分析，針對第二型糖尿病併有慢性腎臟病患者在急性心肌梗塞之後所做的研究，Sitagliptin 雖然沒有增加心血管死亡、缺血性中風或心臟衰竭住院的風險，但卻增加了 73% 復發性心肌梗塞及 43% 經皮冠狀動脈血管重建 (percutaneous coronary revascularization) 的風險 [193]。

根據台灣健保資料庫分析結果，DPP-4 抑制劑對於心血管事件的影響在台灣的研究並沒有定論，包括北榮王岡陵和中醫大洪逸芷等醫師的分析，顯示 DPP-4 抑制劑有增加心臟衰竭住院的風險 [194,195]，而台大曾慶孝醫師的分析，顯示 DPP-4 抑制劑在短期內會增加心臟衰竭住院的風險，但長期則有減少其風險 [196]，但是成大歐凰姿等學者的分析，卻顯示 DPP-4 抑制劑有減少心臟衰竭風險 [197]，同時北市立醫院詹尚易等醫師分析第二型糖尿病併慢性腎衰竭患者，顯示 DPP-4 抑制劑有減少總死亡率但對於心肌梗塞和心臟衰竭住院的減少並無幫助 [198]。至於第二型糖尿病合併有心肌梗塞或腦血管疾病的患者，Wang 和 Chen 等醫師根據台灣健保資料庫分析結果，顯示 DPP-4 抑制劑並沒有增加心血管事件的風險 [199,200]。台大張家勳等醫師在 2016 年也根據台灣健保資料庫分析，顯示 Sitagliptin、Saxagliptin 和 Vildagliptin 其粗心臟衰竭每 100 個人年發生比例分別為 2.77、2.63 和 1.91，同時以 Acarbose 做為參照組的輔助分析顯示這三種 DPP-4 抑制劑並沒有增加心臟衰竭的風險，其中又以 Vildagliptin 造成的心臟衰竭的風險是最低的 [201]。從這些研究歸納起來，DPP-4 抑制劑對於心血管事件影響從台灣健保資料庫研究並沒有定論，可能的因素包括：(1) 研究設計和分析方法不同，例如研究設計包括世代研究、縱向研究等；分析方法包括 multivariable Cox proportional hazards regression analysis、time-varying Cox proportional hazards regression analysis、multivariable logistic regression analysis 和 Cox regression incorporated with the inverse probability of treatment weighting using propensity score 等。(2) 有些只針對單一種 DPP-4 抑制劑來研究，特別是在 Sitagliptin 的探討，這可能與它是台灣最早上市的 DPP-4 抑制劑有關，所以有較完整資料可供分析。但有些純粹以 DPP-4 抑制劑來與其它降血糖藥物做探討，並沒有明確指出確切的 DPP-4 抑制劑，也許不同種類的 DPP-4 抑制劑本身對於心血管事件的影響存在著異質性有關，當然這需要後續更多的研究來佐證。(3) 糖尿病期間的長短也是一個影響因子。一般來說，糖尿病期間越長，病患得到大小血管病變的風險也就越高，平均糖尿病期間有些研究較長，有些較短，甚至有些則沒有提及。(4) 研究觀察的時間不一，有些研究花較長時間觀察，但有些研究花較短時間觀察，當然最終的結果也會不一樣。例如台大曾慶孝醫師的分析，顯示 DPP-4 抑制劑在一年以內短時間會增加心臟衰竭住院的風險 [196]，臆測可能與 DPP-4 抑制劑本身特性有關或其它未知因素有關，但一年以上的長時間則有減少其風險，推測可能與 DPP-4 抑制劑潛藏有保護心臟衰竭的作用，這可以從 Santos 等人的研究得到佐證，該研究發現心臟衰竭的患者血中 DPP-4 濃度增加了大約 130%，更進一步發現心臟衰竭的患者血清 DPP-4 活性與左心室射出率呈現逆相關，另外在其試驗老鼠的研究也發現長期 DPP-4 抑制劑可以減輕心臟衰竭的發生和進展 [202]。類似的研究在以豬為模組也顯示 DPP-4 抑制劑在心臟衰竭的有利的好處 [203]。(5) DPP-4 抑制劑的劑量，只有少數有提到使用劑量，大都數都沒提到劑量的議題。例如在洪逸芷等醫師的分析，顯示低、中或高劑量的 Sitagliptin 相對於對照組，心臟衰竭的風險分別增加 1.35、2.16 及 2.57 倍 [195]。(6) 除了 DPP-4 抑制劑之外，關於病患使用其它多種降血糖藥物的比率不一，故在這些研究無法互相比較 DPP-4 抑制劑對於心血管事件的利或弊。(7). 病患的共病與其藥物治療，在不同的研究設計裡呈現不同相貌，無法相互比較，也許對於探討最後結論有所影響。總之，若依據台灣健保資料庫，

也許不同種類的 DPP-4 抑制劑對於心血管事件的影響確實存在著異質性，當然這需往後更多的研究來佐證。另外在 2014 年的二篇統合分析及 2016 年的觀察性研究，顯示 DPP-4 抑制劑會增加 13%~19% 心臟衰竭的風險，雖然其造成的真正機轉目前仍不確定，不過推測可能與糖尿病患者本身的高齡、慢性腎臟衰竭病史、潛在的心臟衰竭、心血管病史和長期糖尿病等等有關 [204-206]。總歸 DPP-4 抑制劑對於心血管疾病的影響，也許要等到目前進行中的 Linagliptin 試驗 (CAROLINA)[207] 結果出爐，DPP-4 抑制劑對於心血管疾病的影響會有更明確的答案。

七、類升糖素肽 -1 受體促效劑 (Glucagon-like peptide-1 receptor agonists)

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) 除了可以用來控制血糖之外，許多的研究推測 GLP-1RAs 對心血管可能具有保護的功用，包括有減重 [208-212]、降低血壓 [212-215]、改善血脂異常 [211,212,216]、降低 PAI-1、BNP (B-type natriuretic peptide) 和 hs-CRP (high sensitive C-reactive protein)[217]、內臟及皮下脂肪組織 [218,219] 和餐後載脂蛋白 B-48 及 CIII (apolipoproteins B-48 and CIII)[220]。許多統合分析顯示 GLP-1RAs 並沒有增加心血管事件風險 [221-223]，但這些大多是回溯性的分析，起初並不是設計用來探討其與心血管疾病發生與否，所以並不能真正反映兩者之間的關聯性。2016 年的一篇世代研究 [224]，顯示 GLP-1RAs 在現實世界中並沒有比其它降血糖藥物有增加心血管疾病的風險。這些 GLP-1RAs 都有心血管疾病危險性評估的縱向性研究發表，兩大型前瞻性隨機臨床研究包括 LEADER trial[225] (Liraglutide and cardiovascular outcomes in type 2 diabetes) 與 SUSTAIN-6 trial[226] (Semaglutide and cardiovascular outcomes in patients with type 2 diabetes) 分別顯示 GLP-1 RA Liraglutide 及 Semaglutide 有顯著降低心血管事件，另一個大型前瞻性隨機臨床研究：ELIXA trial (Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome) 顯示 GLP-1 RA Lixisenatide 沒有增加心血管事件 [227]。這三個大型臨床試驗由於納入研究的條件不同，所以無法進一步比較其各自的優劣性。有趣的是非致命性腦中風在 SUSTAIN-6 trial 比在 LEADER trial 顯著減少，推測與其收縮壓降低較多有關 [228]。GLP-1RAs 是否會造成病患心臟衰竭的問題也是當前大家討論的議題。Halbirk 等學者 2010 年針對有缺血性心臟病併有心臟衰竭的非糖尿病的患者的研究，顯示注射 GLP-1 後 48 小時並沒有改變心臟指數 (cardiac index, CI) 或左心室射出率 (left ventricular ejection fraction, LVEF)[229]。Kumarathurai 等學者 2016 年針對第二型糖尿病患併有穩定的心血管疾病所做的交叉研究，顯示 GLP-1 RA Liraglutide 並沒有改善 LVEF 功能 [230]。最近 Lepore 等學者針對心臟衰竭患者所做的 12 週隨機性研究，顯示 GLP-1 RA albiglutide 並沒有改善心臟功能 [231]。但是 Munaf 等學者在 2012 年的一篇統合分析則顯示 GLP-1RAs 有改善心臟衰竭病患的 LVEF 功能，但是對於 BNP 指數並沒有顯著的改善 [232]。2016 年 Li 等學者匯集 20 個臨床試驗第 II/III 期分析，顯示 GLP-1RAs 相較於對照組有較低心臟衰竭的風險 [233]。這些不同的研究結果說明了 GLP-1RAs 對於強心的作用需要有更多的研究來佐證，另外這些都是侷限在小族群研究且短時間觀察，無法真正反映 GLP-1RAs 對心臟衰竭的影響。最近一些大型前瞻性的研究，顯示 ELIXA[227] 和 LEADER[225] 分別可以減少 4% 及 13% 心臟衰竭住院的風險，而在 SUSTAIN-6[226] 反而增加了 11% 心臟衰竭住院的風險，但這三個研究與其各自的安慰劑比較結果臨床差異不顯著。因心臟衰竭而住院在這三個大型前瞻性的研究結果有些歧異性，目前仍然不是很清楚，推測除了各自納入研究的條件不同，此外可惜的是這三個研究均沒有像 EXAMINE 與 SAVOR-TIMI 53 試驗事先有測量 pro-BNP 數值，因此也就無法判斷這些病患是否事先就屬於心臟衰竭的高危險群。為此，2016 年發表的一篇 FIGHT 試驗 (Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial)，針

對患有末期心臟衰竭與減少 LVEF (≦ 40%) 之第二型糖尿病患者，GLP-1 RA Liraglutide 對於安慰劑雖然有增加 30% 因心臟衰竭再住院的風險，但是兩者之間並沒有顯著的差異 [234]。此與針對有高風險心血管疾病的第二型糖尿病為對象的 LEADER 試驗所顯示 Liraglutide 並沒有增加心臟衰竭風險之結果相異，這或許暗示著 GLP-1RAs 使用在有後期心臟衰竭及明顯減少 LVEF 的患者需要更加留意。不過針對 GLP-1RAs 使用在這些組群的利與弊，也許仍需要更久的追蹤來評估這些新藥對心血管疾病的影響。

八、第二型鈉 - 葡萄糖轉運蛋白抑制劑 (Sodium-Glucose Co-transporter 2 Inhibitors)

Sodium-Glucose Co-transporter 2 Inhibitors (SGLT-2 inhibitors) 主要是利用增加腎臟葡萄糖排泄方式來達到控制血糖，此與藉由刺激貝他細胞分泌胰島素以達到血糖控制的一般口服降血糖藥物的作用機轉不同，可以提供一種新穎獨特的治療概念。許多臨床研究顯示 SGLT-2 inhibitors 也有心血管保護作用：減少體脂肪 [235,236]、減重 [235-238]、降低血壓 [239-241]、降低尿酸 [242-244] 和降低胰島素阻抗 [245]。目前也有愈來愈多的研究在探討 SGLT-2 inhibitors 與心血管事件的關係。EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) 是在 2015 年所發表的大型前瞻性臨床試驗，顯示 SGLT-2 inhibitor Empagliflozin 可以分別減少心血管死亡率相對風險 38%、心臟衰竭住相對風險 35% 及整體死亡率相對風險 32% [246]。Wu 等人 2016 年的統合分析，顯示 SGLT-2 inhibitors 可以分別減少心血管事件、心血管死亡率、心臟衰竭及整體死亡率 [247]。2017 年由歐美等六個國家所共同參與的 CVD-REAL Study (Comparative effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)[248]，總共收集了 309056 位病人，比較 SGLT-2 inhibitors 與其它降血糖藥物，顯示 SGLT-2 inhibitors 可以顯著減少心臟衰竭住院風險及整體死亡率)。從 CVD-REAL 與 EMPA-REG OUTCOME 一致結果，顯示 SGLT-2 inhibitors 有助於減少心臟衰竭住院及整體死亡率的風險，另外推測 SGLT-2 inhibitors 間存在著所謂的 class effect，因此在 CVD-REAL 研究雖然在不同國家使用的 SGLT2 抑制劑的比例不一，但其結果並沒有顯著的異質性，此外值得一提的是在 CVD-REAL 研究中約 87% 病患本是沒有心血管病史，暗示 SGLT-2 inhibitors 在沒有或具有低風險心血管疾病的患者身上使用是安全的，這樣的結果與先前 SAVOR-TIMI 53 及 EXAMINE 次分析在心臟衰竭住院風險評估的結論不同。2018 年由亞太、中東和北美區域等六個國家所共同參與的 CVD-REAL 2 Study[249]，總共收集了 470128 位病人，其中亞洲人比率高達 87%，大約 73% 病患本身是沒有心血管疾病之病史。以 1:1 方式分配，比較 SGLT-2 inhibitors 與其它降血糖藥物，顯示 SGLT-2 inhibitors 可以顯著減少心血管事件，包括整體死亡率、心臟衰竭住院和動脈粥樣硬化等。從 CVD-REAL 到 CVD-REAL 2 的結果顯示 SGLT-2 inhibitors 對於心血管的益處可以運用在廣泛的不同種族身上。最近瑞典的研究 [250]，比較兩種新的口服降血糖藥物：SGLT-2 inhibitor 或 DPP-4 inhibitor 與胰島素，顯示該兩種口服降血糖藥相對於胰島素可以降低整體死亡率、心血管疾病及低血糖風險分別為 44%、15% 及 74%，就個別的口服降血糖藥與胰島素比較，SGLT-2 inhibitor Dapagliflozin 可以降低整體死亡率與心血管疾病分別為 56% 與 49%，但 DPP-4 inhibitor 只降低整體死亡率 41%，並沒有降低心血管疾病。似乎 SGLT-2 inhibitor 在心血管疾病的保護方面略勝 DPP-4 inhibitor 一籌，不過 SGLT-2 inhibitor 是在 2013 年才開始上市，有關其對心血管疾病影響之相關臨床研究仍是有限。另外 2017 年發表的大型前瞻性研究 CANVAS (Canagliflozin Cardiovascular Assessment Study)，針對同時有第二型糖尿病和高風險心血管疾病的患者，Canagliflozin 相對於安慰劑可以降低整體死亡率、心肌梗塞及心臟衰竭住院風險分別為 13%、11% 及 33%，而有過去有截肢或

周邊血管疾病的患者，則增加 1.97 倍截肢的風險 [251]。目前正在進行中的大型前瞻性研究包括 DECLARE (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; NCT01730534) 及 VERTIS (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease; NCT01986881) 等，如果其對於心血管事件風險的結論與 CVD-REAL、EMPA-REG OUTCOME 及 CANVAS 一致性的話，也許 SGLT-2 inhibitors 在治療第二型糖尿病的臨床策略上，尤其有心血管病史的患者會有不同的考量。

結論

儘管醫療照護日新月異，心血管疾病仍然是第二型糖尿病的第一死因 [252]，主要是肇因於患者長期血糖控制不佳及合併症所致。除了生活飲食型態的調整之外，利用各種降血糖藥物，來達到理想的血糖控制以避免後續大小血管併發症的產生是目前臨床醫師治療糖尿病患者首要目標。此外在選擇降血糖藥物治療的同時，除了應個別化考量血糖控制及避免因發生低血糖而增加心血管事件風險之外，也應該思考其是否有增加心血管疾病的風險 (表一)。傳統的口服降血糖藥物包括雙胍類有大量的實證醫學佐證可降低心血管疾病發生率。磺醯尿素類可能增加心血管疾病風險，需要更多針對心血管安全性的研究來探討，而美格替耐類對整體心血管安全因缺乏大型長期臨床試驗證實，目前尚無定論。甲型葡萄糖酶抑制劑對於心血管疾病的風險評估目前仍缺乏較大規模前瞻性的研究，故其對心血管事件之預後尚無一致性的結論。TZD 在心血管疾病的角色最受爭議，其中 Rosiglitazone 在上市後因有研究發現有伴隨增加心血管疾病的風險，因而在許多國家被禁用，但從近期許多相關研究及次級分析指出 Rosiglitazone 並沒有顯著增加心血管疾病的發生率，儘管如此，由於整體分析目前仍缺乏一致性的結論，仍需後續更多的臨床研究才能有較明確的答案。至於另一個目前仍在使用中的 TZD 藥物 Pioglitazone，雖然多數臨床研究認為整體上其對心血管疾病是有所助益的，但對於患有後期心臟衰竭病史的患者而言，Pioglitazone 的使用需更加謹慎以免加重心臟衰竭住院的風險。關於目前市面上使用已有 10 年左右時間的 DPP-4 抑制劑，雖然近期的 SAVOR TIMI 53、EXAMINE 和 TECOS 等大型的前瞻性臨床研究指出均能夠改善心血管疾病的發生率，但是從 SAVOR TIMI 53 及 EXAMINE 試驗的次級分析顯示 DPP-4 抑制劑對於有潛在心臟衰竭的患者應謹慎使用，以避免增加心臟衰竭住院的發生率。而近期大型的 GLP-1 RAs 臨床研究雖然顯示能夠減少心血管疾病的發生率，但是相關大型前瞻性臨床研究數量仍稍顯不足，目前臨床證據稍嫌薄弱，需更長期追蹤研究來佐證。至於新藥 SGLT-2 抑制劑由於上市時間不長，雖然近來有些大型研究顯示 SGLT-2 抑制劑也有改善心血管疾病的發生率，甚至其改善效果有明顯優於 DPP-4 抑制劑，但是其仍有許多的大型前瞻性臨床試驗目前仍處於研究階段，所以有關 SGLT-2 抑制劑對心血管疾病是否有所助益，可能須看未來幾年的研究而定了。

表一：降血糖藥物之心血管效應

藥物	體重	低血糖	心臟血管	心臟衰竭	整體心血管安全
雙胍類 (Metformin)	減少或中立	無	可能有心臟保護作用 (減少心肌梗塞面積、冠狀動脈硬化保護作用、減少發炎反應和氧化壓力、避免血管纖維和重塑化)	可能減少心臟衰竭風險	對心血管安全整體是有好處
磺醯尿素類 (Sulfonylurea)	增加	是	低血糖造成缺血性心血管疾病 可能抑制心肌缺血前制約效應保護作用造成心肌細胞傷害增加 增加心血管疾病風險	可能增加心臟衰竭風險	可能增加心血管疾病風險，需要更多針對心血管安全性的研究來探討
美格替耐類 (Meglitinide)	增加	是	低血糖造成缺血性心血管疾病較少有因抑制心肌缺血前制約效應保護作用造成心肌細胞傷害增加	目前尚無定論，缺乏大型長期臨床試驗證實	目前尚無定論，缺乏大型長期臨床試驗證實
噻唑烷二酮類衍生物 (Thiazolidinedione)	增加 (水份滯留、體脂肪重分佈)	無	水份滯留增加心臟衰竭風險 Pioglitazone 有減少發炎指數、改善心血管風險因子和改善冠狀動脈粥樣硬化程度 Rosiglitazone 可能有增加心肌梗塞風險	可能增加心臟衰竭風險	Pioglitazone 對心血管安全整體是有好處，不過在有心臟疾病的患者要特別留意，尤其是有心臟衰竭的病史 Rosiglitazone 有增加心血管疾病風險
甲型醣苷酶抑制劑 (α-glucosidase inhibitors)	中立	無	可能有心血管疾病護 (降低三酸甘油脂、減少血漿 PAI-1 和纖維蛋白原、減少餐後凝血因子活化和改善高血壓) 對於心血管疾病風險之次級預防可能沒有幫助	缺乏大型長期臨床試驗證實	目前尚無定論，缺乏大型長期臨床試驗證實
雙肽基肽酶 -4 抑制劑 (Dipeptidyl peptidase 4 Inhibitors)	中立	無	可能有心血管保護 (改善動脈硬化、血壓、血脂、發炎係數和頸動脈內膜中層厚度) 可能有利於血管生成或新生血管	可能增加心臟衰竭風險	沒有增加心血管疾病風險，目前仍有大型臨床試驗正在進中
類升糖素肽 -1 受體促效劑 (Glucagon-like peptide-1 receptor agonist)	減少	無	可能有心血管保護 (減重、降壓、改善血脂異常、降低 PAI-1、BNP 和 hs-CRP、內臟及皮下脂肪組織和餐後載脂蛋白 B-48 及 CIII) 可能有改善 LVEF 功能	目前尚無定論 (有些研究認為有減少心臟衰竭住院風險 (如 ELIXA 和 LEADER)，有些研究認為有增加心臟衰竭住院風險 (如 SUSTAIN-6 和 FIGHT))	可能對心血管安全整體是有好處，目前仍有大型臨床試驗正在進中
第二型鈉 - 葡萄糖轉運蛋白抑制劑 (Sodium-glucose co-transporter-2 Inhibitors)	減少	無	可能有心血管保護 (減少體脂肪、減重、降壓、降尿酸和降胰島素阻抗)	可能減少心臟衰竭風險	可能對心血管安全整體是有好處，目前仍有大型臨床試驗正在進中

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Non-insulin Anti-diabetic Drugs and Cardiovascular Safety

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In this review, we examine the effect of oral (metformin, sulfonylureas, meglitinides, a-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and sodium-glucose co-transporter-2 inhibitors) and injectable (glucagon-like peptide-1 receptor agonists) glucose-lowering drugs on long-term studies of cardiovascular (CV) safety. Available evidence indicates that metformin does not exert adverse effects on cardiovascular disease (CVD) in patients with type 2 diabetes mellitus (T2DM); because it improves some cardiovascular risk factors (CVRFs), metformin may reduce CVD morbidity and mortality. It remains unclear at the present time whether or not sulfonylureas are associated with an increased CVD risk. Many studies, mostly retrospective analyses of large databases but some prospective, have demonstrated an increased CVD risk in T2DM patients treated with sulfonylureas. However, UKPDS (United Kingdom Prospective Diabetes Study), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and ACCORD (Action to Control Cardiovascular Risk in Diabetes) trials failed to demonstrate an increase in either CVD mortality or morbidity in sulfonylurea-treated T2DM patients. Recent meta-analyses also have generated conflicting results with some purporting to show an increase in cardiovascular mortality, while another concluded that there was no increase in CV disease. The ongoing CAROLINA (Cardiovascular Outcome Trial of Linagliptin Versus Glimepiride in Type 2 Diabetes) trial, might help to clarify and define the CV safety of these drugs. Meglitinides has no any effect on classic CVRFs, although a decrease in Lipoprotein(a) has been reported with repaglinide. Monotherapy with repaglinide in T2DM patients with and without previous myocardial infarction, seems to be associated without increased major cardiovascular events, cardiovascular mortality and all-cause mortality compared with metformin. Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular cause. Pioglitazone exerts beneficial effects on a number of CVRFs and may slow the progression of atherogenesis and reduces CV events. In IRIS (the Insulin Resistance Intervention after Stoke) trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or transient ischemic attack,

pioglitazone was associated with a lower risk of stroke or myocardial infarction. The release of ACE (the Acarbose Cardiovascular Evaluation) trial showed that acarbose did not reduce the risk of major adverse cardiovascular events. Subsequent CV outcome trials with DPP-4 inhibitors (saxagliptin, alogliptin, and sitagliptin) showed noninferiority but failed to demonstrate any superiority in patients with T2DM and high CV risk. An unexpected higher risk of hospitalization for heart failure (HF) was reported with saxagliptin. Among glucagon-like peptide-1 receptor agonists (GLP-1 RA), Lixisenatide, did not show CV benefits in patients with T2DM and acute coronary syndrome. Extended-release exenatide was also not significantly better for CV outcomes. By contrast, long-acting GLP-1 RA (liraglutide) and longer-acting GLP-1 RA (semaglutide), both decreased the incidence of major adverse CV events and mortality. 2 Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors empagliflozin and canagliflozin showed a significant reduction in triple major cardiovascular events, all-cause mortality and hospitalization for HF (and also CV mortality for empagliflozin). In CVD-REAL study (Comparative Effectives of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransport-2 Inhibitors), SGLT-2 inhibitors were associated with a lower risk of hospitalization for HF and all-cause mortality. A further sub-analysis of CVD-REAL showed that SGLT-2 inhibitors were associated with a modestly lower risk of myocardial infarction and stoke. Confirmatory findings were reported in another similar study performed in other countries (CVD-REAL 2). In conclusion, treatment of T2DM is an individualized and complex challenge in which targeting cardiovascular risk factors is an important component in the decision making. (J Intern Med Taiwan 2019; 30: 107-131)