doi:10.1093/eurheartj/ehab177

Where diabetes care meets cardiovascular research: our cardiovascular perspective at a Centre devoted to diabetes research and care

Gian Paolo Fadini [1,2]*, Saula Vigili de Kreutzenberg[1], and Angelo Avogaro[1]

Department of Medicine, Section of Metabolic Disease, University Hospital of Padova, Via Giustiniani 2, Padua 35128, Italy; and Veneto Institute of Molecular Medicine, Laboratory of Experimental Diabetology, Padua 35128, Italy

Cardiovascular disease at the fore of a diabetologist's point of view

Professionals who are involved in diabetes research and care will sooner or later encounter cardiologists and cardiovascular scientists. No matter if you treat type 1 or type 2 diabetes, whether your main area of research is retinopathy, nephropathy, neuropathy, or foot disease, patients' heart problems will inevitably come into your horizon.

Despite the better glycaemic control with newer drugs, continuous glucose monitoring devices, and insulin delivery systems, diabetes remains a major risk factor for coronary artery disease and heart failure. Prevention and treatment of cardiovascular disease in people with diabetes is top one priority of diabetes care and a major focus of diabetes research. On the other side, the growing complexity of diabetes pharmacotherapy can confuse a cardiologist's perspective, especially considering how many new drugs provided with cardioprotective effects have been approved in the last few years. Those working side-by-side with diabetologists will manage to get the best cardiovascular protection from diabetes medications.

The Padua's model

At the University Hospital of Padua (North–East Italy), we have a long-standing tradition of 'cardio-diabetology' with prominent ramifications in research and clinical care. Founders of the Padua metabolic school were the first to describe the metabolic syndrome in 1967. Since then, the intertwined relations between insulin resistance, vascular function, and cardiovascular disease became a core area of investigation in our Centre as in the rest of the world.

In the last 20 years, the research team based in Padua contributed to a new understanding of vascular diabetic complications based on the exhaustion of regenerative cells from the haematopoietic system. Nourished by the close physical connections between the diabetes outpatient clinic, the Hospital inpatient ward, and the Laboratory of Experimental Diabetology (*Figure 1*), the Centre has always pursued a strong contamination between routine clinical care and translational research. Over these years, we ping-ponged between pathophysiology, treatment, and epidemiology, trying to fill the many knowledge gaps that still prevent us from effectively tackling cardiovascular disease in diabetes.

How diabetes specialists can contribute to knowledge in the cardiovascular field

Research conducted by the wide diabetology community has always fuelled great developments in the cardiovascular research field.

In the 2000s, building on seminal works by Takayuki Asahara from Tokyo and Stefanie Dimmeler from Frankfurt, we pioneered the study of endothelial progenitor cells in diabetes. This was a brand-new research avenue driving an extraordinary change in the way we think about vascular disease, bringing failure of endogenous reparative process on the foreground.[1] While the great expectations on progenitor cell-based regenerative therapies remained mostly unmet, we have learnt a lot on how the haematopoietic, metabolic, and cardiovascular systems interact. Shortage of haematopoietic stem/progenitor cells in the blood has primed us to look at the bone marrow as a central housekeeper of the body's self-repair capacity. We linked the impaired traffic of stem cells to myelopoiesis induced by gluco- and lipotoxicity. Such anti-regenerative milieu propagates to the vessel wall, explaining why patients with low levels of blood stem cells have an exaggerated risk of cardiovascular events.[2] These achievements could not be possible without the close connections between clinical care and preclinical research we have set up in Padua.

The obvious next step was understanding therapeutic implications. In spite of having shown that dipeptidyl peptidase-4, a class of oral diabetes medications, rescued stem/progenitor cell defects,[3] we could not ignore such drugs were not providing diabetic patients with the expected cardiovascular benefits. While some exciting results on stem cell traffic were being obtained with pioglitazone,[4] game-changing data on sodium-glucose cotransporter-2 inhibitors (SGLT2i) almost wiped away competitor therapies. Early evidence of cardiorenal benefits from SGLT2i seemed too good to be true, but an unprecedented amount of consistent data now makes SGLT2i a most-wanted drug class by cardiologists. Besides digging into their complex and multifaceted mechanism of action, we turned to pharmacoepidemiology, by building region-wide and nation-wide cohorts.[5] Mining such big data, we confirmed in routine clinical practice several key effects shown by SGLT2i in trials. Even more importantly, we explored what trials did not: treating diabetes with SGLT2i resulted in better cardiovascular outcomes than treating with glucagon like peptide-1 (GLP-1) receptor

*Prof. Gian Paolo Fadini, MD PhD, University Hospital of Padua, Department of Medicine, Via Giustiniani 2, 35128 Padova, Italy. Tel: +39 049 8214318, Fax: +39 049 8212184, Email: gianpaolo.fadini@unipd.it

agonists,[6] the top-tier competitors. Still, GLP-1 receptor agonists provide a consistent protection against stroke, where SGLT2i are, at best, neutral. Where and when to choose one over the other of these two treatments is still a matter of debate and is certainly an area where the diabetologist–cardiologist link can make the difference (*Figure 2*).[7]

Yet, the enthusiasm on SGLT2i comes at the expense of some downside cardiologists need to be aware of, before getting their hands on. By inducing glycosuria, SGLT2i favours genitourinary tract symptoms sometimes leading to discontinuation and rarely progressing to life-threatening infections. Other rare but serious adverse events can occur during therapy with SGLT2i, which we have explored in pharmacovigilance databases.[8] Like for statins in the past decades, cardiologists and diabetologists will need to work together to get the most out of SGLT2i, while protecting patients' safety.

Figure 1 Clone connections between diabetes clinics and research centres at the Padua University Hospital area. The map shows close physical connections of diabetes inpatient (red) and outpatient (blue) clinics with the laboratory of experimental diabetology, hosted at the Venetian Institute of Molecular Medicine (www.vimm.com).

All in all, addressing cardiovascular prevention at the diabetes clinic can be challenging. Italy has a unique organization of diabetes care, which is provided through hundreds of specialized outpatient clinics spread all over the country. There, diabetes specialists struggle while managing glycaemic control, education, foot care, but have a limited armamentarium against retinopathy and neuropathy. These microangiopathies remain unmet needs and their presence is strongly correlated with cardiovascular morbidity. In this complex scenario, though, proper cardiovascular risk assessment may be overlooked. Clinical audits with observational data can highlight models of care that are effective in improving cardiovascular outcomes. Whether taking older or newer drugs, patients receiving high-quality and comprehensive care at a diabetes centre, including a complete cardiovascular workup, experienced better outcomes than those following a fragmented model of care, where they wander among unlinked specialists.[9]

A vision for the future

Diabetes care and research have so many connections with cardiology that new professional figures may be needed to fully unlock the potentials of such interaction. Knowledge in multiple medical and biological areas can foster transformative research, as we have witnessed when cardiologists and diabetologists came close to haematologists to address the mystery of endothelial progenitor cells. The advent of SGLT2i and GLP-1 receptor agonists, along with their undisputed cardiovascular benefits, is another striking example of how much the diabetology and cardiology communities can learn from each other.

We envisage that big medical Universities and teaching hospitals promote tracks for 'cardio-diabetologists' and 'metabolic cardiologists'. The combined MD–PhD course of study, now available in many countries,[10] would be ideal for candidates wishing such accomplishment as physician–scientists. Chairs in this discipline will fertilize the environment for nourishing students and boosting this research area to a new level.

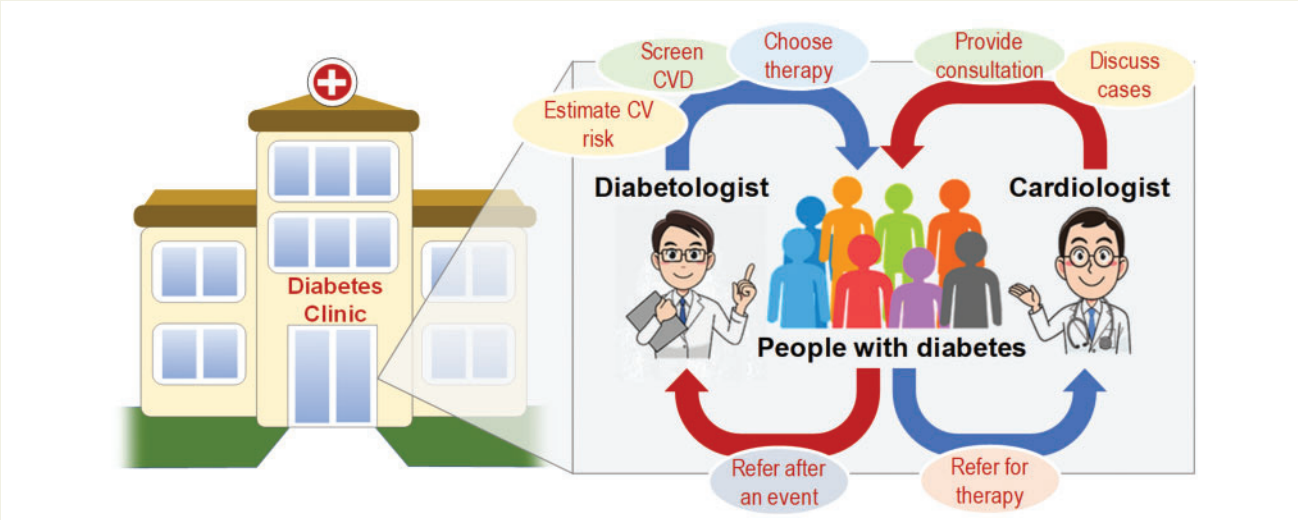

Figure 2 Close collaborations between diabetologists and cardiologists at the diabetes clinic. CV, cardiovascular; CVD, cardiovascular disease.

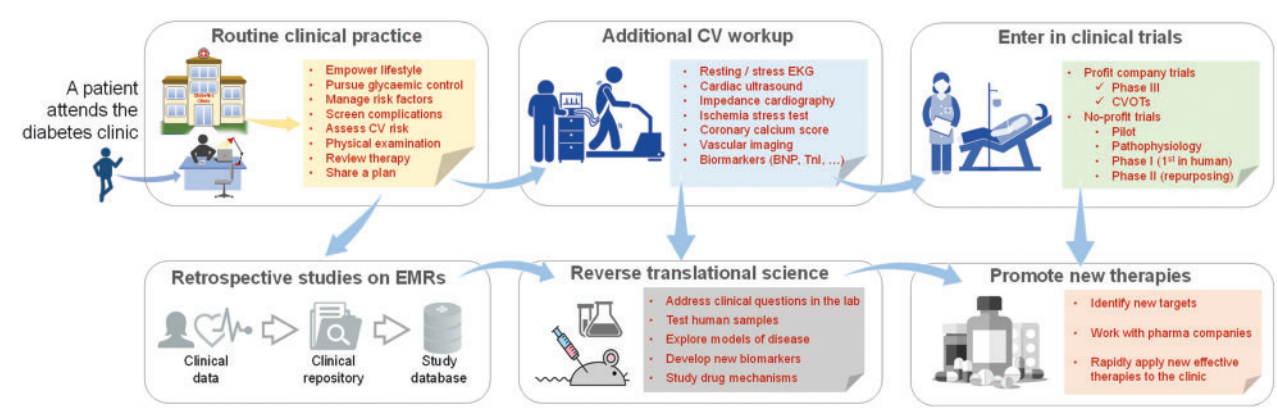

Figure 3 Model of research and care at top-level cardio-diabetology centres. BNP, B-type natriuretic peptide; CV, cardiovascular; CVOT, cardiovascular outcome trial; EKG, electrocardiogram; EMR, electronic medical records; TnI, troponin I.

In parallel, we believe it is essential to deliver the highest quality of specialized care to people with diabetes at the very same place where front-line clinical-translational research in the cardiovascular and diabetes field is pursued (*Figure 3*). Men and women with diabetes will most likely appreciate attending outpatient clinics where cardiovascular prevention receives the same attention as glycaemic control does, the continuum of micro- and macro-angiopathy is well recognized, innovation is promoted in diagnosis and care, with fast uptake of new effective pharmacotherapies. Patients would be offered participation in profit and no-profit clinical trials, including pathophysiological studies, phase I and first-in-human trials with incoming products of research. Physician–scientists would oversee patients' care and the inexhaustible amount of data generated from routine practice would fuel registries and observational cohort studies to complement data from trials and inform pre-clinical research. A reverse translational science approach should be the driver of such environment, putting patients at the centre of research and care.

There might be places in the world where cardio-diabetology centres already exist. They should be built wherever the need to counter cardiovascular disease in diabetes is recognized as a priority, most likely in all industrialized countries.

Conflict of interest: G.P.F. received grants, honoraria, or lecture fees from Abbott, Astrazeneca, Boehringer, Lilly, Novo Nordisk, and Sanofi. S.V.d.K. declares no conflict of interest. A.A. received research grants, lecture, or advisory board fees from Merck Sharp & Dome, AstraZeneca, Novartis, Boehringer-Ingelheim, Sanofi, Mediolanum, Janssen, Novo Nordisk, Lilly, Servier, and Takeda.

References

1. Avogaro A, Albiero M, Menegazzo L, de Kreutzenberg S, Fadini GP. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. *Diabetes Care* 2011;**34**(Suppl 2):S285–S290.
2. Fadini GP, Mehta A, Dhindsa DS, Bonora BM, Sreejit G, Nagareddy P, Quyyumi AA. Circulating stem cells and cardiovascular outcomes: from basic science to the clinic. *Eur Heart J* 2020;**41**:4271–4282.
3. Fadini GP, Boscaro E, Albiero M, Menegazzo L, Frison V, de Kreutzenberg S, Agostini C, Tiengo A, Avogaro A. The oral dipeptidyl peptidase-4 inhibitor sitagliptin increases circulating endothelial progenitor cells in patients with type 2 diabetes: possible role of stromal-derived factor-1alpha. *Diabetes Care* 2010;**33**:1607–1609.
4. Tedesco S, Ciciliot S, Menegazzo L, D'Anna M, Scattolini V, Cappellari R, Cignarella A, Avogaro A, Albiero M, Fadini GP. Pharmacologic PPAR-gamma activation reprograms bone marrow macrophages and partially rescues HSPC mobilization in human and murine diabetes. *Diabetes* 2020;**69**:1562–1572.
5. Fadini GP, Avogaro A, Degli Esposti L, Russo P, Saragoni S, Buda S, Rosano G, Pecorelli S, Pani L, OsMed Health-DB Network. Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database. *Eur Heart J* 2015;**36**:2454–2462.
6. Longato E, Di CB, Sparacino G, Gubian L, Avogaro A, Fadini GP. Cardiovascular outcomes of type 2 diabetic patients treated with sglt-2 inhibitors versus GLP-1 receptor agonists in real-life. *BMJ Open Diabetes Res Care* 2020;**8**:e001451.
7. Bailey CJ. Choosing GLP-1 receptor agonists or SGLT-2 inhibitors by cardiorenal risk. *Lancet Diabetes Endocrinol* 2020;**8**:97–99.
8. Fadini GP, Avogaro A. SGLT2 inhibitors and amputations in the US FDA adverse event reporting system. *Lancet Diabetes Endocrinol* 2017;**5**:680–681.
9. Morieri ML, Longato E, Mazzucato M, Di Camillo B, Cocchiglia A, Gubian L, Sparacino G, Avogaro A, Fadini GP, Vigili de Kreutzenberg S. Improved long-term cardiovascular outcomes after intensive versus standard screening of diabetic complications: an observational study. *Cardiovasc Diabetol* 2019;**18**:117.
10. The M.D.-Ph.D. Track: the triathlon of medical research training. *Science magazine blog.* 2010. https://blogs.sciencemag.org/sciencecareers/2010/07/the-mdphd-track.html (March 2021).