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REVIEW

Everolimus in kidney transplant recipients at high cardiovascular risk: a narrative review

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Abstract

Kidney transplant recipients (KTRs) are at increased risk of cardiovascular (CV) morbidity and mortality, and side effects induced by immunosuppressive therapy may be a major contributor to this risk, together with traditional CV risk factors. Many strategies have been considered in order to reduce CV risk in KTRs, such as steroid and/or calcineurin inhibitor (CNI) minimization, but current data are inconclusive. The introduction of mammalian target of rapamycin (mTOR) inhibitors, the cornerstone of CNI minimization, in the immunosuppressive protocol may reduce both the incidence and severity of CNI-associated side effects; however, whether this strategy has an impact on CV risk after kidney transplantation needs to be evaluated. To this end, a panel of Italian experts in the field of transplantation was convened in a series of meetings to assess the current literature on the potential of the mTOR inhibitor everolimus as a cardioprotective agent. This narrative review summarizes the panel's round-table discussions and provides recommendations for CV risk management in KTRs.

Keywords Kidney transplant recipients · Cardiovascular risk · mTOR inhibitors · Calcineurin inhibitors · Everolimus

Introduction

Cardiovascular disease remains the major cause of mortality among kidney transplant recipients (KTRs) who have a functioning graft [1], with an estimated risk of cardiovascular (CV) events about 50-fold that of the general population [2].

Both pre- and post-transplant factors may be involved in this increased CV risk [3].

Although, globally, accurate CV status assessment is performed in all patients before considering them eligible for a kidney transplant program [3], current available guidelines on CV risk after grafting only suggest managing CV disease at least as intensively in KTRs as in the general population [4].

An important issue in CV risk after kidney transplantation is the role of immunosuppressive therapy, which can adversely affect kidney function and give rise to important side effects such as dyslipidemia, hypertension, and post-transplant diabetes mellitus. These are all well-known factors involved in the pathogenesis of CV disease and could account for the unfavorable CV scenario observed after kidney transplantation [5, 6].

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Many strategies have been considered in order to reduce CV risk in KTRs, such as steroid and/or calcineurin inhibitor (CNI) minimization, but current data are inconclusive [7].

The cornerstone of CNI minimization is the introduction of mammalian target of rapamycin (mTOR) inhibitors in the immunosuppressive protocol. However, whether this strategy has an impact on CV risk after kidney transplantation needs to be evaluated.

Moreover, in order to prevent the risk of acute rejection as a possible effect of CNI minimization, introduction of mTOR inhibitors in immunosuppressive protocols is often associated with prolonged steroid therapy maintenance.

Several studies have shown that long-term steroid therapy is associated with increased risk of new-onset diabetes after transplantation (NODAT), hypertension and dyslipidemia [5, 8], all well-known cardiovascular risk factors. It is therefore conceivable that prolonged therapy with steroids in the case of CNI minimization and the adoption of an mTOR inhibitor such as everolimus (EVR) may, at least in part, counterbalance the potential cardioprotective effect of EVR in KTRs.

However, although little information is provided on the effects of mTOR inhibitor-based immunosuppressive therapy combined with steroid withdrawal, evidence exists showing the adoption of this therapeutic strategy could be associated with an increased rate of acute rejection [9, 10].

The Italian ENTROPIA Project was launched with the aim of focusing on the potential of everolimus as a cardioprotective agent for CV risk management in KTRs. The project consisted of a series of round-table discussions of current evidence on the topic, among a panel of Italian experts in the field of transplantation, and a final meeting where results emerging from the discussions were collected and then summarized. The search for relevant original articles for the review was carried out by accessing the PubMed database in May 2018 using different combinations of pertinent keywords. Papers were considered for discussion according to their topic relevance, as judged by the members of the expert panel.

Cardiovascular risk factors in kidney transplantation

Renal function

Impaired renal function can increase CV risk in KTRs [11–15]. A recent post hoc analysis of the Folic Acid for Vascular Outcome Reduction In Transplantation (FAVORIT) trial showed an association between lower estimated glomerular filtration rate (eGFR; less than 45 ml/min/1.73 m^2) and CV adverse events [16]; decreased renal function was associated with increased risk of cardiac death in a post hoc analysis of the Assessment of LEscol in Renal Transplantation (ALERT) trial [17]. These findings are further supported by the Patient Outcomes in Renal Transplantation (PORT) study, which showed a correlation between lower eGFR and increased coronary heart disease in KTRs [18]. CNI therapy is closely associated with worsening of renal function. Chronic CNI nephrotoxicity, which is largely non-specific in appearance, with often coexisting interstitial fibrosis, intimal hyalinosis and glomerulosclerosis [19], progresses over time [20]. Although a recent study showed a less nephrotoxic effect with tacrolimus compared with cyclosporine in KTRs [21], both CNIs appeared to have similar toxicity profiles in terms of progressive eGFR reduction [22].

Diabetes mellitus after transplantation

NODAT is a frequent complication in the KTR population, affecting up to 42% of KTRs within the first 3 years after transplantation, as reported by the US Renal Data System Annual Data Report [1], and is associated with increased CV risk. A direct association was, in fact, shown between increased fasting glucose levels and CV events, regardless of the presence of other CV risk factors [23], and CV death [24], whereas NODAT was shown to be associated with greater risk of posttransplant myocardial infarction in a large cohort including more than 35,000 patients [25]. Furthermore, an association between post-transplant diabetes and death with graft function was also reported, surprisingly showing diabetes had a greater impact on patient survival than acute rejection within the first year [26]. Steroid therapy is a major risk factor for NODAT, as clearly shown by a lower post-transplant diabetes incidence in KTRs treated with steroid-sparing or avoidance strategies [27]. Furthermore, NODAT occurred more frequently in tacrolimus (TAC)- than in cyclosporine A (CsA)-treated patients [22, 28, 29], especially in the first post-transplant year [30].

Dyslipidemia

Alongside concurrent medications and pre-existing risk factors, immunosuppressive therapy plays a major role in the dyslipidemia of KTRs, even though tacrolimus therapy appears to be associated with a lower prevalence of lipid profile alterations [31–33]. Cyclosporine influences lipid metabolism in a dose-dependent manner; it alters bile-acid metabolism limiting the clearance of cholesterol, reduces hepatic lipase and lipoprotein lipase activity, downregulates expression of low-density lipoprotein (LDL) receptors, and increases LDL oxidation. All these actions contribute to the increase in total cholesterol, very low-density lipoprotein (VLDL) cholesterol, LDL cholesterol, and triglyceride levels, and to the decrease in high-density lipoprotein (HDL) cholesterol levels [5, 34].

The ALERT study, which evaluated the impact of fluvastatin on CV outcome in KTRs, showed a reduction in major adverse cardiac event occurrence, which emerged in the extended follow-up of the study [35]. Interestingly, in the ALERT cohort, total cholesterol level was an independent predictor of the risk of myocardial infarction and both cardiac and non-cardiac death; further, fluvastatin therapy was effective also in patients at low CV risk, and early initiation of statin therapy was associated with better CV outcomes [17, 36].

Hypertension

Hypertension, either systolic or diastolic, was an independent predictor of graft failure, according to results from the Collaborative Transplant Study [37]. This finding is quite compelling, as hypertension is highly prevalent among KTRs, with more than 50% of transplant recipients administered at least two antihypertensive medications 1 year after grafting [38]. Moreover, any 10 mmHg increase in systolic blood pressure was associated with a 12–18% increase in the risk of graft failure, and all-cause mortality. The tight association of increased systolic blood pressure with CV death was particularly seen in KTRs younger than 50 years, in whom a beneficial effect of lowering blood pressure was, indeed, shown on graft and patient survival outcomes [39].

Cardioprotective potential of mTOR inhibitors

Although both in vitro and animal studies showed a substantial advantage of everolimus relative to sirolimus with regards to inhibitory effects on mTOR pathways, anti-inflammatory properties, and endothelial and smooth cell function, it is unclear how these preclinical findings can be translated into the clinical setting as directly comparative clinical studies are lacking [40].

Everolimus may exert cardioprotection both indirectly and directly: indirectly, by allowing minimization of CNI exposure to reduce the detrimental effect of either TAC or CsA on renal function and by avoiding or at least lessening the incidence of well-known CV risk factors related to CNI therapy; and directly, by improving vascular function and regressing left ventricular hypertrophy.

All these potential benefits must, of course, be balanced by the increased risk of acute rejection and of mTOR inhibitor-related side effects, which, in turn, could affect the CV prognosis of KTRs (Fig. 1).

Renal graft function

Four strategies have been tested in clinical practice in kidney transplantation to offset CNI-induced nephrotoxicity leading to GFR reduction: CNI avoidance, CNI withdrawal, full conversion to another class of immunosuppressants, and CNI minimization [41]. The cornerstone of these strategies is the introduction of mTOR inhibitors to the immunosuppressive protocol. Among these strategies, CNI avoidance was mainly tested in protocols adopting sirolimus.

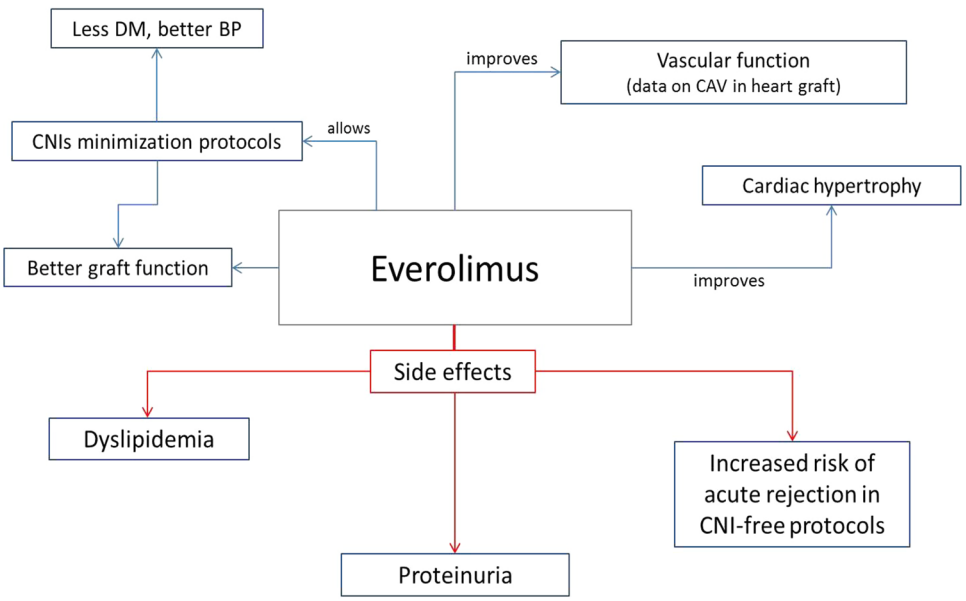

Fig. 1 The potential association of everolimus with cardiovascular risk factors. BP: blood pressure; CAV: cardiac allograft vasculopathy; CNIs: calcineurin inhibitors; DM: diabetes mellitus

In patients randomized to receive sirolimus in the Rapamune Maintenance Regimen Study, eGFR was significantly better than in those allocated to standard CNI therapy [42].

More recently, by contrast, sirolimus was associated with lower graft survival and higher adverse event rates in the ELITE-Symphony Trial [43], and with no positive effect on graft function in the ORION study [44], thus raising concerns over the safety of such a CNI-free regimen. In fact, a large randomized trial including 475 patients was prematurely interrupted due to the high incidence of acute rejection and lower survival rates registered at an interim analysis [45].

Everolimus has been evaluated in numerous CNI-sparing strategies, with heterogenous outcomes (Table 1). In the HERAKLES study, a large randomized controlled study, the CNI-free arm was characterized by eGFR improvement, which was confirmed in the more prolonged follow-up study [46, 47], but this finding was not confirmed when renal outcome was adjudicated as a composite of biopsy-proven acute rejection (BPAR), graft loss and death in the SOCRATES study [9]. Better GFR was shown in the everolimus arm of the ZEUS study, with no significant difference in BPAR incidence after 5 years of follow-up [48]. In the CENTRAL study [49] significant difference in renal outcome was observed in everolimus-treated KTRs compared with those on standard CNI treatment. Moreover, in the ASCERTAIN trial, an improved eGFR was shown in patients with a creatinine clearance of more than 50 ml/min after CNI discontinuation 6 months post-transplantation [50]. More recently, the ELEVATE trial failed to demonstrate a renoprotective effect with use of an mTOR inhibitor, even raising caution because of an

Table 1 Renal graft function in comparative studies evaluating everolimus

Author, year (study name)	Study design	Study period/ EVR initiation	EGFR difference between groups
Budde 2017 (HERAKLES) [46]	STD-CNI + MPA: 165 pts EVR + MPA: 171 pts reduced CNI + EVR: 161 pts	1y/3 m	Better in EVR + MPA than in STD-CNI and reduced CNI; similar in reduced CNI and STD-CNI
Sommerer 2018 (HERAKLES) [47]	4-year extension study of HERAKLES: 417 pts	5y/3m	Better in EVR + MPA than in STD-CNI and reduced CNI; similar in reduced CNI and STD-CNI
Budde 2015 (ZEUS) [48]	EVR + MPA: 123 pts CNI + MPA: 109 pts	5y/4.5 m	Better in EVR + MPA
Chadban 2014 (SOCRATES) [9]	EVR + CNI-withdrawal: 49 pts EVR + CNI + S-withdrawal: 30 pts CNI + MPA + S: 47 pts	1y/2w	Not significantly different; EVR + CNI + S-Withdrawal arm halted
Mjornstedt 2015 (CENTRAL) [49]	CNI + MPA : 100 pts EVR + MPA: 102 pts	3y/7w	Better in EVR, lower in CNI
Holdaas 2011 (ASCERTAIN) [50]	EVR + CNI withdrawal: 127 pts EVR + reduced CNI: 144 pts Control: 123 pts	2y/post 6 m	NS (when CrCl > 50 mL/min greater increase in CNI withdrawal arm)
De Fijter 2017 (ELEVATE) [51]	EVR: 359 pts CNI: 356 pts	2y/10–14 w	Not significantly different
Tedesco Silva 2010 [52]	EVR (TL 3-8 ng/ml) + reduced CNI : 277 pts EVR (TL 6-12 ng/ml) + reduced CNI: 279 pts STD-CNI + MPA: 277 pts	2y/de novo	Not significantly different
Langer 2012 (ASSET) [53]	EVR + TAC TL 1.5–3 ng/ml: 107 pts EVR + TAC TL 4–7 ng/ml: 117 pts	1y/de novo	NS (probably due to overlapping of achieved tacrolimus exposure levels)
Salvadori 2009 [54]	STD-EVR + low-exposure CNI: 143 pts Higher-EVR exposure + very low-exposure CNI: 142 pts	1y/de novo	Not significantly different
Pascual (TRANSFORM) [56]	EVR + reduced CNI: 1022 pts MPA + STD-CNI: 1015 pts	1y/de novo	Not significantly different
Bemelman 2017 (MECANO) [55]	P + CNI: 89 pts P + MPA 39 pts P + EVR 96 pts	2y/6 m	Better in EVR arm (P + MPA arm halted)

CNI: calcineurin inhibitors; CrCl: creatinine clearance; eGFR: estimated glomerular filtration rate; EVR: everolimus; m: months; MPA: mycophenolate; P, prednisolone; pt: patients; S: steroids; STD: standard; TAC: tacrolimus; TL: trough level; w: week; y: year

increased incidence of treated BPAR in patients receiving everolimus [51].

CNI-minimization protocols are the most widely reported strategies: Tedesco Silva and colleagues did not find significant differences in renal function, graft loss and death when comparing mTOR inhibitors and reduced-exposure CNI with standard CNI [52]; similar findings were reported by Langer and colleagues in the ASSET study, although the authors pointed out that results might be influenced by difficulties in maintaining adequate trough levels of TAC in patients on reduced CNI treatment [53]. The EVEREST trial showed no difference in eGFR between everolimus plus low CsA and everolimus plus very low CsA, but an evident advantage in graft survival in patients allocated to receive lower exposure to CNI [54]. Higher 2-year eGFR and decreased evidence of fibrosis and inflammation on biopsy was reported in KTRs administered everolimus compared with those on CsA and those on mycophenolic acid (MPA) in the MECANO trial, with no significant increase in acute rejection rate in patients allocated to the mTOR inhibitor [55].

More recently, the TRANSFORM study, the largest trial ever designed in kidney transplantation, which included 2037 patients randomized to receive standard-exposure CNI treatment plus MPA and steroids, or reduced-exposure CNI treatment and everolimus plus steroids, reported that everolimus was non-inferior to MPA in terms of treated BPAR, graft loss and death, and renal function [56].

Furthermore, as a recent study highlighted, everolimus in association with low-dose CNIs showed good outcomes regarding renal function and safety, and may be selected as a de novo protocol in transplant recipients of kidneys from very old donors [57].

Consistent with a recent review that analyzed immunosuppressive protocols designed to reduce CNI exposure, it appears that minimization regimens including mTOR inhibitors allow better renal outcomes compared with protocols adopting standard-dose CNI regimens; especially if initiated within the first 6 months after transplantation, even though there is increased risk of BPAR [41].

A large meta-analysis including more than 16,000 KTRs confirmed that low-dose CNIs combined with mTOR inhibitors may improve renal function and reduce graft loss, with no difference in both death and acute rejection rate [58].

Last, taken together, these findings highlight the impact on renal graft function of reduced-exposure CNI protocols adopting everolimus. They support the hypothesis of a cardioprotective role of the mTOR inhibitor, given the reportedly better CV outcomes observed in KTRs, with less compromised renal function, that has emerged from large observational studies [16–18].

Vascular damage

Both macro- and micro-vascular damage is highly prevalent and associated with adverse outcome and mortality in patients with renal disease [59, 60]. Morphologic and functional vascular alterations often persist after kidney transplantation, thus affecting both general and CV outcomes [61].

Endothelial cells have a central role in producing regulatory vascular factors: impairment in endothelial function promotes leukocyte adhesion, thrombotic dysfunction, and alters vasomotor tone; it also causes vascular smooth cells to proliferate and migrate to the intima [62, 63]. Whereas CNIs induced endothelial damage [64, 65], everolimus was shown to exert a positive effect on endothelial function in an animal model [65]. Endothelial dysfunction has been recently identified as an early manifestation of atherosclerosis [66], and proper evaluation of endothelial function has been shown to predict CV events, regardless of traditional risk factors [67, 68].

In experimental animal models, mTOR inhibitors have shown a beneficial effect in slowing progression of atherosclerosis; and, inhibition of mTOR complex 1 (mTORC1) improves endothelial function, decreases smooth-cell proliferation, and decreases lipid deposition in atherosclerotic plaque [69]. Administration of everolimus markedly decreases monocyte chemotaxis and subsequent macrophage content in atherosclerotic lesions, key factors in atherosclerosis process initiation and development [70]. Moreover, since matrix metalloproteinases have decreased activity on collagen, mTOR inhibitors may promote plaque stability [71, 72].

Of course, translating evidence derived from experimental models to the clinical setting may be misleading and requires caution. However, cardiac allograft vasculopathy (CAV), which is a peculiar condition affecting heart transplant recipients and characterized by diffuse narrowing of coronary arteries due to initial endothelial injury followed by intimal hyperplasia and proliferation of vascular smooth cells [73], can be considered a reliable clinical model to understand the positive effect of everolimus on endothelial function. Both immunological events that trigger the host immune system and non-immunological factors such as infections, ischemia–reperfusion injury, hyperlipidemia and old donor age appear to promote CAV [74–76]. Many studies have demonstrated that mTOR inhibitors may reduce the incidence and severity of CAV [76, 77]. It is noteworthy that mTOR inhibitors may be helpful in CAV early prevention, since CAV appears to be initially induced by immunomediated injury, eventually leading to endothelial proliferation. No significant results were found regarding late everolimus introduction, thus implying that metabolic risk factors have a major role in

late CAV pathogenesis. Moreover, an early altered lipid profile was not associated with outcome [78]; these findings further support the hypothesis that everolimus may play a protective role in atherosclerosis development, independent of altered lipid metabolism.

A well-established vascular predictor of CV events and mortality in the general population is arterial stiffness [79], which can be evaluated indirectly by means of aortic pulse wave velocity (aPWV) assessment; in fact, aPWV measurement appears to enhance CV risk-prediction accuracy in the general population [80].

Previous studies showed progressive increases in PWV in KTRs on CsA therapy, whereas mTOR inhibitors were associated with no further worsening or even a reduction of this index, suggesting a protective effect of mTOR inhibitors on arterial distensibility [81, 82]. It is conceivable that the decrease in vascular calcification, a main determinant of arterial stiffness [83], associated with rapamycin-induced Klotho upregulation shown in an animal model [84] may also play a role in the clinical setting, even though more-recent evidence emerging from the ELEVATE study has failed to confirm these findings [85].

Hypertension and left ventricular hypertrophy

Although a CNI-withdrawal regimen has been associated with a lower prevalence of hypertension relative to a standard-CNI exposure regimen, only a marginal reduction in blood pressure was reported in studies comparing low-dose with standard-dose CNI. Furthermore, small differences were reported in the blood pressure profiles of patients on mTOR inhibitors with lower exposure to CNIs in comparison with KTRs undergoing standard CNI therapy [58].

The RMR study comparing a sirolimus-based regimen with a standard CNI regimen is the only available study showing significantly lower systolic blood pressure associated with mTOR inhibitor therapy and full CNI withdrawal 3 months after grafting [42]. More recently, the ELEVATE trial, which evaluated blood pressure by means of ambulatory blood pressure monitoring (ABPM), the gold standard for assessing blood pressure profile in renal transplantation [86], showed a decrease in diastolic blood pressure in the everolimus arm after 12 months [85]. This is noteworthy, given that diastolic blood pressure load, as assessed by ABPM, proved to be a significant predictor of both renal and CV outcome in a large cohort of patients with chronic kidney disease [87]. However, no differences were detectable after 24 months in KTRs enrolled into the ELEVATE trial [86], raising concerns over whether mTOR inhibitors could provide additional blood pressure control benefit in KTRs. Notably, what seems to be highlighted by available studies is that a CNI-free regimen may potentiate better control of arterial hypertension in KTRs.

Left ventricular hypertrophy (LVH) is a common complication among KTRs, mainly because it is frequently prevalent in patients with end-stage kidney disease undergoing kidney transplantation. Indeed, the presence or persistence of LVH in the first year post-transplantation was shown to be associated with lower survival [88]. Moreover, it is the strongest predictor of the risk of subsequent congestive heart failure, a CV complication that negatively affects the general outcome of KTRs [88].

Preliminary interventional studies have shown regression of LVH in KTRs converted from a CNI- to an mTOR inhibitor-based immunosuppressive regimen in both cardiac- and kidney-transplanted patients [89, 90].

The rationale for testing mTOR inhibitors in this setting emerged from studies conducted in animal models, where this class of drugs proved to be effective in reducing cardiac hypertrophic response to aortic constriction, and in reversing it in spontaneously hypertensive rats and in mice in which cardiac hypertrophy was induced by surgically induced renal injury [91, 92].

LVH regression was then confirmed in a randomized controlled trial comparing 10 patients with proven LVH who received low-dose CsA and everolimus, and 20 controls receiving standard CsA therapy. After 1 year, a significant decrease in left ventricular mass (LVM) index was detected only in everolimus-treated patients, regardless of blood pressure change, mainly due to a reduction in parietal thickness, thus further highlighting the anti-proliferative effect of mTOR inhibitors in this setting [93]. These findings were confirmed [94], but two larger randomized controlled trials failed to demonstrate a change in LVM in KTRs allocated to everolimus therapy [85, 95]. However, an important limitation must be recognized in both of these trials: baseline LVM was near to normal in enrolled patients, in both treatment and control arms, thus making it quite difficult to appreciate any everolimus-dependent LVM-lowering effect in patients without LVH at the start of observation [96]. This led to the conclusion that a bias in patient selection was the reason for the LVM endpoint finding in these two studies.

Diabetes mellitus

Although mTOR inhibitors can induce diabetes, the relationship of NODAT with mTOR inhibitor therapy remains controversial.

The mechanisms by which mTOR inhibitors may induce glucose metabolism disorder are: the onset of insulin resistance in adipose tissue and skeletal muscle; increased hepatic gluconeogenesis; impaired insulin secretion; and direct action towards pancreatic beta cells through inhibition of mTORC1 and mTORC2. There are discrepancies between

the effect of mTOR inhibitors in vivo and in vitro; it was hypothesized that the correlation between mTORC1 activity and glucose metabolism may follow a U-shaped curve, where a smaller mTORC1 activation and a greater mTORC1 activation have a detrimental effect on metabolic homoeostasis [97]. Interestingly, prolonged treatment with mTOR inhibitors in mice is correlated with a better glucose profile [97].

Sirolimus was shown to be associated with impaired glucose metabolism in a large registry study including more than 20,000 patients [98], whereas a large review showed NODAT occurred in up to 38% of transplant recipients who were administered mTOR inhibitors and low-dose TAC [99]. By contrast, a recent meta-analysis including 2083 patients showed no significant increase in NODAT incidence after conversion to mTOR inhibitor therapy [100], a finding also confirmed in a larger meta-analysis analyzing protocols of CNI withdrawal or tapering in KTRs [58]. Last, no significant difference in NODAT incidence between everolimus and CNIs has been demonstrated in recent trials (Table 2); in fact, a lower prevalence of either impaired fasting glucose or post-transplant diabetes mellitus was reported in patients who were administered mTOR inhibitors compared with those administered CNIs [101].

mTOR inhibitors and adverse effects

Taken together, the above findings indicate the potential for everolimus adoption in an effort to reduce the CV risk of KTRs who are exposed to several factors that may affect CV outcome. However, mTOR inhibitor therapy is also associated with side effects that could counter this CV benefit and possibly even increase the CV risk of transplanted patients.

Dyslipidemia

The actual impact of everolimus on dyslipidemia in KTRs remains a challenge, as most available studies lack information on statin management in these patients [102].

By contrast, numerous studies have demonstrated dyslipidemia to occur more frequently in patients on mTOR inhibitors compared with those administered CNIs. Tedesco Silva and Pascual showed a greater prevalence of hypercholesterolemia in patients administered everolimus, and total cholesterol and triglyceride levels were lower in patients on standard CNI therapy in the ASCERTAIN trial [50, 52, 56], although other large studies have failed to demonstrate an association (Table 2). Recently, a large meta-analysis showed a greater incidence of hypercholesterolemia in KTRs after conversion from a CNI- to an mTOR inhibitor-based protocol [58]. A similar finding was reported in a smaller meta-analysis, although no significant difference was detected between everolimus and sirolimus [100], and in two randomized studies a dose-dependent effect on total cholesterol levels was shown [103].

Rapalogs are known to increase lipophagy and expression of hormone-sensitive lipase (HSL) and adipose triglyceride lipase (ATGL) leading to lipolysis. In addition, they heighten PCSK9 expression and downregulate LDL receptor expression, resulting in raised LDL values, whereas lipidic deposits are decreased by peroxisome proliferator-activated receptor gamma (PPARg) downregulation [104]. It is noteworthy that everolimus pharmacokinetics are not affected by

Table 2 Blood pressure, new-onset diabetes, and dyslipidemia incidence in comparative studies evaluating everolimus

Author, year (study name)	Blood pressure	NODAT	Dyslipidemia
Budde 2017 (HERAKLES) [46]	NS	NS	NS
Sommerer 2018 (HERAKLES) [47]	NS	NS	NS
Budde 2015 (ZEUS) [48]	NS	NS	NS
Chadban SJ, 2014 (SOCRATES) [9]		NS	NS
Mjornstedt 2015 (CENTRAL) [49]		NS	NS
Holdaas 2011 (ASCERTAIN) [50]	NS	NS	Higher in CNI elimination and reduced CNI arm
De Fijter 2017 (ELEVATE) [51]	DBP lower at m12, but not at m24 in EVR arm	NS	Higher in EVR
Tedesco Silva 2010 [52]		NS	Higher in EVR
Langer 2012 (ASSET) [53]	NS	NS, higher in TAC TL 4–7 ng/ml	NS, higher in TAC TL 4–7 ng/ml
Salvadori 2009 [54]	NS		
Pascual 2018 (TRANSFORM) [56]			Higher in EVR: RR 1.86 (1.59 to 2.17)
Bemelman 2017 (MECANO) [55]			NS

CNI: calcineurin inhibitors; DBP: diastolic blood pressure; EVR: everolimus; m: months; NODAT: new-onset diabetes mellitus after transplantation; NS: not significantly different; RR: relative risk; TAC: tacrolimus; TL: trough level

co-administration of atorvastatin, which supports evidence that statin therapy may be efficacious in counteracting dyslipidemia induced by mTOR inhibitors [105]. Moreover, the combination of fluvastatin and everolimus was shown to induce a prominent and synergistic antiproliferative effect on vascular smooth muscle cells (VSMCs) [106], which may play a pathogenic role in the atherosclerotic process.

Acute rejection

Acute rejection may affect graft survival [107], as an effect of subsequent renal function worsening [108]. In addition, acute rejection is included in the PORT equation as it is a predictor of the risk of coronary heart disease [18], thus highlighting its potential role also as a CV risk factor; this has been confirmed in other studies [109, 110, 117].

The risk of BPAR in patients administered mTOR inhibitors has been largely investigated, mainly as a secondary endpoint or in post hoc analyses, in studies aimed at assessing the efficacy of such therapy in preventing CNI-nephrotoxicity.

Interestingly, in patients on mTOR inhibitor therapy, the risk of BPAR was found to be greatly influenced by 24-h exposure to the drug. In fact, the rate of BPAR was significantly higher when everolimus trough levels were below 3 ng/ml; furthermore, BPAR rates were comparable with those in regimens of mycophenolic acid with standard-exposure CNI when everolimus trough levels were within the recommended range of 3–8 ng/ml [111, 112]. In trials investigating the potential of mTOR inhibitors as a de novo substitute for CNIs, a high rate of BPAR was shown [43, 44, 113], whereas with early conversion from a CNI- to an mTOR inhibitor-based regimen only a slightly higher risk of BPAR was found [46, 51, 114, 115] (Table 3).

Last, reduced-exposure CNIs combined with mTOR inhibitors have been never associated with a higher risk of BPAR when compared with standard therapy [46, 54], even with prolonged follow-up [116]. This strategy, therefore, should be considered for KTRs at low immunological risk, taking into account the potential for graft function preservation.

Proteinuria

Proteinuria negatively affects both patient and graft survival [117–119], and is also an independent predictor of adverse

Table 3 Adverse side effects in comparative studies evaluating everolimus

Author, year (trial)	BPAR	Any adverse event rate	Discontinuation rate	Proteinuria
Budde 2017 (HERAKLES) [46]	NS	Similar	Higher in EVR + MPA	EVR + MPA: 6.5% Reduced CNI: 4.5% STD-CNI: 0%
Sommerer 2018 (HERAKLES) [47]	NS		High conversion to STD-CNI	EVR + MPA: 15.3% Reduced CNI: 12.4% STD-CNI: 10.5%
Budde 2015 (ZEUS) [48]	BPAR NS, AR higher in EVR arm	Similar		Higher in EVR
Chadban 2014 (SOCRATES) [9]	Higher in CNI withdrawal, trend vs CTFE	Similar	Higher in CNI withdrawal	NS
Mjornstedt 2015 (CENTRAL) [49]	NS, DSA NS	Similar	Higher in EVR	NS, higher in EVR
Holdaas 2011 (ASCERTAIN) [50]	NS, NS composite efficacy endpoint	Similar	Higher in CNI elimination and reduced CNI	Higher in CNI elimination at month 12, NS at month 24
De Fijter 2017 (ELEVATE) [51]	Higher in EVR	Similar	Higher in EVR	Higher in EVR
Tedesco Silva 2010 [52]	NS	Similar	Higher in EVR	Higher in EVR 3 mg
Langer 2012 (ASSET) [53]	NS	Similar	Higher in TAC TL 1.5–3 ng/ml	Higher in TAC TL 1.5–3 ng/ml
Salvadori 2009 [54]	NS		Greater in higher EVR exposure + very low exposure CsA	
Pascual 2018 (TRANSFORM) [56]	NS, de novo DSA incidence and AMR rate NS	Similar	Higher in EVR	Higher in EVR (RR 2.24)
Bemelman 2017 (MECANO) [55]	NS, DSA NS	SAE higher with EVR	Higher in EVR	NS

AMR: antibody-mediated rejection; AR: acute rejection; BPAR: biopsy-proven acute rejection; CNI: calcineurin inhibitors; CsA: cyclosporine A; CTFE: composite treatment failure; DSA: donor-specific antibody; EVR: everolimus; MPA: mycophenolate; NS: no significant difference; RR: relative risk; SAE: serious adverse events; STD: standard; TAC: tacrolimus; TL: trough level

CV events and mortality [117, 120, 121]. This was recently confirmed by a cohort analysis of the FAVORIT trial in which urine albumin-creatinine ratio (ACR) greater than 30 mg/g was independently correlated with graft failure, CV events, and all-cause death [122].

Many studies have evaluated the incidence of proteinuria in patients on mTOR inhibitor therapy (Table 3).

Nephrotic-range proteinuria was reported in 64% of KTRs who converted from a CNI- to an mTOR inhibitor-based immunosuppressive regimen [123]. The underlying mechanism is still unknown, even though several studies have emphasized the role of podocytes in the pathogenesis of proteinuria and glomerular damage [124, 125]. Stallone and colleagues demonstrated that mTOR inhibitors can induce a blockade of the expression of the main components of podocyte cytoskeletons and slit diaphragm proteins, the expression of which in graft biopsies was shown to be directly correlated with blood mTOR inhibitor levels [126]. These data support the observation that high sirolimus dose may induce de novo focal segmental glomerulosclerosis, a glomerular disease characterized by significant podocyte alterations [127].

By contrast, evidence exists that sirolimus may exert beneficial effects in proteinuric nephropathy [128], probably by reducing the extent of interstitial fibrosis, the expression of pro-fibrotic genes [128, 129], and blocking proliferation of renal epithelial cells in response to proteinuria [130], at doses considerably lower than those adopted in immunosuppressive protocols. Thus, the crucial point seems to be the dose of mTOR inhibitor, since all the potential side effects of this class of drugs are dose-dependent [131]. Taking this into account, it is conceivable that the combination of mTOR inhibitors with CNI, both at low-doses, could allow adequate protection from rejection and from drug-induced side effects.

Conclusions and perspectives

KTRs are at increased risk of CV morbidity and mortality, and side effects induced by immunosuppressive therapy may be a major contributor to this risk, together with traditional CV risk factors.

mTOR inhibitors have proved to be effective in reducing cytomegalovirus and, to a lesser extent, BK polyomavirus infections in KTRs [132]. In addition, this class of drugs shows anti-oncogenic properties, especially in non-melanoma skin cancer and, furthermore, in other tumors, with an overall reduced incidence of cancer reported in recent studies [133, 134]. Accordingly, everolimus is adopted in immunosuppressive protocols for KTRs at low immunological risk, because of these potential protective effects.

Together with direct anti-proliferative action, possibly explaining at least in part the reduced risk of malignancies, sparing CNIs by introducing mTOR inhibitors could play a major beneficial role in KTRs.

As infection, malignancies and CV disease are the main causes of graft dysfunction in KTRs, the possibility of coupling infection and cancer prevention to CV protection should be of interest to clinicians wanting to improve the overall prognoses of KTRs.

Last, kidney transplant has been suggested as a model of accelerated CV aging. The mTOR pathway regulates many aspects of cellular aging, including autophagy, mitochondrial functions, oxidative phosphorylation, and apoptosis [135]. Furthermore, mTOR is a key modulator of aging and age-related disease [132], and mTOR inhibitors may significantly delay CV aging, as clearly demonstrated in several experimental models and molecular biology of aging endothelial cells [136].

In conclusion, KTRs at higher risk for CV events could be advantaged by mTOR inhibitor introduction in immunosuppressive protocols. This strategy could also be adopted with the aim of minimizing CNI exposure and thus reducing both the incidence and severity of CNI-associated side effects, such as diabetes and hypertension which may increase the risk of adverse CV events and negatively affect both general and graft outcome.

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Compliance with ethical standards

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